Medical Marijuana Program

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

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

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

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

Section A: Petitioner's Information

Name (First, Middle, Last): [redacted]

Home Address (including Apartment or Suite #): [redacted]

City: [redacted] | State: CT | Zip Code: [redacted]

Telephone Number: [redacted] | E-mail Address: [redacted]

Section B: Medical Condition, Medical Treatment or Disease

Please specify the medical condition, medical treatment or disease that you are seeking to add to the list of debilitating medical conditions under the Act. Be as precise as possible in identifying the condition, treatment or disease. I have polyneuropathy. TREATMENT IS Lyrica 400mg. I had A Kidney Transplant so I cannot take Anymore. Goes Thru Kidney.

Section C: Background

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

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

Neuropathy is Explain By DR [redacted] A Neurologist. And DR [redacted] of [redacted] HOSPITAL. ATTACHed my DCTORS.

Section D: Negative Effects of Current Treatment

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

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

Neuropathy Treament is Accepted But Im mild Cases only. My CASe is VERY Painful, SleepTime AT night Generaly 1-2AM To 5:15.

Medical Marijuana Program

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

Section E: Negative Effects of Condition or Treatment

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

- Attach additional pages as necessary. My Feet + Legs ARE in constant unberable pain. I can barely walk w/out assistance From cane/walker. I am basicly Homebound.

Section F: Conventional Therapies

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

- Attach additional pages as necessary. Lyrica is used to treat it, But i am limited to the dosage because of kidney Transplant. No other treatments are safe with my kidney transplant.

Section G: General Evidence of Support for Medical Marijuana Treatment

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

- Attach additional pages as necessary. See attached articles.

Section H: Scientific Evidence of Support for Medical Marijuana Treatment

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

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

Section I: Professional Recommendations for Medical Marijuana Treatment

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

Medical Marijuana Program

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

Section J: Submission of Petition

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

- Attach additional pages as necessary.

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

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

Signature	Date Signed:
[redacted]	12-14-18

266306-388

[redacted]

Department of Neurology

Patient Name: [redacted]
Medical Record #: [redacted]
Today's Date: 7/5/2016 Birth Date: [redacted] Age: [redacted]
[redacted] MD:

Referring Physician: [redacted]

Dear [redacted]

CHIEF COMPLAINT
This is a report of my findings in the case of this [redacted]-year-old right-handed male whom I saw in neurological consultation on July 5, 2016 per your request for the chief compliant of painful discomfort and numbness in the extremities.
As you know, the patient has been followed by [redacted] over the last 20-25 years. [redacted] was referred to specialist for evaluation and treatment of numbness and tingling sensation in the hands and feet. After extensive evaluation, which included nerve conduction study and blood work, the patient was diagnosed with sensorimotor polyneuropathy. [redacted] was treated with amitriptyline and gabapentin in the past. Presently he takes Lyrica. The medication provides him with moderate relief of the pain. After each dose of Lyrica the patient appreciate almost complete resolution of pain and numbness in the feet, but for a few hours only.
[redacted] reports painful discomfort in the knees and the right thigh. He does not appreciate any significant loss of strength in the extremities.
The patient reports no headaches, double vision, difficulties with speech and swallowing.

PAST MEDICAL HISTORY
Arthritis, kidney failure status post kidney transplant, hypertension, neuropathy.

PAST SURGICAL HISTORY
Hernia repair, hip replacement, kidney transplant, carpal tunnel release bilaterally.

MEDICATIONS
Tacrolimus 0.5 mg 3 capsules twice a day, allopurinol 100 mg a day, Ambien 5 mg a day, who amlodipine 5 mg a day, carvedilol 12.5 mg twice per day, doxazosin 2 mg a day, prednisone 5 mg a day, magnesium oxide 400 mg a day, Lyrica totally 350 mg a day, sodium bicarbonate 650 mg 2 times a day, tramadol 50 mg every 6 hours as needed.

ALLERGY
NKDA

SOCIAL HISTORY
The patient is married. He lives with his wife. He drinks alcohol rarely and doesn't smoke.

FAMILY HISTORY
Father with history of stroke and mother with history of dementia.

SYSTEM REVIEW
Swelling the feet, shortness of breath, hearing loss.

PHYSICAL EXAMINATION

Patient Name: [redacted]
Medical Record #: [redacted]
Today's Date: 7/5/2016 Birth Date: [redacted] Age: [redacted]

[redacted] is a well-developed, mildly overweight male in no apparent distress. His head is normocephalic and atraumatic.
The neck is supple with no evidence of bruit.
The patient was evaluated sitting comfortably on the examining table.
His blood pressure is 124/70, pulse is 59, respiratory rate is 18 per minute.

NEUROLOGICAL EXAMINATION

MENTAL STATUS
The patient is alert and oriented to person, place and time. Recent and remote memories are normal. Attention and concentration are normal.
Comprehension and expressive speech are normal.

CRANIAL NERVES
Pupils are equal and reactive to light bilaterally. No afferent pupillary defect. Extraocular movements are normal. Visual fields are full to confrontation.
Funduscopic examination shows no evidence of optic nerve edema or atrophy.
Facial sensation is normal. There is no evidence of facial weakness.
Hearing is diminished bilaterally. There is no weakness of soft palate or tongue.

MOTOR EXAM
Muscle bulk and tone are normal.
Strength in the upper and lower extremities is normal bilaterally, except for 4/5 weakness of right hip flexors due to right leg pain.
Deep tendon reflex are 1+ and symmetrical in the upper extremities. Could not obtain DTRs from the legs..
Babinski sign is negative.

COORDINATIVE TESTING
Rapid alternating hand movements are normal. Finger- to -nose maneuver is normal. The patient has antalgic gait. He walks with a cane.

SENSORY EXAMINATION
There is reduction of all primary sensory modalities in the distal lower extremities.

IMPRESSION:
The patient has evidence of distal sensory motor polyneuropathy. Was intention to achieve further reduction of discomfort, I recommended to try Cymbalta 30 mg a day. I encouraged patient to supplement his diet with megadose of vitamins of group B. I instructed him to start taking alpha- lipoic acid 600 mg a day.
I will reevaluate [redacted] in my office in 3-4 months.
Thank you for giving me the opportunity to see this patient and participate in his care with you.

Yours truly,

[redacted]

266306-388

[redacted]

Department of Neurology

Patient Name: [redacted]
Medical Record #: [redacted]
Office visit date: 10/4/2016 Birth Date: [redacted] Age: [redacted]
[redacted] MD:

To: [redacted]

HISTORY OF PRESENT ILLNESS
[redacted] was seen for neurological follow-up on October 4, 2016. The patient could not appreciate any noticeable reduction of discomfort in his legs with introduction of initial dose of Cymbalta. As earlier, patient grades his level of discomfort as 9/10 on 0-10 scale. He is more uncomfortable at the end of the day and at night.
I was able to review patient's most recent blood work. Except for slight elevation of level of potassium, all test results were fairly normal.

MEDICAL/SURGICAL HISTORY
Arthritis, kidney failure status post kidney transplant, hypertension, neuropathy.

PAST SURGICAL HISTORY
Hernia repair, hip replacement, kidney transplant, carpal tunnel release bilaterally.

MEDICATIONS
Tacrolimus 0.5 mg 3 capsules twice a day, allopurinol 100 mg a day, Ambien 5 mg a day, who amlodipine 5 mg a day, carvedilol 12.5 mg twice per day, doxazosin 2 mg a day, prednisone 5 mg a day, magnesium oxide 400 mg a day, Lyrica totally 450 mg a day, sodium bicarbonate 650 mg 2 times a day, alpha lipoic acid, Cymbalta 30 mg a day, tramadol 50 mg every 6 hours as needed.

GENERAL EXAMINATION
[redacted] is well-developed, well-nourished male in no apparent distress. He was evaluated sitting comfortably on the chair.
Blood pressure is 125/52, pulse is 58, respiratory rate is 18 per minute.

NEUROLOGICAL EXAMINATION
MENTAL STATUS
The patient is alert and oriented to person, place and time. Recent and remote memories are normal. Attention and concentration are normal.
Comprehension and expressive speech are normal.

CRANIAL NERVES
Pupils are equal and reactive to light bilaterally. Extraocular movements are normal. Visual fields are full to confrontation.
Funduscopic examination shows no evidence of optic nerve edema or atrophy.
Facial sensation is normal. There is no evidence of facial weakness.
Hearing is diminished bilaterally. There is no weakness of soft palate or tongue.

MOTOR EXAM
Muscle bulk and tone are normal.
Strength in the upper and lower extremities is normal bilaterally, except for 4/5 weakness of right hip flexors due to right leg pain.

Patient Name: [redacted]
Medical Record #: [redacted]
Office visit date: 10/4/2016 Birth Date: [redacted] Age: [redacted]

Deep tendon reflex are 1+ and symmetrical in the upper extremities. No DTRs couldn't be obtainable from the lower extremities.
Babinski sign is negative.

COORDINATIVE TESTING
Rapid alternating hand movements are normal. Finger- to -nose maneuver is normal. There is reduction of stride.

SENSORY EXAMINATION
There is reduction of all primary sensory modalities in the distal lower extremities.

IMPRESSION/PLAN
My recommendation was to increase the dose of Cymbalta to 60 mg a day. In 2-3 weeks [redacted] will try to increase it up to 90 mg a day.
I recommended patient take 1200 mg of alpha-lipoic acid.
His daily dose of Lyrica will be redistributed as 150 mg every 8 hours.
I will reevaluate [redacted] in my office in 3 months.

[redacted]

[redacted]

[redacted]

266306-388

[redacted]

Department of Neurology

Patient Name: [redacted]
Medical Record #: [redacted]
Office visit date: 1/3/2017 Birth Date: [redacted] Age: [redacted]
[redacted] MD:

To: [redacted]

HISTORY OF PRESENT ILLNESS
[redacted] was seen for neurological follow-up on January 3, 2017. The patient was able to grade the degree of discomfort in his legs as 8/10 on 0-10 pain scale. As being said earlier, [redacted] appreciates painful discomfort in he is legs at the end of the day and at night.
At the time of evaluation today patient does not appreciate any leg pain.

