MMP-008

New Jersey Department of Health
Medicinal Marijuana Program
PO 360
Trenton, NJ 08625-0360

MEDICINAL MARIJUANA PETITION
(N.J.A.C. 8:64-5.1 et seq.)

INSTRUCTIONS

This petition form is to be used only for requesting approval of an additional medical condition or treatment thereof as a "debilitating medical condition" pursuant to the New Jersey Compassionate Use Medical Marijuana Act, N.J.S.A. 24:6I-3. Only one condition or treatment may be identified per petition form. For additional conditions or treatments, a separate petition form must be submitted.

NOTE: This Petition form tracks the requirements of N.J.A.C. 8:64-5.3. Note that if a petition does not contain all information required by N.J.A.C. 8:64-5.3, the Department will deny the petition and return it to petitioner without further review. For that reason the Department strongly encourages use of the Petition form.

*This completed petition **must** be postmarked **August 1 through August 31, 2016** and sent by **certified mail** to:*

New Jersey Department of Health
Office of Commissioner - Medicinal Marijuana Program
Attention: Michele Stark
369 South Warren Street
Trenton, NJ 08608

Please complete each section of this petition. If there are any supportive documents attached to this petition, you should reference those documents in the text of the petition. If you need additional space for any item, please use a separate piece of paper, number the item accordingly, and attach it to the petition.

---

1. **Petitioner Information**

Name: [redacted]

Street Address: [redacted]

City, State, Zip Code: [redacted]

Telephone Number: [redacted]

Email Address: [redacted]

2. **Identify the medical condition or treatment thereof proposed. Please be specific. Do not submit broad categories (such as "mental illness").**

sporadic hemiplegic migraine (SHM)

3. **Do you wish to address the Medical Marijuana Review Panel regarding your petition?**

☐ Yes, in Person

☐ Yes, by Telephone

☒ No

4. **Do you request that your personally identifiable information or health information remain confidential?**

☒ Yes

☐ No

If you answer "Yes" to Question 4, your name, address, phone number, and email, as well as any medical or health information specific to you, will be redacted from the petition before forwarding to the panel for review.

RECEIVED
AUG 22 2016
OFFICE OF THE CHIEF OF STAFF

5. **Describe the extent to which the condition is generally accepted by the medical community and other experts as a valid, existing medical condition.**

Taken from http://www.healthline.com/health/migraine-rare-and-extreme-types-of-migraines

Hemiplegic migraine affects 0.03 percent of Americans. People with hemiplegic migraines experience paralysis or weakness on one side of the body, disturbances in speech and vision, and other symptoms that often mimic a stroke. The paralysis is usually temporary, but it can last for several days. Two types of hemiplegic migraine exist:

- Familial Hemiplegic Migraine (FHMR): FHM is an inherited genetic migraine disorder that causes hemiplegic migraines. (Genetic testing can determine if a person has the gene mutations that are associated with this migraine variant.) If a parent, sibling, or child has FMR, the chances you will have FHM are higher.
- Sporadic Hemiplegic Migraine (SHM): SHM is associated with hemiplegic migraines that occur in people without the genetic disorder and without a family history of hemiplegic migraines. Both FHM and SHM are diagnosed after a person has symptoms of a hemiplegic migraine on several occasions. However, if that person does not have a relative with diagnosed hemiplegic migraines, doctors may believe the person has SHM—both present the same way; the only difference is the presence of the known genetic risk.

6. **If one or more treatments of the condition, rather than the condition itself, are alleged to be the cause of the patient's suffering, describe the extent to which the treatments causing suffering are generally accepted by the medical community and other experts as valid treatments for the condition.**

Coventional treatments for migraine headaches are ineffective. Treatments do not cause or contribute to the suffering, but are also non-effective.

7. **Describe the extent to which the condition itself and/or the treatments thereof cause severe suffering, such as severe and/or chronic pain, severe nausea and/or vomiting or otherwise severely impair the patient's ability to carry on activities of daily living.**

Abortive and Pain Relief: Migraine-specific abortives, the triptans and ergotamines, are currently contraindicated in the treatment of hemiplegic migraine because of their vasoconstrictive properties and concerns about stroke.

For me personally, each episode is identical symptomatically.
1. Each episode begins with an aura. My vision becomes impaired. From experience, I have about 20 minutes before I become physically impaired. This is especially critical if I am driving at the time this starts.
2. The indescribable migraine pain begins and continues for 4-6 hours.
3. I lose motor function on one side of my body. I can't control my arm and leg, they go limp.
4. I lose the ability to speak. I am speaking in my mind, but the words are mumbled and come out unintelligibly.
5. After approximately 20-30 minutes go by, periods of vomiting begin. After each vomiting session, there is a temporary relief of the headache pain for a few minutes where I regain speech and motor functions temporarilly. The vomiting sessions repeat about once every hour until the migraine subsides.
6. The pain starts again and the cycle repeats for 4-6 hours.
7. Once the episode ends, I am physically exhausted and need the next day to rest and recuperate. The after affects can last for several says.

Each time I have been taken to various emergency rooms for treatment with poor success. Many are unfamiliar with the condition and the fear is that it may be misdiagnosed as a stroke and treated improperly with trip tans or ergotamine's. I carry a letter from my doctor to explain my condition to the ER doctor, but at times, the physician on ER duty has refused to follow my doctor's instructions, which is the danger that the wrong treatment may make my condition worse or irrecoverable.

My mother wrote a chronological history of the migraine episodes I have suffered since birth and I have attached it as well.

8. **Describe the availability of conventional medical therapies other than those that cause suffering to alleviate suffering caused by the condition and/or the treatment thereof.**

   There are no FDA approved treatments for hemiplegic migraine and little likelihood that any will be developed, due to the rarity of the condition. The most commonly prescribed abortive migraine drugs are contraindicated for hemiplegic migraine.

9. **Describe the extent to which evidence that is generally accepted among the medical community and other experts supports a finding that the use of marijuana alleviates suffering caused by the condition and/or the treatment thereof.** *[**Note:** You may attach articles published in peer-reviewed scientific journals reporting the results of research on the effects of marijuana on the medical condition or treatment of the condition and supporting why the medical condition should be added to the list of debilitating medical conditions.]*

   Attached to this form are hard copies relevant to answering the question above and here are the links:

   http://www.ncbi.nlm.nih.gov/pubmed/26749285

   http://www.blisstree.com/2008/04/30/mental-health-well-being/marijuana-for-migraine-276/

   http://www.livescience.com/53461-medical-marijuana-reduces-migraine-frequency.html

   http://medicalmarijuana.procon.org/view.answers.php?questionID=000218

10. **Attach letters of support from physicians or other licensed health care professionals knowledgeable about the condition. List below the number of letters attached and identify the authors.**

    In 2013, I tried to get approval for medical marijuana by reaching out to a NJ physician authorized to prescribe medical marijuana. My treating physician was Dr. Mark Green, Director of Headache and Pain Medication at Mount Sinai School of Medicine in New York. Dr Green wrote a letter to the NJ physician describing my condition and recommending that I be treated with medical marijuana. I have attached a copy of that letter for your review. My request was not approved despite Dr Green's letter recomending this treatment

    Excerpts from his letter:
    "I explained that triptans and ergots were contraindicated."
    "The medical management was unsuccessful."
    "There are no FDA approved treatments for hemiplegic migraine and little likelihood that any will be developed, due to the rarity of the condition. The most commonly prescribed abortive migraine drugs are contraindicated."

    Also, I have attached the results from my initial consultation with Dr Green in 2006

I certify, under penalty of perjury, that I am 18 years of age or older; that the information provided in this petition is true and accurate to the best of my knowledge; and that the attached documents are authentic.

Signature of Petitioner	[redacted]	Date August 15, 2016

Columbia University College of Physicians and Surgeons

Mark W. Green, MD
Director of Headache Medicine

Clinical Professor of Neurology

16 East 60th St., Suite 310

New York, NY 10022
Office: 212.326.8456
Fax: 212-326-8530

Patient name: [redacted]
Date: [redacted]
DOB:
Physicians: Dr. Muenzen (report sent)
Accompanied By:

CC: 18-year-old right handed, non-diabetic, non-hypertensive male, headaches since age 3, getting worse last few years.

HPI: Attacks every few years. First aura is an aura; gets a fortification spectra with a scotoma right side. That lasts 45 minutes. Then cannot speak (posterior aphasia), that lasts up to 6 hours. Then numbness whole right side. Headache begins at that point, gets nauseated and vomits. Pain is generalized and severe and he is immobilized. Gets very tired and tries to fall asleep, but often vomits and cannot sleep. Attacks often triggered by bump on head.

Has been using Advil or hydrocodone 7.5.

Treatment present: Preventive: see intake
Acute:

Treatment in past: Preventive:
Acute:

Testing: MRI: Ophthalmologic: Cervical spine: Bloods: Other: MRI brain age 10. Never redone

Other Medical History/ROS: (see questionnaire for negatives, personally discussed with patient), has weight loss this year, no cause found

Mood: normal
Allergies: none
Medications: nothing in addition

Social/Work History: Occupation: starting [redacted] next month Family: with children.
Habits: Caffeine: very little ETOH: Tobacco: none Exercise: swimming Diet:

Significant Family Medical History: see intake sheet: no family history of dementias or hemiplegic migraine
Mother age 50 had migraines Father age 53 Brothers ages Sisters ages Offspring ages

Examination: Height: 5 6 Weight: 133

General: This is a thin young male, who is afebrile, fully ambulatory and alert. Posture and gross motor behavior are normal. Personal hygiene is good and dress is appropriate. Facial expression at rest is normal and varies appropriately with emotion. There are no cranial or skeletal malformations. The sclera and conjunctiva are normal. No TMJ clicks, no paranasal sinus tenderness.

ENT: Soft palate: Retropharyngeal space: Nasal airway:

Mental Status: Oriented to person, place, and date. Memory and calculations intact (see questionnaire). Euthymic. Speech is of normal clarity, inflection, pace and volume. Thought content is coherent, organized, and relevant without tangentiality; ideas of reference, delusions or hallucinations.

Cardiovascular: BP: 100/70 HR: 60 regular. Peripheral pulses are normal and there is no clubbing, cyanosis or edema. No carotid or thyroid bruits. Good symmetrical pulsations of the temporal arteries with no tenderness.

Cranial Nerves:

II, III, IV, VI: VA: VF's grossly normal: PERLA. EOMI. No nystagmus. Normal pursuit and saccades. Fundoscopy reveals flat discs with good venous pulsations, no hemorrhages or exudates. OKNs normal

V and VII: Facial sensation and motor function are normal.

VIII: Weber midline RP ~4 256 TF equal bilaterally

IX: The palate rises symmetrically on volition and reflex.

XI: Shoulder shrug normal bilaterally. SCM power normal bilaterally.

XII: The tongue protrudes midline without atrophy or fasciculations.

Neuromuscular: Power is intact, 5/5 throughout. Reflexes: biceps, brachioradialis, triceps, quadriceps femoris and Achilles all 2+ bilaterally. Jaw jerk: There is no pronator drift. Normal gait and arm swing. Normal tone. No tremor. RAM, FN, HKS normal. Normal station. Romberg normal. Atavistic reflexes: snout: Myerson's: Hoffman's: palmomental: grasp: Babinski:

Sensory: ST, PP, temperature and vibration normal throughout.

Musculoskeletal: Posture: Hip tilt: Jaw/TMJ: normal range of motion without popping, dislocation or tenderness. Cervical spine: full ROM without tenderness

Assessment: hemiplegic migraine; sporadic, not familial

Plan/Treatment changes:

Medications: consider verapamil, based on BP, and use 81 mg aspirin daily.
Alternatives would be Depakote or Topamax
For an attack in ER, use IV prochlorperazine 10 mg over 5 minutes and repeat in 20 minutes and use concomitant Benadryl or IV Depacon 1 gram in 50 cc of normal saline administered rapidly over 5 minutes

Testing: MRI scan with gad to evaluate for T2 lesions (then use acetazolamide)
Although I explained that triptans are contraindicated, there is no evidence that it is harmful and some evidence that it is helpful; but more studies needed

Other:

Next appointment: prn

Total time: 1 ½ hours.

Mark W. Green MD

Mark W. Green, MD
Professor of Neurology and Anesthesiology

Director of Headache and Pain Medicine
Department of Neurology
Mount Sinai School of Medicine

5 East 98th Street, 7th Floor, Box 1139
New York, NY 10029

212 241-2726

[redacted] 2013

Walter Husar MD
170 East Main Street
Rockaway, NJ 07866

Re: [redacted]

Dear Dr Husar:

I am writing to you in support of [redacted] request to use medical marijuana for his hemiplegic migraines. He has been using marijuana at home for over a year initiating it as soon as the migraine aura begins, and has successfully aborted the attacks. In the past, he was treated in various emergency rooms with poor success.

I first evaluated him on [redacted] 2006 when I served as director of Headache Medicine at Columbia University. The diagnosis of sporadic (non-familial) hemiplegic migraine was made and various medication suggestions were made including verapamil, divalproex and topiramate. I explained that triptans and ergots were contraindicated.

I last evaluated [redacted] at Mt Sinai on [redacted], 2013 where he described typical scotoma in his right visual field, lasting 30 minutes and followed by a stabbing headache lasting 6 hours and hemiplegic spells. The medical management was unsuccessful.

The medical literature on the use of marijuana in migraine is extensive, and studies have largely positive but of poor quality. The pharmaceutic industry is working to develop cannabinoid receptor agents specifically for the treatment of migraine.

There are no FDA approved treatments for hemiplegic migraine and little likelihood that any will be developed, due to the rarity of the condition. The most commonly prescribed abortive migraine drugs are contraindicated.

In view of these facts, I hope that you will be willing to care for [redacted] and permit him to use medical marijuana.

[redacted] MIGRAINE JOURNAL

Born - [redacted]**/88-** [redacted] is my second son. He was two weeks late. I had a normal nine month pregnancy, but had problems with allergies and with my nose being stuffy the last few months once the buds came on the trees. I had a normal vaginal delivery free of all drugs for mother and child. [redacted] had normal development, except was born with dry skin. He has Ichthyosis Vulgaris "X" linked. My sister's second son has the same thing.

[redacted] was a good baby, slept well and never complained about anything. When he was three he was running around outside with a playmate when he tripped and hit his forehead on a step and cut his forehead. He did not have a concussion, just needed to be stitched up by a surgeon. He recovered very well and seemed fine after that. When he was 4, I put him in the nursery school by our house. This was to aid in his social development. He was signed up for only two afternoons a week. He was only there for a few times when I picked him up one day and found him bleeding from the nose.

[redacted]**/92-** (4 years 3 months old) He had fallen at the Nursery school. He had blood coming from his nose when I picked him up. I asked the teachers what happened and everyone said they did not see anything. That night he was very tired and went to bed early. In the morning while feeding him he started to vomit and said his head hurt. I called my friend who was nurse and she said his eyes showed he had a concussion. I called the school and still no one would admit they had seen anything but they paid for his hospital stay.

1995- (6 years old) We discovered that he became allergic to shrimp, although he ate shrimp previously with no effects.

[redacted]**/95** [redacted]**/95** (6 years old) He had been playing with his brother jumping off the couch. He hit the left side of his head on the side of the couch. Within a half hour he was complaining of a headache and not being able to feel his right hand. Then his speech began to be slurred. He breathing seemed shallow. We took him to the local Emergency Room and they put him in the Trauma unit, gave him oxygen and watched his vital signs. They took him for a CAT scan and it showed no signs of concussion. After throwing up, his speech became clear again and his feeling in his arm returned. In the morning they released him. He was tired and sore for a few days.

[redacted]**/95-** Playing outside was hit in the head with a football. I noticed the same pattern, a half hour after being hurt, he starts to vomit and complain of head pain and the slurring speech and the arm feels heavy with pins and needles. I called the doctor and I kept him home and stayed up all night watching him. When he woke in the morning, he complained of a sore head and was very tired.

[redacted]**/96-** He was playing outside catching lighting bugs. We thought he must have hit his head while searching, but he said he knew he did not hit his head. He said he started seeing a black spot in front of his eye. He started to get scared and complained of his head starting to hurt. In a half hour he started vomiting. He continues to vomit till he gets the dry heaves. He has trouble talking and saying words. His eyes were going around and he complains his arm is feeling heavy seems confused. Says his leg is feeling funny on the same side. Can't sit wants to lay flat. When he throws up the pressure seems to get better and he is able to talk better. When calling the doctor, she says to keep an eye on him if I can wake him and sees if he will talk once every hour. So I watched him through the night. At 4:00 in the morning he said he had to go to the bathroom. He got up and walked on his own and took some water, but was very tired and went back to sleep. At 9 am I wake him and he said he was still tired and his head was still sore.

[redacted]**/96** – (8 years old) Birthday spent the morning having a MRI. Nothing was abnormal was also seeing a neurologist. Dr. Feldman in Hackensack.

[redacted] –EEG was normal, both tests did not show anything.

[redacted]**/97** - [redacted] –Snow day at school. He woke up at 7:15 and asked if there was school. I told him no and to go back to bed. He complained that his hand felt like pins and needles. I said he must have slept wrong and the he should try to get more sleep. He returned to bed until 8:30. He had some bagel and then started to play. About 10:30 he said he could not see well out of his right eye. At 11:00 he said he started to feel funny. He was getting a headache. I gave him Tylenol. By 11:30 he started to vomit and screaming of pain behind his right eye. He vomited till bile came up. His arm was heavy also speech became slurred. He can't seem to focus as his eyes roll around. He said he was hot, then cold. When I touched him he said my hand was real hot. I gave him feverall in the butt to stop him from vomiting. In sleep he was panting and grinding his teeth. By one o'clock he was talking better but felt cold. He said he felt a bit dizzy a few days before this happened. At 4:45 came out of bed and said his head was still sore. Both my doctors were away on vacation. I called the nurse 2-3 times over the course of the day.

[redacted]**/97**- 7:16 at night. Said he felt a numb feeling in his hand. I gave him Excedrin. By 7:45 said he saw spots. His speech started to get funny. He started to cry and get upset because by now he knew what was coming. His head did not hurt yet but there was some pain on the right side that comes and goes. By 8:45 he was vomiting. Pain got worse and he was panting. Once he throws up he says the pain is less. Seems very sensitive to noises and very restless he is sensitive to touch. He said he was hot. He kept smacking his lips. By 9:20 resting better he went to sleep he slept the whole night and woke at 7:00 he still has dull pain in his head when bending over it hurts. I gave him more Excedrin. Let him stay home from school. Said he still sees some spots.

2 years went by and he had no migraines. We thought it was over.

[redacted]**/99** [redacted] - While playing ran into his brother. Hit his eyebrow on brother's hip while playing baseball in the yard. At 8:00 had spots in front of his eyes. Took 1 Excedrin. A half hour later took another Excedrin. After another half hour he started vomiting. Up till 12pm then went to sleep was hot and cold and confused, he could not talk. He seems to be itchy and kept putting his hand down his pants. Talking and not able to make any sense of what he is saying. Extreme pain in his head. Shallow breathing and grinding teeth, smacking his lips. The next day said head was sore. Stayed home for two days. Said he was dizzy a few days ago.

3 years go by with only small headaches that go away with Advil or Tylenol, Excedrin migraine, etc. But when the spot comes first he knows that he has 20 minutes, before things start to happen.

[redacted]**/03**-[redacted] A kid at school shook him against a locker. A half hour later he started the migraine. It was very bad. I gave him some Excedrin when I brought him home. But all he did was lie on the floor next to the toilet and complain and scream in pain. The worst I have ever seen him. I called our Doctor, he said take him to the emergency room. He had the speech slurred and the vomiting. I got him in the car with a bucket and took him to the E.R. After a CAT scan they did not see anything, they gave him a shot of Demerol. In about an hour he started to seem better. They kept him for about six hours and let him go home. He stayed out of school for two days.

[redacted]**/04** Had surgery on his knee dislocated it at school. Prior to surgery, found the heart has a loose floppy valve. Dr. will keep an eye on it, says he may have a connective tissue disorder?? On the [redacted] started a migraine.

[redacted]/04- He started with saying he felt a headache coming on, his speech started to get slurred and confused. I called the Doctor and asked if I could try giving him one of the Hydocodone pills he had from the surgery. He said try it. He did have some vomiting but he did not seem to be in as bad pain as other times. He seemed to get out of it faster. But still complained of soreness the next day.

[redacted]/04 - [redacted] was at work, (4 miles from home) he got the spot in front of his eye. He told work he had to leave right away and get home. [redacted] was home and gave him the Hydocodone and kept an eye on him until I came home. I was glued to the phone all the way home listening to everything and it seemed that he did not suffer as much since he took the pill right away. We still wonder if he gets enough into him before the vomiting starts, maybe we can stop it from happening. He was sleeping when I got home and was able to say a few words, so I let him go back to sleep. Still sore the next day which was Saturday. But he went back to school on Monday.

2005- No migraines to report (started to drive). But during the summer had problems with his stomach and had several blood tests, and sample test but had to get a colonoscopy in Sept. after loosing 30 lbs for no reason. They found nothing and said it must have been a virus in his system??

[redacted]/06- [redacted] - off school. While over a friends house at 5:50 pm. He called me to say he had a spot in front of his eyes that looked like a backwards number six. He said it had some colors coming form it with some ripples like a water effect. I asked him to get some Tylenol or Excedrin or something like that to take. They had Aleve, so he took two. I drove over to pick him up which was 15- 20 min.later. He was just starting with his speech. We got him home and I called the Doctor. I had no more Hydocodone left. The doctor said if he gets back bring him to the E.R. for a shot of Demerol.

We knew he was going to start vomiting and he did not seem too bad but then got much worse. By 9:30 we got him ready to go to the ER. At the hospital we had the same doctor that treated him in 2003 and we explained the history. He gave him anti nausea and Demerol. But after a few hours, [redacted] was still unable to speak clearly and the words that were coming out were all wrong and he was not getting any relief form the vomiting. He was not loosing the pressure and was having a hard time trying to talk. He would be pulling on his hair as if he wanted to pull it out of this head and was screaming in pain.

When he was at a resting state he had some trouble breathing. So they put oxygen on him. They gave him a second shot and some more meds for the vomiting. He did not show some good signs until about 4:30 in the morning. They were going to do a CAT scan but decided he was looking better. They let him go home at 6:30 in the morning on the [redacted]. They had taken 4 vials of blood and also urine and all the test results they took they said were normal. This seemed to be the worst episode we have had. [redacted] stayed out of school for two days. He said his stomach is sore from vomiting so hard and his head feels sore and he slept for two days almost around the clock. I woke him to eat and to drink so that he did not become dehydrated.

[redacted]/09- Last episode on record since treatment with marijuana. Same as other attacks in the past. Trouble breathing, called ambulance, was given oxygen and transported to ER. Treatment same as in the past, no drugs administered.

Subsequent onset of attacks treated with marijuana immediately upon onset of symptoms. No attacks suffered since starting this regime in the last 7 years although there have been many instances where the migraine symptoms started and were abated.

Neuroendocrinology Letters Nos.1/2, Feb-Apr Vol.25, 2004
 ISSN 0172–780X www.nel.edu

REVIEW ARTICLE

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

Ethan B. Russo

Senior Medical Advisor, GW Pharmaceuticals, 2235 Wylie Avenue, Missoula, MT 59802, USA

Correspondence to: Ethan B. Russo, M.D.
Senior Medical Advisor, GW Pharmaceuticals
2235 Wylie Avenue
Missoula, MT 59802, USA
VOICE: +1 406-542-0151
FAX: +1 406-542-0158
EMAIL: erusso@montanadsl.net

Submitted: *December 1, 2003*
Accepted: *February 2, 2004*

Key words: **cannabis; cannabinoids; medical marijuana; analgesia; migraine; headache; irritable bowel syndrome; fibromyalgia; causalgia; allodynia; THC; CBD**

Neuroendocrinol Lett 2004; 25(1/2):31–39 NEL251204R02 *Copyright® Neuroendocrinology Letters www.nel.edu*

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.

Abbreviations

AEA:	arachidonylethanolamide, anandamide
2-AG:	2-arachidonylglycerol
CB_1:	cannabinoid 1 receptor
CBD:	cannabidiol
CECD:	clinical endocannabinoid deficiency
CGRP:	calcitonin gene-related peptide
CNS:	central nervous system
CRP:	complex regional pain
ECT:	electroconvulsive therapy
FAAH:	fatty acid amide hydrolase
fMRI:	functional magnetic resonance imaging
5-HT:	5-hydroxytryptamine, serotonin
GI:	gastrointestinal
IBS:	irritable bowel syndrome
NMDA:	N-methyl-d-aspartate
PAG:	periaqueductal gray
PET:	positron emission tomography
PTSD:	post-traumatic stress disorder
RSD:	reflex sympathetic dystrophy
THC:	Δ^9-tetrahydrocannabinol
TMJ:	temporomandibular joint
VR_1:	vanilloid 1 receptor

Introduction

In the initial lines of his 1895 work, *Project for a Scientific Psychology,* Sigmund Freud stated [1] (p. 295), "The intention is to furnish a psychology that shall be a natural science: that is, to represent psychical processes as quantitatively determinate states of specifiable material particles, thus making those processes perspicuous and free from contradiction." Freud was frustrated in this effort, and found that available science at the twilight of the 19th century was not capable of providing biochemical explanations for cerebral processes, leading him to pursue psychodynamic theory alternatively.

At the dawn of the 21st century, despite astounding progress in psychopharmacology, medicine remains challenged in its attempts to understand and successfully treat a large number of recalcitrant syndromes, noteworthy among them, migraine, fibromyalgia, and irritable bowel syndrome (IBS). For many physicians these problematic entities suggest a psychosomatic or "functional" etiology that remains shorthand for a diagnosis where our biochemical understanding and therapeutic vigor fall short of the mark.

In the last fifteen years, however, the discovery of the endogenous cannabinoid (endocannabinoid) system [2] has provided new insights into a neuromodulatory scheme that portends to provide better explanations of, and treatments for, a wide variety of previously intractable disorders, particularly painful conditions (reviewed in [3; 4]).

After all, for each neurotransmitter system there are pathological conditions attributable to its deficiency: dementia in Alzheimer disease due to loss of acetylcholine activity, Parkinsonism due to dopamine deficiency, depression secondary to lowered levels of serotonin, norepinephrine or other amines, etc. Should the situation be any different for the endocannabinoid system, whose receptor density is in fact greater than many of the others? This article will explore that question and propose a concept first articulated in prior publications [5; 6], that a clinical endocannabinoid deficiency (CECD), whether congenital or acquired may help to explain the pathophysiology of certain diagnostic pitfalls, especially those characterized by hyperalgesia, and thereby provide a basis for their treatment with cannabinoid medicines.

Mechanisms of action of cannabis and THC have recently been elucidated with the discovery of cannabinoid receptors and an endogenous ligand, arachidonylethanolamide, nicknamed anandamide, from the Sanskrit word *ananda,* or "bliss" [7]. Anandamide (AEA) inhibits cyclic AMP mediated through G-protein coupling in target cells, which cluster in nociceptive areas of the CNS [8]. Preliminary tests of its pharmacological action and behavioral activity support similarity of AEA to THC [9], and both entities are partial agonists at the CB_1 receptor. Pertwee [4] has examined the pharmacology of cannabinoid receptors and pain in detail.

Methods

Available literature was reviewed, and literature searches pursued via the National Library of Medicine database and other Internet resources.

Results

Migraine

Migraine is a public health issue of astounding societal cost. There are an estimated 23 million sufferers in the USA [10], with an economic impact of $1.2 to $17.2 billion annually [11]. The neurochemistry of migraine is among the most complex of any human malady, and its relation to cannabinoid mechanisms has been examined previously in brief [12] and in depth [5].

Serotonergic pathways are considered integral to migraine pathogenesis and treatment. Numerous points of intersection with cannabinoid mechanisms are evident: THC inhibits serotonin release from the platelets of human migraineurs [13]; THC stimulates 5-HT synthesis, inhibits synaptosomal uptake, and promotes its release [14]; AEA and CB_1 agonists inhibit rat serotonin type 3 ($5\text{-}HT_3$) receptors [15] involved in emetic and pain responses. Additionally, AEA produces an 89% relative potentiation of the $5\text{-}HT_{1A}$ receptor response, and a 36% inhibition of the $5\text{-}HT_{2A}$ receptor response [16]. Another endocannabinoid, 2-arachidonylglycerol (2-AG) inhibited $5\text{-}HT_{2A}$ by 28%. Recently, mild but significant similar activity on $5\text{-}HT_{2A}$ has been demonstrated for cannabidiol [17], and cannabis terpenoids [18]. Higher concentrations of anandamide decreased serotonin and ketanserin binding (the latter being a $5\text{-}HT_{2A}$ antagonist) [19]. These observations support putative efficacy of therapeutic cannabinoids in acute migraine (agonistic activity at $5\text{-}HT_{1A}$ or D) and in its prophylactic treatment (antagonistic activity at $5\text{-}HT_{2A}$) [20].

The importance of dopaminergic mechanisms in migraine has also been explored [21]. 6-hydroxydopamine, which causes degeneration of catecholamine

terminals, blocked THC antinociception [22]. AEA stimulates nitric oxide formation through inhibition of presynaptic dopamine release [23]. Dopamine blocking and modulatory effects of cannabis and THC have been demonstrated in studies of Tourette syndrome [24; 25], and schizophrenia in Germany [26], suggesting that THC may similarly modulate dopaminergic imbalances in headache.

Inflammatory mechanisms affected by cannabis are legion (reviewed [27–31]. THC and cannabinoids inhibit prostaglandin E-2 synthesis [32]; smoked cannabis reduces platelet aggregation [33]; THC demonstrated an oral potency as an anti-inflammatory 20 times that of aspirin and twice that of hydrocortisone [34], and cannabidiol (CBD) inhibited both cyclooxygenase and lipoxygenase. Similarly, anandamide and metabolites are substrates for brain lipoxygenase [35]. Opiates, cannabinoids and eicosanoids signal through common nitric acid coupling [36], while THC blocks the conversion of arachidonate into metabolites derived by cyclooxygenase activity, and stimulates lipoxygenase, promoting down-regulation of inflammation.

CNS beta-endorphin levels are depleted during migraine attacks [37], but THC experimentally increases them [38]. THC additionally regulates substance P and enkephalin mRNA levels in the basal ganglia [39]. THC affects an analgesic brainstem circuit in the rostral ventromedial medulla that interacts with opiate pathways [40], mediating antinociception after activation of neurons in the midbrain periaqueductal grey matter (PAG), a putative migraine generator area [41], wherein THC and other cannabinoids are antinociceptive [42]. The PAG is an integral processor of ascending and descending pain pathways, fear and anxiety [43]. Additional support is provided by studies demonstrating tritiated sumatriptan binding in human PAG [44], and that THC administration elevates proenkephalin gene expression in the PAG [45]. Most compelling is data supporting tonic activity of anandamide in the PAG with production of analgesia, and hyperalgesia upon cannabinoid antagonism [46].

Cannabinoids may represent a therapeutic advantage over opiates, particularly in treatment of neuropathic pain [47]. Opiates commonly aggravate migraine or even provoke its appearance [48], as observed therapeutic doses of morphine failed to alleviate acute attack and increased hyperalgesia in migraineurs during inter-ictal periods.

A trigeminovascular system has long been implicated as integral to the pain, inflammation and secondary vascular effects of migraine, linked through the NMDA/glutamate system [49]. Cannabinoid agonists inhibit voltage-gated calcium channels, and activate potassium channels to produce presynaptic inhibition of glutamate release [50], without dissociative effects noted with other NMDA inhibitors, such as ketamine. Subsequently, THC was shown to modulate glutamatergic transmission through a reduction without blockade [51]. NMDA antagonism was felt to be effective in eliminating hyperalgesia associated with migraine [52], as well a "secondary hyperalgesia" with exaggerated responses to noxious stimuli in areas adjacent to the pain. NMDA blockade was recommended to treat chronic daily headache [53]. This group also addressed how a genetic predisposition ("third hyperalgesia") may lead to a "chronicization" of migraine through NMDA stimulation [54].

THC and CBD phytocannabinoids also act as neuroprotective antioxidants against glutamate neurotoxicity and cell death mediated via NMDA, AMPA and kainate receptors [55], independently of cannabinoid receptors, and exceed the antioxidant potency of vitamins C and E.

Migraine is a complex neurochemical disorder with myriad effects beyond pain. Its tendency to produce photophobia and phonophobia, even between discreet attacks [56], may be considered suggestive of a "sensory hyperalgesia," as these normally tolerated sensations take on painful proportions.

The combination of endocannabinoids and their inactive precursors have been dubbed an entourage effect [57], and an analogous synergy of phytocannabinoids, cannabis terpenoids and flavonoids has also been suggested and analyzed at some length [58]. The unique attributes of cannabis to affect serotonergic, dopaminergic, opioid, anti-inflammatory, and NMDA mechanisms of migraine, both acutely and prophylactically, have rendered it a proposed "ideal drug" for its treatment [5].

Migraine is a strongly genetic disorder, but similar symptoms are acquired under conditions of closed head injury, where the "post-traumatic syndrome" displays similar symptoms. A protective role of endocannabinoids in such settings is evident in the findings that 2-AG is elevated after experimental brain injury, and that it plays an important neuroprotective role [59].

Unfortunately, no organized clinical trials of cannabis in migraine have been performed. While documentation of the use of cannabis for migraine suggests a 4000 year history, and it was a major indication for cannabis medicines in Western society between 1842 and 1942 [5], there have been few modern studies beyond the "anecdotal" [5; 60–62]. Surveys in California indicate that of 2480 patients served by the Oakland Cannabis Buyers' Club, 127, or 5%, sought cannabis for treatment of chronic migraines [63]. Success rates of some 80% with North American strains of cannabis have been estimated based on clinical contact [5]. Experience in prophylactic use of Marinol® (synthetic THC) in some ten patients was disappointing, with some decrement in frequency and severity of attacks, but not total remission or "cures" claimed by 19th century authors with extracts of Indian hemp [5]. The difference may well be due to a nearly total dearth of cannabidiol in North American cannabis strains [64] (see discussion below), and the observed possibility of CBD modulation of serotonergic function [17]. More formal documentation of clinical efficacy would be distinctly welcome.

Fibromyalgia

Fibromyalgia, or myofascial pain syndrome, is an extremely common but controversial condition, whose very basis has been questioned, particularly among neurologists [65]. Even this author must admit to past prejudice in labeling it a "semi-mythical pseudo-disease." Notwithstanding these opinions, the condition is the most frequent diagnosis in American rheumatology practices. Bennett has provided an excellent review [66], emphasizing new insights into fibromyalgia as a condition indicative of "central sensitization" and amplification of somatic nociception. While no clear chemical or anatomical pathology has been clarified in tender muscle points, these present a self-sustaining and amplifying influence on pain perception in the brain over time, and lead to a concomitant disturbances in restful sleep, manifestations of dysautonomia, and prevalent secondary depression. Interestingly, the application of standard antidepressant medication to the latter, and pharmacotherapy in general, provide disappointing results in fibromyalgia treatment. Has a promising therapeutic avenue been missed?

Returning to the work of Nicolodi and Sicuteri, the "secondary hyperalgesia" manifested by an increased response to noxious stimuli in areas adjacent to the pain is common to migraine and fibromyalgia (see below). These authors suggested NMDA blockade as an approach to pain in defects of serotonergic analgesia in fibromyalgia [67].

Several studies of Richardson and her group provide key support for a relation of fibromyalgia and similar conditions to a clinical endocannanabinoid deficiency. An initial study [68] demonstrated that intrathecal injection of SR141716A, a powerful cannabinoid antagonist/inverse agonist, resulted in thermal hyperalgesia in mice. This suggests that the endocannabinoid system regulates nociceptive thresholds, and that absence of such regulation, or endocannabinoid hypofunction, underlies hyperalgesia and related chronic pain conditions. In a subsequent study [69], oligonucleotides directed against CB_1 mRNA produced significant hyperalgesia. Additionally, the hyperalgesic effect of SR141716A was blocked in a dose-dependent manner by co-administration of two NMDA receptor antagonists, again supporting tonic activity of the endocannabinoid system under normal conditions. On this basis, it was suggested that cannabinoid agonists would be applicable to treatment of chronic pain conditions unresponsive to opioid analgesics.

Further investigation demonstrated that intrathecal AEA totally blocked carrageenan-induced spinal thermal hyperalgesia, while having no effect on normal thermal sensory and antinociceptive thresholds [70]. Additionally, AEA inhibited K^+ and capsaicin-evoked calcitonin gene-related peptide (CGRP) release, and CB_1 receptors were identified in rat sensory neurons and trigeminal ganglion. On this basis, the authors recommended cannabinoids for disorders driven by a primary afferent barrage (e.g., allodynia, visceral hyperalgesia, temporomandibular joint pain (TMJ), and reflex sympathetic dystrophy (RSD)), and that such treatment could be effective a sub-psychoactive dosages.

Another study examined peripheral mechanisms [71], wherein AEA acted on CB_1 to reduce hyperalgesia and inflammation via inhibition of CGRP neurosecretion in capsaicin activated nerve terminals. This is akin to mechanisms of "sterile inflammation" observed centrally in migraine, where CGRP is felt to be an important mediator [5]. Overall the results supported the notion that endocannabinoids modulate neurogenic inflammation through inhibition of peripheral terminal neurosecretion in capsaicin-sensitive fibers. AEA demonstrated anti-edema effects in addition to anti-hyperalgesia. Similar implications were provided by another study [72], in which WIN 55,212–2, a powerful CB_1 agonist, blocked capsaicin-induced hyperalgesia in rat paws. Once more, the benefit occurred at a dosage that did not produce analgesia or motor impairment, suggesting therapeutic benefit of cannabinoids without adverse effects. Similarly, local THC administration was evaluated in capsaicin-induced pain in rhesus monkeys [73], where, once more, pain was effectively reduced at low dosage, and was blocked by a CB_1 antagonist.

Another concept that is important to understanding of fibromyalgia is "wind-up," a central sensitization of posterior horn neurons in pain pathways that occurs secondarily to tonic impulses form nociceptive afferent C fibers dependent on NMDA and substance P synaptic mechanisms in the spinal cord [74]. Similar mechanisms were implicated in TMJ dysfunction and RSD/CRP syndromes. The authors felt that some unknown peripheral tonic mechanism maintains allodynia, hyperalgesia, central sensitization and enhanced wind-up. Unfortunately, an obvious explanation was overlooked. In a previous publication [75], it was demonstrated that of wind-up was decreased in dose-dependent fashion by WIN 55,212 in spinal wide dynamic range and nociceptive-specific neurons. Thus, cannabinoids were able to suppress facilitation of spinal responses after repetitive noxious stimuli without impairment of non-nociceptive functions.

On a practical level, once more there have been no formal clinical trials of cannabis or THC in treatment of fibromyalgia. However, 21 California patients listed fibromyalgia and 11 myofascial pain (1.3% of a clinical population of 2480 subjects) as primary diagnoses leading to their usage of clinical cannabis [63]. Anecdotal reports to this author and other clinicians support unique efficacy of cannabis beyond conventional pharmacotherapy for alleviation of pain, dysphoria and sleep disturbances.

Irritable Bowel Syndrome (IBS)

IBS is another difficult clinical syndrome for patients and their physicians. It is characterized by fluctuating symptoms of gastrointestinal pain, spasm, distention, and varying degrees of constipation or especially diarrhea. These may be triggered by infection,

but dietary indiscretions also figure prominently in discrete attacks. Although many clinicians regard it as a "diagnostic wastebasket," irritable bowel syndrome represents the most frequent referral diagnosis for American gastroenterologists. Once more, a wide variety of treatments including atropinic agents, antidepressants and others affecting a myriad of neurotransmitter systems are prescribed, often with inadequate clinical benefits.

That endocannabinoids are important in GI function was powerfully underlined by the fact that 2-arachidonylglycerol (2-AG) was first isolated in canine gut [76].

In a recent review [77], the concept of "functional" bowel disorders as disturbances displaying "visceral hypersensitivity" was emphasized, involving a veritable symphony of neuroactive and pro-inflammatory modulators. In the susceptible subject, these lead to gastrointestinal allodynia and hyperalgesia to stimuli that would not discomfit the unaffected individual. The role of vanilloid mechanisms in IBS was also explored, and it is worth emphasizing that anandamide is an endogenous agonist at VR_1 receptors, as is the phytocannabinoid cannabidiol (CBD) [78]. Repetitive VR_1 stimulation rapidly produces a sensory neuron refractory state that would be a clinical advantage in treatment of visceral hypersensitivity.

Pertwee has examined the relationship of cannabinoids to gastrointestinal function in depth [79]. To summarize: The enteric nervous systems of mammals express CB_1 and stimulation depresses gastrointestinal motility, especially through inhibition of contractile neurotransmitter release. Observed effects include delayed gastric emptying, some decrease in peptic acid production, and slowed enteric motility, inhibition of stimulated acetylcholine release, peristalsis, and both cholinergic and non-adrenergic non-cholinergic (NANC) contractions of smooth muscle, whether circular or longitudinal. These effects are mediated at the brain level as well as in the GI tract (This supports a chestnut frequently invoked by this author, "The brain and the gut speak the same language."). These effects are opposed by CB_1 antagonists (e.g., SR141716A). This would strongly support the notion that GI motility is under tonic control of the endocannabinoid system. The latter concept was reinforced by additional investigation from the same laboratory [80], in which it was demonstrated that the virtually all of the immunoreactive myenteric neurons in the ganglia of rat and guinea pig expressed CB_1 receptors, and that there was a close correlation of such receptors to fibers labeled for synaptic protein, suggesting a fundamental role in neurotransmitter release. Additionally, it has been shown that chronic intestinal inflammation results in an up-regulation or sensitization of cannabinoid receptors [81]. CBD has little effect on intestinal motility on its own, but synergizes the effect of THC in slowing transit of a charcoal meal when used in concert [82].

In the basis of available data, Di Carlo and Izzo recommended the application of cannabinoid drugs in treatment of IBS in humans [83]. To date, those studies have not eventuated, but cannabis has a long history in treating cholera, intestinal colic and related disorders (reviewed in [84]), and cannabis figures prominently in IBS treatment in testimonials on the Internet. Though anecdotal, reports suggest unique efficacy of symptomatic relief at cannabis dosages that do not impair activities of daily living. In comparison, recent trends in pharmacotherapy provide interesting contrasts. Alosetron, a $5\text{-}HT_3$ receptor antagonist marketed for females with diarrhea-predominant IBS produces only a 12–17% therapeutic gain [85], and was temporarily removed from the American market due to fatal cases of ischemic colitis with attendant obstipation. Tegaserod, a $5\text{-}HT_4$ receptor agonist marketed to women with constipation-predominant IBS, is reportedly well tolerated, but provides only a 5–15% improvement over placebo [85]. This "push-pull" dichotomy of serotonergic function in IBS is strongly suggestive that such efforts are barking up the wrong neurotransmitter tree. Rational analysis suggests that endocannabinoids may well be the more likely therapeutic neuromodulatory target, and that phytocannabinoid treatment might represent a more efficacious and safer therapeutic approach. In particularly severe IBS cases, the employment of a foaming rectal preparation of a whole cannabis extract might be considered.

Comorbidities of Migraine, Fibromyalgia and Irritable Bowel Syndrome

Further examination of pertinent literature supports that there are very interesting relationships between migraine, fibromyalgia and IBS. Recently, a syndrome of cutaneous allodynia associated with migraine has been reported [86], and experimentally, repetitive noxious stimulation of the skin in migraineurs between attacks facilitates pain perception [87]. Nicolodi, Sicuteri et al. similarly noted a decreased pain threshold in migraineurs tested with over-distension of upper extremity veins, but not mere pressure from a sphygmomanometer cuff [88], meriting a label for migraine as a "visceral systemic sensory disorder." The same team noted a baseline fragility of serotonergic systems in migraine and fibromyalgia [89], plus the co-occurrence of primary headache in 97% of 201 fibromyalgia patients. In a later study [67], they supported the concept that both disorders represented a failure of serotonergic analgesia and NMDA-mediated neuronal plasticity. Other observations included the induction of fibromyalgic symptoms by the drug fenclonine in migraineurs but not others, and the production of migraine *de novo* in fibromyalgia patients without prior history after administration of nitroglycerine 0.6 mg sublingually. Similarly, an American group [90] examined 101 patients with the transformed migraine form of chronic daily headache, and were able to diagnose 35.6% as having comorbid fibromyalgia. Similarly, a high lifetime prevalence of migraine, IBS, depression and panic disorder were observed in 33 women meeting American College of Rheumatology criteria of fibromyalgia [91].

Sperber et al. examined separate groups of IBS and fibromyalgia patients [92]. Of the IBS cohort, 31.6% had fibromyalgia with significant numbers of tender muscle points compared to controls. Similarly, 32% of fibromyalgia patients met diagnostic criteria of IBS. In addition to these correlations, Bennett added irritable bladder syndrome to the comorbidities of fibromyalgia [66], supporting a concomitant visceral hyperalgesia [93; 94] in a condition where cannabis extracts have already proven efficacious [95].

Most recently, in an experimental protocol, it was demonstrated that IBS patients displayed cutaneous hyperalgesia that was suppressed by temporary rectal anesthesia with lidocaine [96], indicating central sensitization.

Broadening the Concept of Clinical Endocannabinoid Deficiency

One may quickly see that certain patients display symptoms of all three disorders, or additional ones considered "functional." With accrual of sufficient numbers of complaints lacking objective medical support, one assigns the label of somatization disorder. Given the above data, however, one might reasonably ask three questions in such contexts: 1) Are there as yet unelucidated biochemical explanations for these disorders? 2) Might endocannabinoid deficiency explain their pathophysiology? 3) Are the symptoms alleviated by clinical cannabis?

Globus hystericus and similar symptoms are frequently relegated to the psychogenic realm, but as a spasmodic disorder, it may well represent an endocannabinoid deficiency (CECD), as muscle tone (and tremor associated with demyelination) have been demonstrated to be under tonic endocannabinoid control in experimental animals [97]. Cannabis extracts have already proven efficacious in treatment of spasticity [98; 99].

Similarly, premature ejaculation in men is conventionally perceived as "psychological." This seems less tenable, when anecdotes support that cannabis prolongs latency, and proof is apparent in the dose responsive delay in ejaculation in rats noted in experiments with HU 210, a powerful CB_1 agonist [100].

A more obvious set of correlating conditions would be those of causalgia, allodynia and phantom limb pain, where application of cannabis based medicine extracts has already proven medically effective [99; 101]. Perhaps it will be demonstrable in the future that such conditions are associated with focal or spinal CECD states.

It has long been known that cannabinoids lower intraocular pressure in glaucoma (reviewed [102]), but only recently noted that that the mechanism is under tonic endocannabinoid control. Glaucoma also represents a vascular retinopathy for which cannabis may be neuroprotective. Perhaps an endocannabinoid deficiency is operative here as well.

Cannabis has had numerous historical applications to obstetrics and gynecology (reviewed [103]). This suggests usage of cannabinoid treatment in spasmodic dysmenorrhea, hyperemesis gravidarum, and regulation of the uterine milieu in fertilization and unexplained fetal wastage, where endocannabinoid mechanisms have been demonstrated or implicated. Further investigation may shed light on whether dysregulation of the system underlies their pathophysiology.

In the pediatric realm, the entity of infantile colic has remained enigmatic. This disturbing anomaly is associated with apparent visceral sensitivity and distinct dysphoria, and is frequently medically recalcitrant to even desperate treatment measures with medications with serious adverse effect profiles. This author posits this to be another developmental endocannabinoid deficiency state that is likely amenable to phytocannabinoid treatment.

Endocannabinoid mechanisms also regulate bronchial function [104], and therapeutic efficacy in asthma treatment with cannabis preparations has been long known [105]. Based on similar analyses of the multi-organ involvement of cystic fibrosis [106], Fride has proposed endocannabinoid deficiencies as underlying the pathophysiology of that disorder, and its treatment with phytocannabinoids.

In the psychiatric realm, bipolar disorder has been therapeutically recalcitrant to high dose antidepressants, but anecdotal data support cannabis efficacy [107]. Whether endocannabinoid tone is too low in the disorder would be conjectural at this time, but in the instance of post-traumatic stress disorder (PTSD), such a foundation seems likely, as endocannabinoids have been demonstrated as essential to the extinction of aversive memories in experimental animals [108].

Recent work by Wallace et al. has also demonstrated that convulsive thresholds are also under endocannabinoid control [109; 110], and that THC prevents 100% of subsequent seizures, far in excess of the capabilities of phenobarbital and phenytoin. Affected rats demonstrated both acute increases in endocannabinoid production and a long-term up-regulation of CB_1 production as apparent compensatory effects counteracting glutamate excitotoxicity. Based on this, one might conjecture that similar changes accrue when seizures are employed therapeutically as electroconvulsive therapy (ECT), in treatment of intractable depression. It seems that the resultant memory loss and prolonged improvement in mood may well be attributable to an increase in endocannabinoid levels rectifying their previous inadequacy.

Recent theory on depression suggests that mere deficiencies of serotonin and norepinephrine may be insufficient explanations of the disorder, but rather, innate neuroplasticity is inherently impaired and requires specific treatment [111]. Cannabinoids certainly seem to enhance that plasticity with their neuroprotective abilities [112; 113], and should be further explored therapeutically.

The apoptotic and anti-angiogenic properties of endo- and phytocannabinoids in various cancers (reviewed [114; 115]) raise the hypothesis that certain people who are especially susceptible to malignancy may be endocannabinoid deficient.

Conclusions

Clinical Endocannabinoid Deficiency: Is It a Provable Concept?

The preceding material has pertained to conjectural and experimental evidence of a conceptual alternative biochemical explanation for certain disease manifestations, but one must ask how these would obtain? Baker et al. have described how endocannabinoids may demonstrate an impairment threshold if too high, and a range of normal function below which a deficit threshold may be crossed [112]. Syndromes of CECD may be congenital or acquired. In the former case, one could posit that genetically-susceptible individuals might produce inadequate endocannabinoids, or that their degradation is too rapid. The same conditions might be acquired in injury or infection. Unfortunately, the regulation of endocannabinoid synthesis and degradation are far from fully elucidated (reviewed [116]). While a single enzyme, anandamide synthase, catalyzes AEA production, its degradation by fatty acid amidohydrolase (FAAH), is shared with many substrates. To complicate matters, an endocannabinoid with antagonistic properties at CB_1 called virodhamine (*virodha*, Sanskrit for "opposition") has recently been discovered [117]. Further research may shed light on these relationships.

In the meantime, a clinical agent that modifies endocannabinoid function will soon be clinically available in the form of cannabidiol. Recent research has demonstrated that although THC does not share VR_1 agonistic activity with AEA, CBD does so to a similar degree as capsaicin [78]. What is more, CBD inhibits uptake of the endocannabinoid anandamide (AEA), and weakly inhibits its hydrolysis. The presence of this component in available cannabis based medicine extracts portends to vastly extend the clinical applications and therapeutic efficacy of this re-emerging modality [118–120].

It is highly likely that additional regulatory roles for endocannabinoids will be discovered for this neuro- and immunomodulatory system. Some simple human experiments may be valuable, such as cerebrospinal fluid assay of AEA and 2-AG before and after ECT treatment. It is likely in the future that positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) for cannabinoid ligands may clarify these concepts.

This article has examined the inter-relationships of three clinical syndromes and biochemical basis in endocannabinoid function, as well as reflecting on other conditions that may display similar correlations. Only time and the scientific method will ascertain whether a new paradigm is applicable to human physiology and treatment of its derangements. Our insight into these possibilities is dependent on the contribution of one unique healing plant, for clinical cannabis has become a therapeutic compass to what modern medicine fails to cure.

REFERENCES

1 Freud S. Project for a scientific psychology. Trans. Strachey J. In: The standard edition of the complete psychological works of Sigmund Freud. Vol. 1, 24 vols. London: Hogarth Press.; 1966. p. 281–343.
2 Di Marzo V. 'Endocannabinoids' and other fatty acid derivatives with cannabimimetic properties: biochemistry and possible physiopathological relevance. Biochim Biophys Acta 1998; **1392**:153–175.
3 Russo EB. Role of cannabis and cannabinoids in pain management. In: Weiner RS, editors. Pain management: A practical guide for clinicians. 6th edit., 2 vols. Boca Raton, FL: CRC Press; 2002. p. 357–375.
4 Pertwee RG. Cannabinoid receptors and pain. Prog Neurobiol 2001; **63**:569–611.
5 Russo EB. Hemp for headache: An in-depth historical and scientific review of cannabis in migraine treatment. Journal of Cannabis Therapeutics 2001; **1**:21–92.
6 Russo EB. Handbook of psychotropic herbs: A scientific analysis of herbal remedies for psychiatric conditions. 2001. Haworth Press, Binghamton, NY.
7 Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 1992; **258**:1946–1949.
8 Herkenham MA. Localization of cannabinoid receptors in brain: relationship to motor and reward systems. In: Korman SG, Barchas JD, editors. Biological Basis of Substance Abuse. London: Oxford University; 1993. p. 187–200.
9 Fride E, Mechoulam R. Pharmacological activity of the cannabinoid receptor agonist, anandamide, a brain constituent. Eur J Pharmacol 1993; **231**:313–314.
10 Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. Journal of the American Medical Association 1992; **267**:64–69.
11 Lipton RB, Stewart WF. Migraine in the United States: A review of epidemiology and health care use. Neurology 1993; **43**:S6–10.
12 Russo E. Cannabis for migraine treatment: The once and future prescription? An historical and scientific review. Pain 1998; **76**:3–8.
13 Volfe Z, Dvilansky A, Nathan I. Cannabinoids block release of serotonin from platelets induced by plasma from migraine patients. Int J Clin Pharmacol Res 1985; **5**:243–246.
14 Spadone C. Neurophysiologie du cannabis [Neurophysiology of cannabis]. Encephale 1991; **17**:17–22.
15 Fan P. Cannabinoid agonists inhibit the activation of 5-HT3 receptors in rat nodose ganglion. Journal of Neurophysiology 1995; **73**: 907–910.
16 Boger DL, Patterson JE, Jin Q. Structural requirements for 5-HT2A and 5-HT1A serotonin receptor potentiation by the biologically active lipid oleamide. Proc Natl Acad Sci U S A 1998; **95**:4102–4107.
17 Hall B, Burnett A, Christians A, Halley C, Parker LA, Russo E, et al. (2004). Pharmacology of cannabidiol at serotonin receptors. Western Pharmacology Society, Honolulu, HI.
18 Russo EB, Macarah CM, Todd CL, Medora R, Parker K. (2000). Pharmacology of the essential oil of hemp at 5HT1A and 5HT2a receptors. 41st Annual Meeting of the American Society of Pharmacognosy, Seattle, WA.
19 Kimura T, Ohta T, Watanabe K, Yoshimura H, Yamamoto I. Anandamide, an endogenous cannabinoid receptor ligand, also interacts with 5-hydroxytryptamine (5-HT) receptor. Biol Pharm Bull 1998; **21**:224–226.
20 Peroutka SJ. The pharmacology of current anti-migraine drugs. Headache 1990; **30**:5–11; discussion 24–18.
21 Peroutka SJ. Dopamine and migraine. Neurology 1997; **49**:650–656.
22 Ferri S, Cavicchini E, Romualdi P, Speroni E, Murari G. Possible mediation of catecholaminergic pathways in the antinociceptive effect of an extract of *Cannabis sativa* L. Psychopharmacology 1986; **89**: 244–247.
23 Stefano GB, Salzet B, Rialas CM, Pope M, Kustka A, Neenan K, et al. Morphine- and anandamide-stimulated nitric oxide production inhibits presynaptic dopamine release. Brain Res 1997; **763**:63–68.
24 Muller-Vahl KR, Schneider U, Prevedel H, Theloe K, Kolbe H, Daldrup T, et al. Delta9-Tetrahydrocannabinol (THC) is Effective in the Treatment of Tics in Tourette Syndrome: a 6-Week Randomized Trial. J Clin Psychiatry 2003; **64**:459–465.

25 Müller-Vahl KR, Schneider U, Kolbe H, Emrich HM. Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol. Am J Psychiatry 1999; **156**:495.
26 Leweke FM, Giuffrida A, Wurster U, Emrich HM, Piomelli D. Elevated endogenous cannabinoids in schizophrenia. Neuroreport 1999; **10**: 1665-1669.
27 Burstein S. Eicosanoids as mediators of cannabinoid action. In: Murphy L, Bartke A, editors. Marijuana/Cannabinoids: Neurobiology and neurophysiology of drug abuse. Boca Raton: CRC Press; 1992. p. 73–91.
28 Evans AT, Formukong EA, Evans FJ. Actions of cannabis constituents on enzymes of arachidonate metabolism: anti-inflammatory potential. Biochem Pharmacol 1987; **36**:2035–2037.
29 Formukong EA, Evans AT, Evans FJ. Analgesic and antiinflammatory activity of constituents of *Cannabis sativa* L. Inflammation 1988; **12**:361–371.
30 Formukong EA, Evans AT, Evans FJ. The inhibitory effects of cannabinoids, the active constituents of *Cannabis sativa* L. on human and rabbit platelet aggregation. J Pharm Pharmacol 1989; **41**: 705–709.
31 McPartland J. Cannabis and eicosanoids: A review of molecular pharmacology. Journal of Cannabis Therapeutics 2001; **1**:71–83.
32 Burstein S, Levin E, Varanelli C. Prostaglandins and cannabis. II. Inhibition of biosynthesis by the naturally occurring cannabinoids. Biochem Pharmacol 1973; **22**:2905–2910.
33 Schaefer CF, Brackett DJ, Gunn CG, Dubowski KM. Decreased platelet aggregation following marihuana smoking in man. J Okla State Med Assoc 1979; **72**:435–436.
34 Evans FJ. Cannabinoids: The separation of central from peripheral effects on a structural basis. Planta Med 1991; **57**:S60–67.
35 Hampson AJ, Hill WA, Zan-Phillips M, Makriyannis A, Leung E, Eglen RM, et al. Anandamide hydroxylation by brain lipoxygenase:metabolite structures and potencies at the cannabinoid receptor. Biochim Biophys Acta 1995; **1259**:173–179.
36 Fimiani C, Liberty T, Aquirre AJ, Amin I, Ali N, Stefano GB. Opiate, cannabinoid, and eicosanoid signaling converges on common intracellular pathways nitric oxide coupling. Prostaglandins Other Lipid Mediat 1999; **57**:23–34.
37 Fettes I, Gawel M, Kuzniak S, Edmeads J. Endorphin levels in headache syndromes. Headache 1985; **25**:37–39.
38 Wiegant VM, Sweep CG, Nir I. Effect of acute administration of delta 1-tetrahydrocannabinol on beta- endorphin levels in plasma and brain tissue of the rat. Experientia 1987; **43**:413–415.
39 Mailleux P, Vanderhaeghen JJ. Delta-9-tetrahydrocannabinol regulates substance P and enkephalin mRNAs levels in the caudate-putamen. Eur J Pharmacol 1994; **267**:R1–3.
40 Meng ID, Manning BH, Martin WJ, Fields HL. An analgesia circuit activated by cannabinoids. Nature 1998; **395**:381–383.
41 Goadsby PJ, Gundlach AL. Localization of 3H-dihydroergotamine-binding sites in the cat central nervous system: relevance to migraine. Ann Neurol 1991; **29**:91–94.
42 Lichtman AH, Martin BR. Spinal and supraspinal components of cannabinoid-induced antinociception. J Pharmacol Exp Ther 1991; **258**:517–523.
43 Behbehani MM. Functional characteristics of the midbrain periaqueductal gray. Prog Neurobiol 1995; **46**:575–605.
44 Castro ME, Pascual J, Romon T, del Arco C, del Olmo E, Pazos A. Differential distribution of [3H]sumatriptan binding sites (5-HT1B, 5- HT1D and 5-HT1F receptors) in human brain: focus on brainstem and spinal cord. Neuropharmacology 1997; **36**:535–542.
45 Manzanares J, Corchero J, Romero J, Fernandez-Ruiz JJ, Ramos JA, Fuentes JA. Chronic administration of cannabinoids regulates proenkephalin mRNA levels in selected regions of the rat brain. Brain Res Mol Brain Res 1998; **55**:126–132.
46 Walker JM, Huang SM, Strangman NM, Tsou K, Sanudo-Pena MC. Pain modulation by the release of the endogenous cannabinoid anandamide. Proceedings of the National Academy of Sciences 1999; **96**: 12198–12203.
47 Hamann W, di Vadi PP. Analgesic effect of the cannabinoid analogue nabilone is not mediated by opioid receptors. Lancet 1999; **353**: 560.
48 Nicolodi M. Painful and non-painful effects of low doses of morphine in migraine sufferers partly depend on excitatory amino acids and gamma- aminobutyric acid. Int J Clin Pharmacol Res 1998; **18**: 79–85.
49 Storer RJ, Goadsby PJ. Trigeminovascular nociceptive transmission involves N-methyl-D-aspartate and non-N-methyl-D-aspartate glutamate receptors. Neuroscience 1999; **90**:1371–1376.
50 Shen M, Piser TM, Seybold VS, Thayer SA. Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. J Neurosci 1996; **16**:4322–4334.
51 Shen M, Thayer SA. Delta-9-tetrahydrocannabinol acts as a partial agonist to modulate glutamatergic synaptic transmission between rat hippocampal neurons in culture. Mol Pharmacol 1999; **55**:8–13.
52 Nicolodi M, Sicuteri F. Exploration of NMDA receptors in migraine: Therapeutic and theoretic implications. Int J Clin Pharmacol Res 1995; **15**:181–189.
53 Nicolodi M, Del Bianco PL, Sicuteri F. Modulation of excitatory amino acids pathway: a possible therapeutic approach to chronic daily headache associated with analgesic drugs abuse. Int J Clin Pharmacol Res 1997; **17**:97–100.
54 Nicolodi M, Sicuteri F. Negative modultors [sic] of excitatory amino acids in episodic and chronic migraine: preventing and reverting chronic migraine. Special lecture 7th INWIN Congress. Int J Clin Pharmacol Res 1998; **18**:93–100.
55 Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-)Delta9-tetrahydrocannabinol are neuroprotective antioxidants. Proc Natl Acad Sci U S A 1998; **95**:8268–8273.
56 Main A, Dowson A, Gross M. Photophobia and phonophobia in migraineurs between attacks. Headache 1997; **37**:492–495.
57 Mechoulam R, Ben-Shabat S. From gan-zi-gun-nu to anandamide and 2-arachidonoylglycerol: The ongoing story of cannabis. Nat Prod Rep 1999; **16**:131–143.
58 McPartland JM, Russo EB. Cannabis and cannabis extracts: Greater than the sum of their parts? Journal of Cannabis Therapeutics 2001; **1**:103–132.
59 Panikashvili D, Simeonidou C, Ben-Shabat S, Hanus L, Breuer A, Mechoulam R, et al. An endogenous cannabinoid (2-AG) is neuroprotective after brain injury. Nature 2001; **413**:527–531.
60 Mikuriya TH. 1997. Chronic migraine headache: Five cases successfully treated with marinol and/or illiciit cannabis.
61 Grinspoon L, Bakalar JB. Marihuana, the forbidden medicine. 1993. Yale University Press, New Haven.
62 el-Mallakh RS. Marijuana and migraine. Headache 1987; **27**:442–443.
63 Gieringer D. Medical use of cannabis: Experience in California. In: Grotenhermen F, Russo E, editors. Cannabis and cannabinoids: Pharmacology, toxicology, and therapeutic potential. Binghamton, NY: Haworth Press; 2001. p. 153–170.
64 Gieringer D. Medical cannabis potency testing project. Bulletin of the Multidisciplinary Association for Psychedelic Studies 1999; **9**: 20–22.
65 Bohr T. Problems with myofascial pain syndrome and fibromyalgia syndrome. Neurology 1996; **46**:593–597.
66 Bennett RM. Rational management of fibromyalgia. Rheum Dis Clin North Am 2002; **28**:xiii–xv.
67 Nicolodi M, Volpe AR, Sicuteri F. Fibromyalgia and headache. Failure of serotonergic analgesia and N-methyl-D-aspartate-mediated neuronal plasticity: Their common clues. Cephalalgia 1998; **18 (Suppl 21)**:41–44.
68 Richardson JD, Aanonsen L, Hargreaves KM. SR 141716A, a cannabinoid receptor antagonist, produces hyperalgesia in untreated mice. Eur J Pharmacol 1997; **319**:R3–4.
69 Richardson JD, Aanonsen L, Hargreaves KM. Hypoactivity of the spinal cannabinoid system results in NMDA-dependent hyperalgesia. J Neurosci 1998; **18**:451–457.
70 Richardson JD, Aanonsen L, Hargreaves KM. Antihyperalgesic effects of spinal cannabinoids. Eur J Pharmacol 1998; **345**:145–153.
71 Richardson JD, Kilo S, Hargreaves KM. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. Pain 1998; **75**:111–119.
72 Li J, Daughters RS, Bullis C, Bengiamin R, Stucky MW, Brennan J, et al. The cannabinoid receptor agonist WIN 55,212-2 mesylate blocks the development of hyperalgesia produced by capsaicin in rats. Pain 1999; **81**:25–33.
73 Ko MC, Woods JH. Local administration of delta9-tetrahydrocannabinol attenuates capsaicin-induced thermal nociception in rhesus monkeys: a peripheral cannabinoid action. Psychopharmacology (Berl) 1999; **143**:322–326.
74 Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. Pain 2001; **91**:165–175.
75 Strangman NM, Walker JM. Cannabinoid WIN 55,212-2 inhibits the activity-dependent facilitation of spinal nociceptive responses. J

Neurophysiol 1999; **82**:472–477.
76 Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol 1995; **50**:83–90.
77 Holzer P. Gastrointestinal afferents as targets of novel drugs for the treatment of functional bowel disorders and visceral pain. Eur J Pharmacol 2001; **429**:177–193.
78 Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol 2001; **134**:845–852.
79 Pertwee RG. Cannabinoids and the gastrointestinal tract. Gut 2001; **48**:859–867.
80 Coutts AA, Irving AJ, Mackie K, Pertwee RG, Anavi-Goffer S. Localisation of cannabinoid CB(1) receptor immunoreactivity in the guinea pig and rat myenteric plexus. J Comp Neurol 2002; **448**: 410–422.
81 Izzo AA, Fezza F, Capasso R, Bisogno T, Pinto L, Iuvone T, et al. Cannabinoid CB1-receptor mediated regulation of gastrointestinal motility in mice in a model of intestinal inflammation. Br J Pharmacol 2001; **134**:563–570.
82 Anderson PF, Jackson DM, Chesher GB. Interaction of delta-9-tetrahydrocannabinol and cannabidiol on intestinal motility in mice. J Pharm Pharmacol 1974; **26**:136–137.
83 Di Carlo G, Izzo AA. Cannabinoids for gastrointestinal diseases: potential therapeutic applications. Expert Opin Investig Drugs 2003; **12**:39–49.
84 Russo E. Cannabinoids in pain management. Study was bound to conclude that cannabinoids had limited efficacy. Brit Med J 2001; **323**:1249–1250; discussion 1250–1241.
85 Talley NJ. Evaluation of drug treatment in irritable bowel syndrome. Br J Clin Pharmacol 2003; **56**:362–369.
86 Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH. An association between migraine and cutaneous allodynia. Ann Neurol 2000; **47**:614–624.
87 Weissman-Fogel I, Sprecher E, Granovsky Y, Yarnitsky D. Repeated noxious stimulation of the skin enhances cutaneous pain perception of migraine patients in-between attacks: clinical evidence for continuous sub-threshold increase in membrane excitability of central trigeminovascular neurons. Pain 2003; **104**:693–700.
88 Nicolodi M, Sicuteri R, Coppola G, Greco E, Pietrini U, Sicuteri F. Visceral pain threshold is deeply lowered far from the head in migraine. Headache 1994; **34**:12–19.
89 Nicolodi M, Sicuteri F. Fibromyalgia and migraine, two faces of the same mechanism. In: Filippini GA, editors. Recent advances in tryptophan research. New York: Plenum Press; 1996. p. 373–379.
90 Peres MF, Young WB, Kaup AO, Zukerman E, Silberstein SD. Fibromyalgia is common in patients with transformed migraine. Neurology 2001; **57**:1326–1328.
91 Hudson JI, Goldenberg DL, Pope HG, Jr., Keck PE, Jr., Schlesinger L. Comorbidity of fibromyalgia with medical and psychiatric disorders. Am J Med 1992; **92**:363–367.
92 Sperber AD, Atzmon Y, Neumann L, Weisberg I, Shalit Y, Abu-Shakrah M, et al. Fibromyalgia in the irritable bowel syndrome: studies of prevalence and clinical implications. Am J Gastroenterol 1999; **94**:3541–3546.
93 Jaggar SI, Hasnie FS, Sellaturay S, Rice AS. The anti-hyperalgesic actions of the cannabinoid anandamide and the putative CB2 receptor agonist palmitoylethanolamide in visceral and somatic inflammatory pain. Pain 1998; **76**:189–199.
94 Jaggar SI, Sellaturay S, Rice AS. The endogenous cannabinoid anandamide, but not the CB2 ligand palmitoylethanolamide, prevents the viscero-visceral hyper-reflexia associated with inflammation of the rat urinary bladder. Neurosci Lett 1998; **253**:123–126.
95 Brady CM, DasGupta R, Wiseman OJ, Berkley KJ, Fowler CJ. (2001). Congress of the International Association for Cannabis as Medicine, Berlin, Germany.
96 Verne GN, Robinson ME, Vase L, Price DD. Reversal of visceral and cutaneous hyperalgesia by local rectal anesthesia in irritable bowel syndrome (IBS) patients. Pain 2003; **105**:223–230.
97 Baker D, Pryce G, Croxford JL, Brown P, Pertwee RG, Huffman JW, et al. Cannabinoids control spasticity and tremor in a multiple sclerosis model. Nature 2000; **404**:84–87.
98 Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet 2003; **362**:1517–1526.
99 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. Clinical Rehabilitation 2003; **17**:18–26.
100 Ferrari F, Ottani A, Giuliani D. Inhibitory effects of the cannabinoid agonist HU 210 on rat sexual behaviour. Physiol Behav 2000; **69**: 547–554.
101 Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmonds S, et al. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 "N of 1" studies. Anaesthesia 2004; **59**:440–452.
102 Jarvinen T, Pate D, Laine K. Cannabinoids in the treatment of glaucoma. Pharmacol Ther 2002; **95**:203.
103 Russo E. Cannabis treatments in obstetrics and gynecology: A historical review. Journal of Cannabis Therapeutics 2002; **2**:5–35.
104 Pertwee RG, Ross RA. Cannabinoid receptors and their ligands. Prostaglandins Leukot Essent Fatty Acids 2002; **66**:101–121.
105 Williams SJ, Hartley JP, Graham JD. Bronchodilator effect of delta1-tetrahydrocannabinol administered by aerosol of asthmatic patients. Thorax 1976; **31**:720–723.
106 Fride E. Cannabinoids and cystic fibrosis: A novel approach. Journal of Cannabis Therapeutics 2002; **2**:59–71.
107 Grinspoon L, Bakalar JB. The use of cannabis as a mood stabilizer in bipolar disorder: anecdotal evidence and the need for clinical research. J Psychoactive Drugs 1998; **30**:171–177.
108 Marsicano G, Wotjak CT, Azad SC, Bisogno T, Rammes G, Cascio MG, et al. The endogenous cannabinoid system controls extinction of aversive memories. Nature 2002; **418**:530–534.
109 Wallace MJ, Martin BR, DeLorenzo RJ. Evidence for a physiological role of endocannabinoids in the modulation of seizure threshold and severity. Eur J Pharmacol 2002; **452**:295–301.
110 Wallace MJ, Blair RE, Falenski KW, Martin BR, DeLorenzo RJ. The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. J Pharmacol Exp Ther 2003; **307**:129–137.
111 Delgado P, Moreno F. Antidepressants and the brain. Int Clin Psychopharmacol 1999; **14 Suppl 1**:S9–16.
112 Baker D, Pryce G, Giovannoni G, Thompson AJ. The therapeutic potential of cannabis. Lancet Neurology 2003; **2**:291–298.
113 Mechoulam R, Panikashvili D, Shohami E. Cannabinoids and brain injury: therapeutic implications. Trends Mol Med 2002; **8**:58–61.
114 Guzman M. Cannabinoids: potential anticancer agents. Nat Rev Cancer 2003; **3**:745–755.
115 Maccarrone M, Finazzi-Agro A. The endocannabinoid system, anandamide and the regulation of mammalian cell apoptosis. Cell Death Differ 2003; **10**:946–955.
116 Hillard CJ, Jarrahian A. Cellular accumulation of anandamide: consensus and controversy. Br J Pharmacol 2003; **140**:802–808.
117 Porter AC, Sauer JM, Knierman MD, Becker GW, Berna MJ, Bao J, et al. Characterization of a novel endocannabinoid, virodhamine, with antagonist activity at the CB1 receptor. J Pharmacol Exp Ther 2002; **301**:1020–1024.
118 Russo EB. Cannabis-From pariah to prescription. Journal of Cannabis Therapeutics 2003; **3**(3):1–29.
119 Whittle BA, Guy GW, Robson P. Prospects for new cannabis-based prescription medicines. Journal of Cannabis Therapeutics 2001; **1**: 183–205.
120 Whittle BA, Guy GW, Robson P. Cannabis and cannabinoids as medicines. 2003. Pharmaceutical Press, London.