MEDICAL/SURGICAL HISTORY
Arthritis, kidney failure status post kidney transplant, hypertension, neuropathy.

PAST SURGICAL HISTORY
Hernia repair, hip replacement, kidney transplant, carpal tunnel release bilaterally.

MEDICATIONS
Tacrolimus 0.5 mg 3 capsules twice a day, allopurinol 100 mg a day, Ambien 5 mg a day, who amlodipine 5 mg a day, carvedilol 12.5 mg twice per day, doxazosin 2 mg a day, prednisone 5 mg a day, magnesium oxide 400 mg a day, Lyrica totally 450 mg a day, Cymbalta 60 mg a day, sodium bicarbonate 650 mg 2 times a day, alpha- lipoic acid, Cymbalta 30 mg a day, tramadol 50 mg every 6 hours as needed.

GENERAL EXAMINATION
[redacted] is well-developed, mildly overweight male in no apparent distress. He was evaluated sitting comfortably on the chair.
His blood pressure is 110/70, pulse is 64/m, respiratory rate is 18 per minute.

NEUROLOGICAL EXAMINATION
MENTAL STATUS
The patient is alert and oriented to person, place and time. Recent and remote memories are normal. Attention and concentration are normal.
Comprehension and expressive speech are normal.

CRANIAL NERVES
Pupils are equal and reactive to light bilaterally. Extraocular movements are normal. Visual fields are full to confrontation.
Funduscopic examination shows no evidence of optic nerve edema or atrophy.
Facial sensation is normal. There is no evidence of facial weakness.
Hearing is diminished bilaterally. There is no weakness of soft palate or tongue.

MOTOR EXAM
Muscle bulk and tone are normal.
Strength in the upper and lower extremities is normal bilaterally, except for 4/5 weakness of right hip flexors due to right leg pain.
Deep tendon reflex are 1+ and symmetrical in the upper extremities. No DTRs couldn't be obtainable from the lower extremities.

Patient Name: [redacted]
Medical Record #: [redacted]
Office visit date: 1/3/2017 Birth Date: [redacted] Age: [redacted]

Babinski sign is negative.

COORDINATIVE TESTING
Rapid alternating hand movements are normal. Finger- to -nose maneuver is normal. There is reduction of stride.

SENSORY EXAMINATION
There is reduction of all primary sensory modalities in the distal lower extremities.

IMPRESSION/PLAN
As we can see, [redacted] still has noticeable discomfort in the legs almost on daily basis. For that, I recommended patient increase his maintenance dose of Cymbalta to 90 mg a day.
Patient should monitor his kidney function. As I understand, [redacted] will see his nephrologist in 2 weeks.
The patient will be reevaluated in my office in 3 months.

[redacted]

266306-388

[redacted]

Department of Neurology

Patient Name: [redacted]
Medical Record #: [redacted]
Office visit date: 4/5/2017 Birth Date: [redacted] Age: [redacted]
[redacted] MD:

To: [redacted]

HISTORY OF PRESENT ILLNESS
[redacted] was seen for neurological follow-up on April 5, 2017. The patient reports that Lyrica provides him with fair control of discomfort in the legs as long as he takes the medication every 4-5 hours. [redacted] did not see any additional pain reduction with increase of Cymbalta.
The patient submitted a copy of his recent blood work. Apparently the study was notable for slight reduction of platelet count and minimal increase of serum potassium.

MEDICAL/SURGICAL HISTORY
Arthritis, kidney failure status post kidney transplant, hypertension, neuropathy.

PAST SURGICAL HISTORY
Hernia repair, hip replacement, kidney transplant, carpal tunnel release bilaterally.

MEDICATIONS
Tacrolimus 0.5 mg 3 capsules twice a day, allopurinol 100 mg a day, Ambien 5 mg a day, who amlodipine 5 mg a day, carvedilol 12.5 mg twice per day, doxazosin 2 mg a day, prednisone 5 mg a day, magnesium oxide 400 mg a day, Lyrica 100 mg in the morning, 50 mg at noon, 50 mg around 3 PM, 100 mg at 6 PM, and 100 or 150 mg at night, Cymbalta 90 mg a day, sodium bicarbonate 650 mg 2 times a day, alpha- lipoic acid, tramadol 50 mg every 6 hours as needed.

GENERAL EXAMINATION
[redacted] is a well-developed, mildly overweight male in no apparent distress. He was evaluated sitting comfortably on the chair.
His blood pressure is 127/66, pulse is 74, respiratory rate is 18 per minute.
NEUROLOGICAL EXAMINATION
MENTAL STATUS
The patient is alert and oriented to person, place and time. Recent and remote memories are normal. Attention and concentration are normal.
Comprehension and expressive speech are normal.

CRANIAL NERVES
Pupils are equal and reactive to light bilaterally. Extraocular movements are normal. Visual fields are full to confrontation.
Funduscopic examination shows no evidence of optic nerve edema or atrophy.
Facial sensation is normal. There is no evidence of facial weakness.
Hearing is diminished bilaterally. There is no weakness of soft palate or tongue.

MOTOR EXAM
Muscle bulk and tone are normal.
Strength in the upper and lower extremities is normal bilaterally, except for 4/5 weakness of right hip flexors due to right leg pain.
Deep tendon reflex are 1+ and symmetrical in the upper extremities. DTRs are negative from the legs.
Babinski sign is negative.

Patient Name: [redacted]
Medical Record #: [redacted]
Office visit date: 4/5/2017 Birth Date: [redacted] Age: [redacted]

COORDINATIVE TESTING
Rapid alternating hand movements are normal. Finger- to -nose maneuver is normal. There is reduction of stride.

SENSORY EXAMINATION
There is reduction of all primary sensory modalities in the distal lower extremities.

IMPRESSION/PLAN
The patient will continue therapy with the Lyrica and Cymbalta. [redacted] will try to make slight adjustment in his dose of Lyrica. I feel that he should be able to increase it up to 450 mg a day as long as he has no apparent reduction of GFR. The patient will be seen for reevaluation in 3-4 months.

[redacted]

[redacted]

[redacted]

Department of Endocrinology

[redacted]

[redacted]
Date of Birth: [redacted] **Age:** [redacted]
MRN: [redacted]
Appointment Date: 07/05/2017
Appointment Provider: [redacted]
Consult Letter

Greetings,
I had the pleasure of seeing our patient, [redacted] in my office today.
My most recent evaluation follows. Thank you for your kind assistance in the care of this patient.
Sincerely,
[redacted]

HPI

[redacted] was seen for neurological follow-up on July 5, 2017.
The patient was able to report that he is blood work lately was remarkable for elevated serum glucose.
I also was informed that [redacted] does not appreciate any noticeable discomfort in his feet during the daytime.
However, in the evening, he frequently feels so uncomfortable that has to take extra 50 mg of Lyrica in the middle of the night.
There is discontinued Cymbalta as the medication was not helpful.

Results

Reviewed related lab results during this encounter.

Abnormal CBC
Abnormal Metabolic Panel

Fall Risk Assessment, Morse
History of falling, immediate or within 3 months? No (0).
Presence of Secondary Diagnosis? No (0). No (0).
Use of Ambulatory Aid? Bed rest/nurse assist (0)
Gait Weak or Impaired? bedrest/uses wheelchair/immobile (0)
Morse Fall Risk Score & Action:

Assessment

Assessed

1. Lower extremity numbness (R20.0)
2. History of arthritis (Z87.39)
3. History of Hernia Repair
4. History of Wrist Surgery

[redacted]

5. Family history of cerebrovascular accident (CVA) (Z82.3) : Father
6. Family history of Advanced dementia : Mother

Plan

1. Start: Lyrica 25 MG Oral Capsule; TAKE 1 CAPSULE DAILY
2. Start: Mexiletine HCl - 150 MG Oral Capsule; take 1 capsule twice a day

Discussion/Summary

The patient has evidence of distal sensorimotor polyneuropathy. Unfortunately, [redacted] could not achieve good control of leg discomfort with 450 mg of Lyrica per day.
He does not appreciate any noticeable relief of discomfort with neuropathy compound cream.
His history is significant for poor response to tricyclics and Cymbalta.
For that, I suggested patient to try mexiletine 150 mg once or twice a day. If [redacted] will show good response to mexiletine, I will titrate the dose up to 300/400 mg a day.
[redacted] will be reevaluated in my office in 2 months.

End of Encounter Meds

Medication Name	Instruction
Allopurinol 100 MG Oral Tablet	
AmLODIPine Besylate 5 MG Oral Tablet	TAKE 1 TABLET BY MOUTH EVERY DAY
Aspirin EC 81 MG Oral Tablet Delayed Release	
Carvedilol 6.25 MG Oral Tablet	
Doxazosin Mesylate 2 MG Oral Tablet	
Lyrica 100 MG Oral Capsule	
Lyrica 25 MG Oral Capsule	TAKE 1 CAPSULE DAILY
Magnesium Oxide 400 MG Oral Tablet	
Mexiletine HCl - 150 MG Oral Capsule	take 1 capsule twice a day
PredniSONE 5 MG Oral Tablet	
Sodium Bicarbonate 650 MG Oral Tablet	
Tacrolimus 0.5 MG Oral Capsule	
Zolpidem Tartrate 5 MG Oral Tablet	TAKE 1 TABLET BY MOUTH EVERY DAY AT BEDTIME AS NEEDED

Signatures

Electronically signed by : [redacted] Jul 5 2017 8:58AM EST

[redacted]

Department of Endocrinology

[redacted]

[redacted]
Date of Birth: [redacted] **Age:** [redacted]
MRN: [redacted]
Appointment Date: 09/06/2017
Appointment Provider: [redacted]
Consult Letter

Greetings,
I had the pleasure of seeing our patient, [redacted] in my office today.
My most recent evaluation follows. Thank you for your kind assistance in the care of this patient.
Sincerely,
[redacted]

HPI

[redacted] was in for neurological follow-up on September 6, 2017. The patient was able to relate that he could not tolerate mexiletine due to severe nausea. [redacted] believes that Lyrica is the most effective medication he tried to control the discomfort in his legs. The patient takes 325 mg of Lyrica per day. On occasions, he takes extra 50 mg of Lyrica in the middle of the night.
About 2-3 times a day [redacted] applies neuropathy lotion on his feet. Unfortunately, each application provides patients only with 1 hour of pain relief.