PAIN

Pain 76 (1998) 3–8

Review Article

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

Ethan Russo*

Department of Neurology, Western Montana Clinic, 515 West Front Street, Missoula, MT 58907-7609, USA

Accepted 26 January 1998

Abstract

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

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

1. Introduction

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

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

This study will examine the history of *Cannabis* use for one indication, that of headache treatment, its scientific rationale, and possible future as an alternative therapeutic agent.

2. Historical and ethnobotanical usage of Cannabis in migraine treatment

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

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

* Tel.: +1 406 3297238; fax: +1 406 3297453;
e-mail: ptm5739@montana.com

0304-3959/98/$19.00
PII S0304-3959(98)00033-5

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

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

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

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

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

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

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

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

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

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

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

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

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

3. Modern research developments on Cannabis

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

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

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

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

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

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

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

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

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

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

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

With respect to behavior, Hollister refuted the tenet that depicted *Cannabis* as a contributor to violent and aggressive behavior. Concerning addiction, he noted minimal withdrawal symptoms of nausea, vomiting, diarrhea, and tremors in some experimental subjects after very heavy chronic usage. Such effects were brief and self-limited.

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

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

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

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

Additional research sheds light on possible mechanisms of therapeutic action of the cannabinoids on migraine. An inhibitory effect of anandamide and other cannabinoid agonists on rat serotonin type 3 ($5\text{-}HT_3$) receptors was demonstrated (Fan, 1995). This receptor has been implicated as a mediator of emetic and pain responses. In 1996, a study in rats demonstrated antinociceptive effects of delta-9-THC and other cannabinoids in the periaqueductal gray matter (Lichtman et al., 1996). The PAG has been frequently cited as a likely anatomic area for migraine generation (Goadsby and Gundlach, 1991).

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

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

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

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

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

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

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

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

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

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

4. Discussion

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

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

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

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

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

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

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

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

5. Conclusions

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

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

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

Acknowledgements

The author would like to thank the following individuals: Rick Doblin and Sylvia Thiessen of the Multidisciplinary Association for Psychedelic Studies (MAPS), for financial support, and continued advice and suggestions. Paulette Cote of Western Montana Clinic Library, and the Inter-Library Loan Department at the Mansfield Library of the University of Montana for wonderful service in locating obscure references. Drs. Tod Mikuriya and Lester Grinspoon for provision of books, suggestions and encouragement. Drs. Keith Parker and Vernon Grund of the Department of Pharmacy, University of Montana for their guidance and good sense. Drs. Varro Tyler and Dennis McKenna for their inspiration and the confidence they engendered. Dr. Donald Abrams for his continuing efforts in pursuit of medical indications for *Cannabis*. The Herbal Research Foundation and NAPRALERT for assistance on ethnobotanical information. Dr. Samir Ross for his initial guidance on my inquiries about experimental research on *Cannabis*. Marie-Josée Thibault, Deborah Somerville, and Penny King for their faithfulness and 'moral support'. Ultimately, to Dr. Mark Russo, for reasons he alone will understand.

References

Agurell, S., Halldin, M., Lindgren, J.-E., Ohlsson, A., Widman, M., Gillespie, H. and Hollister, L., Pharmacokinetics and metabolism of delta-1-tetrahydrocannabinol and other cannabinoids with emphasis on man, Pharmacol. Rev., 38 (1986) 21–43.

AJPH, Access to therapeutic marijuana/cannabis, Am. J. Public Health, 86 (1996) 441–442.

Brunner, T.F., Marijuana in ancient Greece and Rome? The literary evidence, J. Psychedel. Drugs, 9 (1977) 221–225.

Camp, W.H., The antiquity of hemp as an economic plant, J. N. Y. Bot. Gard., 37 (1936) 110–114.

Chait, L.D. and Zacny, J.P., Reinforcing and subjective effects of oral delta-9-THC and smoked marijuana in humans, Psychopharmacology, 107 (1992) 255–262.

Chiang, C.N. and Barnett, G., Marijuana effect and delta-9-tetrahydrocannabinol plasma level, Clin. Pharm. Ther., 36 (1984) 234–238.
Chopra, I.C. and Chopra, R.W., The use of cannabis drugs in India, Bull. Narcotics, 9 (1957) 4–29.
Co, B.T., Goodwin, D.W., Gado, M., Mikhael, M. and Hill, S.Y., Absence of cerebral atrophy in chronic cannabis users by computerized transaxial tomography, J. Am. Med. Assoc., 237 (1977) 1229–1230.
Cohen, S., The 94-day cannabis study, Ann. N. Y. Acad. Sci., 282 (1976) 211–220.
Comitas, L., Cannabis and work in Jamaica: a refutation of the amotivational syndrome, Ann. N. Y. Acad. Sci., 282 (1976) 211–220.
Darmsteter, J. (trans.), The Zend-Avesta, Part I, The Vendîdâd, Oxford, London, 1895, 389 pp.
Devane, W.A., Hanus, L., Breuer, A., Pertwee, R.G., Stevenson, L.A., Griffin, G., Gibson, D., Mandelbaum, A., Etinger, A. and Mechoulam, R., Isolation and structure of a brain constituent that binds to the cannabinoid receptor, Science, 258 (1992) 1946–1949.
Dwarakanath, C., Use of opium and cannabis in the traditional systems of medicine in India, Bull. Narcotics, 17 (1965) 15–19.
El-Mallakh, R.F., Marijuana and migraine, Headache, 27 (1987) 442–443.
Fan, P., Cannabinoid agonists inhibit the activation of 5-HT3 receptors in rat nodose ganglion neurons, J. Neurophysiol., 73 (1995) 907–910.
Ferrari, M.D. and Saxena, P.R., 5-HT1 receptors in migraine pathophysiology and treatment, Eur. J. Neurol., 2 (1995) 5–21.
Fishbein, M., Migraine associated with menstruation, J. Am. Med. Assoc., 237 (1942) 326.
Fisher, M.A. and Glass, S., Butorphanol (Stadol): a study in problems of current drug information and control, Neurology, 48 (1997) 1156–1160.
Foltin, R.W., Fischman, M.W. and Byrne, M.F., Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory, Appetite, 11 (1988) 1–14.
Fride, E. and Mechoulam, R., Pharmacological activity of the cannabinoid receptor agonist, anandamide, a brain constituent, Eur. J. Pharmacol., 231 (1993) 313–314.
Gieringer, D., Waterpipe study, Bull. Multidisc. Assoc. Psychedel. Stud., 6 (1996) 59–63.
Goadsby, P.J. and Gundlach, A.L., Localization of [^{3}H]-dihydroergotamine binding sites in the cat central nervous system: relevance to migraine, Ann. Neurol., 29 (1991) 91–94.
Grinspoon, L. and Bakalar, J.B., Marihuana: The Forbidden Medicine, Yale University, New Haven, CT, 1993, 184 pp.
Grinspoon, L. and Bakalar, J.B., Marihuana as medicine: a plea for reconsideration, J. Am. Med. Assoc., 273 (1995) 1875.
Hall, W., Solowij, N. and Lemon, J., The Health and Psychological Consequences of Cannabis Use, National Drug Strategy Monograph Series No. 25, National Drug and Alcohol Research Centre, Australia, 1995.
Herkenham, M.A., Localization of cannabinoid receptors in brain: relationship to motor and reward systems. In: S.G. Koreman and J.D. Barchas (eds.), Biological Basis of Substance Abuse, Oxford University Press, London, 1993, pp. 187–200.
Hollister, L.E., Health aspects of cannabis, Pharmacol. Rev., 38 (1986) 1–20.
Kuehnle, J., Mendelson, J.H., Davis, K.R. and New, P.F.J., Computed tomographic examination of heavy marihuana smokers, J. Am. Med. Assoc., 237 (1977) 1231–1232.
Li, H.-L., An archaeological and historical account of cannabis in China, Econ. Bot., 28 (1974) 437–448.
Lichtman, A.H., Cook, S.A. and Martin, B.R., Investigation of brain sites mediating cannabinoid-induced antinociception in rats: evidence supporting periaqueductal gray involvement, J. Pharmacol. Exp. Ther., 276 (1996) 585–593.
Linet, M.S., Stewart, W.F. and Celentano, D.D., An epidemiological study of headache among adolescents and young adults, J. Am. Med. Assoc., 261 (1989) 2211–2216.
Lipton, R.B. and Stewart, W.F., Migraine in the United States: epidemiology and health care use, Neurology, 43 (suppl.)(1993) 6–10.
Martin, B.R., Cellular effects of cannabinoids, Pharmacol. Rev., 38 (1986) 45–74.
Mason, A.P. and McBay, A.J., Cannabis: pharmacology and interpretation of effects, J. Forens. Sci., 30 (1985) 615–631.
Mathew, N.T., Serotonin 1D (5-HT 1D) agonists and other agents in acute migraine, Neurol. Clinics, 15 (1997) 61–83.
Mikuriya, T.H. (Ed.), Marijuana: Medical Papers 1839–1972, Medi-Comp Press, Oakland, CA, 1973, 465 pp.
Milstein, S.L., MacCannell, K., Karr, G. and Clark, S., Marijuana-produced changes in pain tolerance: experienced and non-experienced subjects, Int. Neuropsychiatr., 10 (1975) 177–182.
Noyes, R. and Baram, D.A., Cannabis analgesia, Comp. Psychiatr., 15 (1974) 531–535.
Noyes, R., Brunk, F., Baram, D.A. and Canter, A., Analgesic effect of delta-9-tetrahydrocannabinol, J. Clin. Pharmacol., 15 (1975a) 134–143.
Noyes, R., Brunk, F., Avery, D.H. and Canter, A., The analgesic properties of delta-9-tetrahydrocannabinol and codeine, Clin. Pharmacol. Ther., 18 (1975b) 84–89.
Osler, W. and McCrae, T., The Principles and Practice of Medicine, Appleton, New York, 1915, 1225 pp.
Peroutka, S.J., Developments in 5-hydroxytryptamine receptor pharmacology in migraine, Neurol. Clinics, 8 (1990) 829–839.
Ratnam, E.V., Cannabis indica, J. Brit. Med Assoc., Ceylon Branch, 13 (1916) 30–34.
Schultes, R.E., Man and marijuana, Nat. Hist., 82 (1973) 59–63, 80, 82.
Schultes, R.E., Klein, W.M., Plowman, T. and Lockwood, T.E., Cannabis: an example of taxonomic neglect, Bot. Mus. Leafl. Harvard Univ., 23 (1974) 337–367.
Sidney, S., Beck, J.E., Tekawa, I.S., Quesenberry, C.P. and Friedman, G.D., Marijuana use and mortality, Am. J. Public Health, 87 (1997) 585–590.
Smith, R., Editorial: the war on drugs, Br. Med. J., 311 (1995) 23–30.
Stewart, W.F., Lipton, R.B. and Celantano, D.D., Prevalence of migraine headache in the United States, J. Am. Med. Assoc., 267 (1992) 64–69.
Volfe, Z., Dvilansky, A. and Nathan, I., Cannabinoids block release of serotonin from platelets by plasma from migraine patients, Int. J. Clin. Pharm. Res., 4 (1985) 243–246.
Voth, E.A. and Schwartz, R.H., Medical applications of delta-9-tetrahydrocannabinol and marijuana, Ann. Intern. Med., 126 (1997) 791–798.
Walton, R.P., Marihuana: America's New Drug Problem: A Sociologic Question with its Basic Explanation Dependent on Biologic and Medical Principles, Lippincott, Philadelphia, PA, 1938, 223 pp.
Young, F.L., In the Matter of Marijuana Rescheduling Petition, Department of Justice, Drug Enforcement Administration. Docket 86-22, Drug Enforcement Administration, Washington, DC, September 6, 1988.

Role of Cannabinoids in Pain Management

18

Ethan B. Russo and Andrea G. Hohmann

Key Points

- Cannabinoids are pharmacological agents of endogenous (endocannabinoids), botanical (phytocannabinoids), or synthetic origin.
- Cannabinoids alleviate pain through a variety of receptor and non-receptor mechanisms including direct analgesic and anti-inflammatory effects, modulatory actions on neurotransmitters, and interactions with endogenous and administered opioids.
- Cannabinoid agents are currently available in various countries for pain treatment, and even cannabinoids of botanical origin may be approvable by FDA, although this is distinctly unlikely for smoked cannabis.
- An impressive body of literature supports cannabinoid analgesia, and recently, this has been supplemented by an increasing number of phase I–III clinical trials.

Introduction

Plants and Pain

It is a curious fact that we owe a great deal of our insight into pharmacological treatment of pain to the plant world [1]. Willow bark from *Salix* spp. led to development of aspirin and eventual elucidation of the analgesic effects of prostaglandins and their role in inflammation. The opium poppy (*Papaver somniferum*) provided the prototypic narcotic analgesic morphine, the first alkaloid discovered, and stimulated the much later discovery of the endorphin and enkephalin systems. Similarly, the pharmacological properties of cannabis (*Cannabis sativa*) prompted the isolation of Δ^9-tetrahydrocannabinol (THC), the major psychoactive ingredient in cannabis, in 1964 [2]. It is this breakthrough that subsequently prompted the more recent discovery of the body's own cannabis-like system, the endocannabinoid system (ECS), which modulates pain under physiological conditions. Pro-nociceptive mechanisms of the endovanilloid system were similarly revealed by phytochemistry of capsaicin, the pungent ingredient in hot chile peppers (*Capsicum annuum* etc.), which activates transient receptor potential vanilloid receptor-1 (TRPV1). Additional plant products such as the mints and mustards activate other TRP channels to produce their physiological effects.

E.B. Russo, M.D. (✉)
GW Pharmaceuticals,
20402 81st Avenue SW, Vashon, WA 98070, USA

Pharmaceutical Sciences, University of Montana,
Missoula, MT, USA
e-mail: ethanrusso@comcast.net

A.G. Hohmann, Ph.D.
Department of Psychological and Brain Sciences, Indiana University,
101 East 10th Street, Bloomington, IN 47405, USA
e-mail: hohmanna@indiana.edu

The Endocannabinoid System

There are three recognized types of cannabinoids: (1) the phytocannabinoids [3] derived from the cannabis plant, (2) synthetic cannabinoids (e.g., ajulemic acid, nabilone, CP55940, WIN55, 212-2) based upon the chemical structure of THC or other ligands which bind cannabinoid receptors, and (3) the endogenous cannabinoids or endocannabinoids. Endocannabinoids are natural chemicals such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG) found in animals whose basic functions are "relax, eat, sleep, forget, and protect" [4]. The endocannabinoid system encompasses the endocannabinoids themselves, their biosynthetic and catabolic enzymes, and their corresponding receptors [5]. AEA is hydrolyzed by the enzyme fatty-acid amide hydrolase (FAAH) into breakdown products arachidonic acid and ethanolamine [6]. By contrast, 2-AG is hydrolyzed primarily by the enzyme monoacylglycerol lipase (MGL) into breakdown products arachidonic acid and glycerol [7] and to a lesser extent by the enzymes ABHD6 and ABHD12. FAAH, a

T.R. Deer et al. (eds.), *Comprehensive Treatment of Chronic Pain by Medical, Interventional, and Integrative Approaches*,
DOI 10.1007/978-1-4614-1560-2_18,

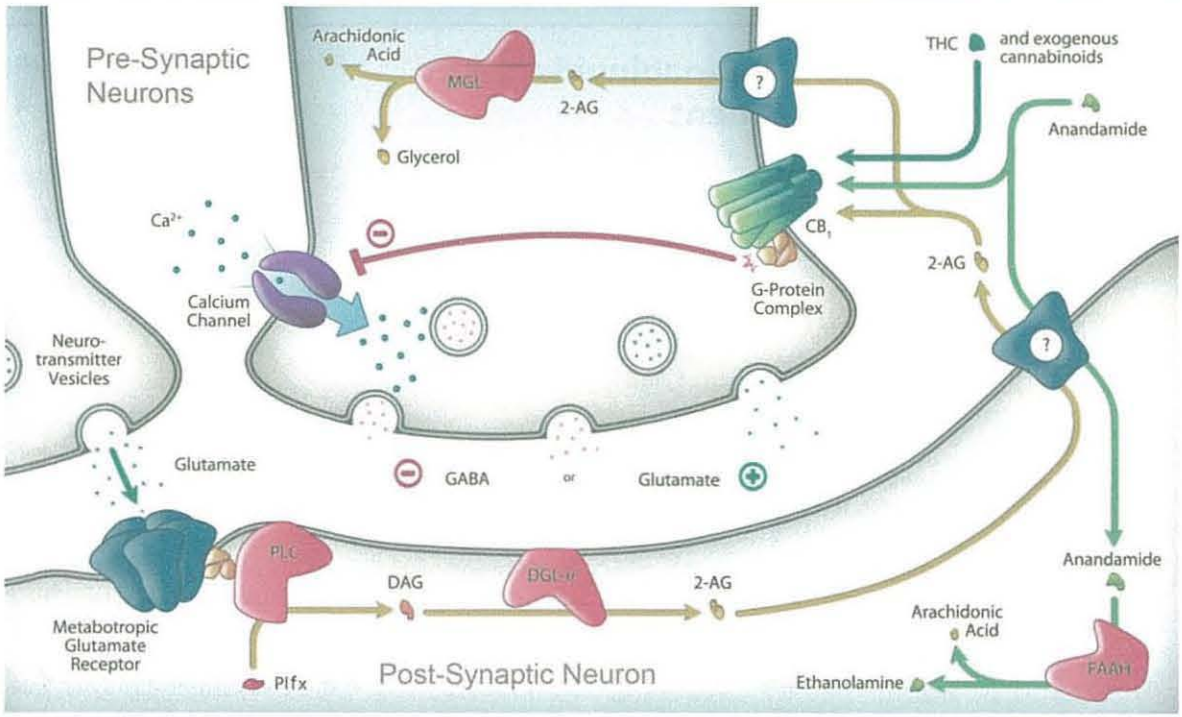


Fig. 18.1 Putative mechanism of endocannabinoid-mediated retrograde signaling in the nervous system. Activation of metabotropic glutamate receptors (*mGluR*) by glutamate triggers the activation of the phospholipase C (*PLC*)-diacylglycerol lipase (*DGL*) pathway to generate the endocannabinoid 2-arachidonoylglycerol (*2-AG*). First, the 2-AG precursor diacylglycerol (*DAG*) is formed from PLC-mediated hydrolysis of membrane phospholipid precursors (*PIPx*). DAG is then hydrolyzed by the enzyme DGL-α to generate 2-AG. 2-AG is released from the postsynaptic neuron and acts as a retrograde signaling molecule. Endocannabinoids activate presynaptic CB_1 receptors which reside on terminals of glutamatergic and GABAergic neurons. Activation of CB_1 by 2-AG, anandamide, or exogenous cannabinoids (e.g., tetrahydrocannabinol, *THC*) inhibits calcium influx in the presynaptic terminal, thereby inhibiting release of the primary neurotransmitter (i.e., glutamate or GABA) from the synaptic vesicle. Endocannabinoids are then rapidly deactivated by transport into cells (via a putative endocannabinoid transporter) followed by intracellular hydrolysis. 2-AG is metabolized by the enzyme monoacylglycerol lipase (*MGL*), whereas anandamide is metabolized by a distinct enzyme, fatty-acid amide hydrolase (*FAAH*). Note that MGL co-localizes with CB_1 in the presynaptic terminal, whereas FAAH is localized to postsynaptic sites. The existence of an endocannabinoid transporter remains controversial. Pharmacological inhibitors of either endocannabinoid deactivation (e.g., FAAH and MGL inhibitors) or transport (i.e., uptake inhibitors) have been developed to exploit the therapeutic potential of the endocannabinoid signaling system in the treatment of pain (Figure by authors with kind assistance of James Brodie, GW Pharmaceuticals)

postsynaptic enzyme, may control anandamide levels near sites of synthesis, whereas MGL, a presynaptic enzyme [8], may terminate 2-AG signaling following CB_1 receptor activation. These enzymes also represent therapeutic targets because inhibition of endocannabinoid deactivation will increase levels of endocannabinoids at sites with ongoing synthesis and release [9]. The pathways controlling formation of AEA remain poorly understood. However, 2-AG is believed to be formed from membrane phospholipid precursors through the sequential activation of two distinct enzymes, phospholipase C and diacylglycerol lipase-α. First, PLC catalyzes formation of the 2-AG precursor diacylglycerol (DAG) from membrane phosphoinositides. Then, DAG is hydrolyzed by the enzyme diacylglycerol lipase-α (DGL-α) to generate 2-AG [199].

There are currently two well-defined cannabinoid receptors, although additional candidate cannabinoid receptors have also been postulated. CB_1, a seven transmembrane spanning G-protein-coupled receptor inhibiting cyclic AMP release, was identified in 1988 [10]. CB_1 is the primary neuromodulatory receptor accounting for psychopharmacological effects of THC and most of its analgesic effects [11]. Endocannabinoids are produced on demand in postsynaptic cells and engage presynaptic CB_1 receptors through a retrograde mechanism [12]. Activation of presynaptic CB_1 receptors then acts as a synaptic circuit breaker to inhibit neurotransmitter release (either excitatory or inhibitory) from the presynaptic neuron (*vide infra*) (Fig. 18.1). CB_2 was identified in 1992, and while thought of primarily as a peripheral immunomodulatory receptor, it also has important

effects on pain. The role of CB_2 in modulating persistent inflammatory and neuropathic pain [13] has been recently reviewed [14, 15]. Activation of CB_2 suppresses neuropathic pain mechanisms through nonneuronal (i.e., microglia and astrocytes) and neuronal mechanisms that may involve interferon-gamma [16]. THC, the prototypical classical cannabinoid, is a weak partial agonist at both CB_1 and CB_2 receptors. Transgenic mice lacking cannabinoid receptors (CB_1, CB_2, GPR55), enzymes controlling endocannabinoid breakdown (FAAH, MGL, ABHD6), and endocannabinoid synthesis (DGL-α, DGL-β) have been generated [17]. These knockouts have helped elucidate the role of the endocannabinoid system in controlling nociceptive processing and facilitated development of inhibitors of endocannabinoid breakdown (FAAH, MGL) as novel classes of analgesics.

A Brief Scientific History of Cannabis and Pain

Centuries of Citations

Cannabis has been utilized in one form or another for treatment of pain for longer than written history [18–21]. Although this documentation has been a major preoccupation of the lead author [22–25], and such information can provide provocative direction to inform modern research on treatment of pain and other conditions, it does not represent evidence of form, content, or degree that is commonly acceptable to governmental regulatory bodies with respect to pharmaceutical development.

Anecdotes Versus Modern Proof of Concept

While thousands of compelling stories of efficacy of cannabis in pain treatment certainly underline the importance of properly harnessing cannabinoid mechanisms therapeutically [26, 27], prescription analgesics in the United States necessitate Food and Drug Administration (FDA) approval. This requires a rigorous development program proving consistency, quality, efficacy, and safety as defined by basic scientific studies and randomized controlled trials (RCT) [28] and generally adhering to recent IMMPACT recommendations [29], provoking our next question.

Can a Botanical Agent Become a Prescription Medicine?

Most modern physicians fail to recognize that pharmacognosy (study of medicinal plants) has led directly or indirectly to an estimated 25 % of modern pharmaceuticals [30]. While the plethora of available herbal agents yield an indecipherable cacophony to most clinicians and consumers alike, it is certainly possible to standardize botanical agents and facilitate their recommendation based on sound science [31]. Botanical medicines can even fulfill the rigorous dictates of the FDA and attain prescription drug status via a clear roadmap in the form of a blueprint document [32], henceforth termed the *Botanical Guidance*: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070491.pdf. To be successful and clinically valuable, botanicals, including cannabis-based medicines, must demonstrate the same quality, clinical analgesic benefit, and appropriately safe adverse event profile as available new chemical entities (NCE) [28].

The Biochemical and Neurophysiological Basis of Pain Control by Cannabinoids

Neuropathic Pain

Thorough reviews of therapeutic effects of cannabinoids in preclinical and clinical domains have recently been published [33, 34]. In essence, the endocannabinoid system (ECS) is active throughout the CNS and PNS in modulating pain at spinal, supraspinal, and peripheral levels. Endocannabinoids are produced on demand in the CNS to dampen sensitivity to pain [35]. The endocannabinoid system is operative in such key integrative pain centers as the periaqueductal grey matter [36, 37], the ventroposterolateral nucleus of the thalamus [38], and the spinal cord [39, 40]. Endocannabinoids are endogenous mediators of stress-induced analgesia and fear-conditioned analgesia and suppress pain-related phenomena such as windup [41] and allodynia [42]. In the periphery and PNS [13], the ECS has key effects in suppressing both hyperalgesia and allodynia via CB_1 [43] and CB_2 mechanisms (Fig. 18.2). Indeed, pathological pain states have been postulated to arise, at least in part, from a dysregulation of the endocannabinoid system.

Antinociceptive and Anti-inflammatory Pain Mechanisms

Beyond the mechanisms previously mentioned, the ECS plays a critical role in peripheral pain, inflammation, and hyperalgesia [43] through both CB_1 and CB_2 mechanisms. CB_1 and CB_2 mechanisms are also implicated in regulation of contact dermatitis and pruritus [44]. A role for spinal CB_2 mechanisms, mediated by microglia and/or astrocytes, is also revealed under conditions of inflammation [45]. Both THC and cannabidiol (CBD), a non-euphoriant phytocannabinoid common in certain cannabis strains, are potent anti-inflammatory antioxidants with activity exceeding that of

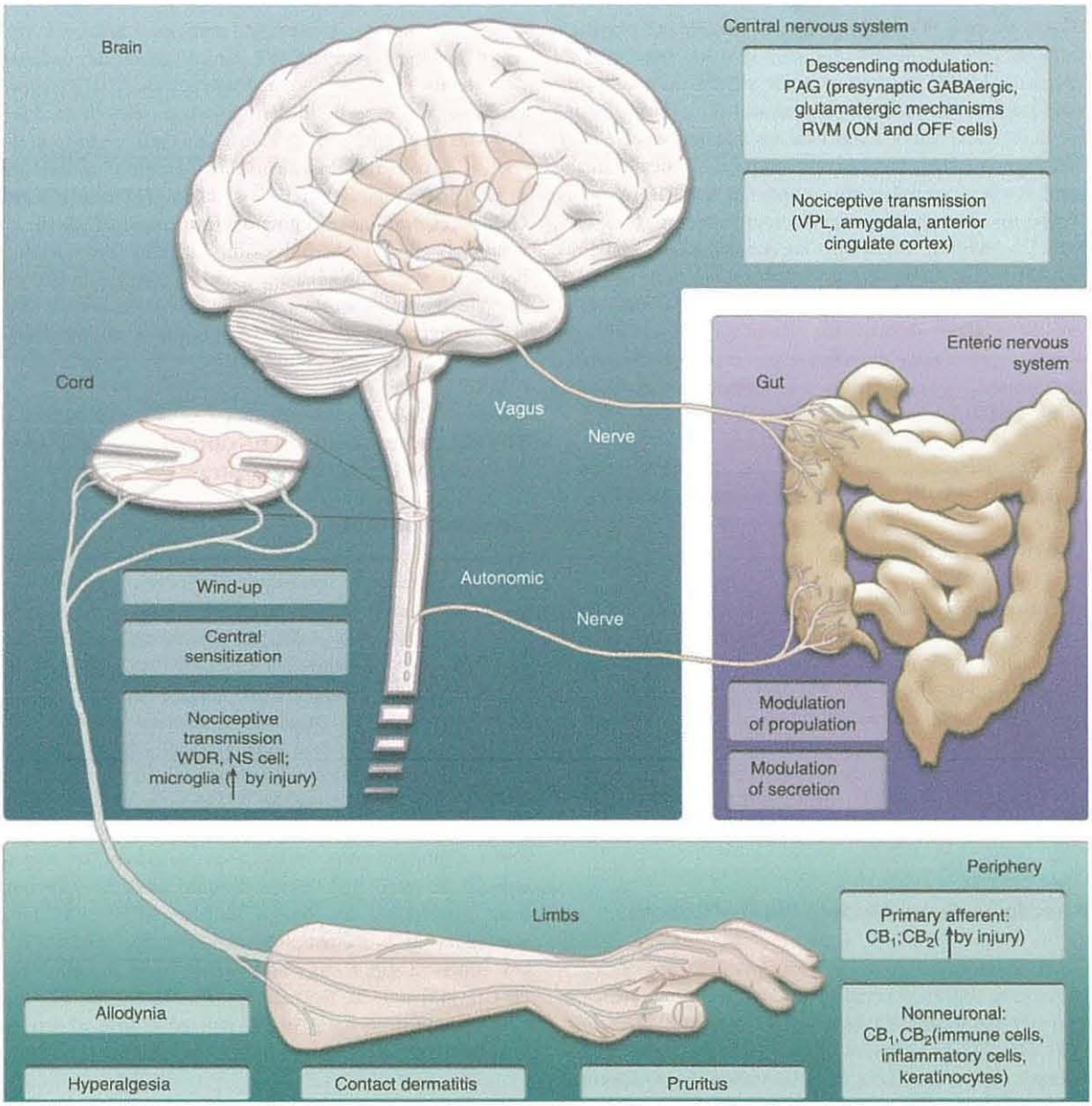


Fig. 18.2 Cannabinoids suppress pain and other pathophysiological (e.g., contact dermatitis, pruritis) and physiological (e.g., gastrointestinal transit and secretion) processes through multiple mechanisms involving CB_1 and CB_2 receptors. Peripheral, spinal, and supraspinal sites of cannabinoid actions are shown. In the periphery, cannabinoids act through both neuronal and nonneuronal mechanisms to control inflammation, allodynia, and hyperalgesia. CB_1 and CB_2 have been localized to both primary afferents and nonneuronal cells (e.g., keratinocytes, microglia), and expression can be regulated by injury. In the spinal cord, cannabinoids suppress nociceptive transmission, windup, and central sensitization by modulating activity in the ascending pain pathway of the spinothalamic tract, including responses of wide dynamic range (*WDR*) and nociceptive specific (*NS*) cells. Similar processes are observed at rostral levels of the neuraxis (e.g., ventroposterolateral nucleus of the thalamus, amygdala, anterior cingulate cortex). Cannabinoids also actively modulate pain through descending mechanisms. In the periaqueductal gray, cannabinoids act through presynaptic glutamatergic and GABAergic mechanisms to control nociception. In the rostral ventromedial medulla, cannabinoids suppress activity in ON cells and inhibit the firing pause of OFF cells, in response to noxious stimulation to produce antinociception (Figure by authors with kind assistance of James Brodie, GW Pharmaceuticals)

vitamins C and E via non-cannabinoid mechanisms [46]. THC inhibits prostaglandin E-2 synthesis [47] and stimulates lipooxygenase [48]. Neither THC nor CBD affects COX-1 or COX-2 at relevant pharmacological dosages [49].

While THC is inactive at vanilloid receptors, CBD, like AEA, is a $TRPV_1$ agonist. Like capsaicin, CBD is capable of inhibiting fatty-acid amide hydrolase (FAAH), the enzyme which hydrolyzes AEA and other fatty-acid amides that do not bind to cannabinoid receptors. CBD additionally inhibits AEA reuptake [50] though not potently. Thus, CBD acts as an endocannabinoid modulator [51], a mechanism that various pharmaceutical firms hope to emulate with new chemical entities (NCEs). CBD inhibits hepatic metabolism of THC to 11-hydroxy-THC, which is possibly more psychoactive, and prolongs its half-life, reducing its psychoactivity and attenuating attendant anxiety and tachycardia [51]; antagonizes psychotic symptoms [52]; and attenuates appetitive effects of THC [53] as well as its effects on short-term memory [54]. CBD also inhibits tumor necrosis factor-alpha (TNF-α) in a rodent model of rheumatoid arthritis [55]. Recently, CBD has been demonstrated to enhance adenosine receptor A2A signaling via inhibition of the adenosine transporter [56].

Recently, GPR18 has been proposed as a putative CBD receptor whose function relates to cellular migration [57]. Antagonism of GPR18 (by agents such as CBD) may be efficacious in treating pain of endometriosis, among other conditions, especially considering that such pain may be endocannabinoid-mediated [58]. Cannabinoids are also very active in various gastrointestinal and visceral sites mediating pain responses [59, 60].

Cannabinoid Interactions with Other Neurotransmitters Pertinent to Pain

As alluded to above, the ECS modulates neurotransmitter release via retrograde inhibition. This is particularly important in NMDA-glutamatergic mechanisms that become hyperresponsive in chronic pain states. Cannabinoids specifically inhibit glutamate release in the hippocampus [61]. THC reduces NMDA responses by 30–40 % [46]. Secondary and tertiary hyperalgesia mediated by NMDA [62] and by calcitonin gene-related peptide [40] may well be targets of cannabinoid therapy in disorders such as migraine, fibromyalgia, and idiopathic bowel syndrome wherein these mechanisms seem to operate pathophysiologically [63], prompting the hypothesis of a "clinical endocannabinoid deficiency." Endocannabinoid modulators may therefore restore homeostasis, leading to normalization of function in these pathophysiological conditions. THC also has numerous effects on serotonergic systems germane to migraine [64], increasing its production in the cerebrum while decreasing reuptake [65]. In fact, the ECS seems to modulate the trigeminovascular system of migraine pathogenesis at vascular and neurochemical levels [66–68].

Cannabinoid-Opioid Interactions

Although endocannabinoids do not bind to opioid receptors, the ECS may nonetheless work in parallel with the endogenous opioid system with numerous areas of overlap and interaction. Pertinent mechanisms include stimulation of beta-endorphin by THC [69] as well as its ability to demonstrate experimental opiate sparing [70], prevent opioid tolerance and withdrawal [71], and rekindle opioid analgesia after loss of effect [72]. Adjunctive treatments that combine opioids with cannabinoids may enhance the analgesic effects of either agent. Such strategies may permit lower doses of analgesics to be employed for therapeutic benefit in a manner that minimizes incidence or severity of adverse side effects.

Clinical Trials, Utility, and Pitfalls of Cannabinoids in Pain

Evidence for Synthetic Cannabinoids

Oral dronabinol (THC) has been available as the synthetic Marinol® since 1985 and is indicated for nausea associated with chemotherapy and appetite stimulation in HIV/AIDS. Issues with its cost, titration difficulties, delayed onset, and propensity to induce intoxicating and dysphoric effects have limited clinical application [73]. It was employed in two open-label studies of chronic neuropathic pain in case studies in 7 [74] and 8 patients [75], but no significant benefit was evident and side effects led to prominent dropout rates (average doses 15–16.6 mg THC). Dronabinol produced benefit in pain in multiple sclerosis [76], but none was evident in postoperative pain (Table 18.1) [77]. Dronabinol was reported to relieve pruritus in three case-report subjects with cholestatic jaundice [78]. Dronabinol was assessed in 30 chronic noncancer pain patients on opioids in double-blind crossover single-day sessions vs. placebo with improvement [79], followed by a 4-week open-label trial with continued improvement (Table 18.1). Associated adverse events were prominent. Methodological issues included lack of prescreening for cannabinoids, 4 placebo subjects with positive THC assays, and 58 % of subjects correctly guessing Marinol dose on test day. An open-label comparison in polyneuropathy examined nabilone patients with 6 obtaining 22.6 % mean pain relief after 3 months, and 5 achieving 28.6 % relief after 6 months, comparable to conventional agents [80]. A pilot study of Marinol in seven spinal cord injury patients with neuropathic pain saw two withdraw, and the remainder appreciate no greater efficacy than with diphenhydramine [81].

Table 18.1 Randomized controlled trials of cannabinoids in pain

Agent	*N*=	Indication	Duration/type	Outcomes/reference
Ajulemic acid	21	Neuropathic pain	7 day crossover	Visual analogue pain scales improved over placebo ($p=0.02$)/Karst et al. [92]
Cannabis, smoked	50	HIV neuropathy	5 days/DB	Decreased daily pain ($p=0.03$) and hyperalgesia ($p=0.05$), 52 % with >30 % pain reduction vs. placebo ($p=0.04$)/ Abrams et al. [94]
Cannabis, smoked	23	Chronic neuropathic pain	5 days/DB	Decreased pain vs. placebo only at 9.4 % THC level ($p=0.023$)/Ware et al. [98]
Cannabis, smoked	38	Neuropathic pain	Single dose/DBC	NSD in pain except at highest cannabis dose ($p=0.02$), with prominent psychoactive effects/Wilsey et al. [95]
Cannabis, smoked	34	HIV neuropathy	5 days /DB	DDS improved over placebo ($p=0.016$), 46 % vs. 18 % improved >30 %, 2 cases toxic psychosis/Ellis et al. [97]
Cannabis, vaporized	21	Chronic pain on opioids	5 days/DB	27 % decrement in pain/Abrams et al. [118]
Cannador	419	Pain due to spasm in MS	15 weeks	Improvement over placebo in subjective pain associated with spasm ($p=0.003$)/ Zajicek et al. [120]
Cannador	65	Postherpetic neuralgia	4 weeks	No benefit observed/Ernst et al. [122]
Cannador	30	Postoperative pain	Single doses, daily	Decreasing pain intensity with increased dose ($p=0.01$)/Holdcroft et al. [123]
Marinol	24	Neuropathic pain in MS	15–21 days/DBC	Median numerical pain ($p=0.02$), median pain relief improved ($p=0.035$) over placebo/Svendsen et al. [76]
Marinol	40	Postoperative pain	Single dose/DB	No benefit observed over placebo/Buggy et al. [77]
Marinol	30	Chronic pain	3 doses, 1 day/DBC	Total pain relief improved with 10 mg ($p<0.05$) and 20 mg ($p<0.01$) with opioids, AE prominent/Narang et al. [79]
Nabilone	41	Postoperative pain	3 doses in 24 h/DB	NSD morphine consumption. Increased pain at rest and on movement with nabilone 1 or 2 mg/Beaulieu [85]
Nabilone	31	Fibromyalgia	2 weeks/DBC	Compared to amitriptyline, nabilone improved sleep, decrease wakefulness, had no effect on pain, and increased AE/ Ware et al. [90]
Nabilone	96	Neuropathic pain	14 weeks/DBC vs. dihydrocodeine	Dihydrocodeine more effective with fewer AE/Frank et al. [88]
Nabilone	13	Spasticity pain	9 weeks/DBC	NRS decreased 2 points for nabilone ($p<0.05$)/Wissel et al. [87]
Nabilone	40	Fibromyalgia	4 weeks/DBC	VAS decreased in pain, Fibromyalgia Impact Questionnaire, and anxiety over placebo (all, $p<0.02$)/Skrabek et al. [89]
Sativex	20	Neurogenic pain	Series of 2-week N-of-1 crossover blocks	Improvement with Tetranabinex and Sativex on VAS pain vs. placebo ($p<0.05$), symptom control best with Sativex ($p<0.0001$)/Wade et al. [132]
Sativex	24	Chronic intractable pain	12 weeks, series of N-of-1 crossover blocks	VAS pain improved over placebo ($p<0.001$) especially in MS ($p<0.0042$)/ Notcutt et al. [133]
Sativex	48	Brachial plexus avulsion	6 weeks in 3 two-week crossover blocks	Benefits noted in Box Scale-11 pain scores with Tetranabinex ($p=0.002$) and Sativex ($p=0.005$) over placebo/Berman et al. [134]
Sativex	66	Central neuropathic pain in MS	5 weeks	Numerical Rating Scale (NRS) analgesia improved over placebo ($p=0.009$)/Rog et al. [135]

(continued)

Table 18.1 (continued)

Agent	*N*=	Indication	Duration/type	Outcomes/reference
Sativex	125	Peripheral neuropathic pain	5 weeks	Improvements in NRS pain levels (p=0.004), dynamic allodynia (p=0.042), and punctuate allodynia (p=0.021) vs. placebo/Nurmikko et al. [136]
Sativex	56	Rheumatoid arthritis	Nocturnal dosing for 5 weeks	Improvements over placebo morning pain on movement (p=0.044), morning pain at rest (p=0.018), DAS-28 (p=0.002), and SF-MPQ pain at present (p=0.016)/Blake et al. [138]
Sativex	117	Pain after spinal injury	10 days	NSD in NRS pain scores, but improved Brief Pain Inventory (p=0.032), and Patients' Global Impression of Change (p=0.001) (unpublished)
Sativex	177	Intractable cancer pain	2 weeks	Improvements in NRS analgesia vs. placebo (p=0.0142), Tetranabinex NSD/ Johnson et al. [139]
Sativex	135	Intractable lower urinary tract symptoms in MS	8 weeks	Improved bladder severity symptoms including pain over placebo (p=0.001) [200]
Sativex	360	Intractable cancer pain	5 weeks/DB	CRA of lower and middle-dose cohorts improved over placebo (p=0.006)/ [201]

Nabilone, or Cesamet®, is a semisynthetic analogue of THC that is about tenfold more potent, and longer lasting [82]. It is indicated as an antiemetic in chemotherapy in the USA. Prior case reports in neuropathic pain [83] and other pain disorders [84] have been published. Sedation and dysphoria are prominent associated adverse events. An RCT of nabilone in 41 postoperative subjects dosed TID actually resulted in increased pain scores (Table 18.1) [85]. An uncontrolled study of 82 cancer patients on nabilone noted improved pain scores [86], but retention rates were limited. Nabilone improved pain ($p<0.05$) vs. placebo in patients with mixed spasticity syndromes in a small double-blind trial (Table 18.1) [87], but was without benefits in other parameters. In a double-blind crossover comparison of nabilone to dihydrocodeine (schedule II opioid) in chronic neuropathic pain (Table 18.1) [88], both drugs produced marginal benefit, but with dihydrocodeine proving clearly superior in efficacy and modestly superior in side-effect profile. In an RCT in 40 patients of nabilone vs. placebo over 4 weeks, it showed significant decreases in VAS of pain and anxiety (Table 18.1) [89]. A more recent study of nabilone vs. amitriptyline in fibromyalgia yielded benefits on sleep, but not pain, mood, or quality of life (Table 18.1) [90]. An open-label trial of nabilone vs. gabapentin found them comparable in pain and other symptom relief in peripheral neuropathic pain [91].

Ajulemic acid (CT3), another synthetic THC analogue in development, was utilized in a phase II RCT in peripheral neuropathic pain in 21 subjects with apparent improvement (Table 18.1) [92]. Whether or not ajulemic acid is psychoactive is the subject of some controversy [93].

Evidence for Smoked or Vaporized Cannabis

Few randomized controlled clinical trials (RCTs) of pain with smoked cannabis have been undertaken to date [94–97]. One of these [96] examined cannabis effects on experimental pain in normal volunteers.

Abrams et al. [94] studied inpatient adults with painful HIV neuropathy in 25 subjects in double-blind fashion to receive either smoked cannabis as 3.56 % THC cigarettes or placebo cigarettes three times daily for 5 days (Table 18.1). The smoked cannabis group had a 34 % reduction in daily pain vs. 17 % in the placebo group (p=0.03). The cannabis cohort also had a 52 % of subjects report a >30 % reduction in pain scores over the 5 days vs. 24 % in the placebo group (p=0.04) (Table 18.1). The authors rated cannabis as "well tolerated" due to an absence of serious adverse events (AE) leading to withdrawal, but all subjects were cannabis experienced. Symptoms of possible intoxication in the cannabis group including anxiety (25 %), sedation (54 %), disorientation (16 %), paranoia (13 %), confusion (17 %), dizziness (15 %), and nausea (11 %) were all statistically significantly more common than in the placebo group. Despite these findings, the authors stated that the values do not represent any serious safety concern in this short-term study. No discussion in the article addressed issues of the relative efficacy of blinding in the trial.

Wilsey et al. [95] examined neuropathic pain in 38 subjects in a double-blind crossover study comparing 7 % THC cannabis, 3.5 % THC cannabis, and placebo cigarettes via a complex cumulative dosing scheme with each dosage given

once, in random order, with at least 3 day intervals separating sessions (Table 18.1). A total of 9 puffs maximum were allowed over several hours per session. Authors stated, "Psychoactive effects were minimal and well-tolerated, but neuropsychological impairment was problematic, particularly with the higher concentration of study medication." Again, only cannabis-experienced subjects were allowed entry. No withdrawals due to AE were reported, but 1 subject was removed due to elevated blood pressure. No significant differences were noted in pain relief in the two cannabis potency groups, but a significant separation of pain reduction from placebo ($p=0.02$) was not evident until a cumulative 9 puffs at 240 min elapsed time. Pain unpleasantness was also reduced in both active treatment groups ($p<0.01$). Subjectively, an "any drug effect" demonstrated a visual analogue scale (VAS) of 60/100 in the high-dose group, but even the low-dose group registered more of a "good drug effect" than placebo ($p<0.001$). "Bad drug effect" was also evident. "Feeling high" and "feeling stoned" were greatest in the high-dose sessions ($p<0.001$), while both high- and low-dose differentiated significantly from placebo ($p<0.05$). Of greater concern, both groups rated impairment as 30/100 on VAS vs. placebo ($p=0.003$). Sedation also demarcated both groups from placebo ($p<0.01$), as did confusion ($p=0.03$), and hunger ($p<0.001$). Anxiety was not considered a prominent feature in this cannabis-experienced population. This study distinguished itself from some others in its inclusion of specific objective neuropsychological measures and demonstrated neurocognitive impairment in attention, learning, and memory, most noteworthy with 7 % THC cannabis. No commentary on blinding efficacy was included.

Ellis et al. [97] examined HIV-associated neuropathic pain in a double-blind trial of placebo vs. 1–8 % THC cannabis administered four times daily over 5 days with a 2-week washout (Table 18.1). Subjects were started at 4 % THC and then titrated upward or downward in four smoking sessions dependent upon their symptom relief and tolerance of the dose. In this study, 96 % of subjects were cannabis-experienced, and 28 out of 34 subjects completed the trial. The primary outcome measure (Descriptor Differential Scale, DDS) was improved in the active group over placebo ($p=0.016$), with >30 % relief noted in 46 % of cannabis subjects vs. 18 % of placebo. While most adverse events (AE) were considered mild and self-limited, two subjects had to leave the trial due to toxicity. One cannabis-naïve subject was withdrawn due to "an acute cannabis-induced psychosis" at what proved to be his first actual cannabis exposure. The other subject suffered intractable cough. Pain reduction was greater in the cannabis-treated group ($p=0.016$) among completers, as was the proportion of subjects attaining >30 % pain reduction (46 % vs. 18 %, $p=0.043$). Blinding was assessed in this study; whereas placebo patients were inaccurate at guessing the investigational product, 93 % of those receiving cannabis guessed correctly. On safety issues, the authors stated that the frequency of some nontreatment-limiting side effects was greater for cannabis than placebo. These included concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation, and thirst.

A Canadian study [98] examined single 25-mg inhalations of various cannabis potencies (0–9.4 % THC) three times daily for 5 days per cycle in 23 subjects with chronic neuropathic pain (Table 18.1). Patients were said to be cannabis-free for 1 year, but were required to have some experience of the drug. Only the highest potency demarcated from placebo on decrements in average daily pain score (5.4 vs. 6.1, $p=0.023$). The most frequent AE in the high-dose group were headache, dry eyes, burning sensation, dizziness, numbness, and cough, but with "high" or "euphoria" reported only once in each cannabis potency group.

The current studies of smoked cannabis are noteworthy for their extremely short-term exposure and would be of uncertain relevance in a regulatory environment. The IMMPACT recommendations on chronic neuropathic pain clinical trials that are currently favored by the FDA [29] generally suggest randomized controlled clinical trials of 12-week duration as a prerequisite to demonstrate efficacy and safety. While one might assume that the degree of pain improvement demonstrated in these trials could be maintained over this longer interval, it is only reasonable to assume that cumulative adverse events would also increase to at least some degree. The combined studies represent only a total of 1,106 patient-days of cannabis exposure (Abrams: 125, Wilsey: 76, Ellis: 560, Ware 345) or 3 patient-years of experience. In contrast, over 6,000 patient-years of data have been analyzed for Sativex between clinical trials, prescription, and named-patient supplies, with vastly lower AE rates (data on file, GW Pharmaceuticals) [28, 99]. Certainly, the cognitive effects noted in California-smoked cannabis studies figure among many factors that would call the efficacy of blinding into question for investigations employing such an approach. However, it is also important to emphasize that unwanted side effects are not unique to cannabinoids. In a prospective evaluation of specific chronic polyneuropathy syndromes and their response to pharmacological therapies, the presence of intolerable side effects did not differ in groups receiving gabapentinoids, tricyclic antidepressants, anticonvulsants, cannabinoids (including nabilone, Sativex), and topical agents [80]. Moreover, no serious adverse events were related to any of the medications.

The current studies were performed in a very select subset of patients who almost invariably have had prior experience of cannabis. Their applicability to cannabis-naïve populations is, thus, quite unclear. At best, the observed benefits might possibly accrue to some, but it is eminently likely that candidates for such therapy might refuse it on any number of

grounds: not wishing to smoke, concern with respect to intoxication, etc. Sequelae of smoking in therapeutic outcomes have had little discussion in these brief RCTs [28]. Cannabis smoking poses substantial risk of chronic cough and bronchitic symptoms [100], if not obvious emphysematous degeneration [101] or increase in aerodigestive cancers [102]. Even such smoked cannabis proponents as Lester Grinspoon has acknowledged are the only well-confirmed deleterious physical effect of marihuana is harm to the pulmonary system [103]. However, population-based studies of cannabis trials have failed to show any evidence for increased risk of respiratory symptoms/chronic obstructive pulmonary disease [100] or lung cancer [102] associated with smoking cannabis.

A very detailed analysis and comparison of mainstream and sidestream smoke for cannabis vs. tobacco smoke was performed in Canada [104]. Of note, cannabis smoke contained ammonia (NH_3) at a level of 720 μg per 775 mg cigarette, a figure 20-fold higher than that found in tobacco smoke. It was hypothesized that this finding was likely attributable to nitrate fertilizers. Formaldehyde and acetaldehyde were generally lower in cannabis smoke than in tobacco, but butyraldehyde was higher. Polycyclic aromatic hydrocarbon (PAH) contents were qualitatively similar in the comparisons, but total yield was lower for cannabis mainstream smoke, but higher than tobacco for sidestream smoke. Additionally, NO, NO_x, hydrogen cyanide, and aromatic amines concentrations were 3–5 times higher in cannabis smoke than that from tobacco. Possible mutagenic and carcinogenic potential of these various compounds were mentioned. More recently, experimental analysis of cannabis smoke with resultant acetaldehyde production has posited its genotoxic potential to be attributable to reactions that produce DNA adducts [105].

Vaporizers for cannabis have been offered as a harm reduction technique that would theoretically eliminate products of combustion and associated adverse events. The Institute of Medicine (IOM) examined cannabis issues in 1999 [106], and among their conclusions was the following (p. 4): "Recommendation 2: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems." One proposed technique is vaporization, whereby cannabis is heated to a temperature that volatilizes THC and other components with the goal of reducing or eliminating by-products of combustion, including potentially carcinogenic polycyclic aromatic hydrocarbons, benzene, acetaldehyde, carbon monoxide, toluene, naphthaline, phenol, toluene, hydrogen cyanide, and ammonia. Space limitations permit only a cursory review of available literature [107–115].

A pilot study of the Volcano vaporizer vs. smoking was performed in the USA in 2007 in 18 active cannabis consumers, with only 48 h of presumed abstinence [116]. NIDA 900-mg cannabis cigarettes were employed (1.7, 3.4, and 6.8 % THC) with each divided in two, so that one-half would be smoked or vaporized in a series of double-blind sessions. The Volcano vaporizer produced comparable or slightly higher THC plasma concentrations than smoking. Measured CO in exhaled vapor sessions diminished very slightly, while it increased after smoking ($p<0.001$). Self-reported visual analogue scales of the associated high were virtually identical in vaporization vs. smoking sessions and increased with higher potency material. A contention was advanced that the absence of CO increase after vaporization can be equated to "little or no exposure to gaseous combustion toxins." Given that no measures of PAH or other components were undertaken, the assertion is questionable. It was also stated that there were no reported adverse events. Some 12 subjects preferred the Volcano, 2 chose smoking, and 2 had no preference as to technique, making the vaporizer "an acceptable system" and providing "a safer way to deliver THC."

A recent [202, 117] examined interactions of 3.2 % THC NIDA cannabis vaporized in the Volcano in conjunction with opioid treatment in a 5-day inpatient trial in 21 patients with chronic pain (Table 18.1). All subjects were prior cannabis smokers. Overall, pain scores were reduced from 39.6 to 29.1 on a VAS, a 27 % reduction, by day 5. Pain scores in subjects on morphine fell from 34.8 to 24.1, while in subjects taking oxycodone, scores dropped from 43.8 to 33.6.

The clinical studies performed with vaporizers to date have been very small pilot studies conducted over very limited timeframes (i.e., for a maximum of 5 days). Thus, these studies cannot contribute in any meaningful fashion toward possible FDA approval of vaporized cannabis as a delivery technique, device, or drug under existing policies dictated by the *Botanical Guidance* [32]. It is likewise quite unlikely that the current AE profile of smoked or vaporized cannabis would meet FDA requirements. The fact that all the vaporization trials to date have been undertaken only in cannabis-experienced subjects does not imply that results would generalize to larger patient populations. Moreover, there is certainly no reason to expect AE profiles to be better in cannabis-naïve patients. Additionally, existing standardization of cannabis product and delivery via vaporization seem far off the required marks. Although vaporizers represent an alternate delivery method devoid of the illegality associated with smoked cannabis, the presence of toxic ingredients such as PAH, ammonia, and acetaldehyde in cannabis vapor are unlikely to be acceptable to FDA in any significant amounts. Existing vaporizers still lack portability or convenience [28]. A large Internet survey revealed that only 2.2 % of cannabis users employed vaporization as their primary cannabis intake method [118]. While studies to date have established that lower temperature vaporization in the Volcano, but not necessarily other devices, can reduce the relative amounts of noxious by-products of combustion, it has yet to be demonstrated that they are totally eliminated. Until or unless this goal is achieved, along with

requisite benchmarks of herbal cannabis quality, safety, and efficacy in properly designed randomized clinical trials, vaporization remains an unproven technology for therapeutic cannabinoid administration.

Evidence for Cannabis-Based Medicines

Cannador is a cannabis extract in oral capsules, with differing THC:CBD ratios [51]. Cannador was utilized in a phase III RCT of spasticity in multiple sclerosis (CAMS) (Table 18.1) [119]. While no improvement was evident in the Ashworth Scale, reduction was seen in spasm-associated pain. Both THC and Cannador improved pain scores in follow-up [120]. Cannador was also employed for postherpetic neuralgia in 65 patients, but without success (Table 18.1) [121, 122]. Slight pain reduction was observed in 30 subjects with postoperative pain (CANPOP) not receiving opiates, but psychoactive side effects were notable (Table 18.1).

Sativex® is a whole-cannabis-based extract delivered as an oromucosal spray that combines a CB_1 and CB_2 partial agonist (THC) with a cannabinoid system modulator (CBD), minor cannabinoids, and terpenoids plus ethanol and propylene glycol excipients and peppermint flavoring [51, 123]. It is approved in Canada for spasticity in MS and under a Notice of Compliance with Conditions for central neuropathic pain in multiple sclerosis and treatment of cancer pain unresponsive to opioids. Sativex is also approved in MS in the UK, Spain, and New Zealand, for spasticity in multiple sclerosis, with further approvals expected soon in some 22 countries around the world. Sativex is highly standardized and is formulated from two *Cannabis sativa* chemovars predominating in THC and CBD, respectively [124]. Each 100 µl pump-action oromucosal spray of Sativex yields 2.7 mg of THC and 2.5 mg of CBD plus additional components. Pharmacokinetic data are available [125–127]. Sativex effects begin within an interval allowing dose titration. A very favorable adverse event profile has been observed in the development program [27, 128]. Most patients stabilize at 8–10 sprays per day after 7–10 days, attaining symptomatic control without undue psychoactive sequelae. Sativex was added to optimized drug regimens in subjects with uncontrolled pain in every RCT (Table 18.1). An Investigational New Drug (IND) application to study Sativex in advanced clinical trials in the USA was approved by the FDA in January 2006 in patients with intractable cancer pain. One phase IIB dose-ranging study has already been completed [201]. Available clinical trials with Sativex have been independently assessed [129, 130].

In a phase II study of 20 patients with neurogenic symptoms [131], significant improvement was seen with both Tetranabinex (high-THC extract without CBD) and Sativex on pain, with Sativex displaying better symptom control ($p<0.0001$), with less intoxication (Table 18.1).

In a phase II study of intractable chronic pain in 24 patients [132], Sativex again produced the best results compared to Tetranabinex ($p<0.001$), especially in MS ($p<0.0042$) (Table 18.1).

In a phase III study of brachial plexus avulsion ($N=48$) [133], pain reduction with Tetranabinex and Sativex was about equal (Table 18.1).

In an RCT of 66 MS subjects, mean Numerical Rating Scale (NRS) analgesia favored Sativex over placebo (Table 18.1) [134].

In a phase III trial ($N=125$) of peripheral neuropathic pain with allodynia [135], Sativex notably alleviated pain levels and dynamic and punctate allodynia (Table 18.1).

In a safety-extension study in 160 subjects with various symptoms of MS [136], 137 patients showed sustained improvements over a year or more in pain and other symptoms [99] without development of any tolerance requiring dose escalation or withdrawal effects in those who voluntarily discontinued treatment suddenly. Analgesia was quickly reestablished upon Sativex resumption.

In a phase II RCT in 56 rheumatoid arthritis sufferers over 5 weeks with Sativex [137], medicine was limited to only 6 evening sprays (16.2 mg THC + 15 mg CBD). By study end, morning pain on movement, morning pain at rest, DAS-28 measure of disease activity, and SF-MPQ pain all favored Sativex (Table 18.1).

In a phase III RCT in intractable cancer pain on opioids ($N=177$), Sativex, Tetranabinex THC-predominant extract, and placebo were compared [138] demonstrating strongly statistically significant improvements in analgesia for Sativex only (Table 18.1). This suggests that the CBD component in Sativex was necessary for benefit.

In a 2-week study of spinal cord injury pain, NRS of pain was not statistically different from placebo, probably due to the short duration of the trial, but secondary endpoints were positive (Table 18.1). Additionally, an RCT of intractable lower urinary tract symptoms in MS also demonstrated pain reduction (Table 18.1).

The open-label study of various polyneuropathy patients included Sativex patients with 3 obtaining 21.56 % mean pain relief after 3 months (2/3 > 30 %), and 4 achieving 27.6 % relief after 6 months (2/4 > 30 %), comparable to conventional agents [80].

A recently completed RCT of Sativex in intractable cancer pain unresponsive to opioids over 5 weeks was performed in 360 subjects (Table 18.1). Results of a Continuous Response Analysis (CRA) showed improvements over placebo in the low-dose ($p=0.08$) and middle-dose cohorts ($p=0.038$) or combined ($p=0.006$). Pain NRS improved over placebo in the low-dose ($p=0.006$) and combined cohorts ($p=0.019$).

Sleep has improved markedly in almost all Sativex RCTs in chronic pain based on symptom reduction, not a hypnotic effect [139].

The adverse event (AE) profile of Sativex has been quite benign with bad taste, oral stinging, dry mouth, dizziness, nausea, or fatigue most common, but not usually prompting discontinuation [128]. Most psychoactive sequelae are early and transient and have been notably lowered by more recent application of a slower, less aggressive titration schedule. While no direct comparative studies have been performed with Sativex and other agents, AE rates were comparable or greater with Marinol than with Sativex employing THC dosages some 2.5 times higher, likely due to the presence of accompanying CBD [28, 51]. Similarly, Sativex displayed a superior AE profile compared to smoked cannabis based on safety-extension studies of Sativex [28, 99], as compared to chronic use of cannabis with standardized government-supplied material in Canada for chronic pain [140] and the Netherlands for various indications [141, 142] over a period of several months or more. All AEs are more frequent with smoked cannabis, except for nausea and dizziness, both early and usually transiently reported with Sativex [27, 28, 128]. A recent meta-analysis suggested that serious AEs associated with cannabinoid-based medications did not differ from placebo and thus could not be attributable to cannabinoid use, further reinforcing the low toxicity associated with activation of cannabinoid systems.

Cannabinoid Pitfalls: Are They Surmountable?

The dangers of COX-1 and COX-2 inhibition by nonsteroidal anti-inflammatory drugs (NSAIDS) of various design (e.g., gastrointestinal ulceration and bleeding vs. coronary and cerebrovascular accidents, respectively) [143, 144] are unlikely to be mimicked by either THC or CBD, which produce no such activity at therapeutic dosages [49].

Natural cannabinoids require polar solvents and may be associated with delayed and sometimes erratic absorption after oral administration. Smoking of cannabis invariably produces rapid spikes in serum THC levels; cannabis smoking attains peak levels of serum THC above 140 ng/ml [145, 146], which, while desirable to the recreational user, has no necessity or advantage for treatment of chronic pain [28]. In contrast, comparable amounts of THC derived from oromucosal Sativex remained below 2 ng/ml with much lower propensity toward psychoactive sequelae [28, 125], with subjective intoxication levels on visual analogue scales that are indistinguishable from placebo, in the single digits out of 100 [100]. It is clear from RCTs that such psychoactivity is not a necessary accompaniment to pain control. In contrast, intoxication has continued to be prominent with oral THC [73].

In comparison to the questionable clinical trial blinding with smoked and vaporized cannabis discussed above, all indications are that such study blinding has been demonstrably effective with Sativex [147, 148] by utilizing a placebo spray with identical taste and color. Some 50 % of Sativex subjects in RCTs have had prior cannabis exposure, but results of two studies suggest that both groups exhibited comparable results in both treatment efficacy and side effect profile [134, 135].

Controversy continues to swirl around the issue of the potential dangers of cannabis use medicinally, particularly its drug abuse liability (DAL). Cannabis and cannabinoids are currently DEA schedule I substances and are forbidden in the USA (save for Marinol in schedule III and nabilone in schedule II) [73]. This is noteworthy in itself because the very same chemical compound, THC, appears simultaneously in schedule I (as THC), schedule II (as nabilone), and schedule III (as Marinol). DAL is assessed on the basis of five elements: intoxication, reinforcement, tolerance, withdrawal, and dependency plus the drug's overall observed rates of abuse and diversion. Drugs that are smoked or injected are commonly rated as more reinforcing due to more rapid delivery to the brain [149]. Sativex has intermediate onset. It is claimed that CBD in Sativex reduces the psychoactivity of THC [28]. RCT AE profiles do not indicate euphoria or other possible reinforcing psychoactive indicia as common problems with its use [99]. Similarly, acute THC effects such as tachycardia, hypothermia, orthostatic hypotension, dry mouth, ocular injection, and intraocular pressure decreases undergo prominent tachyphylaxis with regular usage [150]. Despite that observation, Sativex has not demonstrated dose tolerance to its therapeutic benefits on prolonged administration, and efficacy has been maintained for up to several years in pain conditions [99].

The existence or severity of a cannabis withdrawal syndrome remains under debate [151, 152]. In contrast to reported withdrawal sequelae in recreational users [153], 24 subjects with MS who volunteered to discontinue Sativex after a year or more suffered no withdrawal symptoms meeting Budney criteria. While symptoms such as pain recurred after some 7–10 days without Sativex, symptom control was rapidly reattained upon resumption [99].

Finally, no known abuse or diversion incidents have been reported with Sativex to date (March 2011). Formal DAL studies of Sativex vs. Marinol and placebo have been completed and demonstrate lower scores on drug liking and similar measures at comparable doses [155].

Cognitive effects of cannabis also remain at issue [155, 156], but less data are available in therapeutic applications. Studies of Sativex in neuropathic pain with allodynia have revealed no changes vs. placebo on Sativex in portions of the Halstead-Reitan Battery [135], or in central neuropathic pain in MS [134], where 80 % of tests showed no significant differences. In a recent RCT of Sativex vs. placebo in MS patients, no cognitive differences of note were observed

[157]. Similarly, chronic Sativex use has not produced observable mood disorders.

Controversies have also arisen regarding the possible association of cannabis abuse and onset of psychosis [156]. However, an etiological relationship is not supported by epidemiological data [158–161], but may well be affected by dose levels and duration, if pertinent. One may speculate that lower serum levels of Sativex combined with antipsychotic properties of CBD [52, 162, 163] might attenuate such concerns. Few cases of related symptoms have been reported in SAFEX studies of Sativex.

Immune function becomes impaired in experimental animals at cannabinoid doses 50–100 times necessary to produce psychoactive effects [164]. In four patients smoking cannabis medicinally for more than 20 years, no changes were evident in leukocyte, CD4, or CD8 cell counts [155]. MS patients on Cannador demonstrated no immune changes of note [165] nor were changes evident in subjects smoking cannabis in a brief trial in HIV patients [166]. Sativex RCTs have demonstrated no hematological or immune dysfunction.

No effects of THC extract, CBD extract, or Sativex were evident on the hepatic cytochrome P450 complex [167] or on human CYP450 [168]. Similarly, while Sativex might be expected to have additive sedative effects with other drugs or alcohol, no significant drug-drug interactions of any type have been observed in the entire development program to date.

No studies have demonstrated significant problems in relation to cannabis affecting driving skills at plasma levels below 5 ng/ml of THC [169]. Four oromucosal sprays of Sativex (exceeding the average single dose employed in therapy) produced serum levels well below this threshold [28]. As with other cannabinoids in therapy, it is recommended that patients not drive nor use dangerous equipment until accustomed to the effects of the drug.

Future Directions: An Array of Biosynthetic and Phytocannabinoid Analgesics

Inhibition of Endocannabinoid Transport and Degradation: A Solution?

It is essential that any cannabinoid analgesic strike a compromise between therapeutic and adverse effects that may both be mediated via CB_1 mechanisms [34]. Mechanisms to avoid psychoactive sequelae could include peripherally active synthetic cannabinoids that do not cross the blood-brain barrier or drugs that boost AEA levels by inhibiting fatty-acid amide hydrolase (FAAH) [170] or that of 2-AG by inhibiting monoacylycerol lipase (MGL). CBD also has this effect [50] and certainly seems to increase the therapeutic index of THC [51].

In preclinical studies, drugs inhibiting endocannabinoid hydrolysis [171, 172] and peripherally acting agonists [173] all show promise for suppressing neuropathic pain. AZ11713908, a peripherally restricted mixed cannabinoid agonist, reduces mechanical allodynia with efficacy comparable to the brain penetrant mixed cannabinoid agonist WIN55,212-2 [173]. An irreversible inhibitor of the 2-AG hydrolyzing enzyme MGL suppresses nerve injury-induced mechanical allodynia through a CB_1 mechanism, although these anti-allodynic effects undergo tolerance following repeated administration [172]. URB937, a brain impermeant inhibitor of FAAH, has recently been shown to elevate anandamide outside the brain and suppress neuropathic and inflammatory pain behavior without producing tolerance or unwanted CNS side effects [171]. These observations raise the possibility that peripherally restricted endocannabinoid modulators may show therapeutic potential as analgesics with limited side-effect profiles.

The Phytocannabinoid and Terpenoid Pipeline

Additional phytocannabinoids show promise in treatment of chronic pain [123, 163, 174]. Cannabichromene (CBC), another prominent phytocannabinoid, also displays anti-inflammatory [175] and analgesic properties, though less potently than THC [176]. CBC, like CBD, is a weak inhibitor of AEA reuptake [177]. CBC is additionally a potent TRPA1 agonist [178]. Cannabigerol (CBG), another phytocannabinoid, displays weak binding at both CB_1 and CB_2 [179, 180] but is a more potent GABA reuptake inhibitor than either THC or CBD [181]. CBG is a stronger analgesic, anti-erythema, and lipooxygenase agent than THC [182]. CBG likewise inhibits AEA uptake and is a TRPV1 agonist [177], a TRPA1 agonist, and a TRPM8 antagonist [178]. CBG is also a phospholipase A2 modulator that reduces PGE-2 release in synovial cells [183]. Tetrahydrocannabivarin, a phytocannabinoid present in southern African strains, displays weak CB_1 antagonism [184] and a variety of anticonvulsant activities [185] that might prove useful in chronic neuropathic pain treatment. THCV also reduced inflammation and attendant pain in mouse experiments [187]. Most North American [187] and European [188, 189] cannabis strains have been bred to favor THC over a virtual absence of other phytocannabinoid components, but the latter are currently available in abundance via selective breeding [124, 190].

Aromatic terpenoid components of cannabis also demonstrate pain reducing activity [123, 163]. Myrcene displays an opioid-type analgesic effect blocked by naloxone [191] and reduces inflammation via PGE-2 [192]. β-Caryophyllene displays anti-inflammatory activity on par with phenylbutazone via PGE-1 [193], but contrasts by displaying gastric cytoprotective activity [194]. Surprisingly, β-caryophyllene has proven to be a phytocannabinoid in its own right as a selective CB_2 agonist [195]. α-Pinene inhibits PGE-1 [196], and linalool acts as a local anesthetic [197].

Summary

Basic science and clinical trials support the theoretical and practical basis of cannabinoid agents as analgesics for chronic pain. Their unique pharmacological profiles with multimodality effects and generally favorable efficacy and safety profiles render cannabinoid-based medicines promising agents for adjunctive treatment, particularly for neuropathic pain. It is our expectation that the coming years will mark the advent of numerous approved cannabinoids with varying mechanisms of action and delivery techniques that should offer the clinician useful new tools for treating pain.