Results

Fall Risk Assessment, Morse
History of falling, immediate or within 3 months? No (0).
Presence of Secondary Diagnosis? No (0). No (0).
Use of Ambulatory Aid? Bed rest/nurse assist (0)
Gait Weak or Impaired? bedrest/uses wheelchair/immobile (0)
Morse Fall Risk Score & Action:

Plan

1. Start: Lyrica 100 MG Oral Capsule; TAKE 1 CAPSULE 4 TIMES DAILY

Discussion/Summary

There is has evidence of distal sensorimotor polyneuropathy. At this point I have no other recommendation for [redacted] rather than continue Lyrica as main therapy for neuropathic discomfort.
The patient to take 100 mg of Lyrica 4 times per day.
He will continue to apply cream on his feet 3-4 times per day.
The patient will be reevaluated in 3-4 months.

End of Encounter Meds

[redacted]

Medication Name	Instruction
Allopurinol 100 MG Oral Tablet	TAKE 1 TABLET BY MOUTH EVERY DAY
AmLODIPine Besylate 5 MG Oral Tablet	TAKE 1 TABLET BY MOUTH EVERY DAY
Aspirin EC 81 MG Oral Tablet Delayed Release	
Carvedilol 6.25 MG Oral Tablet	TAKE 1 TABLET TWICE DAILY WITH MEALS.
Doxazosin Mesylate 2 MG Oral Tablet	
Lyrica 100 MG Oral Capsule	TAKE 1 CAPSULE 4 TIMES DAILY
Lyrica 100 MG Oral Capsule	TAKE 1 CAPSULE TWICE DAILY.
Lyrica 25 MG Oral Capsule	TAKE 1 CAPSULE DAILY
Lyrica 50 MG Oral Capsule	TAKE 1 CAPSULE DAILY
Magnesium Oxide 400 MG Oral Tablet	
Mexiletine HCl - 150 MG Oral Capsule	take 1 capsule twice a day
PredniSONE 5 MG Oral Tablet	
Sodium Bicarbonate 650 MG Oral Tablet	
Tacrolimus 0.5 MG Oral Capsule	
Zolpidem Tartrate 5 MG Oral Tablet	TAKE 1 TABLET BY MOUTH AT BEDTIME AS NEEDED FOR SLEEP

Signatures
Electronically signed by : [redacted] Sep 6 2017 4:41PM EST

[redacted]

Department of Endocrinology

[redacted]

[redacted]
Date of Birth: [redacted] **Age:** [redacted]
MRN: [redacted]
Appointment Date: 12/05/2017
Appointment Provider: [redacted]
Consult Letter

Greetings,
I had the pleasure of seeing our patient, [redacted] in my office today.
My most recent evaluation follows. Thank you for your kind assistance in the care of this patient.
Sincerely,
[redacted]

HPI

[redacted] was in for neurological follow-up on December 5, 2017. The patient came to my office reporting an increase of painful discomfort in the legs. He also was able to appreciate some spread of the numbness and tingling sensation from the feet up to the knees. On a few occasions, [redacted] was able to appreciate noticeable painful discomfort in the left hip. To control the pain, [redacted] has been taking up to 400 mg of Lyrica per day. Apparently, the patient is aware of the fact that he cannot take full dose of Lyrica Lyrica due to his renal problems. Some nights, the pain is so bad that [redacted] has difficulties to sleep and has to take Tylenol.

Results

Fall Risk Assessment, Morse
History of falling, immediate or within 3 months? No (0).
Presence of Secondary Diagnosis? No (0). No (0).
Use of Ambulatory Aid? Bed rest/nurse assist (0)
Gait Weak or Impaired? bedrest/uses wheelchair/immobile (0)
Morse Fall Risk Score & Action:

Plan

1. ALT - 10236; Status:Active; Requested for:05Dec2017;
2. AST - 10235; Status:Active; Requested for:05Dec2017;
3. CBC AUTO 3PT DIFF; Status:Active; Requested for:05Dec2017;
4. Valproic Acid (Depakote) - 11793; Status:Active; Requested for:05Dec2017;
5. Start: Divalproex Sodium 250 MG Oral Tablet Delayed Release; TAKE 1 TABLET BY MOUTH TWICE A DAY FOR FIRST WK THEN 2TAB TWICE A DAY
6. Start: Hydrocodone-Acetaminophen 5-325 MG Oral Tablet (Norco); TAKE 1 TABLET DAILY
7. Renew: Lyrica 25 MG Oral Capsule; TAKE 1 CAPSULE DAILY

Discussion/Summary

[redacted] has long history of polyneuropathy. As we can see, the patient is very uncomfortable despite of maximum

[redacted]

dose of Lyrica. From the history, he did not respond to tricyclic antidepressants and Cymbalta. I warned [redacted] that he cannot take high dose of Lyrica due to his kidney problems.
I suggested patient to complete a trial of Depakote. He will introduce 250 mg of Depakote twice a day and will titrate a dose up to 500 mg twice a day in 1 week. [redacted] should check Depakote level, liver enzymes, and CBC in 3-4 weeks.
I also gave patient prescription for 20 pills of Norco 5/325. He will use it for breakthrough pains at night.
I will see [redacted] for follow-up in 2 months.

End of Encounter Meds

Medication Name	Instruction
Allopurinol 100 MG Oral Tablet	TAKE 1 TABLET BY MOUTH EVERY DAY
AmLODIPine Besylate 5 MG Oral Tablet	TAKE 1 TABLET BY MOUTH EVERY DAY
Aspirin EC 81 MG Oral Tablet Delayed Release	TAKE 1 TABLET DAILY.
Carvedilol 12.5 MG Oral Tablet	TAKE 1 TABLET BY MOUTH TWICE DAILY
Divalproex Sodium 250 MG Oral Tablet Delayed Release	TAKE 1 TABLET BY MOUTH TWICE A DAY FOR FIRST WK THEN 2TAB TWICE A DAY
Doxazosin Mesylate 2 MG Oral Tablet	TAKE 1 TABLET DAILY AS DIRECTED.
Hydrocodone-Acetaminophen 5-325 MG Oral Tablet (Norco)	TAKE 1 TABLET DAILY
Lyrica 100 MG Oral Capsule	TAKE 1 CAPSULE 3 TIMES DAILY
Lyrica 25 MG Oral Capsule	TAKE 1 CAPSULE DAILY
Lyrica 50 MG Oral Capsule	TAKE 2 CAPSULE DAILY
Magnesium Oxide 400 MG Oral Tablet	TAKE 1 TABLET DAILY.
PredniSONE 5 MG Oral Tablet	TAKE 1 TABLET DAILY.
Prograf 1 MG Oral Capsule (Tacrolimus)	
Sodium Bicarbonate 650 MG Oral Tablet	TAKE 1 TABLET TWICE DAILY WITH MEALS.
Tacrolimus 0.5 MG Oral Capsule	
Zolpidem Tartrate 5 MG Oral Tablet	TAKE 1 TABLET BY MOUTH EVERY DAY AT BEDTIME

Signatures

Electronically signed by : [redacted]; Dec 5 2017 9:43AM EST

[redacted]
Department of Endocrinology

[redacted]

[redacted]
Date of Birth: [redacted] **Age:** [redacted]
MRN: [redacted]
Appointment Date: 02/06/2018
Appointment Provider: [redacted]
Consult Letter

HPI

[redacted] was seen for neurological follow-up on February 6, 2018. According to patient the degree of discomfort in his feet continues to be very high. He grades that as 9/10 on 0-to-10 scale.
[redacted] has been taking around 400 mg of Lyrica per day. Some days, he takes 425 mg.
According to patient, among all medications he tried to address the discomfort in his feet, Lyrica has been the most effective.

Results

Fall Risk Assessment, Morse
History of falling, immediate or within 3 months? No (0)..
Presence of Secondary Diagnosis? No (0). No (0)..
Use of Ambulatory Aid? Bed rest/nurse assist (0)
Gait Weak or Impaired? bedrest/uses wheelchair/immobile (0)
Morse Fall Risk Score & Action:

Plan

1. Start: Nortriptyline HCl - 10 MG Oral Capsule; 1-2 capsules po qPM

Discussion/Summary

[redacted] has evidence of distal sensorimotor polyneuropathy. Taking into consideration the fact that he has significant discomfort in the feet on high dose of Lyrica, I recommended patient to add another medication frequently use for neuropathic discomfort. Specifically, I suggested patient to introduce 10 mg of nortriptyline with intention to double the dose in 1 week. Nortriptyline could be titrated up to 50 or 100 mg a day to see the maximum of the effectiveness.
The patient should order 5 mg of l-methylfolate.
I will see [redacted] for reevaluation in 4-6 months.

End of Encounter Meds

Medication Name	Instruction
Allopurinol 100 MG Oral Tablet	TAKE 1 TABLET BY MOUTH EVERY DAY
AmLODIPine Besylate 5 MG Oral Tablet	TAKE 1 TABLET BY MOUTH EVERY DAY
Aspirin EC 81 MG Oral Tablet Delayed Release	TAKE 1 TABLET DAILY.
Carvedilol 12.5 MG Oral Tablet	TAKE 1 TABLET BY MOUTH TWICE DAILY

[redacted]

Divalproex Sodium 250 MG Oral Tablet Delayed Release	TAKE 1 TABLET BY MOUTH TWICE A DAY FOR FIRST WK THEN 2TAB TWICE A DAY
Doxazosin Mesylate 2 MG Oral Tablet	TAKE 1 TABLET DAILY AS DIRECTED.
Hydrocodone-Acetaminophen 5-325 MG Oral Tablet (Norco)	TAKE 1 TABLET DAILY
Lyrica 100 MG Oral Capsule	TAKE 1 CAPSULE 4 TIMES DAILY
Lyrica 25 MG Oral Capsule	TAKE 1 CAPSULE DAILY
Lyrica 50 MG Oral Capsule	TAKE 2 CAPSULE DAILY
Magnesium Oxide 400 MG Oral Tablet	TAKE 1 TABLET DAILY.
Nortriptyline HCl - 10 MG Oral Capsule	1-2 capsules po qPM
PredniSONE 5 MG Oral Tablet	TAKE 1 TABLET DAILY.
Prograf 1 MG Oral Capsule (Tacrolimus)	
Sodium Bicarbonate 650 MG Oral Tablet	TAKE 1 TABLET TWICE DAILY WITH MEALS.
Tacrolimus 0.5 MG Oral Capsule	
Zolpidem Tartrate 5 MG Oral Tablet	TAKE 1 TABLET AT BEDTIME AS NEEDED.