References

1. Di Marzo V, Bisogno T, De Petrocellis L. Endocannabinoids and related compounds: walking back and forth between plant natural products and animal physiology. Chem Biol. 2007;14(7):741–56.
2. Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. J Am Chem Soc. 1964;86: 1646–7.
3. Pate D. Chemical ecology of cannabis. J Int Hemp Assoc. 1994;2: 32–7.
4. Di Marzo V, Melck D, Bisogno T, De Petrocellis L. Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action. Trends Neurosci. 1998;21(12):521–8.
5. Pacher P, Batkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev. 2006;58(3): 389–462.
6. Cravatt BF, Giang DK, Mayfield SP, Boger DL, Lerner RA, Gilula NB. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. Nature. 1996;384(6604):83–7.
7. Dinh TP, Freund TF, Piomelli D. A role for monoglyceride lipase in 2-arachidonoylglycerol inactivation. Chem Phys Lipids. 2002;121(1–2):149–58.
8. Gulyas AI, Cravatt BF, Bracey MH, et al. Segregation of two endocannabinoid-hydrolyzing enzymes into pre- and postsynaptic compartments in the rat hippocampus, cerebellum and amygdala. Eur J Neurosci. 2004;20(2):441–58.
9. Mangieri RA, Piomelli D. Enhancement of endocannabinoid signaling and the pharmacotherapy of depression. Pharmacol Res. 2007;56(5):360–6.
10. Howlett AC, Johnson MR, Melvin LS, Milne GM. Nonclassical cannabinoid analgetics inhibit adenylate cyclase: development of a cannabinoid receptor model. Mol Pharmacol. 1988;33(3): 297–302.
11. Zimmer A, Zimmer AM, Hohmann AG, Herkenham M, Bonner TI. Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB1 receptor knockout mice. Proc Natl Acad Sci USA. 1999;96(10):5780–5.
12. Wilson RI, Nicoll RA. Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. Nature. 2001;410(6828): 588–92.
13. Ibrahim MM, Porreca F, Lai J, et al. CB2 cannabinoid receptor activation produces antinociception by stimulating peripheral release of endogenous opioids. Proc Natl Acad Sci USA. 2005;102(8): 3093–8.
14. Guindon J, Hohmann AG. Cannabinoid CB2 receptors: a therapeutic target for the treatment of inflammatory and neuropathic pain. Br J Pharmacol. 2008;153(2):319–34.
15. Pacher P, Mechoulam R. Is lipid signaling through cannabinoid 2 receptors part of a protective system? Prog Lipid Res. 2011;50:193–211.
16. Racz I, Nadal X, Alferink J, et al. Interferon-gamma is a critical modulator of CB(2) cannabinoid receptor signaling during neuropathic pain. J Neurosci. 2008;28(46):12136–45.
17. Guindon J, Hohmann AG. The endocannabinoid system and pain. CNS Neurol Disord Drug Targets. 2009;8(6):403–21.
18. Fankhauser M. History of cannabis in Western medicine. In: Grotenhermen F, Russo EB, editors. Cannabis and cannabinoids: pharmacology, toxicology and therapeutic potential. Binghamton: Haworth Press; 2002. p. 37–51.
19. Russo EB. History of cannabis as medicine. In: Guy GW, Whittle BA, Robson P, editors. Medicinal uses of cannabis and cannabinoids. London: Pharmaceutical Press; 2004. p. 1–16.
20. Russo EB. History of cannabis and its preparations in saga, science and sobriquet. Chem Biodivers. 2007;4(8):2624–48.
21. Mechoulam R. The pharmacohistory of *Cannabis sativa*. In: Mechoulam R, editor. Cannabinoids as therapeutic agents. Boca Raton: CRC Press; 1986. p. 1–19.
22. Russo E. Cannabis treatments in obstetrics and gynecology: a historical review. J Cannabis Ther. 2002;2(3–4):5–35.
23. Russo EB. Hemp for headache: an in-depth historical and scientific review of cannabis in migraine treatment. J Cannabis Ther. 2001;1(2):21–92.
24. Russo EB. The role of cannabis and cannabinoids in pain management. In: Cole BE, Boswell M, editors. Weiner's pain management: a practical guide for clinicians. 7th ed. Boca Raton: CRC Press; 2006. p. 823–44.
25. Russo EB. Cannabis in India: ancient lore and modern medicine. In: Mechoulam R, editor. Cannabinoids as therapeutics. Basel: Birkhäuser Verlag; 2005. p. 1–22.
26. ABC News, USA Today, Stanford Medical Center Poll. Broad experience with pain sparks search for relief. 9 May 2005.
27. Russo EB. Cannabinoids in the management of difficult to treat pain. Ther Clin Risk Manag. 2008;4(1):245–59.
28. Russo EB. The solution to the medicinal cannabis problem. In: Schatman ME, editor. Ethical issues in chronic pain management. Boca Raton: Taylor & Francis; 2006. p. 165–94.
29. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113(1–2):9–19.
30. Tyler VE. Phytomedicines in Western Europe: potential impact on herbal medicine in the United States. In: Kinghorn AD, Balandrin MF, editors. Human medicinal agents from plants (ACS symposium, No. 534). Washington, D.C.: American Chemical Society; 1993. p. 25–37.
31. Russo EB. Handbook of psychotropic herbs: a scientific analysis of herbal remedies for psychiatric conditions. Binghamton: Haworth Press; 2001.
32. Food and Drug Administration. Guidance for industry: botanical drug products. In: Services UDoHaH, editor. US Government; 2004. p. 48. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070491.pdf.
33. Walker JM, Hohmann AG. Cannabinoid mechanisms of pain suppression. Handb Exp Pharmacol. 2005;168:509–54.
34. Rahn EJ, Hohmann AG. Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside. Neurotherapeutics. 2009;6(4):713–37.
35. Richardson JD, Aanonsen L, Hargreaves KM. SR 141716A, a cannabinoid receptor antagonist, produces hyperalgesia in untreated mice. Eur J Pharmacol. 1997;319(2–3):R3–4.
36. Walker JM, Huang SM, Strangman NM, Tsou K, Sanudo-Pena MC. Pain modulation by the release of the endogenous cannabinoid anandamide. Proc Natl Acad Sci. 1999;96(21):12198–203.
37. Walker JM, Hohmann AG, Martin WJ, Strangman NM, Huang SM, Tsou K. The neurobiology of cannabinoid analgesia. Life Sci. 1999;65(6–7):665–73.
38. Martin WJ, Hohmann AG, Walker JM. Suppression of noxious stimulus-evoked activity in the ventral posterolateral nucleus of the

thalamus by a cannabinoid agonist: correlation between electrophysiological and antinociceptive effects. J Neurosci. 1996;16:6601–11.
39. Hohmann AG, Martin WJ, Tsou K, Walker JM. Inhibition of noxious stimulus-evoked activity of spinal cord dorsal horn neurons by the cannabinoid WIN 55,212-2. Life Sci. 1995;56(23–24):2111–8.
40. Richardson JD, Aanonsen L, Hargreaves KM. Antihyperalgesic effects of spinal cannabinoids. Eur J Pharmacol. 1998;345(2):145–53.
41. Strangman NM, Walker JM. Cannabinoid WIN 55,212-2 inhibits the activity-dependent facilitation of spinal nociceptive responses. J Neurophysiol. 1999;82(1):472–7.
42. Rahn EJ, Makriyannis A, Hohmann AG. Activation of cannabinoid CB(1) and CB(2) receptors suppresses neuropathic nociception evoked by the chemotherapeutic agent vincristine in rats. Br J Pharmacol. 2007;152:765–77.
43. Richardson JD, Kilo S, Hargreaves KM. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. Pain. 1998;75(1):111–9.
44. Karsak M, Gaffal E, Date R, et al. Attenuation of allergic contact dermatitis through the endocannabinoid system. Science. 2007;316(5830):1494–7.
45. Luongo L, Palazzo E, Tambaro S, et al. 1-(2',4'-Dichlorophenyl)-6-methyl-N-cyclohexylamine-1,4-dihydroindeno[1,2-c]pyrazole-3-carboxamide, a novel CB2 agonist, alleviates neuropathic pain through functional microglial changes in mice. Neurobiol Dis. 2010;37(1):177–85.
46. Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-) Delta9-tetrahydrocannabinol are neuroprotective antioxidants. Proc Natl Acad Sci USA. 1998;95(14):8268–73.
47. Burstein S, Levin E, Varanelli C. Prostaglandins and cannabis. II. Inhibition of biosynthesis by the naturally occurring cannabinoids. Biochem Pharmacol. 1973;22(22):2905–10.
48. Fimiani C, Liberty T, Aquirre AJ, Amin I, Ali N, Stefano GB. Opiate, cannabinoid, and eicosanoid signaling converges on common intracellular pathways nitric oxide coupling. Prostaglandins Other Lipid Mediat. 1999;57(1):23–34.
49. Stott CG, Guy GW, Wright S, Whittle BA. The effects of cannabis extracts Tetranabinex & Nabidiolex on human cyclo-oxygenase (COX) activity. Paper presented at: Symposium on the Cannabinoids, Clearwater, June 2005.
50. Bisogno T, Hanus L, De Petrocellis L, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol. 2001;134(4):845–52.
51. Russo EB, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Med Hypotheses. 2006;66(2):234–46.
52. Morgan CJ, Curran HV. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. Br J Psychiatry. 2008;192(4):306–7.
53. Morgan CJ, Freeman TP, Schafer GL, Curran HV. Cannabidiol attenuates the appetitive effects of delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis. Neuropsychopharmacology. 2010;35(9):1879–85.
54. Morgan CJ, Schafer G, Freeman TP, Curran HV. Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study. Br J Psychiatry. 2010;197(4):285–90.
55. Malfait AM, Gallily R, Sumariwalla PF, et al. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. Proc Natl Acad Sci USA. 2000;97(17):9561–6.
56. Carrier EJ, Auchampach JA, Hillard CJ. Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. Proc Natl Acad Sci USA. 2006;103(20):7895–900.
57. McHugh D, Hu SS, Rimmerman N, et al. N-arachidonoyl glycine, an abundant endogenous lipid, potently drives directed cellular migration through GPR18, the putative abnormal cannabidiol receptor. BMC Neurosci. 2010;11:44.
58. Dmitrieva N, Nagabukuro H, Resuehr D, et al. Endocannabinoid involvement in endometriosis. Pain. 2010;151(3):703–10.
59. Izzo AA, Camilleri M. Emerging role of cannabinoids in gastrointestinal and liver diseases: basic and clinical aspects. Gut. 2008;57(8):1140–55.
60. Izzo AA, Sharkey KA. Cannabinoids and the gut: new developments and emerging concepts. Pharmacol Ther. 2010;126(1):21–38.
61. Shen M, Piser TM, Seybold VS, Thayer SA. Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. J Neurosci. 1996;16(14):4322–34.
62. Nicolodi M, Volpe AR, Sicuteri F. Fibromyalgia and headache. Failure of serotonergic analgesia and N-methyl-D-aspartate-mediated neuronal plasticity: their common clues. Cephalalgia. 1998;18 Suppl 21:41–4.
63. Russo EB. Clinical endocannabinoid deficiency (CECD): Can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? Neuroendocrinol Lett. 2004;25(1–2):31–9.
64. Russo E. Cannabis for migraine treatment: the once and future prescription? An historical and scientific review. Pain. 1998;76(1–2):3–8.
65. Spadone C. Neurophysiologie du cannabis [neurophysiology of cannabis]. Encéphale. 1991;17(1):17–22.
66. Akerman S, Holland PR, Goadsby PJ. Cannabinoid (CB1) receptor activation inhibits trigeminovascular neurons. J Pharmacol Exp Ther. 2007;320(1):64–71.
67. Akerman S, Kaube H, Goadsby PJ. Anandamide is able to inhibit trigeminal neurons using an in vivo model of trigeminovascular-mediated nociception. J Pharmacol Exp Ther. 2003;309(1):56–63.
68. Akerman S, Kaube H, Goadsby PJ. Anandamide acts as a vasodilator of dural blood vessels in vivo by activating TRPV1 receptors. Br J Pharmacol. 2004;142:1354–60.
69. Manzanares J, Corchero J, Romero J, Fernandez-Ruiz JJ, Ramos JA, Fuentes JA. Chronic administration of cannabinoids regulates proenkephalin mRNA levels in selected regions of the rat brain. Brain Res Mol Brain Res. 1998;55(1):126–32.
70. Cichewicz DL, Martin ZL, Smith FL, Welch SP. Enhancement of mu opioid antinociception by oral delta9-tetrahydrocannabinol: dose-response analysis and receptor identification. J Pharmacol Exp Ther. 1999;289(2):859–67.
71. Cichewicz DL, Welch SP. Modulation of oral morphine antinociceptive tolerance and naloxone-precipitated withdrawal signs by oral delta 9-tetrahydrocannabinol. J Pharmacol Exp Ther. 2003;305(3):812–7.
72. Cichewicz DL, McCarthy EA. Antinociceptive synergy between delta(9)-tetrahydrocannabinol and opioids after oral administration. J Pharmacol Exp Ther. 2003;304(3):1010–5.
73. Calhoun SR, Galloway GP, Smith DE. Abuse potential of dronabinol (Marinol). J Psychoactive Drugs. 1998;30(2):187–96.
74. Clermont-Gnamien S, Atlani S, Attal N, Le Mercier F, Guirimand F, Brasseur L. Utilisation thérapeutique du delta-9-tétrahydrocannabinol (dronabinol) dans les douleurs neuropathiques réfractaires. The therapeutic use of D9-tetrahydrocannabinol (dronabinol) in refractory neuropathic pain. Presse Med. 2002;31(39 Pt 1):1840–5.
75. Attal N, Brasseur L, Guirimand D, Clermond-Gnamien S, Atlami S, Bouhassira D. Are oral cannabinoids safe and effective in refractory neuropathic pain? Eur J Pain. 2004;8(2):173–7.
76. 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.
77. 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(1–2):169–72.
78. Neff GW, O'Brien CB, Reddy KR, et al. Preliminary observation with dronabinol in patients with intractable pruritus secondary to cholestatic liver disease. Am J Gastroenterol. 2002;97(8):2117–9.

79. Narang S, Gibson D, Wasan AD, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. J Pain. 2008;9(3):254–64.
80. Toth C, Au S. A prospective identification of neuropathic pain in specific chronic polyneuropathy syndromes and response to pharmacological therapy. Pain. 2008;138(3):657–66.
81. Rintala DH, Fiess RN, Tan G, Holmes SA, Bruel BM. Effect of dronabinol on central neuropathic pain after spinal cord injury: a pilot study. Am J Phys Med Rehabil. 2010;89(10):840–8.
82. Lemberger L, Rubin A, Wolen R, et al. Pharmacokinetics, metabolism and drug-abuse potential of nabilone. Cancer Treat Rev. 1982;9(Suppl B):17–23.
83. Notcutt W, Price M, Chapman G. Clinical experience with nabilone for chronic pain. Pharm Sci. 1997;3:551–5.
84. Berlach DM, Shir Y, Ware MA. Experience with the synthetic cannabinoid nabilone in chronic noncancer pain. Pain Med. 2006;7(1):25–9.
85. Beaulieu P. Effects of nabilone, a synthetic cannabinoid, on postoperative pain: Les effets de la nabilone, un cannabinoide synthetique, sur la douleur postoperatoire. Can J Anaesth. 2006;53(8):769–75.
86. Maida V. The synthetic cannabinoid nabilone improves pain and symptom management in cancer patietns. Breast Cancer Res Treat. 2007;103(Part 1):121–2.
87. Wissel J, Haydn T, Muller J, et al. Low dose treatment with the synthetic cannabinoid nabilone significantly reduces spasticity-related pain: a double-blind placebo-controlled cross-over trial. J Neurol. 2006;253(10):1337–41.
88. 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.
89. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. J Pain. 2008;9(2):164–73.
90. 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(2):604–10.
91. Bestard JA, Toth CC. An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. Pain Pract. 2011;11:353–68. Epub 2010 Nov 18.
92. Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. JAMA. 2003;290(13):1757–62.
93. Dyson A, Peacock M, Chen A, et al. Antihyperalgesic properties of the cannabinoid CT-3 in chronic neuropathic and inflammatory pain states in the rat. Pain. 2005;116(1–2):129–37.
94. 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.
95. 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.
96. 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.
97. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology. 2009;34(3):672–80.
98. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ. 2010;182(14):E694–701.
99. Wade DT, Makela PM, House H, Bateman C, Robson PJ. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. Mult Scler. 2006;12:639–45.
100. Tashkin DP. Smoked marijuana as a cause of lung injury. Monaldi Arch Chest Dis. 2005;63(2):93–100.
101. Tashkin DP, Simmons MS, Sherrill DL, Coulson AH. Heavy habitual marijuana smoking does not cause an accelerated decline in FEV1 with age. Am J Respir Crit Care Med. 1997;155(1):141–8.
102. 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 Biomarkers Prev. 2006;15(10):1829–34.
103. Grinspoon L, Bakalar JB. Marihuana, the forbidden medicine. Rev. and exp. edn. New Haven: Yale University Press; 1997.
104. Moir D, Rickert WS, Levasseur G, et al. A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. Chem Res Toxicol. 2008;21(2):494–502.
105. Singh R, Sandhu J, Kaur B, et al. Evaluation of the DNA damaging potential of cannabis cigarette smoke by the determination of acetaldehyde derived N2-ethyl-2′-deoxyguanosine adducts. Chem Res Toxicol. 2009;22(6):1181–8.
106. Joy JE, Watson SJ, Benson Jr JA. Marijuana and medicine: assessing the science base. Washington D.C.: Institute of Medicine; 1999.
107. Gieringer D. Marijuana waterpipe and vaporizer study. MAPS Bull. 1996;6(3):59–66.
108. Gieringer D. Cannabis "vaporization": a promising strategy for smoke harm reduction. J Cannabis Ther. 2001;1(3–4):153–70.
109. Storz M, Russo EB. An interview with Markus Storz. J Cannabis Ther. 2003;3(1):67–78.
110. Gieringer D, St. Laurent J, Goodrich S. Cannabis vaporizer combines efficient delivery of THC with effective suppression of pyrolytic compounds. J Cannabis Ther. 2004;4(1):7–27.
111. Hazekamp A, Ruhaak R, Zuurman L, van Gerven J, Verpoorte R. Evaluation of a vaporizing device (Volcano) for the pulmonary administration of tetrahydrocannabinol. J Pharm Sci. 2006;95(6):1308–17.
112. Van der Kooy F, Pomahacova B, Verpoorte R. Cannabis smoke condensate I: the effect of different preparation methods on tetrahydrocannabinol levels. Inhal Toxicol. 2008;20(9):801–4.
113. Bloor RN, Wang TS, Spanel P, Smith D. Ammonia release from heated 'street' cannabis leaf and its potential toxic effects on cannabis users. Addiction. 2008;103(10):1671–7.
114. Zuurman L, Roy C, Schoemaker RC, et al. Effect of intrapulmonary tetrahydrocannabinol administration in humans. J Psychopharmacol (Oxford, England). 2008;22(7):707–16.
115. Pomahacova B, Van der Kooy F, Verpoorte R. Cannabis smoke condensate III: the cannabinoid content of vaporised *Cannabis sativa*. Inhal Toxicol. 2009;21(13):1108–12.
116. 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.
117. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. Clinical pharmacology and therapeutics. 2011;90(6):844–51.
118. Earleywine M, Barnwell SS. Decreased respiratory symptoms in cannabis users who vaporize. Harm Reduct J. 2007;4:11.
119. 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.
120. 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.
121. Ernst G, Denke C, Reif M, Schnelle M, Hagmeister H. Standardized cannabis extract in the treatment of postherpetic neuralgia: a randomized, double-blind, placebo-controlled cross-over study. Paper presented at: international association for cannabis as medicine. Leiden, 9 Sept 2005.
122. Holdcroft A, Maze M, Dore C, Tebbs S, Thompson S. A multicenter dose-escalation study of the analgesic and adverse effects

of an oral cannabis extract (Cannador) for postoperative pain management. Anesthesiology. 2006;104(5):1040–6.
123. McPartland JM, Russo EB. Cannabis and cannabis extracts: greater than the sum of their parts? J Cannabis Ther. 2001; 1(3–4):103–32.
124. de Meijer E. The breeding of cannabis cultivars for pharmaceutical end uses. In: Guy GW, Whittle BA, Robson P, editors. Medicinal uses of cannabis and cannabinoids. London: Pharmaceutical Press; 2004. p. 55–70.
125. Guy GW, Robson P. A phase I, double blind, three-way crossover study to assess the pharmacokinetic profile of cannabis based medicine extract (CBME) administered sublingually in variant cannabinoid ratios in normal healthy male volunteers (GWPK02125). J Cannabis Ther. 2003;3(4):121–52.
126. Karschner EL, Darwin WD, McMahon RP, et al. Subjective and physiological effects after controlled Sativex and oral THC administration. Clin Pharmacol Ther. 2011;89(3):400–7.
127. Karschner EL, Darwin WD, Goodwin RS, Wright S, Huestis MA. Plasma cannabinoid pharmacokinetics following controlled oral delta9-tetrahydrocannabinol and oromucosal cannabis extract administration. Clin Chem. 2011;57(1):66–75.
128. Russo EB, Etges T, Stott CG. Comprehensive adverse event profile of Sativex. 18th annual symposium on the cannabinoids. Vol Aviemore, Scotland: International Cannabinoid Research Society; 2008. p. 136.
129. Barnes MP. Sativex: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain. Expert Opin Pharmacother. 2006;7(5):607–15.
130. Pérez J. Combined cannabinoid therapy via na oromucosal spray. Drugs Today. 2006;42(8):495–501.
131. 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;17:18–26.
132. Notcutt W, Price M, Miller R, et al. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 "N of 1" studies. Anaesthesia. 2004;59:440–52.
133. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain. 2004;112(3):299–306.
134. Rog DJ, Nurmiko T, Friede T, Young C. Randomized controlled trial of cannabis based medicine in central neuropathic pain due to multiple sclerosis. Neurology. 2005;65(6):812–9.
135. 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.
136. 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.
137. 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(1):50–2.
138. 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 Manage. 2010;39(2):167–79.
139. 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(8):1729–43.
140. Lynch ME, Young J, Clark AJ. A case series of patients using medicinal marihuana for management of chronic pain under the Canadian Marihuana Medical Access Regulations. J Pain Symptom Manage. 2006;32(5):497–501.
141. Janse AFC, Breekveldt-Postma NS, Erkens JA, Herings RMC. Medicinal gebruik van cannabis: PHARMO instituut. Institute for Drug Outcomes Research; 2004.
142. Gorter RW, Butorac M, Cobian EP, van der Sluis W. Medical use of cannabis in the Netherlands. Neurology. 2005;64(5):917–9.
143. Fitzgerald GA. Coxibs and cardiovascular disease. N Engl J Med. 2004;10:6.
144. Topol EJ. Failing the public health – rofecoxib, Merck, and the FDA. N Engl J Med. 2004;10:6.
145. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet. 2003;42(4):327–60.
146. Huestis MA, Henningfield JE, Cone EJ. Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. J Anal Toxicol. 1992;16(5): 276–82.
147. Wright S. GWMS001 and GWMS0106: maintenance of blinding. London: GW Pharmaceuticals; 2005.
148. Clark P, Altman D. Assessment of blinding in phase III Sativex spasticity studies. GW Pharmaceuticals; 2006.
149. Samaha AN, Robinson TE. Why does the rapid delivery of drugs to the brain promote addiction? Trends Pharmacol Sci. 2005;26(2):82–7.
150. Jones RT, Benowitz N, Bachman J. Clinical studies of cannabis tolerance and dependence. Ann N Y Acad Sci. 1976;282:221–39.
151. 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.
152. Smith NT. A review of the published literature into cannabis withdrawal symptoms in human users. Addiction. 2002;97(6): 621–32.
153. Solowij N, Stephens RS, Roffman RA, et al. Cognitive functioning of long-term heavy cannabis users seeking treatment. JAMA. 2002;287(9):1123–31.
154. Schoedel KA, Chen N, Hilliard A, et al. A randomized, double-blind, placebo-controlled, crossover study to evaluate the abuse potential of nabiximols oromucosal spray in subjects with a history of recreational cannabis use. Hum Psychopharmacol. 2011;26:224–36.
155. Russo EB, Mathre ML, Byrne A, et al. Chronic cannabis use in the Compassionate Use Investigational New Drug Program: an examination of benefits and adverse effects of legal clinical cannabis. J Cannabis Ther. 2002;2(1):3–57.
156. Fride E, Russo EB. Neuropsychiatry: schizophrenia, depression, and anxiety. In: Onaivi E, Sugiura T, Di Marzo V, editors. Endocannabinoids: the brain and body's marijuana and beyond. Boca Raton: Taylor & Francis; 2006. p. 371–82.
157. Aragona M, Onesti E, Tomassini V, et al. Psychopathological and cognitive effects of therapeutic cannabinoids in multiple sclerosis: a double-blind, placebo controlled, crossover study. Clin Neuropharmacol. 2009;32(1):41–7.
158. Degenhardt L, Hall W, Lynskey M. Testing hypotheses about the relationship between cannabis use and psychosis. Drug Alcohol Depend. 2003;71(1):37–48.
159. Macleod J, Davey Smith G, Hickman M. Does cannabis use cause schizophrenia? Lancet. 2006;367(9516):1055.
160. Macleod J, Hickman M. How ideology shapes the evidence and the policy: what do we know about cannabis use and what should we do? Addiction. 2010;105:1326–30.
161. Hickman M, Vickerman P, Macleod J, et al. If cannabis caused schizophrenia–how many cannabis users may need to be prevented in order to prevent one case of schizophrenia? England and Wales calculations. Addiction. 2009;104(11):1856–61.

162. Zuardi AW, Guimaraes FS. Cannabidiol as an anxiolytic and antipsychotic. In: Mathre ML, editor. Cannabis in medical practice: a legal, historical and pharmacological overview of the therapeutic use of marijuana. Jefferson: McFarland; 1997. p. 133–41.
163. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol. 2011;163:1344–64.
164. Cabral G. Immune system. In: Grotenhermen F, Russo EB, editors. Cannabis and cannabinoids: pharmacology, toxicology and therapeutic potential. Binghamton: Haworth Press; 2001. p. 279–87.
165. Katona S, Kaminski E, Sanders H, Zajicek J. Cannabinoid influence on cytokine profile in multiple sclerosis. Clin Exp Immunol. 2005; 140(3):580–5.
166. Abrams DI, Hilton JF, Leiser RJ, et al. Short-term effects of cannabinoids in patients with HIV-1 infection. A randomized, placebo-controlled clinical trial. Ann Intern Med. 2003;139:258–66.
167. Stott CG, Guy GW, Wright S, Whittle BA. The effects of cannabis extracts Tetranabinex and Nabidiolex on human cytochrome P450-mediated metabolism. Paper presented at: Symposium on the Cannabinoids, Clearwater, 27 June 2005.
168. Stott CG, Ayerakwa L, Wright S, Guy G. Lack of human cytochrome P450 induction by Sativex. 17th annual symposium on the cannabinoids. Saint-Sauveur, Quebec: International Cannabinoid Research Society; 2007. p. 211.
169. Grotenhermen F, Leson G, Berghaus G, et al. Developing limits for driving under cannabis. Addiction. 2007;102(12):1910–7.
170. Hohmann AG, Suplita 2nd RL. Endocannabinoid mechanisms of pain modulation. AAPS J. 2006;8(4):E693–708.
171. Clapper JR, Moreno-Sanz G, Russo R, et al. Anandamide suppresses pain initiation through a peripheral endocannabinoid mechanism. Nat Neurosci. 2010;13:1265–70.
172. Schlosburg JE, Blankman JL, Long JZ, et al. Chronic monoacylglycerol lipase blockade causes functional antagonism of the endocannabinoid system. Nat Neurosci. 2010;13(9):1113–9.
173. Yu XH, Cao CQ, Martino G, et al. A peripherally restricted cannabinoid receptor agonist produces robust anti-nociceptive effects in rodent models of inflammatory and neuropathic pain. Pain. 2010;151(2):337–44.
174. Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. Trends Pharmacol Sci. 2009;30(10):515–27.
175. Wirth PW, Watson ES, ElSohly M, Turner CE, Murphy JC. Anti-inflammatory properties of cannabichromene. Life Sci. 1980; 26(23):1991–5.
176. Davis WM, Hatoum NS. Neurobehavioral actions of cannabichromene and interactions with delta 9-tetrahydrocannabinol. Gen Pharmacol. 1983;14(2):247–52.
177. Ligresti A, Moriello AS, Starowicz K, et al. Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. J Pharmacol Exp Ther. 2006;318(3):1375–87.
178. De Petrocellis L, Starowicz K, Moriello AS, Vivese M, Orlando P, Di Marzo V. Regulation of transient receptor potential channels of melastatin type 8 (TRPM8): effect of cAMP, cannabinoid CB(1) receptors and endovanilloids. Exp Cell Res. 2007;313(9):1911–20.
179. Gauson LA, Stevenson LA, Thomas A, Baillie GL, Ross RA, Pertwee RG. Cannabigerol behaves as a partial agonist at both CB1 and CB2 receptors. 17th annual symposium on the cannabinoids. Vol Saint-Sauveur, Quebec: International Cannabinoid Research Society; 2007, p. 206.
180. Cascio MG, Gauson LA, Stevenson LA, Ross RA, Pertwee RG. Evidence that the plant cannabinoid cannabigerol is a highly potent alpha2-adrenoceptor agonist and moderately potent 5HT1A receptor antagonist. Br J Pharmacol. 2010;159(1):129-41.
181. Banerjee SP, Snyder SH, Mechoulam R. Cannabinoids: influence on neurotransmitter uptake in rat brain synaptosomes. J Pharmacol Exp Ther. 1975;194(1):74–81.
182. Evans FJ. Cannabinoids: the separation of central from peripheral effects on a structural basis. Planta Med. 1991;57(7):S60–7.
183. Evans AT, Formukong E, Evans FJ. Activation of phospholipase A2 by cannabinoids. Lack of correlation with CNS effects. FEBS Lett. 1987;211(2):119–22.
184. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol. 2008; 153(2):199–215.
185. Hill AJ, Weston SE, Jones NA, et al. Delta-tetrahydrocannabivarin suppresses in vitro epileptiform and in vivo seizure activity in adult rats. Epilepsia. 2010;51(8):1522–32.
186. Bolognini D, Costa B, Maione S, et al. The plant cannabinoid delta9-tetrahydrocannabivarin can decrease signs of inflammation and inflammatory pain in mice. Br J Pharmacol. 2010; 160(3):677–87.
187. Mehmedic Z, Chandra S, Slade D, et al. Potency trends of delta(9)-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. J Forensic Sci. 2010;55:1209–17.
188. King LA, Carpentier C, Griffiths P. Cannabis potency in Europe. Addiction. 2005;100(7):884–6.
189. Potter DJ, Clark P, Brown MB. Potency of delta 9-THC and other cannabinoids in cannabis in England in 2005: implications for psychoactivity and pharmacology. J Forensic Sci. 2008;53(1): 90–4.
190. Potter D. Growth and morphology of medicinal cannabis. In: Guy GW, Whittle BA, Robson P, editors. Medicinal uses of cannabis and cannabinoids. London: Pharmaceutical Press; 2004. p. 17–54.
191. Rao VS, Menezes AM, Viana GS. Effect of myrcene on nociception in mice. J Pharm Pharmacol. 1990;42(12):877–8.
192. Lorenzetti BB, Souza GE, Sarti SJ, Santos Filho D, Ferreira SH. Myrcene mimics the peripheral analgesic activity of lemongrass tea. J Ethnopharmacol. 1991;34(1):43–8.
193. Basile AC, Sertie JA, Freitas PC, Zanini AC. Anti-inflammatory activity of oleoresin from Brazilian Copaifera. J Ethnopharmacol. 1988;22(1):101–9.
194. Tambe Y, Tsujiuchi H, Honda G, Ikeshiro Y, Tanaka S. Gastric cytoprotection of the non-steroidal anti-inflammatory sesquiterpene, beta-caryophyllene. Planta Med. 1996;62(5):469–70.
195. Gertsch J, Leonti M, Raduner S, et al. Beta-caryophyllene is a dietary cannabinoid. Proc Natl Acad Sci USA. 2008;105(26): 9099–104.
197. Gil ML, Jimenez J, Ocete MA, Zarzuelo A, Cabo MM. Comparative study of different essential oils of Bupleurum gibraltaricum Lamarck. Pharmazie. 1989;44(4):284–7.
198. Re L, Barocci S, Sonnino S, et al. Linalool modifies the nicotinic receptor-ion channel kinetics at the mouse neuromuscular junction. Pharmacol Res. 2000;42(2):177–82.
199. Gregg, L.C, Jung, K.M., Spradley, J.M., Nyilas, R., Suplita II, R.L., Zimmer, A., Watanabe, M., Mackie, K., Katona, I., Piomelli, D. and Hohmann, A.G. (2012) Activation of type-5 metabotropic glutamate receptors and diacylglycerol lipase-alpha initiates 2-arachidonoylglycerol formation and endocannabinoid-mediated analgesia in vivo. The Journal of Neuroscience, in press [DOI:10.1523/JNEUROSCI.0013-12.2012].
200. Kavia R, De Ridder D, Constantinescu C, Stott C, Fowler C. Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis. Mult Scler. 2010;16(11):1349–59.
201. Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012;13(5):438–49.
202. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. Clinical pharmacology and therapeutics. 2011;90(6):844–51.

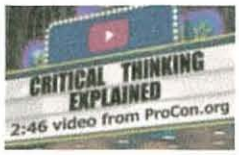
Attached to this form are hard copies relevant to answering the question above and here are the links:

http://www.ncbi.nlm.nih.gov/pubmed/26749285

http://www.blisstree.com/2008/04/30/mental-health-well-being/marijuana-for-migraine-276/

http://www.livescience.com/53461-medical-marijuana-reduces-migraine-frequency.html

http://medicalmarijuana.procon.org/view.answers.php?questionID=000218



Is Marijuana an Effective Treatment for Migraines?

CITE FACEBOOK TWITTER GOOGLE+ EMAIL PRINT

General Reference (not clearly pro or con)

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

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

June 26, 2006 - MedlinePlus ☆

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

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

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

Is Marijuana an Effective Treatment for Migraines?

PRO (yes)

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

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

June 2, 2005 - Philip Denney, MD ☆☆☆☆

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

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

Nov. 2000 - Jack Herer ☆

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

> "In closing, a unique dance of medical science

CON (no)

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

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

Summer 2002 - Journal of Palliative Care ☆☆

The Institute of Medicine published in its Mar. 1999 report titled "Marijuana and Medicine: Assessing the Science Base":

> "Marijuana has been proposed numerous times as a treatment for migraine headaches, but there are almost no clinical data on the use of marijuana or cannabinoids for migraine.
>
> Our search of the literature since 1975 yielded only one scientific publication on the subject. It presents three cases of cessation of daily marijuana smoking followed by migraine attacks – not convincing evidence that marijuana relieves migraine headaches.
>
> The same result could have been found if migraine headaches were a consequence of

18. Source Biographies
19. Glossary
20. Notices Archive
21. Site Map
+ Additional Resources
Get free email updates:
OK
PLEASE DONATE
Keep critical thinking alive!

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

2001 - Ethan Russo, MD ☆☆☆☆

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

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

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

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

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

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

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

---

marijuana withdrawal. While there is no evidence that marijuana withdrawal is followed by migraines, when analyzing the strength of reports such as these it is important to consider all logical possibilities.

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

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

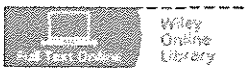
William Young, MD, Director of the In-Patient Program at the Jefferson Headache Center, and Mary Paolone, RN, wrote in the Summer 2003 *Headache*, the newsletter of the American Council for Headache Education:

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

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

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

Summer 2003 - William Young, MD ☆☆☆☆



Pharmacotherapy. 2016 May;36(5):505-10. doi: 10.1002/phar.1673. Epub 2016 Jan 9.

Effects of Medical Marijuana on Migraine Headache Frequency in an Adult Population.

Rhyne DN[1], Anderson SL[1], Gedde M[2], Borgelt LM[1,3].

Author information

Abstract

STUDY OBJECTIVE: No clinical trials are currently available that demonstrate the effects of marijuana on patients with migraine headache; however, the potential effects of cannabinoids on serotonin in the central nervous system indicate that marijuana may be a therapeutic alternative. Thus, the objective of this study was to describe the effects of medical marijuana on the monthly frequency of migraine headache.

DESIGN: Retrospective chart review.

SETTING: Two medical marijuana specialty clinics in Colorado.

PATIENTS: One hundred twenty-one adults with the primary diagnosis of migraine headache who were recommended migraine treatment or prophylaxis with medical marijuana by a physician, between January 2010 and September 2014, and had at least one follow-up visit.

MEASUREMENTS AND RESULTS: The primary outcome was number of migraine headaches per month with medical marijuana use. Secondary outcomes were the type and dose of medical marijuana used, previous and adjunctive migraine therapies, and patient-reported effects. Migraine headache frequency decreased from 10.4 to 4.6 headaches per month ($p<0.0001$) with the use of medical marijuana. Most patients used more than one form of marijuana and used it daily for prevention of migraine headache. Positive effects were reported in 48 patients (39.7%), with the most common effects reported being prevention of migraine headache with decreased frequency of migraine headache (24 patients [19.8%]) and aborted migraine headache (14 patients [11.6%]). Inhaled forms of marijuana were commonly used for acute migraine treatment and were reported to abort migraine headache. Negative effects were reported in 14 patients (11.6%); the most common effects were somnolence (2 patients [1.7%]) and difficulty controlling the effects of marijuana related to timing and intensity of the dose (2 patients [1.7%]), which were experienced only in patients using edible marijuana. Edible marijuana was also reported to cause more negative effects compared with other forms.

CONCLUSION: The frequency of migraine headache was decreased with medical marijuana use. Prospective studies should be conducted to explore a cause-and-effect relationship and the use of different strains, formulations, and doses of marijuana to better understand the effects of medical marijuana on migraine headache treatment and prophylaxis.

PMID: 26749285 DOI: 10.1002/phar.1673

[PubMed - in process]

LinkOut - more resources

PubMed Commons

PubMed Commons home

0 comments

How to join PubMed Commons

Medical Marijuana May Reduce Frequency of Migraines

By Agata Blaszczak-Boxe, Contributing Writer | January 22, 2016 04:25pm ET

Credit: Headache photo via Shutterstock

Medical marijuana might help migraine sufferers reduce the frequency of their headaches, a new study suggests.

In the study of 121 people with migraines, 103 said they had fewer migraines after they began using marijuana, the researchers found. Another 15 people said the frequency of their headaches remained the same during the treatment, and three said the frequency of their headaches increased.

Among the people who noticed improvement, the frequency of their migraine headaches decreased from 10.4 headaches per month to 4.6 headaches per month, on average, the researchers found.

"There was a substantial improvement for patients in their ability to function and feel better," study author Laura Borgelt, a professor of clinical pharmacy at the University of Colorado Anschutz Medical Campus, said in a statement.

However, "Like any drug, marijuana has potential benefits and potential risks," Borgelt noted. "It's important for people to be aware that using medical marijuana can also have adverse effects." [Ouch: 10 Odd Causes of Headaches]

In the study, the researchers looked at the number of migraines per month among patients in Colorado whose doctors had recommended that they use medical marijuana to treat and prevent their migraines, between January 2010 and September 2014. The people who had at

least one follow-up visit with a doctor were included in the study.

Most people in the study used more than one form of marijuana, including inhaled, smoked and edible forms, the researchers said. The people tended to prefer inhaled marijuana to treat acute migraines, and preferred to use edible marijuana to prevent future migraines from occurring. About half of the people in the study were also using prescription migraine drugs, in addition to marijuana, to treat their headaches, Borgelt noted.

Fourteen people in the study reported experiencing side effects during treatment, such as sleepiness, bad dreams and nausea, the researchers said. There were more side effects associated with the use of edible marijuana than with its other forms.

The researchers said they don't know for sure why or how exactly marijuana may work to treat or prevent migraines. In fact, even the mechanisms of migraine as a condition are still not fully understood. In the study, the researchers were trying to evaluate the result of the treatment, even though they do not fully understand how it may work, Borgelt said.

However, there are several pathways that could explain why marijuana might work for patients with migraines, the researchers said. For example, some researchers have proposed that migraines might have something to do with a problem with receptors in the brain called cannabinoid receptors, which affect some crucial neurotransmitters such as serotonin. Compounds in marijuana may also affect these receptors, they said.

It's also possible that serotonin itself plays a role in migraine headaches, Borgelt said, and some research has shown that THC, the ingredient in marijuana that's responsible for most of its psychological effects, may affect serotonin levels.

People with migraines should not try to self-medicate using marijuana, Borgelt stressed. "Any treatment decision should involve a conversation with their [health care] providers," she told Live Science.

The new study was published Jan. 9 in the journal Pharmacotherapy.

Follow Agata Blaszczak-Boxe on Twitter. Follow Live Science @livescience, Facebook & Google+. Originally published on Live Science.

Editor's Recommendations

- 5 Surprising Facts About Pain
- 11 Odd Facts About Marijuana
- 5 Experts Answer: Does Caffeine Cause or Cure Headaches?

Author Bio

Agata Blaszczak-Boxe, Contributing Writer

Agata Blaszczak-Boxe is a contributing writer for Live Science. She covers health, psychology and paleontology, as well as other science topics. Agata has a Master of Arts degree from the City University of New York Graduate School of Journalism. When she is not writing, she can be found reading food blogs, lifting weights or playing with her two attention-hungry cats. Follow Agata on Twitter.

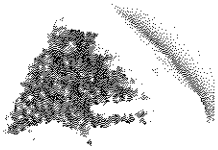
Science Newsletter: Subscribe

enter email here

submit

Follow Us

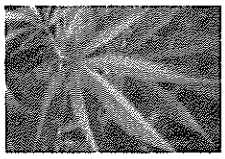
Most Popular



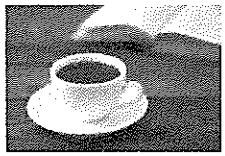
11 Odd Facts About Marijuana

7 Ways Marijuana May Affect the Brain

Migraines: Causes, Symptoms & Relief



Legalized Pot: Smoke It or Eat It?



Coffee Pot: What Happens When You Mix Marijuana & Caffeine?

BLACK+DECKER CM2045 40V MAX Lithium Mower, 20"

☆ ☆ ☆ ☆ ☆

$299.00

Buy Now
Amazon

Home About Us

FOLLOW US

SUBSCRIBE

enter email here ... SUBMIT

The Regina Georges Of The World Will Pay For Being Mean Later In Life, Study Promises

This Gross Shower Maneuver Is Actually Really Good For Your Sex Life

This Company Is Trying To One-Up Uber's Kitten Delivery Service By Bringing You Champagne

These Pants Could Stop Your iPhone From Dying

This Is How You Stop A Burglary At A Sandwich Shop

The End Of The Slutburger? Carl's Jr. To Feature Ronda Rousey In Newest Commercial

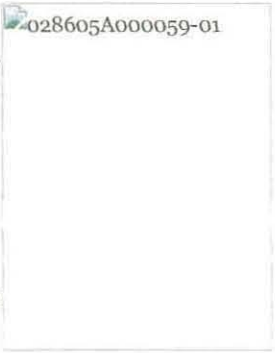
← Previous Post Next Post →

Marijuana for Migraine?

8 years ago by Marijke Durning, RN 16 Comments Share a Tip

With all the talk of using marijuana to manage chronic pain, how useful could it be to help manage migraines?

Migraine pain can be devastating and debilitating. Many migraineurs have tried anything and everything that can help relieve pain without finding relief. I find it particularly interesting, that I can find very little information about studies or anything on the use of medicinal marijuana in treating migraine.



I was able to find a study published in the journal *Headache* in 1987 – we're talking 21 years ago – that suggested there may be a role for marijuana in preventing migraines. More recently, in the journal *Pain*, an article reviewed the use of marijuana in the early 1900s for the relief of migraine pain.

At the beginning of that century, Sir William Osler, considered one of the fathers of modern medicine, said that marijuana was effective for both prevention of migraine, as well as for treatment. Yet, pot was declared an illegal substance in the United States in 1937, despite opposition from the American Medical Association.

In 1999, Dr. Ethan Russo, often considered a "pot pioneer," made an application with the FDA to study the effects of pot on migraines. While finally approved (after many tries), the study still couldn't go on because in February 2000, a supply of marijuana was refused.

Image: Newscom

~~~~~~~~~

If you are interested in the topic of medicinal pot, I will be interviewing the author of a book on medicinal marijuana. We will also have, in the next few weeks, a copy of the book to give away.

~~~~~~~

Technorati Tags: medicinal marijuana,medicinal pot,marijuana for migraine pain,marijuana to prevent migraines,ethan russo,Sir William Osler,relief of migraine pain

Share This Post: Tweet G+ Share 0

Related Topics: FEEL

16 Comments Blisstree.com Login

Recommend Share Sort by Best

Join the discussion...

jimmy • 7 years ago

I am 35 and have suffered from migraines since age 5. They have lately gotten nearly daily. I quit smoking nearly 3 years ago, due to probation. When I used to smoke I had very few migraines. Now I have many. Since I am near the end of my probation and pretty well in the clear I have smoked some to see how it effects my daily migraines. Well, they went away. When I smoke I have no chronic daily migraine. I wonder, why can't this be my medicine (I live in Illinois). Instead I am forced to take very strong medicine such as imitrex way more than I should, but without them I am literally disabled. Prescription drugs kill how many people a year? And what about tylenol, the #1 cause of liver failure in US now in case you didn't know. So, after probation... They can keep all their $30 migraine pills, which add up to over $500 a month.
And, I'll stick to my smoke again.
But, stay away from METH! It will steal your medicine away from you.

1 ^ v • Reply • Share ›

maggie • 6 years ago

I just recovered from a 2-day migraine. I take maxalt - mlt 10mg. I used 2 doses for this go round -- I have medical insurance but each pill costs approximately $27 each. I usually get them in batches of three ($80) and even with that my insurance limits me to 9 a year! So I use them sparingly and suffer greatly losing days of my life.

So this morning when i am finally able to see the light again I wondered about medical marijuana and found this sight. I wish I had the option to try it. It sound like those of you who disagree with the use of it may have a substance problem. I can understand your reluctance and I acknowledge your wok with recovery. There are many substances that are addictive and not illegal. Nicotine, booze, sugar, all of these are addictive to certain people. It is hard to say who will get hooked.

I hope for the day that medical marijuana is an option for those who suffer with chronic pain. My 80-year old mother suffers with severe arthritis pain, cannot have a knee replacement because of her heart condition, never smoked, rarely drank and I mean maybe a taste of wine at holiday but would consider taking medical marijuana for her pain.

As noted before, the cost of migraine meds is high. I would love to know if the big drug companies are stopping the legalization of marijuana. They certainly would have a lot to lose if marijuana is legalized for medical use. I just do not understand the lack of availability. Medical marijuana would still be a controlled substance. So please make it available.

^ v • Reply • Share ›

Jay • 8 years ago

i have severe migraine attacks since i was 7 years old, i am now 21 years and i have tried

hundreds of medicines that didnt give me enough hope to eliminate the pain. only 2 yrs ago i read an article about marijuana and its minimal side effects and its power to heal migraine, and guess what, now i only use marijuana to prevent and treat my pain. It doesnt only take away the pain but it gives me a happy and peaceful state of mind. the best prescription for migraine attacks is 2 small joints at day and 2 at night. only when i have migraine. As for the treatment i found that a joint everydays is enough to prevent migraine attacks.

Legalize the HERB

^ v • Reply • Share ›

finallyfree • 8 years ago

I started getting Hemiplegic Migraines 2 years ago, and have tried EVERYTHING to no avail. After being told to prepare myself for Oxycotin I found a doctor who suggested I take just 1-2 hits of pot, I have NEVER done it before and never thought I would. But I have to say that it was gone within a couple of minutes both times I've tried it. I just started using and for now only use it for a rescue although I have heard of it being a good preventitive. I'm a recovering alcoholic so this is a slippery slope for me, but Oxycotin would be far worse. I had no life before I started this, I couldn't work anymore and had to have help with my daughter, I would have bouts of paraylsis for hours at a time and the pain is just indiscribable. The last 2 years have been spent at least 80% in my bed. After pot I have my life back, I feel wonderful and no negitive effects. The only side effects I get are welcomed, my fear and anxiety go away (I'm a tightly wound person) I also get a sex drive (that has been a problem sence my hysterectomy 4 years ago) it treats not just the pain of my migraine but so far my one sided weakness, nausia (instant, before I exhale) I haven't had paraylsis yet so I can't say on that one but I can guarentee I was headed there last time, the signs were there. It was just a matter of time. I understand that some people this makes them worse, others no effect, but I know of a few that it has given them their life back and I'm one. This has changed my past views on pot completely, at least for medicinal use.

^ v • Reply • Share ›

MC • 8 years ago

I dont know why it is not legal and belive it should be. It baffles me that cigarettes are legal and it kills people - My dad is one of its many victims. I am a hard working 9 to 5 american and instead of drinking a beer (Not knocking it)or smoking a cigarette I kick back and relax with a little smokums. I have suffered with migraines for years and every pill I ever took made me feel worse and sick in different ways with all the side effects- smoking however, has taken the pain away. I sleep better at night and I am in a better mood. I dont do it all the time, just once in a while and its awesome. I am healthy and happy and alot of other hard working americans would be too if the US of A would only make it legal. what a happier, calmer country this would be and it would help on other fronts too such as using it for developing gas, taking the power away from thugs and into the hands of american people, help sick people in physical pain, hey PETA would probably love if the fashion industry adopted it for making clothes instead of fur... Think of the money saved from growing something natural than making a pill in a lab... We dont hate tea that we drink why should be hate on this?? there are so many good things that come from this natural plant that God/mother earth gave to us... Make it legal and all you poeple who complain - try some clean good stuff again, froma good source or grow it yourself and try it one more time - then make your oppinion. Even if there are people who doesnt like it, I can understand- I strongly believe the majority of the population does it and loves it. Make it legal USA! Save the MJ save the USA!

^ v • Reply • Share ›

kristina b • 8 years ago

Hi,

I unfortunately am not in a state where it is legal but I am able to get it quite easily through friends. More people use it more than one would think for various reasons. It

is almost as common as alcohol and I and my friends are in the 35 and above range. The funny thing is my father, who is in his 70's, read an article where it helped a man with MS and chronic headaches, and he recommended it to me. Never thought in my life my father would be telling me to smoke pot. LOL, but it worked and I dont use it very often just when the headaches get stuck in my head and my abortives dont work.

Krisitna

^ v • Reply • Share ›

Marijke Durning, RN • 8 years ago

Hi Kristina - do you have any trouble getting hold of it or are you in a state where it is possible?

^ v • Reply • Share ›

kristina b • 8 years ago

I myself have used marijuana for my migraines and pretty much 90% of the time it has worked fabulously. No residual leftover in the morning like I have with my migraine medicine and no rebound of the headache. It doesnt always work immediately but while I am sleeping it seems to do the trick.

^ v • Reply • Share ›

Marijke Durning, RN • 8 years ago

Hey Joey - there was just a big snowfall in western Canada last week. ;-)

^ v • Reply • Share ›

Diana Lee • 8 years ago

I have friends who swear by marijuana for preventing and treating their migraines. It never made much of a difference for me.

^ v • Reply • Share ›

Mark • 8 years ago

Well Marijke... I don't think I can really say :)

I would imagine that THC in a purer form, i.e., produced under strict guidelines, might have the same effect as what we smoked from off the street.

I still think, and again based on experience, that the better the quality, the heavier that "thumping" in the brain might be. Or, the lower the quality or... oh heck, no, I don't think it would help but I'm simply one person with one experience.

I just remembered - we'd always search for a "higher" high. I.E. we moved from Vietnamese Red to Mexican to Hawaii Electric etc. etc. but the headaches always came, for me.

And now that I've romanced it, I'm going to a meeting - later! :)

^ v • Reply • Share ›

Joey • 8 years ago

I haven't touched "pot" in years and don't plan to return to it, but it really is silly that it's illegal. That being said I have to take a second to marvel at the fact that a blog post was made on the issue of medical marijuana and a comment argument hasn't erupted yet!

looks outside for snow in April

^ v • Reply • Share ›

Marijke Durning, RN • 8 years ago

Merry, your last line made me literally laugh out loud.

^ v • Reply • Share ›

Marijke Durning, RN • 8 years ago

Mark, do you think that if the pot was a controlled substance, meaning it was manufactured in such a way that we knew what was in it - with no extra "stuff" - that would change your mind?

^ v • Reply • Share ›

Merry • 8 years ago

What about other countries where it's not illegal? My first impulse would be to agree with Mark, but the hypothesis should be tested in a scientific environment rather than letting the gubbermint make a decision regardless of factual evidence. (On the other hand, why break with tradition? ;)

^ v • Reply • Share ›

Mark • 8 years ago

First Things First - thank God I haven't touched that "stuff" for almost 19 years!

Secondly - from personal experience (look up "paraquat"), medicinal might be one thing but street marijuana NEVER helped any physical headache I had, only made them worse. Then... you get to experience all the "other" headaches that come with the "territory."

My feelings would be that those "experts" are wrong.

^ v • Reply • Share ›

Role of Cannabinoids in Pain Management

18

Ethan B. Russo and Andrea G. Hohmann

Key Points

- Cannabinoids are pharmacological agents of endogenous (endocannabinoids), botanical (phytocannabinoids), or synthetic origin.
- Cannabinoids alleviate pain through a variety of receptor and non-receptor mechanisms including direct analgesic and anti-inflammatory effects, modulatory actions on neurotransmitters, and interactions with endogenous and administered opioids.
- Cannabinoid agents are currently available in various countries for pain treatment, and even cannabinoids of botanical origin may be approvable by FDA, although this is distinctly unlikely for smoked cannabis.
- An impressive body of literature supports cannabinoid analgesia, and recently, this has been supplemented by an increasing number of phase I–III clinical trials.

Introduction

Plants and Pain

It is a curious fact that we owe a great deal of our insight into pharmacological treatment of pain to the plant world [1]. Willow bark from *Salix* spp. led to development of aspirin and eventual elucidation of the analgesic effects of prostaglandins and their role in inflammation. The opium poppy (*Papaver somniferum*) provided the prototypic narcotic analgesic morphine, the first alkaloid discovered, and stimulated the much later discovery of the endorphin and enkephalin systems. Similarly, the pharmacological properties of cannabis (*Cannabis sativa*) prompted the isolation of Δ^9-tetrahydrocannabinol (THC), the major psychoactive ingredient in cannabis, in 1964 [2]. It is this breakthrough that subsequently prompted the more recent discovery of the body's own cannabis-like system, the endocannabinoid system (ECS), which modulates pain under physiological conditions. Pro-nociceptive mechanisms of the endovanilloid system were similarly revealed by phytochemistry of capsaicin, the pungent ingredient in hot chile peppers (*Capsicum annuum* etc.), which activates transient receptor potential vanilloid receptor-1 (TRPV1). Additional plant products such as the mints and mustards activate other TRP channels to produce their physiological effects.

E.B. Russo, M.D. (✉)
GW Pharmaceuticals,
20402 81st Avenue SW, Vashon, WA 98070, USA

Pharmaceutical Sciences, University of Montana,
Missoula, MT, USA
e-mail: ethanrusso@comcast.net

A.G. Hohmann, Ph.D.
Department of Psychological and Brain Sciences, Indiana University,
101 East 10th Street, Bloomington, IN 47405, USA
e-mail: hohmanna@indiana.edu

The Endocannabinoid System

There are three recognized types of cannabinoids: (1) the phytocannabinoids [3] derived from the cannabis plant, (2) synthetic cannabinoids (e.g., ajulemic acid, nabilone, CP55940, WIN55, 212-2) based upon the chemical structure of THC or other ligands which bind cannabinoid receptors, and (3) the endogenous cannabinoids or endocannabinoids. Endocannabinoids are natural chemicals such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG) found in animals whose basic functions are "relax, eat, sleep, forget, and protect" [4]. The endocannabinoid system encompasses the endocannabinoids themselves, their biosynthetic and catabolic enzymes, and their corresponding receptors [5]. AEA is hydrolyzed by the enzyme fatty-acid amide hydrolase (FAAH) into breakdown products arachidonic acid and ethanolamine [6]. By contrast, 2-AG is hydrolyzed primarily by the enzyme monoacylglycerol lipase (MGL) into breakdown products arachidonic acid and glycerol [7] and to a lesser extent by the enzymes ABHD6 and ABHD12. FAAH, a

T.R. Deer et al. (eds.), *Comprehensive Treatment of Chronic Pain by Medical, Interventional, and Integrative Approaches*,
DOI 10.1007/978-1-4614-1560-2_18, © American Academy of Pain Medicine 2013

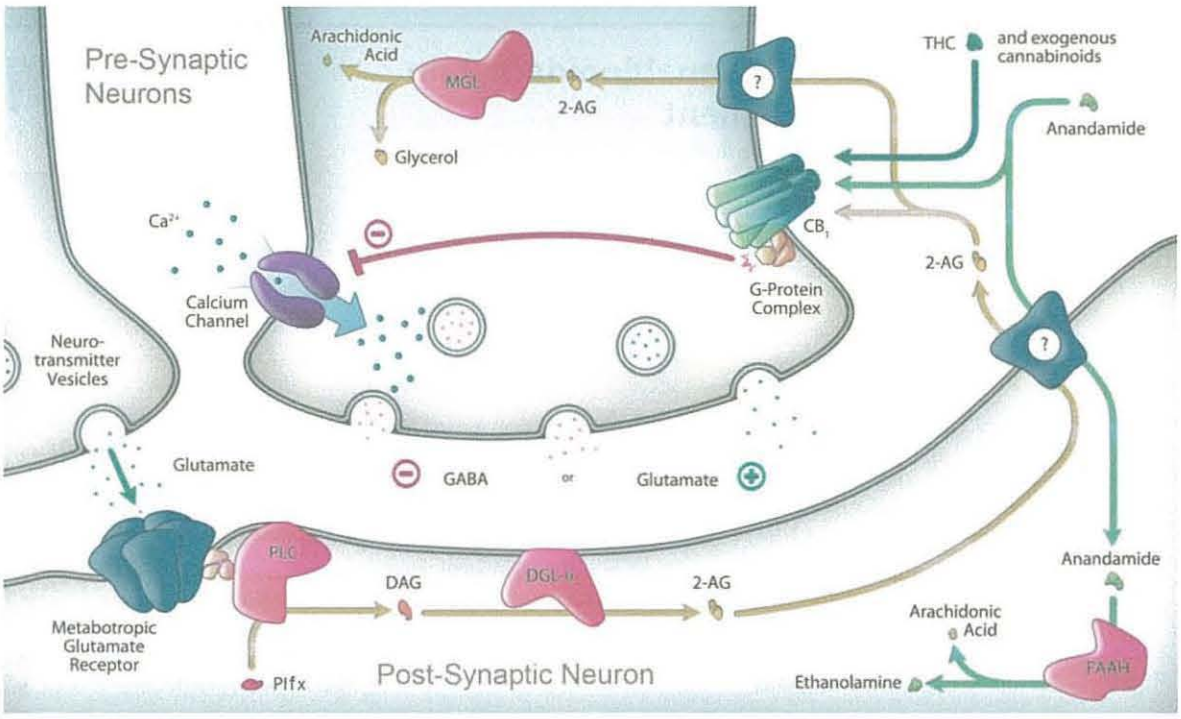


Fig. 18.1 Putative mechanism of endocannabinoid-mediated retrograde signaling in the nervous system. Activation of metabotropic glutamate receptors (*mGluR*) by glutamate triggers the activation of the phospholipase C (*PLC*)-diacylglycerol lipase (*DGL*) pathway to generate the endocannabinoid 2-arachidonoylglycerol (*2-AG*). First, the 2-AG precursor diacylglycerol (*DAG*) is formed from PLC-mediated hydrolysis of membrane phospholipid precursors (*PIPx*). DAG is then hydrolyzed by the enzyme DGL-α to generate 2-AG. 2-AG is released from the postsynaptic neuron and acts as a retrograde signaling molecule. Endocannabinoids activate presynaptic CB_1 receptors which reside on terminals of glutamatergic and GABAergic neurons. Activation of CB_1 by 2-AG, anandamide, or exogenous cannabinoids (e.g., tetrahydrocannabinol, *THC*) inhibits calcium influx in the presynaptic terminal, thereby inhibiting release of the primary neurotransmitter (i.e., glutamate or GABA) from the synaptic vesicle. Endocannabinoids are then rapidly deactivated by transport into cells (via a putative endocannabinoid transporter) followed by intracellular hydrolysis. 2-AG is metabolized by the enzyme monoacylglycerol lipase (*MGL*), whereas anandamide is metabolized by a distinct enzyme, fatty-acid amide hydrolase (*FAAH*). Note that MGL co-localizes with CB_1 in the presynaptic terminal, whereas FAAH is localized to postsynaptic sites. The existence of an endocannabinoid transporter remains controversial. Pharmacological inhibitors of either endocannabinoid deactivation (e.g., FAAH and MGL inhibitors) or transport (i.e., uptake inhibitors) have been developed to exploit the therapeutic potential of the endocannabinoid signaling system in the treatment of pain (Figure by authors with kind assistance of James Brodie, GW Pharmaceuticals)

postsynaptic enzyme, may control anandamide levels near sites of synthesis, whereas MGL, a presynaptic enzyme [8], may terminate 2-AG signaling following CB_1 receptor activation. These enzymes also represent therapeutic targets because inhibition of endocannabinoid deactivation will increase levels of endocannabinoids at sites with ongoing synthesis and release [9]. The pathways controlling formation of AEA remain poorly understood. However, 2-AG is believed to be formed from membrane phospholipid precursors through the sequential activation of two distinct enzymes, phospholipase C and diacylglycerol lipase-α. First, PLC catalyzes formation of the 2-AG precursor diacylglycerol (DAG) from membrane phosphoinositides. Then, DAG is hydrolyzed by the enzyme diacylglycerol lipase-α (DGL-α) to generate 2-AG [199].

There are currently two well-defined cannabinoid receptors, although additional candidate cannabinoid receptors have also been postulated. CB_1, a seven transmembrane spanning G-protein-coupled receptor inhibiting cyclic AMP release, was identified in 1988 [10]. CB_1 is the primary neuromodulatory receptor accounting for psychopharmacological effects of THC and most of its analgesic effects [11]. Endocannabinoids are produced on demand in postsynaptic cells and engage presynaptic CB_1 receptors through a retrograde mechanism [12]. Activation of presynaptic CB_1 receptors then acts as a synaptic circuit breaker to inhibit neurotransmitter release (either excitatory or inhibitory) from the presynaptic neuron (*vide infra*) (Fig. 18.1). CB_2 was identified in 1992, and while thought of primarily as a peripheral immunomodulatory receptor, it also has important

effects on pain. The role of CB_2 in modulating persistent inflammatory and neuropathic pain [13] has been recently reviewed [14, 15]. Activation of CB_2 suppresses neuropathic pain mechanisms through nonneuronal (i.e., microglia and astrocytes) and neuronal mechanisms that may involve interferon-gamma [16]. THC, the prototypical classical cannabinoid, is a weak partial agonist at both CB_1 and CB_2 receptors. Transgenic mice lacking cannabinoid receptors (CB_1, CB_2, GPR55), enzymes controlling endocannabinoid breakdown (FAAH, MGL, ABHD6), and endocannabinoid synthesis (DGL-α, DGL-β) have been generated [17]. These knockouts have helped elucidate the role of the endocannabinoid system in controlling nociceptive processing and facilitated development of inhibitors of endocannabinoid breakdown (FAAH, MGL) as novel classes of analgesics.

A Brief Scientific History of Cannabis and Pain

Centuries of Citations

Cannabis has been utilized in one form or another for treatment of pain for longer than written history [18–21]. Although this documentation has been a major preoccupation of the lead author [22–25], and such information can provide provocative direction to inform modern research on treatment of pain and other conditions, it does not represent evidence of form, content, or degree that is commonly acceptable to governmental regulatory bodies with respect to pharmaceutical development.

Anecdotes Versus Modern Proof of Concept

While thousands of compelling stories of efficacy of cannabis in pain treatment certainly underline the importance of properly harnessing cannabinoid mechanisms therapeutically [26, 27], prescription analgesics in the United States necessitate Food and Drug Administration (FDA) approval. This requires a rigorous development program proving consistency, quality, efficacy, and safety as defined by basic scientific studies and randomized controlled trials (RCT) [28] and generally adhering to recent IMMPACT recommendations [29], provoking our next question.

Can a Botanical Agent Become a Prescription Medicine?

Most modern physicians fail to recognize that pharmacognosy (study of medicinal plants) has led directly or indirectly to an estimated 25 % of modern pharmaceuticals [30]. While the plethora of available herbal agents yield an indecipherable cacophony to most clinicians and consumers alike, it is certainly possible to standardize botanical agents and facilitate their recommendation based on sound science [31]. Botanical medicines can even fulfill the rigorous dictates of the FDA and attain prescription drug status via a clear roadmap in the form of a blueprint document [32], henceforth termed the *Botanical Guidance*: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070491.pdf. To be successful and clinically valuable, botanicals, including cannabis-based medicines, must demonstrate the same quality, clinical analgesic benefit, and appropriately safe adverse event profile as available new chemical entities (NCE) [28].

The Biochemical and Neurophysiological Basis of Pain Control by Cannabinoids

Neuropathic Pain

Thorough reviews of therapeutic effects of cannabinoids in preclinical and clinical domains have recently been published [33, 34]. In essence, the endocannabinoid system (ECS) is active throughout the CNS and PNS in modulating pain at spinal, supraspinal, and peripheral levels. Endocannabinoids are produced on demand in the CNS to dampen sensitivity to pain [35]. The endocannabinoid system is operative in such key integrative pain centers as the periaqueductal grey matter [36, 37], the ventroposterolateral nucleus of the thalamus [38], and the spinal cord [39, 40]. Endocannabinoids are endogenous mediators of stress-induced analgesia and fear-conditioned analgesia and suppress pain-related phenomena such as windup [41] and allodynia [42]. In the periphery and PNS [13], the ECS has key effects in suppressing both hyperalgesia and allodynia via CB_1 [43] and CB_2 mechanisms (Fig. 18.2). Indeed, pathological pain states have been postulated to arise, at least in part, from a dysregulation of the endocannabinoid system.

Antinociceptive and Anti-inflammatory Pain Mechanisms

Beyond the mechanisms previously mentioned, the ECS plays a critical role in peripheral pain, inflammation, and hyperalgesia [43] through both CB_1 and CB_2 mechanisms. CB_1 and CB_2 mechanisms are also implicated in regulation of contact dermatitis and pruritus [44]. A role for spinal CB_2 mechanisms, mediated by microglia and/or astrocytes, is also revealed under conditions of inflammation [45]. Both THC and cannabidiol (CBD), a non-euphoriant phytocannabinoid common in certain cannabis strains, are potent anti-inflammatory antioxidants with activity exceeding that of

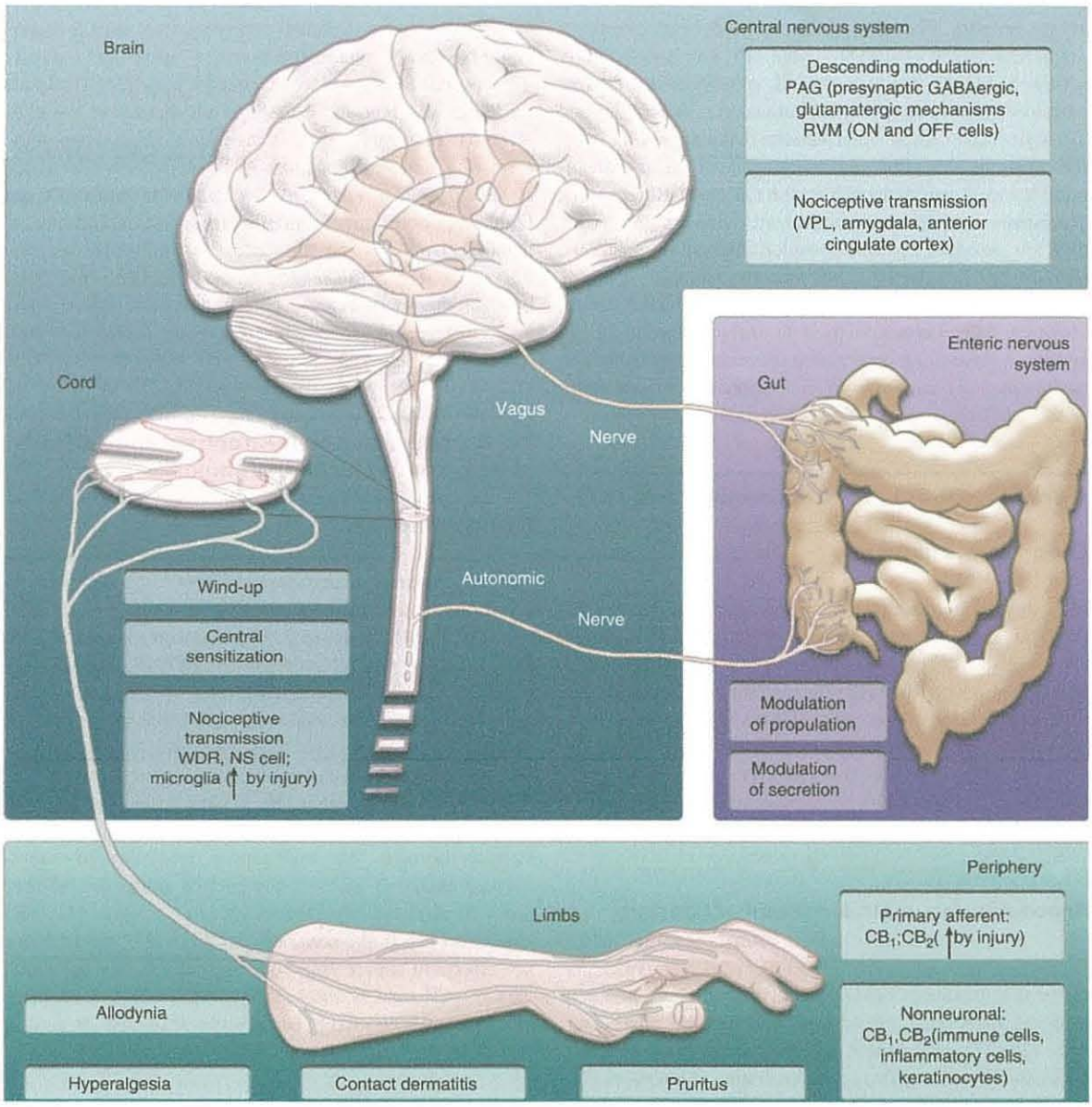


Fig. 18.2 Cannabinoids suppress pain and other pathophysiological (e.g., contact dermatitis, pruritis) and physiological (e.g., gastrointestinal transit and secretion) processes through multiple mechanisms involving CB_1 and CB_2 receptors. Peripheral, spinal, and supraspinal sites of cannabinoid actions are shown. In the periphery, cannabinoids act through both neuronal and nonneuronal mechanisms to control inflammation, allodynia, and hyperalgesia. CB_1 and CB_2 have been localized to both primary afferents and nonneuronal cells (e.g., keratinocytes, microglia), and expression can be regulated by injury. In the spinal cord, cannabinoids suppress nociceptive transmission, windup, and central sensitization by modulating activity in the ascending pain pathway of the spinothalamic tract, including responses of wide dynamic range (*WDR*) and nociceptive specific (*NS*) cells. Similar processes are observed at rostral levels of the neuraxis (e.g., ventroposterolateral nucleus of the thalamus, amygdala, anterior cingulate cortex). Cannabinoids also actively modulate pain through descending mechanisms. In the periaqueductal gray, cannabinoids act through presynaptic glutamatergic and GABAergic mechanisms to control nociception. In the rostral ventromedial medulla, cannabinoids suppress activity in ON cells and inhibit the firing pause of OFF cells, in response to noxious stimulation to produce antinociception (Figure by authors with kind assistance of James Brodie, GW Pharmaceuticals)

vitamins C and E via non-cannabinoid mechanisms [46]. THC inhibits prostaglandin E-2 synthesis [47] and stimulates lipooxygenase [48]. Neither THC nor CBD affects COX-1 or COX-2 at relevant pharmacological dosages [49].