Signatures
Electronically signed by : [redacted]; Feb 6 2018 8:54AM EST

[redacted]

Department of Endocrinology

[redacted]

[redacted]
Date of Birth: [redacted] **Age:** [redacted]
MRN: [redacted]
Appointment Date: 07/03/2018
Appointment Provider: [redacted]
Consult Letter

Greetings,
I had the pleasure of seeing our patient, [redacted] in my office today.
My most recent evaluation follows. Thank you for your kind assistance in the care of this patient.
Sincerely,
[redacted]

HPI

[redacted] was seen for neurological follow-up on July 3, 2018. The patient continued to struggle from almost continuous painful discomfort in the feet. As earlier, [redacted] was able to grade his pain severity as 9/10 on 0-to-10 scale. The discomfort in patient's leg affects his ability to be physically active. As a result of that, [redacted] believe that he is getting weaker.
The patient still takes about 400 mg of Lyrica per day. Some days, he takes 425 mg. He is aware of that Lyrica should be limited due to his kidney problem. However, he does not feel like any other medications give him any noticeable pain control. [redacted] tried to take hydrocodone for pain control. However, he had difficulties tolerating pain medications due to GI discomfort.

Results

Depression Questionnaire (PHQ-9)
Over the past 2 weeks, how often have you been bothered by the following problems?
TOTAL SCORE: severity of depression is mild.

Fall Risk Assessment, Morse
History of falling, immediate or within 3 months? No (0).
Presence of Secondary Diagnosis? No (0). No (0).
Use of Ambulatory Aid? uses crutches/cane/walker (15)
Gait Weak or Impaired? Impaired; short steps with a shuffle; may have difficulty arising from chair; head down; significantly impaired balance; requiring furniture, support person or walking aid to walk (20)
Mental Status: Oriented to own abilities and limitations (0).
Morse Fall Risk Score & Action: Completed today.

Plan

1. Start: Buprenorphine 5 MCG/HR Transdermal Patch Weekly; apply weekly

Discussion/Summary

[redacted]

[redacted] suffers from painful distal sensorimotor polyneuropathy. As a mentioned early, [redacted] could not appreciate any apparent pain control from a wide variety of medications except from Lyrica. At this point, I feel that patient should consider to reduce daily dose of Lyrica due to his renal insufficiency. With intention to reduce patient's pain severity, I suggested [redacted] to try 5 mcg/h Butrans patch.
I will see [redacted] for reevaluation in 2 months.

End of Encounter Meds

Medication Name	Instruction
Allopurinol 100 MG Oral Tablet	TAKE 1 TABLET BY MOUTH EVERY DAY
AmLODIPine Besylate 5 MG Oral Tablet	TAKE 1 TABLET BY MOUTH EVERY DAY
Aspirin EC 81 MG Oral Tablet Delayed Release	TAKE 1 TABLET DAILY.
Buprenorphine 5 MCG/HR Transdermal Patch Weekly	apply weekly
Carvedilol 12.5 MG Oral Tablet	TAKE 1 TABLET BY MOUTH TWICE DAILY
Doxazosin Mesylate 2 MG Oral Tablet	TAKE 1 TABLET DAILY AS DIRECTED.
Hydrocodone-Acetaminophen 5-325 MG Oral Tablet (Norco)	TAKE 1 TABLET DAILY
Magnesium Oxide 400 MG Oral Tablet	TAKE 1 TABLET DAILY.
PredniSONE 5 MG Oral Tablet	TAKE 1 TABLET DAILY.
Prograf 1 MG Oral Capsule (Tacrolimus)	take 1 capsule twice a day
Sodium Bicarbonate 650 MG Oral Tablet	TAKE 1 TABLET TWICE DAILY WITH MEALS.
Tacrolimus 0.5 MG Oral Capsule	take 1 capsule twice a day
Zolpidem Tartrate 5 MG Oral Tablet	TAKE 1 TABLET BY MOUTH AT BEDTIME AS NEEDED
Lyrica 25 MG Oral Capsule	TAKE 1 CAPSULE DAILY

Signatures

Electronically signed by : [redacted]; Jul 3 2018 9:25AM EST

Smoked cannabis for chronic neuropathic pain: a randomized controlled trial

Mark A. Ware MBBS, Tongtong Wang PhD, Stan Shapiro PhD, Ann Robinson RN, Thierry Ducruet MSc, Thao Huynh MD, Ann Gamsa PhD, Gary J. Bennett PhD, Jean-Paul Collet MD PhD

Previously published at www.cmaj.ca

See related commentary by McQuay at www.cmaj.ca

Abstract

Background: Chronic neuropathic pain affects 1%–2% of the adult population and is often refractory to standard pharmacologic treatment. Patients with chronic pain have reported using smoked cannabis to relieve pain, improve sleep and improve mood.

Methods: Adults with post-traumatic or postsurgical neuropathic pain were randomly assigned to receive cannabis at four potencies (0%, 2.5%, 6% and 9.4% tetrahydrocannabinol) over four 14-day periods in a crossover trial. Participants inhaled a single 25-mg dose through a pipe three times daily for the first five days in each cycle, followed by a nine-day washout period. Daily average pain intensity was measured using an 11-point numeric rating scale. We recorded effects on mood, sleep and quality of life, as well as adverse events.

Results: We recruited 23 participants (mean age 45.4 [standard deviation 12.3] years, 12 women [52%]), of whom 21 completed the trial. The average daily pain intensity, measured on the 11-point numeric rating scale, was lower on the prespecified primary contrast of 9.4% v. 0% tetrahydrocannabinol (5.4 v. 6.1, respectively; difference = 0.7, 95% confidence interval [CI] 0.02–1.4). Preparations with intermediate potency yielded intermediate but nonsignificant degrees of relief. Participants receiving 9.4% tetrahydrocannabinol reported improved ability to fall asleep (easier, $p = 0.001$; faster, $p < 0.001$; more drowsy, $p = 0.003$) and improved quality of sleep (less wakefulness, $p = 0.01$) relative to 0% tetrahydrocannabinol. We found no differences in mood or quality of life. The most common drug-related adverse events during the period when participants received 9.4% tetrahydrocannabinol were headache, dry eyes, burning sensation in areas of neuropathic pain, dizziness, numbness and cough.

Conclusion: A single inhalation of 25 mg of 9.4% tetrahydrocannabinol herbal cannabis three times daily for five days reduced the intensity of pain, improved sleep and was well tolerated. Further long-term safety and efficacy studies are indicated. (International Standard Randomised Controlled Trial Register no. ISRCTN68314063)

DOI:10.1503/cmaj.091414

Chronic neuropathic pain has a prevalence of 1%–2%,[1] and treatment options are limited.[2] Pharmacotherapy includes anticonvulsants, antidepressants, opioids and local anesthetics,[3,4] but responses vary and side effects limit compliance.

Cannabis sativa has been used to treat pain since the third millennium BC.[5] An endogenous pain-processing system has been identified, mediated by endogenous cannabinoid ligands acting on specific cannabinoid receptors.[6] These findings, coupled with anecdotal evidence of the analgesic effects of smoked cannabis,[7] support a reconsideration of cannabinoid agents as analgesics.

Oral cannabinoids such as tetrahydrocannabinol, cannabidiol and nabilone have, alone and in combination, shown efficacy in central[8,9] and peripheral[10] neuropathic pain, rheumatoid arthritis[11] and fibromyalgia.[12]

The analgesic effects of smoked cannabis remain controversial, although it is used by 10%–15% of patients with chronic noncancer pain[13] and multiple sclerosis.[14] Clinical trials are needed to evaluate these effects, given that the risks and benefits of inhaled cannabinoids may differ from oral agents. To date, three small clinical trials of the analgesic efficacy of smoked cannabis have been reported.[15–17] All studies were conducted in residential laboratories, and participants smoked multiple doses of the drug at each time point. No study adequately reported data related to adverse events.

We conducted a clinical trial using a standardized single-dose delivery system to explore further the safety and efficacy of smoked cannabis in outpatients with chronic neuropathic pain.

Methods

Participants

The study was approved by the McGill University Health Centre Research Ethics Committee, and all participants gave written informed consent. Participants were recruited at the McGill University Health Centre.

Those eligible were men and women aged 18 years or older with neuropathic pain of at least three months in duration caused by trauma or surgery, with allodynia or hyperalgesia,

From the Department of Anesthesia (Ware), the Department of Family Medicine (Ware), the Department of Epidemiology, Biostatistics and Occupational Health (Wang, Shapiro), the Department of Medicine (Huynh) and the Alan Edwards Centre for Research on Pain (Gamsa, Bennett), McGill University, Montréal, Que.; Boreal Primum (Robinson, Ducruet), Montréal, Que.; and the Centre for Applied Health Research and Evaluation (Collet), University of British Columbia, Vancouver, BC

and with an average weekly pain intensity score greater than 4 on a 10-cm visual analogue scale. Participants had a stable analgesic regimen and reported not having used cannabis during the year before the study (Appendix 1, available at www.cmaj.ca/cgi/content/full/cmaj.091414/DC1). Potential participants had to have normal liver function (defined as aspartate aminogransferase less than three times normal), normal renal function (defined as a serum creatinine level < 133 μmol/L), normal hematocrit (> 38%) and a negative result on β human chorionic gonadotropin pregnancy test (if applicable). Women of child-bearing potential consented to use adequate contraception during the study and for three months afterward.

Exclusion criteria were pain due to cancer or nociceptive causes, presence of significant cardiac or pulmonary disease, current substance abuse or dependence (including abuse of or dependence on cannabis), history of psychotic disorder, current suicidal ideation, pregnancy or breastfeeding, participation in another clinical trial within 30 days of enrolment in our trial, and ongoing insurance claims.

Study design

We used a randomized, double-blind, placebo-controlled, four-period crossover design. Each period was 14 days in duration, beginning with five days on the study drug followed by a nine-day washout period. Eligible participants were randomized to a sequence of treatment periods based on a Latin square design.

Cannabis was obtained from Prairie Plant Systems Inc. (Saskatoon, Sask.) and the United States National Institute of Drug Abuse. Prairie Plant Systems Inc. blended cannabis flowers and leaves to prepare three different potencies of active drug (2.5%, 6.0% and 9.4% tetrahydrocannabinol). The US National Institute of Drug Abuse used ethanolic extraction of cannabinoids to prepare the 0% tetrahydrocannabinol product. Intermediate doses (2.5% and 6.0% tetrahydrocannabinol) were used to increase the likelihood of successful blinding. Doses of 25 mg (± 1 mg) were prepared in opaque gelatin capsules by the study pharmacist. A panel of nine independent personnel examined the appearance of the four cannabis preparations and found no association between estimated and true potency (data not shown).

Cannabis doses were delivered as single smoked inhalations using a titanium pipe (RayDiaTor, Mori Designs, Auburn, WA, USA). The first dose of each period was self-administered under observation in a ventilated room. For dose delivery, one capsule of the assigned potency was opened and the cannabis tipped into the bowl of the pipe. Participants were instructed to inhale for five seconds while the cannabis was lit, hold the smoke in their lungs for ten seconds, and then exhale. The beginning of inhalation was recorded as the onset of the exposure. Subsequent doses were self-administered in the same manner three times daily at home for the first five days of each period.

Routine medications were continued throughout the trial. Use of breakthrough analgesia (acetaminophen) was allowed.

Study protocol

The study nurse explained the study to each participant, sought signed informed consent, obtained a medical history and performed a chart review. The study physician conducted a physical examination. Urinary drug screening was performed. Participants were contacted by telephone on three occasions during the first five days of the screening phase to calculate a baseline average pain score. A psychological evaluation was conducted by a clinical psychologist.

On the first day of each period, participants were followed for three hours. Vital signs and ratings of pain, "high," relaxation, stress, happiness and heart rate were recorded, and blood was collected for tetrahydrocannabinol assays. On days one and five of each study period, blood was collected for hematologic and biochemical analyses. At the end of their first visit, participants were given four labelled containers for urine collection and 13 cannabis doses for the five days of treatment.

During the first five days of each period, participants were contacted daily by telephone to administer questionnaires on pain intensity, sleep, medication and adverse effects. Participants collected early morning urine samples daily. They returned on day five to return the urine samples, to undergo urinary and blood tests, and to complete questionnaires on pain quality, mood, quality of life and assessments of potency. At the end of the study, participants completed final adverse event reports and potency assessments. Participants were advised not to drive a vehicle or operate heavy machinery while under the influence of the study drug.

Outcome measures

Outcome measures were selected following published recommendations for clinical trials of chronic pain.[18] Pain intensity was measured using an 11-item numeric rating scale, with "no pain" and "worst pain possible" as anchors. The numeric rating scale was administered once daily for present, worst, least and average pain intensity during the previous 24 hours. As per protocol, the average pain intensity score over the five days on study drug constituted the primary outcome. Acute effects on pain intensity were measured using a 100-mm visual analogue scale. Pain quality was assessed using the McGill Pain Questionnaire.[19] Sleep was assessed using the Leeds Sleep Evaluation Questionnaire.[20] The short-form Profile of Mood States was used to examine mood effects.[21] Quality of life was assessed using the EQ-5D health outcome instrument.[22] The items "high," "relaxed," "stressed," and "happy" were measured using a 100-mm visual analogue scale (0 = not at all, 10 = extremely).[23–25] Potency assessments were conducted by asking participants on the fifth day of each period to guess which potency they had received. At the end of the trial, participants were asked to guess the order in which they received the treatments. Standard assays for plasma tetrahydrocannabinol assays were used (Appendix 1).

Statistical analysis

Our primary hypothesis was that smoked cannabis containing 9.4% tetrahydrocannabinol is superior to 0% tetrahydrocannabinol in reducing average pain intensity. The comparison of within-patient average weekly pain intensity when assigned 9.4% tetrahydrocannabinol cannabis compared with placebo was the contrast of primary interest. A sample size of 32 patients was targeted assuming a within-patient difference

of 10 mm[26] in the primary outcome between active and placebo drug, on a 100 mm scale, with a standard deviation of 20 mm, and with 80% power and 5% significance.

A generalized linear model including drug, period and first-order carryover effects was fitted. If the carryover effect or period effect was not significant, then a reduced model was refitted. Nine-five per cent confidence intervals were generated. Significance tests were performed at a 5% level. An identical procedure to that described above for the primary outcome was performed to assess the secondary outcomes, including the McGill Pain Questionnaire, the Leeds Sleep Evaluation Questionnaire, the Profile of Mood States, and EQ-5D. Statistical procedures for day one assessments and EQ-5D analyses are shown in Appendix 1. Data from all randomized participants were included in all safety and efficacy analyses.

All reported adverse events were classified according to severity, seriousness and relationship to the study drug. An independent data-monitoring committee monitored the safety-related aspects of the trial.

Regulatory considerations

In conducting the study, we followed the Good Clinical Practice guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.[27] The trial was registered with the International Standard for Randomised Controlled Trials Register (ISRCTN683140063).

Results

Participants

We screened 116 potential participants over a 30-month period (August 2003 to January 2006), of whom 93 were ineligible. Twenty-three participants underwent random assignment to treatment, of whom 21 completed all four cycles. Two participants withdrew within the first five days of the study; one (who was receiving placebo at the time) withdrew because of a positive result on urinary screening for cannabinoid and the other (who was receiving 6% tetrahydrocannabinol at the time) because of increased pain (Figure 1). Demographic and baseline pain characteristics of participants are shown in Table 1.

Primary outcome

We found no evidence of significant carryover or period effects for any outcome. The average daily pain intensity was significantly lower on 9.4% tetrahydrocannabinol cannabis (5.4) than on 0% tetrahydrocannabinol (6.1) ($p = 0.023$; difference = 0.7, 95% CI 0.02–1.4). All pairwise differences between groups are shown with 95% CIs in Table 2. The average daily pain scores for each level of tetrahydrocannabinol, along with other secondary outcomes, are shown in Table 2.

Secondary outcomes

There was a trend toward improvement in all outcomes with increasing tetrahydrocannabinol content (Table 3). Participants using 9.4% tetrahydrocannabinol cannabis reported significantly more drowsiness and reported getting to sleep more easily, faster and with fewer periods of wakefulness compared with those using placebo ($p < 0.05$). Anxiety and depression were improved in the 9.4% tetrahydrocannabinol

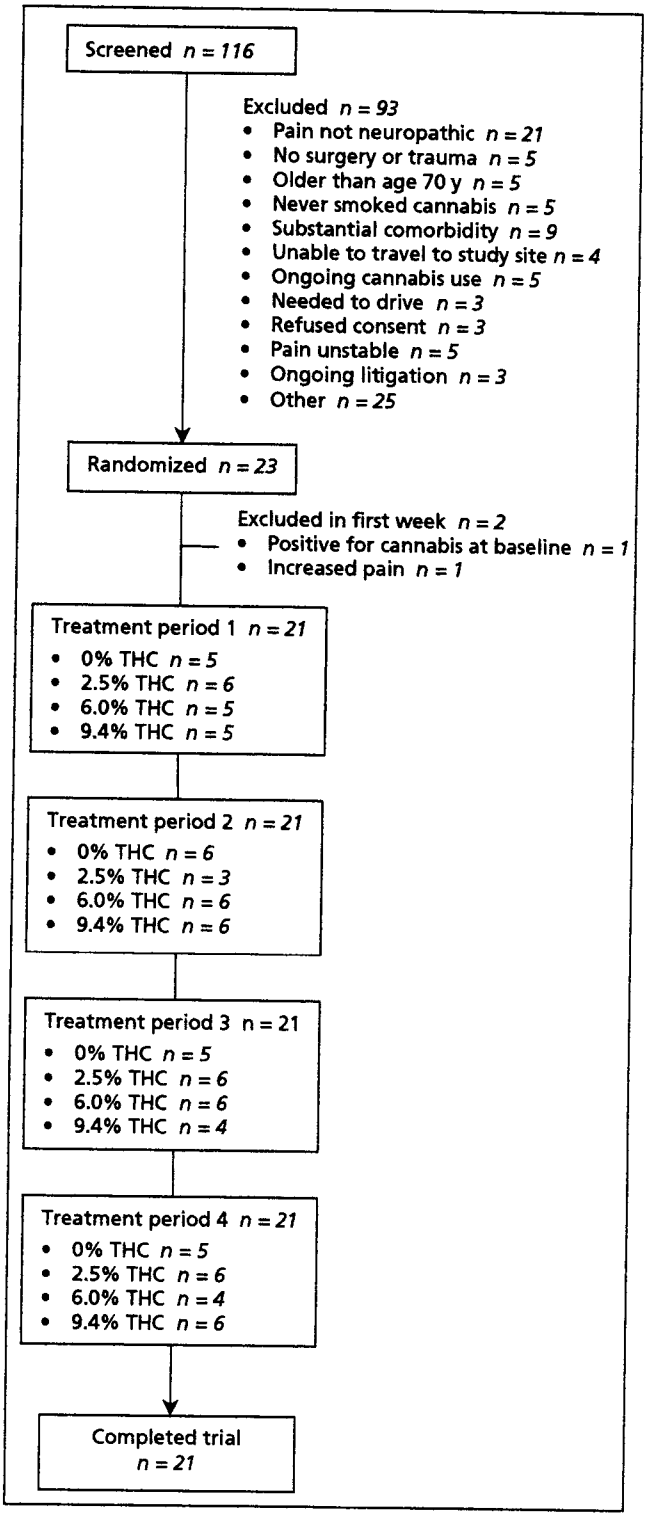


Figure 1: Flow of patients through the randomized controlled trial.