While THC is inactive at vanilloid receptors, CBD, like AEA, is a $TRPV_1$ agonist. Like capsaicin, CBD is capable of inhibiting fatty-acid amide hydrolase (FAAH), the enzyme which hydrolyzes AEA and other fatty-acid amides that do not bind to cannabinoid receptors. CBD additionally inhibits AEA reuptake [50] though not potently. Thus, CBD acts as an endocannabinoid modulator [51], a mechanism that various pharmaceutical firms hope to emulate with new chemical entities (NCEs). CBD inhibits hepatic metabolism of THC to 11-hydroxy-THC, which is possibly more psychoactive, and prolongs its half-life, reducing its psychoactivity and attenuating attendant anxiety and tachycardia [51]; antagonizes psychotic symptoms [52]; and attenuates appetitive effects of THC [53] as well as its effects on short-term memory [54]. CBD also inhibits tumor necrosis factor-alpha (TNF-α) in a rodent model of rheumatoid arthritis [55]. Recently, CBD has been demonstrated to enhance adenosine receptor A2A signaling via inhibition of the adenosine transporter [56].

Recently, GPR18 has been proposed as a putative CBD receptor whose function relates to cellular migration [57]. Antagonism of GPR18 (by agents such as CBD) may be efficacious in treating pain of endometriosis, among other conditions, especially considering that such pain may be endocannabinoid-mediated [58]. Cannabinoids are also very active in various gastrointestinal and visceral sites mediating pain responses [59, 60].

Cannabinoid Interactions with Other Neurotransmitters Pertinent to Pain

As alluded to above, the ECS modulates neurotransmitter release via retrograde inhibition. This is particularly important in NMDA-glutamatergic mechanisms that become hyperresponsive in chronic pain states. Cannabinoids specifically inhibit glutamate release in the hippocampus [61]. THC reduces NMDA responses by 30–40 % [46]. Secondary and tertiary hyperalgesia mediated by NMDA [62] and by calcitonin gene-related peptide [40] may well be targets of cannabinoid therapy in disorders such as migraine, fibromyalgia, and idiopathic bowel syndrome wherein these mechanisms seem to operate pathophysiologically [63], prompting the hypothesis of a "clinical endocannabinoid deficiency." Endocannabinoid modulators may therefore restore homeostasis, leading to normalization of function in these pathophysiological conditions. THC also has numerous effects on serotonergic systems germane to migraine [64], increasing its production in the cerebrum while decreasing reuptake [65]. In fact, the ECS seems to modulate the trigeminovascular system of migraine pathogenesis at vascular and neurochemical levels [66–68].

Cannabinoid-Opioid Interactions

Although endocannabinoids do not bind to opioid receptors, the ECS may nonetheless work in parallel with the endogenous opioid system with numerous areas of overlap and interaction. Pertinent mechanisms include stimulation of beta-endorphin by THC [69] as well as its ability to demonstrate experimental opiate sparing [70], prevent opioid tolerance and withdrawal [71], and rekindle opioid analgesia after loss of effect [72]. Adjunctive treatments that combine opioids with cannabinoids may enhance the analgesic effects of either agent. Such strategies may permit lower doses of analgesics to be employed for therapeutic benefit in a manner that minimizes incidence or severity of adverse side effects.

Clinical Trials, Utility, and Pitfalls of Cannabinoids in Pain

Evidence for Synthetic Cannabinoids

Oral dronabinol (THC) has been available as the synthetic Marinol® since 1985 and is indicated for nausea associated with chemotherapy and appetite stimulation in HIV/AIDS. Issues with its cost, titration difficulties, delayed onset, and propensity to induce intoxicating and dysphoric effects have limited clinical application [73]. It was employed in two open-label studies of chronic neuropathic pain in case studies in 7 [74] and 8 patients [75], but no significant benefit was evident and side effects led to prominent dropout rates (average doses 15–16.6 mg THC). Dronabinol produced benefit in pain in multiple sclerosis [76], but none was evident in postoperative pain (Table 18.1) [77]. Dronabinol was reported to relieve pruritus in three case-report subjects with cholestatic jaundice [78]. Dronabinol was assessed in 30 chronic noncancer pain patients on opioids in double-blind crossover single-day sessions vs. placebo with improvement [79], followed by a 4-week open-label trial with continued improvement (Table 18.1). Associated adverse events were prominent. Methodological issues included lack of prescreening for cannabinoids, 4 placebo subjects with positive THC assays, and 58 % of subjects correctly guessing Marinol dose on test day. An open-label comparison in polyneuropathy examined nabilone patients with 6 obtaining 22.6 % mean pain relief after 3 months, and 5 achieving 28.6 % relief after 6 months, comparable to conventional agents [80]. A pilot study of Marinol in seven spinal cord injury patients with neuropathic pain saw two withdraw, and the remainder appreciate no greater efficacy than with diphenhydramine [81].

Table 18.1 Randomized controlled trials of cannabinoids in pain

Agent	*N*=	Indication	Duration/type	Outcomes/reference
Ajulemic acid	21	Neuropathic pain	7 day crossover	Visual analogue pain scales improved over placebo ($p=0.02$)/Karst et al. [92]
Cannabis, smoked	50	HIV neuropathy	5 days/DB	Decreased daily pain ($p=0.03$) and hyperalgesia ($p=0.05$), 52 % with >30 % pain reduction vs. placebo ($p=0.04$)/ Abrams et al. [94]
Cannabis, smoked	23	Chronic neuropathic pain	5 days/DB	Decreased pain vs. placebo only at 9.4 % THC level ($p=0.023$)/Ware et al. [98]
Cannabis, smoked	38	Neuropathic pain	Single dose/DBC	NSD in pain except at highest cannabis dose ($p=0.02$), with prominent psychoactive effects/Wilsey et al. [95]
Cannabis, smoked	34	HIV neuropathy	5 days /DB	DDS improved over placebo ($p=0.016$), 46 % vs. 18 % improved >30 %, 2 cases toxic psychosis/Ellis et al. [97]
Cannabis, vaporized	21	Chronic pain on opioids	5 days/DB	27 % decrement in pain/Abrams et al. [118]
Cannador	419	Pain due to spasm in MS	15 weeks	Improvement over placebo in subjective pain associated with spasm ($p=0.003$)/ Zajicek et al. [120]
Cannador	65	Postherpetic neuralgia	4 weeks	No benefit observed/Ernst et al. [122]
Cannador	30	Postoperative pain	Single doses, daily	Decreasing pain intensity with increased dose ($p=0.01$)/Holdcroft et al. [123]
Marinol	24	Neuropathic pain in MS	15–21 days/DBC	Median numerical pain ($p=0.02$), median pain relief improved ($p=0.035$) over placebo/Svendsen et al. [76]
Marinol	40	Postoperative pain	Single dose/DB	No benefit observed over placebo/Buggy et al. [77]
Marinol	30	Chronic pain	3 doses, 1 day/DBC	Total pain relief improved with 10 mg ($p<0.05$) and 20 mg ($p<0.01$) with opioids, AE prominent/Narang et al. [79]
Nabilone	41	Postoperative pain	3 doses in 24 h/DB	NSD morphine consumption. Increased pain at rest and on movement with nabilone 1 or 2 mg/Beaulieu [85]
Nabilone	31	Fibromyalgia	2 weeks/DBC	Compared to amitriptyline, nabilone improved sleep, decrease wakefulness, had no effect on pain, and increased AE/ Ware et al. [90]
Nabilone	96	Neuropathic pain	14 weeks/DBC vs. dihydrocodeine	Dihydrocodeine more effective with fewer AE/Frank et al. [88]
Nabilone	13	Spasticity pain	9 weeks/DBC	NRS decreased 2 points for nabilone ($p<0.05$)/Wissel et al. [87]
Nabilone	40	Fibromyalgia	4 weeks/DBC	VAS decreased in pain, Fibromyalgia Impact Questionnaire, and anxiety over placebo (all, $p<0.02$)/Skrabek et al. [89]
Sativex	20	Neurogenic pain	Series of 2-week N-of-1 crossover blocks	Improvement with Tetranabinex and Sativex on VAS pain vs. placebo ($p<0.05$), symptom control best with Sativex ($p<0.0001$)/Wade et al. [132]
Sativex	24	Chronic intractable pain	12 weeks, series of N-of-1 crossover blocks	VAS pain improved over placebo ($p<0.001$) especially in MS ($p<0.0042$)/ Notcutt et al. [133]
Sativex	48	Brachial plexus avulsion	6 weeks in 3 two-week crossover blocks	Benefits noted in Box Scale-11 pain scores with Tetranabinex ($p=0.002$) and Sativex ($p=0.005$) over placebo/Berman et al. [134]
Sativex	66	Central neuropathic pain in MS	5 weeks	Numerical Rating Scale (NRS) analgesia improved over placebo ($p=0.009$)/Rog et al. [135]

(continued)

Table 18.1 (continued)

Agent	*N*=	Indication	Duration/type	Outcomes/reference
Sativex	125	Peripheral neuropathic pain	5 weeks	Improvements in NRS pain levels (p=0.004), dynamic allodynia (p=0.042), and punctuate allodynia (p=0.021) vs. placebo/Nurmikko et al. [136]
Sativex	56	Rheumatoid arthritis	Nocturnal dosing for 5 weeks	Improvements over placebo morning pain on movement (p=0.044), morning pain at rest (p=0.018), DAS-28 (p=0.002), and SF-MPQ pain at present (p=0.016)/Blake et al. [138]
Sativex	117	Pain after spinal injury	10 days	NSD in NRS pain scores, but improved Brief Pain Inventory (p=0.032), and Patients' Global Impression of Change (p=0.001) (unpublished)
Sativex	177	Intractable cancer pain	2 weeks	Improvements in NRS analgesia vs. placebo (p=0.0142), Tetranabinex NSD/ Johnson et al. [139]
Sativex	135	Intractable lower urinary tract symptoms in MS	8 weeks	Improved bladder severity symptoms including pain over placebo (p=0.001) [200]
Sativex	360	Intractable cancer pain	5 weeks/DB	CRA of lower and middle-dose cohorts improved over placebo (p=0.006)/ [201]

Nabilone, or Cesamet®, is a semisynthetic analogue of THC that is about tenfold more potent, and longer lasting [82]. It is indicated as an antiemetic in chemotherapy in the USA. Prior case reports in neuropathic pain [83] and other pain disorders [84] have been published. Sedation and dysphoria are prominent associated adverse events. An RCT of nabilone in 41 postoperative subjects dosed TID actually resulted in increased pain scores (Table 18.1) [85]. An uncontrolled study of 82 cancer patients on nabilone noted improved pain scores [86], but retention rates were limited. Nabilone improved pain ($p<0.05$) vs. placebo in patients with mixed spasticity syndromes in a small double-blind trial (Table 18.1) [87], but was without benefits in other parameters. In a double-blind crossover comparison of nabilone to dihydrocodeine (schedule II opioid) in chronic neuropathic pain (Table 18.1) [88], both drugs produced marginal benefit, but with dihydrocodeine proving clearly superior in efficacy and modestly superior in side-effect profile. In an RCT in 40 patients of nabilone vs. placebo over 4 weeks, it showed significant decreases in VAS of pain and anxiety (Table 18.1) [89]. A more recent study of nabilone vs. amitriptyline in fibromyalgia yielded benefits on sleep, but not pain, mood, or quality of life (Table 18.1) [90]. An open-label trial of nabilone vs. gabapentin found them comparable in pain and other symptom relief in peripheral neuropathic pain [91].

Ajulemic acid (CT3), another synthetic THC analogue in development, was utilized in a phase II RCT in peripheral neuropathic pain in 21 subjects with apparent improvement (Table 18.1) [92]. Whether or not ajulemic acid is psychoactive is the subject of some controversy [93].

Evidence for Smoked or Vaporized Cannabis

Few randomized controlled clinical trials (RCTs) of pain with smoked cannabis have been undertaken to date [94–97]. One of these [96] examined cannabis effects on experimental pain in normal volunteers.

Abrams et al. [94] studied inpatient adults with painful HIV neuropathy in 25 subjects in double-blind fashion to receive either smoked cannabis as 3.56 % THC cigarettes or placebo cigarettes three times daily for 5 days (Table 18.1). The smoked cannabis group had a 34 % reduction in daily pain vs. 17 % in the placebo group (p=0.03). The cannabis cohort also had a 52 % of subjects report a >30 % reduction in pain scores over the 5 days vs. 24 % in the placebo group (p=0.04) (Table 18.1). The authors rated cannabis as "well tolerated" due to an absence of serious adverse events (AE) leading to withdrawal, but all subjects were cannabis experienced. Symptoms of possible intoxication in the cannabis group including anxiety (25 %), sedation (54 %), disorientation (16 %), paranoia (13 %), confusion (17 %), dizziness (15 %), and nausea (11 %) were all statistically significantly more common than in the placebo group. Despite these findings, the authors stated that the values do not represent any serious safety concern in this short-term study. No discussion in the article addressed issues of the relative efficacy of blinding in the trial.

Wilsey et al. [95] examined neuropathic pain in 38 subjects in a double-blind crossover study comparing 7 % THC cannabis, 3.5 % THC cannabis, and placebo cigarettes via a complex cumulative dosing scheme with each dosage given

once, in random order, with at least 3 day intervals separating sessions (Table 18.1). A total of 9 puffs maximum were allowed over several hours per session. Authors stated, "Psychoactive effects were minimal and well-tolerated, but neuropsychological impairment was problematic, particularly with the higher concentration of study medication." Again, only cannabis-experienced subjects were allowed entry. No withdrawals due to AE were reported, but 1 subject was removed due to elevated blood pressure. No significant differences were noted in pain relief in the two cannabis potency groups, but a significant separation of pain reduction from placebo ($p=0.02$) was not evident until a cumulative 9 puffs at 240 min elapsed time. Pain unpleasantness was also reduced in both active treatment groups ($p<0.01$). Subjectively, an "any drug effect" demonstrated a visual analogue scale (VAS) of 60/100 in the high-dose group, but even the low-dose group registered more of a "good drug effect" than placebo ($p<0.001$). "Bad drug effect" was also evident. "Feeling high" and "feeling stoned" were greatest in the high-dose sessions ($p<0.001$), while both high- and low-dose differentiated significantly from placebo ($p<0.05$). Of greater concern, both groups rated impairment as 30/100 on VAS vs. placebo ($p=0.003$). Sedation also demarcated both groups from placebo ($p<0.01$), as did confusion ($p=0.03$), and hunger ($p<0.001$). Anxiety was not considered a prominent feature in this cannabis-experienced population. This study distinguished itself from some others in its inclusion of specific objective neuropsychological measures and demonstrated neurocognitive impairment in attention, learning, and memory, most noteworthy with 7 % THC cannabis. No commentary on blinding efficacy was included.

Ellis et al. [97] examined HIV-associated neuropathic pain in a double-blind trial of placebo vs. 1–8 % THC cannabis administered four times daily over 5 days with a 2-week washout (Table 18.1). Subjects were started at 4 % THC and then titrated upward or downward in four smoking sessions dependent upon their symptom relief and tolerance of the dose. In this study, 96 % of subjects were cannabis-experienced, and 28 out of 34 subjects completed the trial. The primary outcome measure (Descriptor Differential Scale, DDS) was improved in the active group over placebo ($p=0.016$), with >30 % relief noted in 46 % of cannabis subjects vs. 18 % of placebo. While most adverse events (AE) were considered mild and self-limited, two subjects had to leave the trial due to toxicity. One cannabis-naïve subject was withdrawn due to "an acute cannabis-induced psychosis" at what proved to be his first actual cannabis exposure. The other subject suffered intractable cough. Pain reduction was greater in the cannabis-treated group ($p=0.016$) among completers, as was the proportion of subjects attaining >30 % pain reduction (46 % vs. 18 %, $p=0.043$). Blinding was assessed in this study; whereas placebo patients were inaccurate at guessing the investigational product, 93 % of those receiving cannabis guessed correctly. On safety issues, the authors stated that the frequency of some nontreatment-limiting side effects was greater for cannabis than placebo. These included concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation, and thirst.

A Canadian study [98] examined single 25-mg inhalations of various cannabis potencies (0–9.4 % THC) three times daily for 5 days per cycle in 23 subjects with chronic neuropathic pain (Table 18.1). Patients were said to be cannabis-free for 1 year, but were required to have some experience of the drug. Only the highest potency demarcated from placebo on decrements in average daily pain score (5.4 vs. 6.1, $p=0.023$). The most frequent AE in the high-dose group were headache, dry eyes, burning sensation, dizziness, numbness, and cough, but with "high" or "euphoria" reported only once in each cannabis potency group.

The current studies of smoked cannabis are noteworthy for their extremely short-term exposure and would be of uncertain relevance in a regulatory environment. The IMMPACT recommendations on chronic neuropathic pain clinical trials that are currently favored by the FDA [29] generally suggest randomized controlled clinical trials of 12-week duration as a prerequisite to demonstrate efficacy and safety. While one might assume that the degree of pain improvement demonstrated in these trials could be maintained over this longer interval, it is only reasonable to assume that cumulative adverse events would also increase to at least some degree. The combined studies represent only a total of 1,106 patient-days of cannabis exposure (Abrams: 125, Wilsey: 76, Ellis: 560, Ware 345) or 3 patient-years of experience. In contrast, over 6,000 patient-years of data have been analyzed for Sativex between clinical trials, prescription, and named-patient supplies, with vastly lower AE rates (data on file, GW Pharmaceuticals) [28, 99]. Certainly, the cognitive effects noted in California-smoked cannabis studies figure among many factors that would call the efficacy of blinding into question for investigations employing such an approach. However, it is also important to emphasize that unwanted side effects are not unique to cannabinoids. In a prospective evaluation of specific chronic polyneuropathy syndromes and their response to pharmacological therapies, the presence of intolerable side effects did not differ in groups receiving gabapentinoids, tricyclic antidepressants, anticonvulsants, cannabinoids (including nabilone, Sativex), and topical agents [80]. Moreover, no serious adverse events were related to any of the medications.

The current studies were performed in a very select subset of patients who almost invariably have had prior experience of cannabis. Their applicability to cannabis-naïve populations is, thus, quite unclear. At best, the observed benefits might possibly accrue to some, but it is eminently likely that candidates for such therapy might refuse it on any number of

grounds: not wishing to smoke, concern with respect to intoxication, etc. Sequelae of smoking in therapeutic outcomes have had little discussion in these brief RCTs [28]. Cannabis smoking poses substantial risk of chronic cough and bronchitic symptoms [100], if not obvious emphysematous degeneration [101] or increase in aerodigestive cancers [102]. Even such smoked cannabis proponents as Lester Grinspoon has acknowledged are the only well-confirmed deleterious physical effect of marihuana is harm to the pulmonary system [103]. However, population-based studies of cannabis trials have failed to show any evidence for increased risk of respiratory symptoms/chronic obstructive pulmonary disease [100] or lung cancer [102] associated with smoking cannabis.

A very detailed analysis and comparison of mainstream and sidestream smoke for cannabis vs. tobacco smoke was performed in Canada [104]. Of note, cannabis smoke contained ammonia (NH_3) at a level of 720 μg per 775 mg cigarette, a figure 20-fold higher than that found in tobacco smoke. It was hypothesized that this finding was likely attributable to nitrate fertilizers. Formaldehyde and acetaldehyde were generally lower in cannabis smoke than in tobacco, but butyraldehyde was higher. Polycyclic aromatic hydrocarbon (PAH) contents were qualitatively similar in the comparisons, but total yield was lower for cannabis mainstream smoke, but higher than tobacco for sidestream smoke. Additionally, NO, NO_x, hydrogen cyanide, and aromatic amines concentrations were 3–5 times higher in cannabis smoke than that from tobacco. Possible mutagenic and carcinogenic potential of these various compounds were mentioned. More recently, experimental analysis of cannabis smoke with resultant acetaldehyde production has posited its genotoxic potential to be attributable to reactions that produce DNA adducts [105].

Vaporizers for cannabis have been offered as a harm reduction technique that would theoretically eliminate products of combustion and associated adverse events. The Institute of Medicine (IOM) examined cannabis issues in 1999 [106], and among their conclusions was the following (p. 4): "Recommendation 2: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-onset, reliable, and safe delivery systems." One proposed technique is vaporization, whereby cannabis is heated to a temperature that volatilizes THC and other components with the goal of reducing or eliminating by-products of combustion, including potentially carcinogenic polycyclic aromatic hydrocarbons, benzene, acetaldehyde, carbon monoxide, toluene, naphthaline, phenol, toluene, hydrogen cyanide, and ammonia. Space limitations permit only a cursory review of available literature [107–115].

A pilot study of the Volcano vaporizer vs. smoking was performed in the USA in 2007 in 18 active cannabis consumers, with only 48 h of presumed abstinence [116]. NIDA 900-mg cannabis cigarettes were employed (1.7, 3.4, and 6.8 % THC) with each divided in two, so that one-half would be smoked or vaporized in a series of double-blind sessions. The Volcano vaporizer produced comparable or slightly higher THC plasma concentrations than smoking. Measured CO in exhaled vapor sessions diminished very slightly, while it increased after smoking ($p<0.001$). Self-reported visual analogue scales of the associated high were virtually identical in vaporization vs. smoking sessions and increased with higher potency material. A contention was advanced that the absence of CO increase after vaporization can be equated to "little or no exposure to gaseous combustion toxins." Given that no measures of PAH or other components were undertaken, the assertion is questionable. It was also stated that there were no reported adverse events. Some 12 subjects preferred the Volcano, 2 chose smoking, and 2 had no preference as to technique, making the vaporizer "an acceptable system" and providing "a safer way to deliver THC."

A recent [202, 117] examined interactions of 3.2 % THC NIDA cannabis vaporized in the Volcano in conjunction with opioid treatment in a 5-day inpatient trial in 21 patients with chronic pain (Table 18.1). All subjects were prior cannabis smokers. Overall, pain scores were reduced from 39.6 to 29.1 on a VAS, a 27 % reduction, by day 5. Pain scores in subjects on morphine fell from 34.8 to 24.1, while in subjects taking oxycodone, scores dropped from 43.8 to 33.6.

The clinical studies performed with vaporizers to date have been very small pilot studies conducted over very limited timeframes (i.e., for a maximum of 5 days). Thus, these studies cannot contribute in any meaningful fashion toward possible FDA approval of vaporized cannabis as a delivery technique, device, or drug under existing policies dictated by the *Botanical Guidance* [32]. It is likewise quite unlikely that the current AE profile of smoked or vaporized cannabis would meet FDA requirements. The fact that all the vaporization trials to date have been undertaken only in cannabis-experienced subjects does not imply that results would generalize to larger patient populations. Moreover, there is certainly no reason to expect AE profiles to be better in cannabis-naïve patients. Additionally, existing standardization of cannabis product and delivery via vaporization seem far off the required marks. Although vaporizers represent an alternate delivery method devoid of the illegality associated with smoked cannabis, the presence of toxic ingredients such as PAH, ammonia, and acetaldehyde in cannabis vapor are unlikely to be acceptable to FDA in any significant amounts. Existing vaporizers still lack portability or convenience [28]. A large Internet survey revealed that only 2.2 % of cannabis users employed vaporization as their primary cannabis intake method [118]. While studies to date have established that lower temperature vaporization in the Volcano, but not necessarily other devices, can reduce the relative amounts of noxious by-products of combustion, it has yet to be demonstrated that they are totally eliminated. Until or unless this goal is achieved, along with

requisite benchmarks of herbal cannabis quality, safety, and efficacy in properly designed randomized clinical trials, vaporization remains an unproven technology for therapeutic cannabinoid administration.

Evidence for Cannabis-Based Medicines

Cannador is a cannabis extract in oral capsules, with differing THC:CBD ratios [51]. Cannador was utilized in a phase III RCT of spasticity in multiple sclerosis (CAMS) (Table 18.1) [119]. While no improvement was evident in the Ashworth Scale, reduction was seen in spasm-associated pain. Both THC and Cannador improved pain scores in follow-up [120]. Cannador was also employed for postherpetic neuralgia in 65 patients, but without success (Table 18.1) [121, 122]. Slight pain reduction was observed in 30 subjects with postoperative pain (CANPOP) not receiving opiates, but psychoactive side effects were notable (Table 18.1).

Sativex® is a whole-cannabis-based extract delivered as an oromucosal spray that combines a CB_1 and CB_2 partial agonist (THC) with a cannabinoid system modulator (CBD), minor cannabinoids, and terpenoids plus ethanol and propylene glycol excipients and peppermint flavoring [51, 123]. It is approved in Canada for spasticity in MS and under a Notice of Compliance with Conditions for central neuropathic pain in multiple sclerosis and treatment of cancer pain unresponsive to opioids. Sativex is also approved in MS in the UK, Spain, and New Zealand, for spasticity in multiple sclerosis, with further approvals expected soon in some 22 countries around the world. Sativex is highly standardized and is formulated from two *Cannabis sativa* chemovars predominating in THC and CBD, respectively [124]. Each 100 µl pump-action oromucosal spray of Sativex yields 2.7 mg of THC and 2.5 mg of CBD plus additional components. Pharmacokinetic data are available [125–127]. Sativex effects begin within an interval allowing dose titration. A very favorable adverse event profile has been observed in the development program [27, 128]. Most patients stabilize at 8–10 sprays per day after 7–10 days, attaining symptomatic control without undue psychoactive sequelae. Sativex was added to optimized drug regimens in subjects with uncontrolled pain in every RCT (Table 18.1). An Investigational New Drug (IND) application to study Sativex in advanced clinical trials in the USA was approved by the FDA in January 2006 in patients with intractable cancer pain. One phase IIB dose-ranging study has already been completed [201]. Available clinical trials with Sativex have been independently assessed [129, 130].

In a phase II study of 20 patients with neurogenic symptoms [131], significant improvement was seen with both Tetranabinex (high-THC extract without CBD) and Sativex on pain, with Sativex displaying better symptom control ($p<0.0001$), with less intoxication (Table 18.1).

In a phase II study of intractable chronic pain in 24 patients [132], Sativex again produced the best results compared to Tetranabinex ($p<0.001$), especially in MS ($p<0.0042$) (Table 18.1).

In a phase III study of brachial plexus avulsion ($N=48$) [133], pain reduction with Tetranabinex and Sativex was about equal (Table 18.1).

In an RCT of 66 MS subjects, mean Numerical Rating Scale (NRS) analgesia favored Sativex over placebo (Table 18.1) [134].

In a phase III trial ($N=125$) of peripheral neuropathic pain with allodynia [135], Sativex notably alleviated pain levels and dynamic and punctate allodynia (Table 18.1).

In a safety-extension study in 160 subjects with various symptoms of MS [136], 137 patients showed sustained improvements over a year or more in pain and other symptoms [99] without development of any tolerance requiring dose escalation or withdrawal effects in those who voluntarily discontinued treatment suddenly. Analgesia was quickly reestablished upon Sativex resumption.

In a phase II RCT in 56 rheumatoid arthritis sufferers over 5 weeks with Sativex [137], medicine was limited to only 6 evening sprays (16.2 mg THC + 15 mg CBD). By study end, morning pain on movement, morning pain at rest, DAS-28 measure of disease activity, and SF-MPQ pain all favored Sativex (Table 18.1).

In a phase III RCT in intractable cancer pain on opioids ($N=177$), Sativex, Tetranabinex THC-predominant extract, and placebo were compared [138] demonstrating strongly statistically significant improvements in analgesia for Sativex only (Table 18.1). This suggests that the CBD component in Sativex was necessary for benefit.

In a 2-week study of spinal cord injury pain, NRS of pain was not statistically different from placebo, probably due to the short duration of the trial, but secondary endpoints were positive (Table 18.1). Additionally, an RCT of intractable lower urinary tract symptoms in MS also demonstrated pain reduction (Table 18.1).

The open-label study of various polyneuropathy patients included Sativex patients with 3 obtaining 21.56 % mean pain relief after 3 months (2/3 > 30 %), and 4 achieving 27.6 % relief after 6 months (2/4 > 30 %), comparable to conventional agents [80].

A recently completed RCT of Sativex in intractable cancer pain unresponsive to opioids over 5 weeks was performed in 360 subjects (Table 18.1). Results of a Continuous Response Analysis (CRA) showed improvements over placebo in the low-dose ($p=0.08$) and middle-dose cohorts ($p=0.038$) or combined ($p=0.006$). Pain NRS improved over placebo in the low-dose ($p=0.006$) and combined cohorts ($p=0.019$).

Sleep has improved markedly in almost all Sativex RCTs in chronic pain based on symptom reduction, not a hypnotic effect [139].

The adverse event (AE) profile of Sativex has been quite benign with bad taste, oral stinging, dry mouth, dizziness, nausea, or fatigue most common, but not usually prompting discontinuation [128]. Most psychoactive sequelae are early and transient and have been notably lowered by more recent application of a slower, less aggressive titration schedule. While no direct comparative studies have been performed with Sativex and other agents, AE rates were comparable or greater with Marinol than with Sativex employing THC dosages some 2.5 times higher, likely due to the presence of accompanying CBD [28, 51]. Similarly, Sativex displayed a superior AE profile compared to smoked cannabis based on safety-extension studies of Sativex [28, 99], as compared to chronic use of cannabis with standardized government-supplied material in Canada for chronic pain [140] and the Netherlands for various indications [141, 142] over a period of several months or more. All AEs are more frequent with smoked cannabis, except for nausea and dizziness, both early and usually transiently reported with Sativex [27, 28, 128]. A recent meta-analysis suggested that serious AEs associated with cannabinoid-based medications did not differ from placebo and thus could not be attributable to cannabinoid use, further reinforcing the low toxicity associated with activation of cannabinoid systems.

Cannabinoid Pitfalls: Are They Surmountable?

The dangers of COX-1 and COX-2 inhibition by nonsteroidal anti-inflammatory drugs (NSAIDS) of various design (e.g., gastrointestinal ulceration and bleeding vs. coronary and cerebrovascular accidents, respectively) [143, 144] are unlikely to be mimicked by either THC or CBD, which produce no such activity at therapeutic dosages [49].

Natural cannabinoids require polar solvents and may be associated with delayed and sometimes erratic absorption after oral administration. Smoking of cannabis invariably produces rapid spikes in serum THC levels; cannabis smoking attains peak levels of serum THC above 140 ng/ml [145, 146], which, while desirable to the recreational user, has no necessity or advantage for treatment of chronic pain [28]. In contrast, comparable amounts of THC derived from oromucosal Sativex remained below 2 ng/ml with much lower propensity toward psychoactive sequelae [28, 125], with subjective intoxication levels on visual analogue scales that are indistinguishable from placebo, in the single digits out of 100 [100]. It is clear from RCTs that such psychoactivity is not a necessary accompaniment to pain control. In contrast, intoxication has continued to be prominent with oral THC [73].

In comparison to the questionable clinical trial blinding with smoked and vaporized cannabis discussed above, all indications are that such study blinding has been demonstrably effective with Sativex [147, 148] by utilizing a placebo spray with identical taste and color. Some 50 % of Sativex subjects in RCTs have had prior cannabis exposure, but results of two studies suggest that both groups exhibited comparable results in both treatment efficacy and side effect profile [134, 135].

Controversy continues to swirl around the issue of the potential dangers of cannabis use medicinally, particularly its drug abuse liability (DAL). Cannabis and cannabinoids are currently DEA schedule I substances and are forbidden in the USA (save for Marinol in schedule III and nabilone in schedule II) [73]. This is noteworthy in itself because the very same chemical compound, THC, appears simultaneously in schedule I (as THC), schedule II (as nabilone), and schedule III (as Marinol). DAL is assessed on the basis of five elements: intoxication, reinforcement, tolerance, withdrawal, and dependency plus the drug's overall observed rates of abuse and diversion. Drugs that are smoked or injected are commonly rated as more reinforcing due to more rapid delivery to the brain [149]. Sativex has intermediate onset. It is claimed that CBD in Sativex reduces the psychoactivity of THC [28]. RCT AE profiles do not indicate euphoria or other possible reinforcing psychoactive indicia as common problems with its use [99]. Similarly, acute THC effects such as tachycardia, hypothermia, orthostatic hypotension, dry mouth, ocular injection, and intraocular pressure decreases undergo prominent tachyphylaxis with regular usage [150]. Despite that observation, Sativex has not demonstrated dose tolerance to its therapeutic benefits on prolonged administration, and efficacy has been maintained for up to several years in pain conditions [99].

The existence or severity of a cannabis withdrawal syndrome remains under debate [151, 152]. In contrast to reported withdrawal sequelae in recreational users [153], 24 subjects with MS who volunteered to discontinue Sativex after a year or more suffered no withdrawal symptoms meeting Budney criteria. While symptoms such as pain recurred after some 7–10 days without Sativex, symptom control was rapidly reattained upon resumption [99].

Finally, no known abuse or diversion incidents have been reported with Sativex to date (March 2011). Formal DAL studies of Sativex vs. Marinol and placebo have been completed and demonstrate lower scores on drug liking and similar measures at comparable doses [155].

Cognitive effects of cannabis also remain at issue [155, 156], but less data are available in therapeutic applications. Studies of Sativex in neuropathic pain with allodynia have revealed no changes vs. placebo on Sativex in portions of the Halstead-Reitan Battery [135], or in central neuropathic pain in MS [134], where 80 % of tests showed no significant differences. In a recent RCT of Sativex vs. placebo in MS patients, no cognitive differences of note were observed

[157]. Similarly, chronic Sativex use has not produced observable mood disorders.

Controversies have also arisen regarding the possible association of cannabis abuse and onset of psychosis [156]. However, an etiological relationship is not supported by epidemiological data [158–161], but may well be affected by dose levels and duration, if pertinent. One may speculate that lower serum levels of Sativex combined with antipsychotic properties of CBD [52, 162, 163] might attenuate such concerns. Few cases of related symptoms have been reported in SAFEX studies of Sativex.

Immune function becomes impaired in experimental animals at cannabinoid doses 50–100 times necessary to produce psychoactive effects [164]. In four patients smoking cannabis medicinally for more than 20 years, no changes were evident in leukocyte, CD4, or CD8 cell counts [155]. MS patients on Cannador demonstrated no immune changes of note [165] nor were changes evident in subjects smoking cannabis in a brief trial in HIV patients [166]. Sativex RCTs have demonstrated no hematological or immune dysfunction.

No effects of THC extract, CBD extract, or Sativex were evident on the hepatic cytochrome P450 complex [167] or on human CYP450 [168]. Similarly, while Sativex might be expected to have additive sedative effects with other drugs or alcohol, no significant drug-drug interactions of any type have been observed in the entire development program to date.

No studies have demonstrated significant problems in relation to cannabis affecting driving skills at plasma levels below 5 ng/ml of THC [169]. Four oromucosal sprays of Sativex (exceeding the average single dose employed in therapy) produced serum levels well below this threshold [28]. As with other cannabinoids in therapy, it is recommended that patients not drive nor use dangerous equipment until accustomed to the effects of the drug.

Future Directions: An Array of Biosynthetic and Phytocannabinoid Analgesics

Inhibition of Endocannabinoid Transport and Degradation: A Solution?

It is essential that any cannabinoid analgesic strike a compromise between therapeutic and adverse effects that may both be mediated via CB_1 mechanisms [34]. Mechanisms to avoid psychoactive sequelae could include peripherally active synthetic cannabinoids that do not cross the blood-brain barrier or drugs that boost AEA levels by inhibiting fatty-acid amide hydrolase (FAAH) [170] or that of 2-AG by inhibiting monoacylycerol lipase (MGL). CBD also has this effect [50] and certainly seems to increase the therapeutic index of THC [51].

In preclinical studies, drugs inhibiting endocannabinoid hydrolysis [171, 172] and peripherally acting agonists [173] all show promise for suppressing neuropathic pain. AZ11713908, a peripherally restricted mixed cannabinoid agonist, reduces mechanical allodynia with efficacy comparable to the brain penetrant mixed cannabinoid agonist WIN55,212-2 [173]. An irreversible inhibitor of the 2-AG hydrolyzing enzyme MGL suppresses nerve injury-induced mechanical allodynia through a CB_1 mechanism, although these anti-allodynic effects undergo tolerance following repeated administration [172]. URB937, a brain impermeant inhibitor of FAAH, has recently been shown to elevate anandamide outside the brain and suppress neuropathic and inflammatory pain behavior without producing tolerance or unwanted CNS side effects [171]. These observations raise the possibility that peripherally restricted endocannabinoid modulators may show therapeutic potential as analgesics with limited side-effect profiles.