Table 1: Demographic and baseline characteristics of participants

Characteristic	No. (%) of subjects* $n = 23$
Age, yr	
Mean (SD)	45.4 (12.3)
Range	25–77
Sex	
Male	11 (47.8)
Female	12 (52.2)
Education	
Primary or elementary	1 (4.3)
Secondary or high school	8 (34.8)
University or college	14 (60.9)
Employment status	
Full-time or part-time	4 (17.4)
Retired	2 (8.7)
Short-term disability or disabled	14 (60.9)
Other	3 (13.0)
Medications	
Opioids	14 (61)
Antidepressants	12 (52)
Anticonvulsants	10 (43)
NSAIDS	10 (43)
Tobacco use	
Never smoked	8 (34.8)
Current smoker	9 (39.1)
Ex-smoker	6 (26.1)
Ever used alcohol	
Yes	14 (60.9)
No	9 (39.1)
Ever used cannabis	
Yes	18 (81.8)
No	4 (18.2)
Average daily pain at baseline	
Mean (SD)	6.89 (1.37)
Range	4.0–9.2

Note: NSAIDS = nonsteroidal anti-inflammatory drugs, SD = standard deviation.
*Unless otherwise indicated.

group compared with placebo on the EQ-5D subscale ($p < 0.05$). No significant differences were noted on the Profile of Mood States. No difference in the "high," "happy," "relaxed" or "stressed" scores on the visual analogue scale were observed between tetrahydrocannabinol potencies.

A total of 248 mild and six moderate adverse events (fall,[2] increased pain,[1] numbness,[1] drowsiness[1] and pneumonia[1]) were reported during the trial (Table 4). No serious or unexpected adverse events were reported. The total number of adverse events and the number of participants reporting at least one adverse event increased with tetrahydrocannabinol potency. The most frequent drug-related adverse events reported in the group receiving 9.4% tetrahydrocannabinol were headache, dry eyes, burning sensation, dizziness, numbness and cough. Feeling "high" and euphoria were reported once in each of the 2.5%, 6% and 9.4% tetrahydrocannabinol periods. No significant changes in vital signs, heart-rate variability, hematological, biochemistry or renal function blood tests were detected.

On day five of the first cycle, 1 of 5 participants (20%) assigned to placebo correctly identified this assignment, while 9 of the 16 participants (56%) who received placebo during later cycles did so. Of the 5 participants administered 9.4% tetrahydrocannabinol in their first cycle, none correctly identified this assignment, while 10 of 16 patients (63%) did so during later cycles. At the end of the trial, 16 (76%) of the participants were able to correctly identify the 9.4% tetrahydrocannabinol period and 13 (62%) were able to identify the 0% tetrahydrocannabinol period, whereas the 6% tetrahydrocannabinol period was identified by 8 participants (38%) and the 2.5% period by 7 (33%).

Compliance with the study was excellent, and all dispensed capsules were returned. With the exception of one participant who withdrew from the study, there were no positive urine tetrahydrocannabinol tests during the 0% tetrahydrocannabinol period or on any day one before exposure (Appendix 1).

Plasma tetrahydrocannabinol assays revealed dose–response pharmacokinetics (Figure 2) and confirmed that participants did not use cannabis during placebo phases (Appendix 1).

Pharmacy dispensing was satisfactory. No legal issues arose during the study and there were no reports or allegations of diversion of the study drug.

Discussion

We found that 25 mg herbal cannabis with 9.4% tetrahydrocannabinol, administered as a single smoked inhalation three

Table 2: Pairwise comparisons of the effects of four potencies of smoked cannabis on average daily pain

Potency, % of THC	Potency, % of THC, mean difference (95% CI)							
	0		2.5		6.0		9.4	
0	–	–	–	–	–	–	–	–
2.5	–0.13	(–0.83 to 0.56)	–	–	–	–	–	–
6.0	–0.09	(–0.78–0.60)	0.04	(–0.64 to 0.73)	–	–	–	–
9.4	–0.71	(–1.40 to –0.02)	–0.58	(–1.27 to 0.11)	–0.63	(–1.30 to 0.06)	–	–

Note: CI = confidence interval, THC = tetrahydrocannabinol.

Table 3: Effects of smoked cannabis and secondary outcomes, by potency of tetrahydrocannabinol (THC) received

Outcome	Potency of THC, %; outcome measure, mean (SD)*			
	0	2.5	6.0	9.4
Pain intensity				
Average daily pain	6.1 (1.6)	5.9 (1.9)	6.0 (1.8)	5.4 (1.7)†
Highest daily pain	7.1 (1.4)	7.0 (1.6)	7.0 (1.5)	6.5 (1.6)
Lowest daily pain	5.1 (2.1)	5.0 (2.4)	4.8 (2.4)	4.4 (2.2)
McGill Pain Questionnaire				
Sensory	17.2 (10.5)	17.1 (9.9)	14.8 (9.2)	15.6 (8.7)
Affective	3.5 (3.0)	3.8 (3.6)	3.3 (3.4)	3.0 (3.1)
Evaluative	2.2 (1.5)	2.8 (1.3)	2.1 (1.5)	1.7 (1.5)
Miscellaneous	6.2 (4.3)	6.8 (4.4)	5.5 (2.9)	4.5 (3.6)
Total score	29.1 (17.0)	30.4 (18.1)	25.8 (14.5)	24.8 (14.7)
Present pain intensity	2.8 (1.2)	3.0 (1.0)	2.8 (1.0)	2.5 (1.1)
Leeds Sleep Evaluation Questionnaire‡				
Getting to sleep				
Harder — easier than usual	5.4 (1.5)	5.5 (1.6)	6.1 (1.5)	6.8 (1.8)†
Slower — faster than usual	5.3 (1.3)	5.6 (1.4)	6.2 (1.7)	6.9 (1.7)†
Less — more drowsy than usual	5.3 (1.1)	5.9 (1.4)	5.7 (1.3)	6.6 (1.5)†
Quality of sleep				
More restless — more restful	5.5 (1.6)	5.4 (1.7)	5.9 (2.0)	6.5 (2.1)
More — less period wakefulness than usual	5.3 (1.5)	5.0 (1.5)	5.5 (1.7)	6.3 (1.8)†
Awakening this morning				
More difficult — easier	4.6 (1.2)	4.4 (0.8)	4.7 (1.4)	4.8 (1.0)
Took longer — shorter	4.4 (0.8)	4.4 (0.9)	1.7 (1.1)	5.0 (1.0)
Feeling on waking-up				
Tired — alert	4.3 (1.9)	4.0 (1.5)	5.2 (1.9)	4.9 (1.9)
Feeling now				
Tired — alert	4.1 (1.5)	1.3 (1.7)	4.9 (2.0)	4.0 (1.7)
Sense of balance				
More — less clumsy than usual	4.9 (0.4)	4.8 (0.4)	4.9 (0.4)	5.0 (1.2)
EQ-5D health outcomes§				
Mobility, no. (%)	10 (48)	11 (52)	11 (52)	11 (55)
Self-care, no. (%)	14 (67)	12 (57)	15 (71)	14 (70)
Usual activities, no. (%)	3 (14)	3 (14)	4 (19)	5 (25)
Pain or discomfort, no. (%)	11 (52)	10 (48)	14 (67)	14 (75)
Anxiety or depression, no. (%)	4 (19)	5 (23)	7 (33)	9 (45)†
State of health, no. (%)	3 (14)	2 (9)	4 (19)	7 (35)
State of health (VAS)	54.1 (19.5)	48.6 (18.9)	52.9 (22.0)	56.3 (20.4)
Profile of Mood States (POMS)¶				
Depression	10.6 (6.5)	10.4 (6.7)	9.3 (6.6)	9.4 (5.7)
Vigour	7.3 (4.3)	7.3 (5.4)	6.2 (4.6)	8.0 (4.6)
Anger	9.2 (7.0)	7.7 (6.3)	7.9 (7.6)	6.5 (6.0)
Tension	8.5 (5.1)	9.3 (4.6)	9.0 (5.6)	7.2 (5.2)
Confusion	6.3 (3.7)	6.7 (4.0)	6.0 (4.3)	5.7 (4.1)
Fatigue	11.9 (4.1)	11.1 (5.0)	11.1 (4.8)	10.5 (5.0)
Total mood disturbance	39.1 (22.7)	38.0 (24.5)	36.9 (25.9)	31.2 (22.4)

Note: EQ-5D = health outcome instrument,[22] SD = standard deviation, VAS = visual analog scale.
*Unless indicated otherwise.
†$p < 0.05$ for the comparison with 0% THC.
‡Higher scores indicate improved sleep parameters.
§Data are presented as a proportion of subjects reporting the most favourable responses; thus, a higher proportion suggests a better health outcome.
¶With the exception of vigour, lower scores represent better mood.

Table 4: Adverse events reported during the study, by potency of tetrahydrocannabinol (THC) (part 1 of 2)

Adverse event	% of THC			
	0 *n = 21*	2.5 *n = 22*	6.0 *n = 21*	9.4 *n = 22*
Nervous system disorders				
Asthenia	1	3	0	2
Decreased motor skill	0	0	0	1
Dizziness	2	3	4	4
Drowsiness	1	2	2	0
Headache	3	3	7	4
Heavy-headed	0	0	0	1
Insomnia	1	1	1	0
Lethargic	0	0	1	0
Lightheaded	1	1	0	1
Migraine	0	1	0	0
Nightmare	1	0	0	0
Not sleeping well	1	0	0	0
Numbness	1	2	1	2
Sleepiness	0	0	1	2
Spasm	1	0	0	0
Tiredness	1	1	1	0
Unbalanced	0	1	0	1
Total	**14**	**18**	**18**	**18**
General disorders and conditions specific to site of administration				
Bad taste in oral cavity	1	1	0	0
Burning sensation	3	2	3	3
Cheeks flushed	0	0	1	0
Chills	1	2	1	0
Diaphoresis	1	0	0	0
Fall	2	1	0	0
Fatigue	2	3	3	2
Heaviness	0	2	0	1
Hematoma	0	0	0	1
Irritation of oral cavities	0	0	0	1
Itchiness	0	0	0	1
Itchiness in face	0	0	0	1
Itchiness of nose	0	0	2	1
Pain	2	2	3	2
Tingling nose	0	0	1	1
Total	**12**	**13**	**14**	**13**
Psychiatric disorders				
Anxiety	0	0	1	0
Craving for sweets	0	0	0	1
Disinterest in surroundings	0	0	0	1
Dysphoria	0	0	0	2
Euphoria	0	1	0	1
Feel high	0	0	1	0
Fidgety fingers	0	0	0	1
Foggy mental state	0	0	1	1
Lack of concentration	1	2	2	2
Less alert	0	0	0	1
Lost in time	0	1	0	0
Paranoia	0	0	0	1
Racing thoughts	0	0	0	1
Stressful	0	1	0	0
Total	**1**	**5**	**5**	**12**

Adverse event	% of THC			
	0 *n = 21*	2.5 *n = 22*	6.0 *n = 21*	9.4 *n = 22*
Psychiatric disorders (continued)				
Feel high	0	0	1	0
Fidgety fingers	0	0	0	1
Foggy mental state	0	0	1	1
Lack of concentration	1	2	2	2
Less alert	0	0	0	1
Lost in time	0	1	0	0
Paranoia	0	0	0	1
Racing thoughts	0	0	0	1
Stressful	0	1	0	0
Total	**1**	**5**	**5**	**12**
Respiratory, thoracic and mediastinal disorders				
Cough	1	1	3	3
Pneumonia	1	0	0	0
Short of breath	0	0	1	1
Throat irritation	3	4	3	3
Total	**5**	**5**	**7**	**7**
Gastrointestinal disorders				
Decreased appetite	1	0	1	0
Dry mouth	0	0	0	1
Gastric acid	0	0	1	0
Increased appetite	0	1	1	2
Loss of appetite	0	1	0	0
Nausea	1	2	2	1
Thirst	0	0	1	0
Vomiting	0	1	0	0
Total	**2**	**5**	**6**	**4**
Ear and labyrinth disorders				
Ear buzzing	0	0	1	0
Total	**1**	**0**	**1**	**0**
Eye disorders				
Blurry vision	1	0	0	0
Dry eyes	0	0	0	1
Eyes red	0	0	1	0
Itchiness of eyes	0	1	2	1
Total	**1**	**1**	**3**	**2**
Musculoskeletal and connective tissue disorders				
Achy bones	0	1	0	0
Bruise on left back shoulder	1	0	0	0
Edema	1	0	0	1
Heaviness in leg	0	0	1	0
Injury to right knee	0	0	0	1
Muscles of jaw contracted	0	0	1	0
Musculoskeletal pain	1	0	0	0
Weakness of right leg	1	0	0	0
Total	**4**	**1**	**2**	**2**

continued

Table 4: Adverse events reported during the study, by potency of tetrahydrocannabinol (THC) (part 2 of 2)

Adverse event	% of THC			
	0 *n = 21*	2.5 *n = 22*	6.0 *n = 21*	9.4 *n = 22*
Infections and infestations				
Fever	0	1	0	0
Total	**0**	**1**	**0**	**0**
Renal and urinary disorders				
Difficulty voiding	0	1	0	0
Total	**0**	**1**	**0**	**0**
Disorders of skin and subcutaneous tissue				
Rash	0	0	0	1
Total	**0**	**0**	**0**	**1**
Surgical and medical procedures				
Minor surgery	1	0	0	0
Total	**1**	**0**	**0**	**0**
Total adverse events	**46**	**61**	**65**	**82**

Note: THC = tetrahydrocannabinol.

times daily for five days, significantly reduced average pain intensity compared with a 0% tetrahydrocannabinol cannabis placebo in adult participants with chronic post-traumatic or postsurgical neuropathic pain. We found significant improvements in measures of sleep quality and anxiety. We have shown the feasibility of a single-dose delivery method for smoked cannabis, and that blinding participants to treatment allocation is possible using this method.

The mean reduction in pain (0.7) from 6.1 to 5.4 on a 10-cm scale that we detected in this study is modest when compared with that from other drugs for chronic neuropathic pain, such as gabapentin (1.2) and pregabalin (1.3).[28,29] However, our study involved participants with refractory pain for which conventional therapies had failed, and this characteristic may have limited the potential for findings of a larger pain reduction.

The effects of cannabinoids on sleep are recognized.[7,9] The consistent trend toward improvement in all other outcomes for 9.4% tetrahydrocannabinol compared with placebo in our trial suggests that the reported effects on pain, mood and sleep may have been part of an overall improvement in many aspects of patients' conditions.

Limitations and strengths

There were several limitations to this trial. The number of participants recruited was smaller than planned, owing to delays in obtaining licences, approvals and the study drug, and to restrictive criteria for eligibility. Most of our participants had prior experience with cannabis, which had been an early ethics requirement; none was using cannabis at the time of enrolment and they were not "experienced" users, so that the lessons learned would be applicable to naive users of medical cannabis. The use of small, fixed doses with a short trial duration may have reduced the effect size. We used a low dose to minimize exposure to smoke and to reduce psychoactive effects. Previous work has shown that a single dose of 0.4 mg/kg can be inhaled in a single lungful from a pipe,[24,30] which for a 70-kg person approximates to 25 mg per dose. The frequency of dosing was based on a duration of action of inhaled tetrahydrocannabinol of two to three hours[31] and was administered three times daily. We used a fixed dosing schedule because the study was too short to allow dose titration and we wanted the tetrahydrocannabinol potency to be the only difference between cycles. Finally, the highest tetrahydrocannabinol-content cannabis (9.4%) legally available at the time of the study was used. Additional studies with higher potencies and flexible dosing strategies are needed to explore dose–response effects.

With respect to our analysis, we are aware of issues surrounding the use of early tests for carryover effects. However, examination of pain scores during the washout period showed that the washout was adequate (data not shown), and therefore we believe our approach was appropriate.

Our trial had several important strengths, including a credible placebo, good compliance and good safety reporting. Finding a suitable placebo for smoked cannabis is not a trivial issue. During protocol reviews, it was stated that participants smoking cannabis would immediately know, based on the acute psychoactive effects, whether they had received active drug; however, our results do not support this view. Instead, our data suggest that short-term placebo-controlled trials of smoked cannabis are feasible.

The safety of smoked cannabis is a concern for patients and

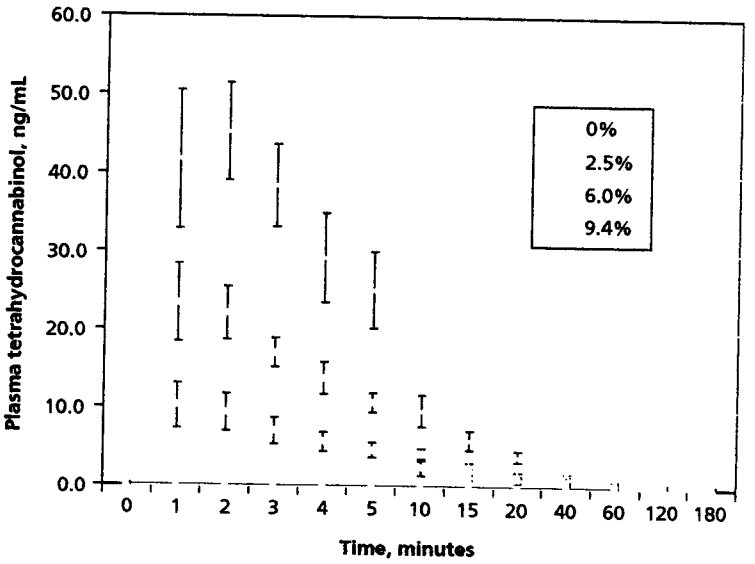


Figure 2: Levels of tetrahydrocannabinol (THC) in plasma after inhalation of a single dose. Data are presented as means and standard deviations.

physicians, and we made a concerted effort to collect data on adverse events and describe short-term physiologic effects. The frequency of adverse events increased with tetrahydrocannabinol potency. Psychoactive effects did not result in participants withdrawing from the study. Euphoria or "high" was reported on only three occasions throughout the trial. There was no evidence of euphoria during the three hours following the first dose of each cycle regardless of tetrahydrocannabinol potency, possibly because plasma levels (mean 45 ng/mL) did not reach levels found with recreational users (> 100 ng/mL).[31]

Conclusion

Our results support the claim that smoked cannabis reduces pain, improves mood and helps sleep. We believe that our trial provides a methodological approach that may be considered for further research. Clinical studies using inhaled delivery systems, such as vaporizers,[32,33] are needed.

This article has been peer reviewed.

Competing interests: None declared.

Contributors: Mark Ware conceived and designed the study, and drafted the manuscript. Stan Shapiro, Jean-Paul Collet, Thierry Ducruet and Gary Bennett were involved in the conception and design of the study. Thierry Ducruet, Ann Robinson, Ann Gamsa and Thao Huynh were involved in the acquisition, analysis and interpretation of data. Tongtong Wang performed analysis of the data with support from Thierry Ducruet and Stan Shapiro. All of the authors were involved in the critical revision of the manuscript, and all of them approved the final draft submitted for publication.

Funding: This trial was supported by the Canadian Institutes of Health Research (grant no. JHM-50014). Financial support for pharmacokinetic assays was received from the Louise and Alan Edwards Foundation.