The Phytocannabinoid and Terpenoid Pipeline

Additional phytocannabinoids show promise in treatment of chronic pain [123, 163, 174]. Cannabichromene (CBC), another prominent phytocannabinoid, also displays anti-inflammatory [175] and analgesic properties, though less potently than THC [176]. CBC, like CBD, is a weak inhibitor of AEA reuptake [177]. CBC is additionally a potent TRPA1 agonist [178]. Cannabigerol (CBG), another phytocannabinoid, displays weak binding at both CB_1 and CB_2 [179, 180] but is a more potent GABA reuptake inhibitor than either THC or CBD [181]. CBG is a stronger analgesic, anti-erythema, and lipooxygenase agent than THC [182]. CBG likewise inhibits AEA uptake and is a TRPV1 agonist [177], a TRPA1 agonist, and a TRPM8 antagonist [178]. CBG is also a phospholipase A2 modulator that reduces PGE-2 release in synovial cells [183]. Tetrahydrocannabivarin, a phytocannabinoid present in southern African strains, displays weak CB_1 antagonism [184] and a variety of anticonvulsant activities [185] that might prove useful in chronic neuropathic pain treatment. THCV also reduced inflammation and attendant pain in mouse experiments [187]. Most North American [187] and European [188, 189] cannabis strains have been bred to favor THC over a virtual absence of other phytocannabinoid components, but the latter are currently available in abundance via selective breeding [124, 190].

Aromatic terpenoid components of cannabis also demonstrate pain reducing activity [123, 163]. Myrcene displays an opioid-type analgesic effect blocked by naloxone [191] and reduces inflammation via PGE-2 [192]. β-Caryophyllene displays anti-inflammatory activity on par with phenylbutazone via PGE-1 [193], but contrasts by displaying gastric cytoprotective activity [194]. Surprisingly, β-caryophyllene has proven to be a phytocannabinoid in its own right as a selective CB_2 agonist [195]. α-Pinene inhibits PGE-1 [196], and linalool acts as a local anesthetic [197].

Summary

Basic science and clinical trials support the theoretical and practical basis of cannabinoid agents as analgesics for chronic pain. Their unique pharmacological profiles with multimodality effects and generally favorable efficacy and safety profiles render cannabinoid-based medicines promising agents for adjunctive treatment, particularly for neuropathic pain. It is our expectation that the coming years will mark the advent of numerous approved cannabinoids with varying mechanisms of action and delivery techniques that should offer the clinician useful new tools for treating pain.

References

1. Di Marzo V, Bisogno T, De Petrocellis L. Endocannabinoids and related compounds: walking back and forth between plant natural products and animal physiology. Chem Biol. 2007;14(7):741–56.
2. Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. J Am Chem Soc. 1964;86: 1646–7.
3. Pate D. Chemical ecology of cannabis. J Int Hemp Assoc. 1994;2: 32–7.
4. Di Marzo V, Melck D, Bisogno T, De Petrocellis L. Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action. Trends Neurosci. 1998;21(12):521–8.
5. Pacher P, Batkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev. 2006;58(3): 389–462.
6. Cravatt BF, Giang DK, Mayfield SP, Boger DL, Lerner RA, Gilula NB. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. Nature. 1996;384(6604):83–7.
7. Dinh TP, Freund TF, Piomelli D. A role for monoglyceride lipase in 2-arachidonoylglycerol inactivation. Chem Phys Lipids. 2002;121(1–2):149–58.
8. Gulyas AI, Cravatt BF, Bracey MH, et al. Segregation of two endocannabinoid-hydrolyzing enzymes into pre- and postsynaptic compartments in the rat hippocampus, cerebellum and amygdala. Eur J Neurosci. 2004;20(2):441–58.
9. Mangieri RA, Piomelli D. Enhancement of endocannabinoid signaling and the pharmacotherapy of depression. Pharmacol Res. 2007;56(5):360–6.
10. Howlett AC, Johnson MR, Melvin LS, Milne GM. Nonclassical cannabinoid analgetics inhibit adenylate cyclase: development of a cannabinoid receptor model. Mol Pharmacol. 1988;33(3): 297–302.
11. Zimmer A, Zimmer AM, Hohmann AG, Herkenham M, Bonner TI. Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB1 receptor knockout mice. Proc Natl Acad Sci USA. 1999;96(10):5780–5.
12. Wilson RI, Nicoll RA. Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. Nature. 2001;410(6828): 588–92.
13. Ibrahim MM, Porreca F, Lai J, et al. CB2 cannabinoid receptor activation produces antinociception by stimulating peripheral release of endogenous opioids. Proc Natl Acad Sci USA. 2005;102(8): 3093–8.
14. Guindon J, Hohmann AG. Cannabinoid CB2 receptors: a therapeutic target for the treatment of inflammatory and neuropathic pain. Br J Pharmacol. 2008;153(2):319–34.
15. Pacher P, Mechoulam R. Is lipid signaling through cannabinoid 2 receptors part of a protective system? Prog Lipid Res. 2011;50:193–211.
16. Racz I, Nadal X, Alferink J, et al. Interferon-gamma is a critical modulator of CB(2) cannabinoid receptor signaling during neuropathic pain. J Neurosci. 2008;28(46):12136–45.
17. Guindon J, Hohmann AG. The endocannabinoid system and pain. CNS Neurol Disord Drug Targets. 2009;8(6):403–21.
18. Fankhauser M. History of cannabis in Western medicine. In: Grotenhermen F, Russo EB, editors. Cannabis and cannabinoids: pharmacology, toxicology and therapeutic potential. Binghamton: Haworth Press; 2002. p. 37–51.
19. Russo EB. History of cannabis as medicine. In: Guy GW, Whittle BA, Robson P, editors. Medicinal uses of cannabis and cannabinoids. London: Pharmaceutical Press; 2004. p. 1–16.
20. Russo EB. History of cannabis and its preparations in saga, science and sobriquet. Chem Biodivers. 2007;4(8):2624–48.
21. Mechoulam R. The pharmacohistory of *Cannabis sativa*. In: Mechoulam R, editor. Cannabinoids as therapeutic agents. Boca Raton: CRC Press; 1986. p. 1–19.
22. Russo E. Cannabis treatments in obstetrics and gynecology: a historical review. J Cannabis Ther. 2002;2(3–4):5–35.
23. Russo EB. Hemp for headache: an in-depth historical and scientific review of cannabis in migraine treatment. J Cannabis Ther. 2001;1(2):21–92.
24. Russo EB. The role of cannabis and cannabinoids in pain management. In: Cole BE, Boswell M, editors. Weiner's pain management: a practical guide for clinicians. 7th ed. Boca Raton: CRC Press; 2006. p. 823–44.
25. Russo EB. Cannabis in India: ancient lore and modern medicine. In: Mechoulam R, editor. Cannabinoids as therapeutics. Basel: Birkhäuser Verlag; 2005. p. 1–22.
26. ABC News, USA Today, Stanford Medical Center Poll. Broad experience with pain sparks search for relief. 9 May 2005.
27. Russo EB. Cannabinoids in the management of difficult to treat pain. Ther Clin Risk Manag. 2008;4(1):245–59.
28. Russo EB. The solution to the medicinal cannabis problem. In: Schatman ME, editor. Ethical issues in chronic pain management. Boca Raton: Taylor & Francis; 2006. p. 165–94.
29. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113(1–2):9–19.
30. Tyler VE. Phytomedicines in Western Europe: potential impact on herbal medicine in the United States. In: Kinghorn AD, Balandrin MF, editors. Human medicinal agents from plants (ACS symposium, No. 534). Washington, D.C.: American Chemical Society; 1993. p. 25–37.
31. Russo EB. Handbook of psychotropic herbs: a scientific analysis of herbal remedies for psychiatric conditions. Binghamton: Haworth Press; 2001.
32. Food and Drug Administration. Guidance for industry: botanical drug products. In: Services UDoHaH, editor. US Government; 2004. p. 48. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070491.pdf.
33. Walker JM, Hohmann AG. Cannabinoid mechanisms of pain suppression. Handb Exp Pharmacol. 2005;168:509–54.
34. Rahn EJ, Hohmann AG. Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside. Neurotherapeutics. 2009;6(4):713–37.
35. Richardson JD, Aanonsen L, Hargreaves KM. SR 141716A, a cannabinoid receptor antagonist, produces hyperalgesia in untreated mice. Eur J Pharmacol. 1997;319(2–3):R3–4.
36. Walker JM, Huang SM, Strangman NM, Tsou K, Sanudo-Pena MC. Pain modulation by the release of the endogenous cannabinoid anandamide. Proc Natl Acad Sci. 1999;96(21):12198–203.
37. Walker JM, Hohmann AG, Martin WJ, Strangman NM, Huang SM, Tsou K. The neurobiology of cannabinoid analgesia. Life Sci. 1999;65(6–7):665–73.
38. Martin WJ, Hohmann AG, Walker JM. Suppression of noxious stimulus-evoked activity in the ventral posterolateral nucleus of the

thalamus by a cannabinoid agonist: correlation between electrophysiological and antinociceptive effects. J Neurosci. 1996;16: 6601–11.
39. Hohmann AG, Martin WJ, Tsou K, Walker JM. Inhibition of noxious stimulus-evoked activity of spinal cord dorsal horn neurons by the cannabinoid WIN 55,212-2. Life Sci. 1995;56(23–24):2111–8.
40. Richardson JD, Aanonsen L, Hargreaves KM. Antihyperalgesic effects of spinal cannabinoids. Eur J Pharmacol. 1998;345(2):145–53.
41. Strangman NM, Walker JM. Cannabinoid WIN 55,212-2 inhibits the activity-dependent facilitation of spinal nociceptive responses. J Neurophysiol. 1999;82(1):472–7.
42. Rahn EJ, Makriyannis A, Hohmann AG. Activation of cannabinoid CB(1) and CB(2) receptors suppresses neuropathic nociception evoked by the chemotherapeutic agent vincristine in rats. Br J Pharmacol. 2007;152:765–77.
43. Richardson JD, Kilo S, Hargreaves KM. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. Pain. 1998;75(1):111–9.
44. Karsak M, Gaffal E, Date R, et al. Attenuation of allergic contact dermatitis through the endocannabinoid system. Science. 2007;316(5830):1494–7.
45. Luongo L, Palazzo E, Tambaro S, et al. 1-(2′,4′-Dichlorophenyl)-6-methyl-N-cyclohexylamine-1,4-dihydroindeno[1,2-c]pyrazole-3-carboxamide, a novel CB2 agonist, alleviates neuropathic pain through functional microglial changes in mice. Neurobiol Dis. 2010;37(1):177–85.
46. Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (-) Delta9-tetrahydrocannabinol are neuroprotective antioxidants. Proc Natl Acad Sci USA. 1998;95(14):8268–73.
47. Burstein S, Levin E, Varanelli C. Prostaglandins and cannabis. II. Inhibition of biosynthesis by the naturally occurring cannabinoids. Biochem Pharmacol. 1973;22(22):2905–10.
48. Fimiani C, Liberty T, Aquirre AJ, Amin I, Ali N, Stefano GB. Opiate, cannabinoid, and eicosanoid signaling converges on common intracellular pathways nitric oxide coupling. Prostaglandins Other Lipid Mediat. 1999;57(1):23–34.
49. Stott CG, Guy GW, Wright S, Whittle BA. The effects of cannabis extracts Tetranabinex & Nabidiolex on human cyclo-oxygenase (COX) activity. Paper presented at: Symposium on the Cannabinoids, Clearwater, June 2005.
50. Bisogno T, Hanus L, De Petrocellis L, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol. 2001;134(4):845–52.
51. Russo EB, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Med Hypotheses. 2006;66(2):234–46.
52. Morgan CJ, Curran HV. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. Br J Psychiatry. 2008;192(4):306–7.
53. Morgan CJ, Freeman TP, Schafer GL, Curran HV. Cannabidiol attenuates the appetitive effects of delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis. Neuropsychopharmacology. 2010;35(9):1879–85.
54. Morgan CJ, Schafer G, Freeman TP, Curran HV. Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study. Br J Psychiatry. 2010;197(4):285–90.
55. Malfait AM, Gallily R, Sumariwalla PF, et al. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. Proc Natl Acad Sci USA. 2000;97(17):9561–6.
56. Carrier EJ, Auchampach JA, Hillard CJ. Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. Proc Natl Acad Sci USA. 2006;103(20):7895–900.
57. McHugh D, Hu SS, Rimmerman N, et al. N-arachidonoyl glycine, an abundant endogenous lipid, potently drives directed cellular migration through GPR18, the putative abnormal cannabidiol receptor. BMC Neurosci. 2010;11:44.
58. Dmitrieva N, Nagabukuro H, Resuehr D, et al. Endocannabinoid involvement in endometriosis. Pain. 2010;151(3):703–10.
59. Izzo AA, Camilleri M. Emerging role of cannabinoids in gastrointestinal and liver diseases: basic and clinical aspects. Gut. 2008;57(8):1140–55.
60. Izzo AA, Sharkey KA. Cannabinoids and the gut: new developments and emerging concepts. Pharmacol Ther. 2010;126(1):21–38.
61. Shen M, Piser TM, Seybold VS, Thayer SA. Cannabinoid receptor agonists inhibit glutamatergic synaptic transmission in rat hippocampal cultures. J Neurosci. 1996;16(14):4322–34.
62. Nicolodi M, Volpe AR, Sicuteri F. Fibromyalgia and headache. Failure of serotonergic analgesia and N-methyl-D-aspartate-mediated neuronal plasticity: their common clues. Cephalalgia. 1998;18 Suppl 21:41–4.
63. Russo EB. Clinical endocannabinoid deficiency (CECD): Can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? Neuroendocrinol Lett. 2004;25(1–2):31–9.
64. Russo E. Cannabis for migraine treatment: the once and future prescription? An historical and scientific review. Pain. 1998;76(1–2):3–8.
65. Spadone C. Neurophysiologie du cannabis [neurophysiology of cannabis]. Encéphale. 1991;17(1):17–22.
66. Akerman S, Holland PR, Goadsby PJ. Cannabinoid (CB1) receptor activation inhibits trigeminovascular neurons. J Pharmacol Exp Ther. 2007;320(1):64–71.
67. Akerman S, Kaube H, Goadsby PJ. Anandamide is able to inhibit trigeminal neurons using an in vivo model of trigeminovascular-mediated nociception. J Pharmacol Exp Ther. 2003;309(1):56–63.
68. Akerman S, Kaube H, Goadsby PJ. Anandamide acts as a vasodilator of dural blood vessels in vivo by activating TRPV1 receptors. Br J Pharmacol. 2004;142:1354–60.
69. Manzanares J, Corchero J, Romero J, Fernandez-Ruiz JJ, Ramos JA, Fuentes JA. Chronic administration of cannabinoids regulates proenkephalin mRNA levels in selected regions of the rat brain. Brain Res Mol Brain Res. 1998;55(1):126–32.
70. Cichewicz DL, Martin ZL, Smith FL, Welch SP. Enhancement of mu opioid antinociception by oral delta9-tetrahydrocannabinol: dose-response analysis and receptor identification. J Pharmacol Exp Ther. 1999;289(2):859–67.
71. Cichewicz DL, Welch SP. Modulation of oral morphine antinociceptive tolerance and naloxone-precipitated withdrawal signs by oral delta 9-tetrahydrocannabinol. J Pharmacol Exp Ther. 2003;305(3):812–7.
72. Cichewicz DL, McCarthy EA. Antinociceptive synergy between delta(9)-tetrahydrocannabinol and opioids after oral administration. J Pharmacol Exp Ther. 2003;304(3):1010–5.
73. Calhoun SR, Galloway GP, Smith DE. Abuse potential of dronabinol (Marinol). J Psychoactive Drugs. 1998;30(2):187–96.
74. Clermont-Gnamien S, Atlani S, Attal N, Le Mercier F, Guirimand F, Brasseur L. Utilisation thérapeutique du delta-9-tétrahydrocannabinol (dronabinol) dans les douleurs neuropathiques réfractaires. The therapeutic use of D9-tetrahydrocannabinol (dronabinol) in refractory neuropathic pain. Presse Med. 2002;31(39 Pt 1):1840–5.
75. Attal N, Brasseur L, Guirimand D, Clermond-Gnamien S, Atlani S, Bouhassira D. Are oral cannabinoids safe and effective in refractory neuropathic pain? Eur J Pain. 2004;8(2):173–7.
76. 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.
77. 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(1–2):169–72.
78. Neff GW, O'Brien CB, Reddy KR, et al. Preliminary observation with dronabinol in patients with intractable pruritus secondary to cholestatic liver disease. Am J Gastroenterol. 2002;97(8): 2117–9.

79. Narang S, Gibson D, Wasan AD, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. J Pain. 2008;9(3):254–64.
80. Toth C, Au S. A prospective identification of neuropathic pain in specific chronic polyneuropathy syndromes and response to pharmacological therapy. Pain. 2008;138(3):657–66.
81. Rintala DH, Fiess RN, Tan G, Holmes SA, Bruel BM. Effect of dronabinol on central neuropathic pain after spinal cord injury: a pilot study. Am J Phys Med Rehabil. 2010;89(10):840–8.
82. Lemberger L, Rubin A, Wolen R, et al. Pharmacokinetics, metabolism and drug-abuse potential of nabilone. Cancer Treat Rev. 1982;9(Suppl B):17–23.
83. Notcutt W, Price M, Chapman G. Clinical experience with nabilone for chronic pain. Pharm Sci. 1997;3:551–5.
84. Berlach DM, Shir Y, Ware MA. Experience with the synthetic cannabinoid nabilone in chronic noncancer pain. Pain Med. 2006;7(1):25–9.
85. Beaulieu P. Effects of nabilone, a synthetic cannabinoid, on postoperative pain: Les effets de la nabilone, un cannabinoide synthetique, sur la douleur postoperatoire. Can J Anaesth. 2006;53(8):769–75.
86. Maida V. The synthetic cannabinoid nabilone improves pain and symptom management in cancer patietns. Breast Cancer Res Treat. 2007;103(Part 1):121–2.
87. Wissel J, Haydn T, Muller J, et al. Low dose treatment with the synthetic cannabinoid nabilone significantly reduces spasticity-related pain: a double-blind placebo-controlled cross-over trial. J Neurol. 2006;253(10):1337–41.
88. 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.
89. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. J Pain. 2008;9(2):164–73.
90. 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(2):604–10.
91. Bestard JA, Toth CC. An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. Pain Pract. 2011;11:353–68. Epub 2010 Nov 18.
92. Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. JAMA. 2003;290(13):1757–62.
93. Dyson A, Peacock M, Chen A, et al. Antihyperalgesic properties of the cannabinoid CT-3 in chronic neuropathic and inflammatory pain states in the rat. Pain. 2005;116(1–2):129–37.
94. 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.
95. 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.
96. 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.
97. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology. 2009;34(3):672–80.
98. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ. 2010;182(14):E694–701.
99. Wade DT, Makela PM, House H, Bateman C, Robson PJ. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. Mult Scler. 2006;12:639–45.
100. Tashkin DP. Smoked marijuana as a cause of lung injury. Monaldi Arch Chest Dis. 2005;63(2):93–100.
101. Tashkin DP, Simmons MS, Sherrill DL, Coulson AH. Heavy habitual marijuana smoking does not cause an accelerated decline in FEV1 with age. Am J Respir Crit Care Med. 1997;155(1):141–8.
102. 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 Biomarkers Prev. 2006;15(10):1829–34.
103. Grinspoon L, Bakalar JB. Marihuana, the forbidden medicine. Rev. and exp. edn. New Haven: Yale University Press; 1997.
104. Moir D, Rickert WS, Levasseur G, et al. A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. Chem Res Toxicol. 2008;21(2):494–502.
105. Singh R, Sandhu J, Kaur B, et al. Evaluation of the DNA damaging potential of cannabis cigarette smoke by the determination of acetaldehyde derived N2-ethyl-2'-deoxyguanosine adducts. Chem Res Toxicol. 2009;22(6):1181–8.
106. Joy JE, Watson SJ, Benson Jr JA. Marijuana and medicine: assessing the science base. Washington D.C.: Institute of Medicine; 1999.
107. Gieringer D. Marijuana waterpipe and vaporizer study. MAPS Bull. 1996;6(3):59–66.
108. Gieringer D. Cannabis "vaporization": a promising strategy for smoke harm reduction. J Cannabis Ther. 2001;1(3–4):153–70.
109. Storz M, Russo EB. An interview with Markus Storz. J Cannabis Ther. 2003;3(1):67–78.
110. Gieringer D, St. Laurent J, Goodrich S. Cannabis vaporizer combines efficient delivery of THC with effective suppression of pyrolytic compounds. J Cannabis Ther. 2004;4(1):7–27.
111. Hazekamp A, Ruhaak R, Zuurman L, van Gerven J, Verpoorte R. Evaluation of a vaporizing device (Volcano) for the pulmonary administration of tetrahydrocannabinol. J Pharm Sci. 2006;95(6):1308–17.
112. Van der Kooy F, Pomahacova B, Verpoorte R. Cannabis smoke condensate I: the effect of different preparation methods on tetrahydrocannabinol levels. Inhal Toxicol. 2008;20(9):801–4.
113. Bloor RN, Wang TS, Spanel P, Smith D. Ammonia release from heated 'street' cannabis leaf and its potential toxic effects on cannabis users. Addiction. 2008;103(10):1671–7.
114. Zuurman L, Roy C, Schoemaker RC, et al. Effect of intrapulmonary tetrahydrocannabinol administration in humans. J Psychopharmacol (Oxford, England). 2008;22(7):707–16.
115. Pomahacova B, Van der Kooy F, Verpoorte R. Cannabis smoke condensate III: the cannabinoid content of vaporised *Cannabis sativa*. Inhal Toxicol. 2009;21(13):1108–12.
116. 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.
117. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. Clinical pharmacology and therapeutics. 2011;90(6):844–51.
118. Earleywine M, Barnwell SS. Decreased respiratory symptoms in cannabis users who vaporize. Harm Reduct J. 2007;4:11.
119. 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.
120. 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.
121. Ernst G, Denke C, Reif M, Schnelle M, Hagmeister H. Standardized cannabis extract in the treatment of postherpetic neuralgia: a randomized, double-blind, placebo-controlled cross-over study. Paper presented at: international association for cannabis as medicine, Leiden, 9 Sept 2005.
122. Holdcroft A, Maze M, Dore C, Tebbs S, Thompson S. A multicenter dose-escalation study of the analgesic and adverse effects

of an oral cannabis extract (Cannador) for postoperative pain management. Anesthesiology. 2006;104(5):1040–6.
123. McPartland JM, Russo EB. Cannabis and cannabis extracts: greater than the sum of their parts? J Cannabis Ther. 2001; 1(3–4):103–32.
124. de Meijer E. The breeding of cannabis cultivars for pharmaceutical end uses. In: Guy GW, Whittle BA, Robson P, editors. Medicinal uses of cannabis and cannabinoids. London: Pharmaceutical Press; 2004. p. 55–70.
125. Guy GW, Robson P. A phase I, double blind, three-way crossover study to assess the pharmacokinetic profile of cannabis based medicine extract (CBME) administered sublingually in variant cannabinoid ratios in normal healthy male volunteers (GWPK02125). J Cannabis Ther. 2003;3(4):121–52.
126. Karschner EL, Darwin WD, McMahon RP, et al. Subjective and physiological effects after controlled Sativex and oral THC administration. Clin Pharmacol Ther. 2011;89(3):400–7.
127. Karschner EL, Darwin WD, Goodwin RS, Wright S, Huestis MA. Plasma cannabinoid pharmacokinetics following controlled oral delta9-tetrahydrocannabinol and oromucosal cannabis extract administration. Clin Chem. 2011;57(1):66–75.
128. Russo EB, Etges T, Stott CG. Comprehensive adverse event profile of Sativex. 18th annual symposium on the cannabinoids. Vol Aviemore, Scotland: International Cannabinoid Research Society; 2008. p. 136.
129. Barnes MP. Sativex: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain. Expert Opin Pharmacother. 2006;7(5):607–15.
130. Pérez J. Combined cannabinoid therapy via na oromucosal spray. Drugs Today. 2006;42(8):495–501.
131. 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;17:18–26.
132. Notcutt W, Price M, Miller R, et al. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 "N of 1" studies. Anaesthesia. 2004;59:440–52.
133. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain. 2004;112(3):299–306.
134. Rog DJ, Nurmiko T, Friede T, Young C. Randomized controlled trial of cannabis based medicine in central neuropathic pain due to multiple sclerosis. Neurology. 2005;65(6):812–9.
135. 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.
136. 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.
137. 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(1):50–2.
138. 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 Manage. 2010;39(2):167–79.
139. 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(8):1729–43.
140. Lynch ME, Young J, Clark AJ. A case series of patients using medicinal marihuana for management of chronic pain under the Canadian Marihuana Medical Access Regulations. J Pain Symptom Manage. 2006;32(5):497–501.
141. Janse AFC, Breekveldt-Postma NS, Erkens JA, Herings RMC. Medicinal gebruik van cannabis: PHARMO instituut. Institute for Drug Outcomes Research; 2004.
142. Gorter RW, Butorac M, Cobian EP, van der Sluis W. Medical use of cannabis in the Netherlands. Neurology. 2005;64(5):917–9.
143. Fitzgerald GA. Coxibs and cardiovascular disease. N Engl J Med. 2004;10:6.
144. Topol EJ. Failing the public health – rofecoxib, Merck, and the FDA. N Engl J Med. 2004;10:6.
145. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet. 2003;42(4):327–60.
146. Huestis MA, Henningfield JE, Cone EJ. Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. J Anal Toxicol. 1992;16(5): 276–82.
147. Wright S. GWMS001 and GWMS0106: maintenance of blinding. London: GW Pharmaceuticals; 2005.
148. Clark P, Altman D. Assessment of blinding in phase III Sativex spasticity studies. GW Pharmaceuticals; 2006.
149. Samaha AN, Robinson TE. Why does the rapid delivery of drugs to the brain promote addiction? Trends Pharmacol Sci. 2005;26(2):82–7.
150. Jones RT, Benowitz N, Bachman J. Clinical studies of cannabis tolerance and dependence. Ann N Y Acad Sci. 1976;282:221–39.
151. 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.
152. Smith NT. A review of the published literature into cannabis withdrawal symptoms in human users. Addiction. 2002;97(6): 621–32.
153. Solowij N, Stephens RS, Roffman RA, et al. Cognitive functioning of long-term heavy cannabis users seeking treatment. JAMA. 2002;287(9):1123–31.
154. Schoedel KA, Chen N, Hilliard A, et al. A randomized, double-blind, placebo-controlled, crossover study to evaluate the abuse potential of nabiximols oromucosal spray in subjects with a history of recreational cannabis use. Hum Psychopharmacol. 2011;26:224–36.
155. Russo EB, Mathre ML, Byrne A, et al. Chronic cannabis use in the Compassionate Use Investigational New Drug Program: an examination of benefits and adverse effects of legal clinical cannabis. J Cannabis Ther. 2002;2(1):3–57.
156. Fride E, Russo EB. Neuropsychiatry: schizophrenia, depression, and anxiety. In: Onaivi E, Sugiura T, Di Marzo V, editors. Endocannabinoids: the brain and body's marijuana and beyond. Boca Raton: Taylor & Francis; 2006. p. 371–82.
157. Aragona M, Onesti E, Tomassini V, et al. Psychopathological and cognitive effects of therapeutic cannabinoids in multiple sclerosis: a double-blind, placebo controlled, crossover study. Clin Neuropharmacol. 2009;32(1):41–7.
158. Degenhardt L, Hall W, Lynskey M. Testing hypotheses about the relationship between cannabis use and psychosis. Drug Alcohol Depend. 2003;71(1):37–48.
159. Macleod J, Davey Smith G, Hickman M. Does cannabis use cause schizophrenia? Lancet. 2006;367(9516):1055.
160. Macleod J, Hickman M. How ideology shapes the evidence and the policy: what do we know about cannabis use and what should we do? Addiction. 2010;105:1326–30.
161. Hickman M, Vickerman P, Macleod J, et al. If cannabis caused schizophrenia–how many cannabis users may need to be prevented in order to prevent one case of schizophrenia? England and Wales calculations. Addiction. 2009;104(11):1856–61.

162. Zuardi AW, Guimaraes FS. Cannabidiol as an anxiolytic and antipsychotic. In: Mathre ML, editor. Cannabis in medical practice: a legal, historical and pharmacological overview of the therapeutic use of marijuana. Jefferson: McFarland; 1997. p. 133–41.
163. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol. 2011;163:1344–64.
164. Cabral G. Immune system. In: Grotenhermen F, Russo EB, editors. Cannabis and cannabinoids: pharmacology, toxicology and therapeutic potential. Binghamton: Haworth Press; 2001. p. 279–87.
165. Katona S, Kaminski E, Sanders H, Zajicek J. Cannabinoid influence on cytokine profile in multiple sclerosis. Clin Exp Immunol. 2005; 140(3):580–5.
166. Abrams DI, Hilton JF, Leiser RJ, et al. Short-term effects of cannabinoids in patients with HIV-1 infection. A randomized, placebo-controlled clinical trial. Ann Intern Med. 2003;139:258–66.
167. Stott CG, Guy GW, Wright S, Whittle BA. The effects of cannabis extracts Tetranabinex and Nabidiolex on human cytochrome P450-mediated metabolism. Paper presented at: Symposium on the Cannabinoids, Clearwater, 27 June 2005.
168. Stott CG, Ayerakwa L, Wright S, Guy G. Lack of human cytochrome P450 induction by Sativex. 17th annual symposium on the cannabinoids. Saint-Sauveur, Quebec: International Cannabinoid Research Society; 2007. p. 211.
169. Grotenhermen F, Leson G, Berghaus G, et al. Developing limits for driving under cannabis. Addiction. 2007;102(12):1910–7.
170. Hohmann AG, Suplita 2nd RL. Endocannabinoid mechanisms of pain modulation. AAPS J. 2006;8(4):E693–708.
171. Clapper JR, Moreno-Sanz G, Russo R, et al. Anandamide suppresses pain initiation through a peripheral endocannabinoid mechanism. Nat Neurosci. 2010;13:1265–70.
172. Schlosburg JE, Blankman JL, Long JZ, et al. Chronic monoacylglycerol lipase blockade causes functional antagonism of the endocannabinoid system. Nat Neurosci. 2010;13(9):1113–9.
173. Yu XH, Cao CQ, Martino G, et al. A peripherally restricted cannabinoid receptor agonist produces robust anti-nociceptive effects in rodent models of inflammatory and neuropathic pain. Pain. 2010;151(2):337–44.
174. Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. Trends Pharmacol Sci. 2009;30(10):515–27.
175. Wirth PW, Watson ES, ElSohly M, Turner CE, Murphy JC. Anti-inflammatory properties of cannabichromene. Life Sci. 1980; 26(23):1991–5.
176. Davis WM, Hatoum NS. Neurobehavioral actions of cannabichromene and interactions with delta 9-tetrahydrocannabinol. Gen Pharmacol. 1983;14(2):247–52.
177. Ligresti A, Moriello AS, Starowicz K, et al. Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. J Pharmacol Exp Ther. 2006;318(3):1375–87.
178. De Petrocellis L, Starowicz K, Moriello AS, Vivese M, Orlando P, Di Marzo V. Regulation of transient receptor potential channels of melastatin type 8 (TRPM8): effect of cAMP, cannabinoid CB(1) receptors and endovanilloids. Exp Cell Res. 2007;313(9):1911–20.
179. Gauson LA, Stevenson LA, Thomas A, Baillie GL, Ross RA, Pertwee RG. Cannabigerol behaves as a partial agonist at both CB1 and CB2 receptors. 17th annual symposium on the cannabinoids. Vol Saint-Sauveur, Quebec: International Cannabinoid Research Society; 2007, p. 206.
180. Cascio MG, Gauson LA, Stevenson LA, Ross RA, Pertwee RG. Evidence that the plant cannabinoid cannabigerol is a highly potent alpha2-adrenoceptor agonist and moderately potent 5HT1A receptor antagonist. Br J Pharmacol. 2010;159(1):129-41.
181. Banerjee SP, Snyder SH, Mechoulam R. Cannabinoids: influence on neurotransmitter uptake in rat brain synaptosomes. J Pharmacol Exp Ther. 1975;194(1):74–81.
182. Evans FJ. Cannabinoids: the separation of central from peripheral effects on a structural basis. Planta Med. 1991;57(7):S60–7.
183. Evans AT, Formukong E, Evans FJ. Activation of phospholipase A2 by cannabinoids. Lack of correlation with CNS effects. FEBS Lett. 1987;211(2):119–22.
184. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol. 2008; 153(2):199–215.
185. Hill AJ, Weston SE, Jones NA, et al. Delta-tetrahydrocannabivarin suppresses in vitro epileptiform and in vivo seizure activity in adult rats. Epilepsia. 2010;51(8):1522–32.
186. Bolognini D, Costa B, Maione S, et al. The plant cannabinoid delta9-tetrahydrocannabivarin can decrease signs of inflammation and inflammatory pain in mice. Br J Pharmacol. 2010; 160(3):677–87.
187. Mehmedic Z, Chandra S, Slade D, et al. Potency trends of delta(9)-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008. J Forensic Sci. 2010;55:1209–17.
188. King LA, Carpentier C, Griffiths P. Cannabis potency in Europe. Addiction. 2005;100(7):884–6.
189. Potter DJ, Clark P, Brown MB. Potency of delta 9-THC and other cannabinoids in cannabis in England in 2005: implications for psychoactivity and pharmacology. J Forensic Sci. 2008;53(1): 90–4.
190. Potter D. Growth and morphology of medicinal cannabis. In: Guy GW, Whittle BA, Robson P, editors. Medicinal uses of cannabis and cannabinoids. London: Pharmaceutical Press; 2004. p. 17–54.
191. Rao VS, Menezes AM, Viana GS. Effect of myrcene on nociception in mice. J Pharm Pharmacol. 1990;42(12):877–8.
192. Lorenzetti BB, Souza GE, Sarti SJ, Santos Filho D, Ferreira SH. Myrcene mimics the peripheral analgesic activity of lemongrass tea. J Ethnopharmacol. 1991;34(1):43–8.
193. Basile AC, Sertie JA, Freitas PC, Zanini AC. Anti-inflammatory activity of oleoresin from Brazilian Copaifera. J Ethnopharmacol. 1988;22(1):101–9.
194. Tambe Y, Tsujiuchi H, Honda G, Ikeshiro Y, Tanaka S. Gastric cytoprotection of the non-steroidal anti-inflammatory sesquiterpene, beta-caryophyllene. Planta Med. 1996;62(5):469–70.
195. Gertsch J, Leonti M, Raduner S, et al. Beta-caryophyllene is a dietary cannabinoid. Proc Natl Acad Sci USA. 2008;105(26): 9099–104.
197. Gil ML, Jimenez J, Ocete MA, Zarzuelo A, Cabo MM. Comparative study of different essential oils of Bupleurum gibraltaricum Lamarck. Pharmazie. 1989;44(4):284–7.
198. Re L, Barocci S, Sonnino S, et al. Linalool modifies the nicotinic receptor-ion channel kinetics at the mouse neuromuscular junction. Pharmacol Res. 2000;42(2):177–82.
199. Gregg, L.C, Jung, K.M., Spradley, J.M., Nyilas, R., Suplita II, R.L., Zimmer, A., Watanabe, M., Mackie, K., Katona, I., Piomelli, D. and Hohmann, A.G. (2012) Activation of type-5 metabotropic glutamate receptors and diacylglycerol lipase-alpha initiates 2-arachidonoylglycerol formation and endocannabinoid-mediated analgesia in vivo. The Journal of Neuroscience, in press [DOI:10.1523/JNEUROSCI.0013-12.2012].
200. Kavia R, De Ridder D, Constantinescu C, Stott C, Fowler C. Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis. Mult Scler. 2010;16(11):1349–59.
201. Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012;13(5):438–49.
202. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. Clinical pharmacology and therapeutics. 2011;90(6):844–51.