REFERENCES

1. Berger A, Dukes EM, Oster G. Clinical characteristics and economic costs of patients with painful neuropathic disorders. *J Pain* 2004;5:143-9.
2. Mendell JR, Sahenk Z. Clinical practice. Painful sensory neuropathy. *N Engl J Med* 2003;348:1243-55.
3. Moulin DE, Clark AJ, Gilron I, et al. Pharmacological management of chronic neuropathic pain — consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manag* 2007;12:13-21.
4. Attal N, Cruccu G, Haanpaa M, et al. EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol* 2006;13:1153-69.
5. Mechoulam R. The pharmacohistory of Cannabis sativa. In: Mechoulam R, editors. *Cannabinoids as therapeutic agents*. Boca Raton (FL): CRC Press; 1986. p. 1-19.
6. Meng ID, Manning BH, Martin WJ, et al. An analgesia circuit activated by cannabinoids. *Nature* 1998;395:381-3.
7. Ware MA, Gamsa A, Persson J, et al. Cannabis for chronic pain: case series and implications for clinicians. *Pain Res Manag* 2002;7:95-9.
8. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ* 2004;329:253.
9. Rog DJ, Nurmikko TJ, Friede T, et al. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 2005;65:812-9.
10. Nurmikko TJ, Serpell MG, Hoggart B, et al. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain* 2007;133:210-20.
11. Blake DR, Robson P, Ho M, et al. 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)* 2005;45:50-2.
12. Skrabek RQ, Galimova L, Ethans K, et al. Nabilone for the treatment of pain in fibromyalgia. *J Pain* 2008;9:164-73.
13. Ware MA, Doyle CR, Woods R, et al. Cannabis use for chronic non-cancer pain: results of a prospective survey. *Pain* 2003;102:211-6.
14. Clark AJ, Ware MA, Yazer E, et al. Patterns of cannabis use among patients with multiple sclerosis. *Neurology* 2004;62:2098-100.
15. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology* 2007;68:515-21.
16. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology* 2009;34:672-80.
17. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain* 2008;9:506-21.
18. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005;113:9-19.
19. Melzack R. The short-form McGill Pain Questionnaire. *Pain* 1987;30:191-7.
20. Parrott AC, Hindmarch I. The Leeds Sleep Evaluation Questionnaire in psychopharmacological investigations — a review. *Psychopharmacology (Berl)* 1980;71:173-9.
21. Shacham S. A shortened version of the Profile of Mood States. *J Pers Assess* 1983;47:305-6.
22. Hurst NP, Kind P, Ruta D, et al. Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). *Br J Rheumatol* 1997;36:551-9.
23. Chait LD, Burke KA. Preference for high- versus low-potency marijuana. *Pharmacol Biochem Behav* 1994;49:643-7.
24. Chait LD, Evans SM, Grant KA, et al. Discriminative stimulus and subjective effects of smoked marijuana in humans. *Psychopharmacology (Berl)* 1988;94:206-12.
25. Chait LD, Zacny JP. Reinforcing and subjective effects of oral delta 9-THC and smoked marijuana in humans. *Psychopharmacology (Berl)* 1992;107:255-62.
26. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008;9:105-21.
27. *Good Clinical Practice: Consolidated Guidelines*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. E6(R1):1996; Switzerland. Available at: www.ich.org/cache/compo/276-254-1.html (accessed 2010 Aug. 18).
28. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA* 1998;280:1831-6.
29. Richter RW, Portenoy R, Sharma U, et al. Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. *J Pain* 2005;6:253-60.
30. Azorlosa JL, Heishman SJ, Stitzer ML, et al. Marijuana smoking: effect of varying delta 9-tetrahydrocannabinol content and number of puffs. *J Pharmacol Exp Ther* 1992;261:114-22.
31. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 2003;42:327-60.
32. Abrams DI, Vizoso HP, Shade SB, et al. Vaporization as a smokeless cannabis delivery system: a pilot study. *Clin Pharmacol Ther* 2007;82:572-8.
33. Zuurman L, Roy C, Schoemaker RC, et al. Effect of intrapulmonary tetrahydrocannabinol administration in humans. *J Psychopharmacol* 2008;22:707-16.

Correspondence to: *Dr. Mark A. Ware, E19.145, Montréal General Hospital, 1650 Cedar Ave., Montréal QC H3G 1A4; mark.ware@muhc.mcgill.ca*

British Journal of Anaesthesia **101** (1): 59–68 (2008)
doi:10.1093/bja/aen119 Advance Access publication May 29, 2008

BJA

Therapeutic potential of cannabis in pain medicine†

R. D. Hosking and J. P. Zajicek*

Neurology Research Group, Peninsula Medical School, Plymouth, UK

**Corresponding author. E-mail: john.zajicek@phnt.swest.nhs.uk*

Advances in cannabis research have paralleled developments in opioid pharmacology whereby a psychoactive plant extract has elucidated novel endogenous signalling systems with therapeutic significance. Cannabinoids (CBs) are chemical compounds derived from cannabis. The major psychotropic CB delta-9-tetrahydrocannabinol (Δ^9-THC) was isolated in 1964 and the first CB receptor (CB_1R) was cloned in 1990. CB signalling occurs via G-protein-coupled receptors distributed throughout the body. Endocannabinoids are derivatives of arachidonic acid that function in diverse physiological systems. Neuronal CB_1Rs modulate synaptic transmission and mediate psychoactivity. Immune-cell CB_2 receptors (CB_2R) may down-regulate neuroinflammation and influence cyclooxygenase-dependent pathways. Animal models demonstrate that CBRs play a fundamental role in peripheral, spinal, and supraspinal nociception and that CBs are effective analgesics. Clinical trials of CBs in multiple sclerosis have suggested a benefit in neuropathic pain. However, human studies of CB-mediated analgesia have been limited by study size, heterogeneous patient populations, and subjective outcome measures. Furthermore, CBs have variable pharmacokinetics and can manifest psychotropism. They are currently licensed as antiemetics in chemotherapy and can be prescribed on a named-patient basis for neuropathic pain. Future selective peripheral CB_1R and CB_2R agonists will minimize central psychoactivity and may synergize opioid anti-nociception. This review discusses the basic science and clinical aspects of CB pharmacology with a focus on pain medicine.

Br J Anaesth 2008; **101**: 59–68

Keywords: analgesics non-opioid, cannabis; pain, experimental; pain, neuropathic; pharmacology, neurotransmission effects; receptors, transmembrane

Cannabis has been of medicinal and social significance for millennia. It is obtained from *Cannabis sativa* and the plant's name reflects its ancient use—*cannabis* may represent a compound of Sanskrit and Hebrew words meaning 'fragrant cane', while *sativa* is Latin for cultivated. Cannabis is also known as hemp. *Marijuana* describes the dried cannabis flowers and leaves which are smoked, while *hashish* refers to blocks of cannabis resin which can be eaten.[6] The great British herbalist Nicholas Culpeper (1616–1654) wrote in his *The English Physitian* (sic) that hemp extract '*allayeth Inflammations in the Head ... eases the pains of the Gout ... Knots in the Joynts, [and] the pains of the Sinews and Hips*'.[10] Culpeper's preparation probably had little psychoactivity as native cannabis grown in northern latitudes has relatively low tetrahydrocannabinol (THC) content.[6] The Irish physician Sir William O'Shaughnessy (1809–1889) made the first scientific study of cannabis while working in Calcutta and popularized its use.[43] The Empress of India (Queen Victoria) was rumoured to have taken cannabis to relieve menstrual discomfort.[25] Tincture of cannabis BPC (British Pharmaceutical Codex) remained available for prescription in the UK until 1971.[54] Ironically, its withdrawal coincided with a resurgence of interest in cannabinoid (CB) pharmacology after chemical characterization of the first CBs.

Cannabis came to be associated with the rise of the drug counter-culture during 1960s and 1970s. In 1965, Britain complied with the United Nations Single Convention on Narcotic Drugs which equated cannabis possession and trafficking with opiates.[6] This Convention established tough penalties under the Dangerous Drugs Act. However, anecdotal reports of symptomatic relief from a variety of medical conditions prompted a reappraisal of its medicinal value in the late 1990s. Evidence submitted by the Royal Pharmaceutical Society to a House of Lords enquiry in 1998 encouraged further research into the use of CBs in multiple sclerosis (MS) and other

†*Declaration of interest.* The authors have received funding from the Medical Research Council and the South West Regional Development Agency.

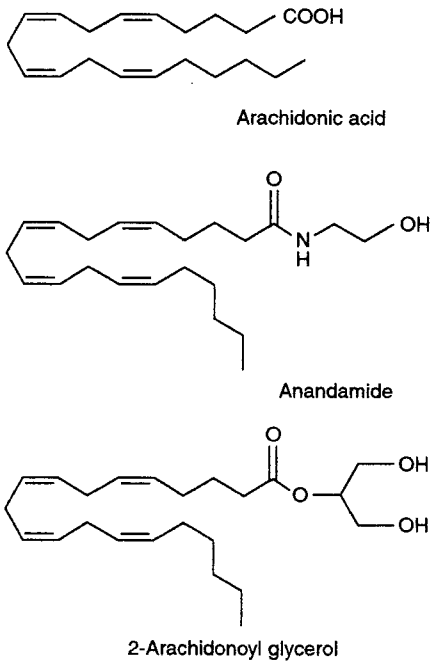


Fig 2 The endocannabinoids anandamide and 2-arachidonoylglycerol are derived from arachidonic acid.

This produces *N*-arachidonoyl-phosphatidyl-ethanolamine (NAPE) from phosphatidyl-ethanolamine (PhosEA) and phosphatidyl-choline (PhosC). NAPE is cleaved by phospholipase D to produce anandamide (AEA). The eCBs then diffuse across the synaptic cleft and bind to pre-synaptic CB_1R, which are negatively coupled to membrane calcium channels. The subsequent decrease in pre-synaptic calcium concentrations reduces the probability of further neurotransmitter release. 2-AG is cleaved to arachidonic acid and glycerol by monoacylglycerol lipase, while anandamide is metabolized to arachidonic acid and ethanolamine by fatty acid amide hydrolase (FAAH).[48]

Seven putative eCBs have been identified:

- Anandamide (arachidonoyl ethanolamide, AEA)
- Dihomo-γ-linolenoylethanolamide (HEA)
- Docosatetraenoylethanolamide (DEA)
- 2-Arachidonoylglycerol (2-AG)
- Noladin ether
- Virodhamine
- *N*-Arachidonolydopamine (NADA)

Cannabinoid pharmacology

Phytocannabinoids (pCBs) obtained from the cannabis plant comprise a range of CBR agonists, partial agonists,

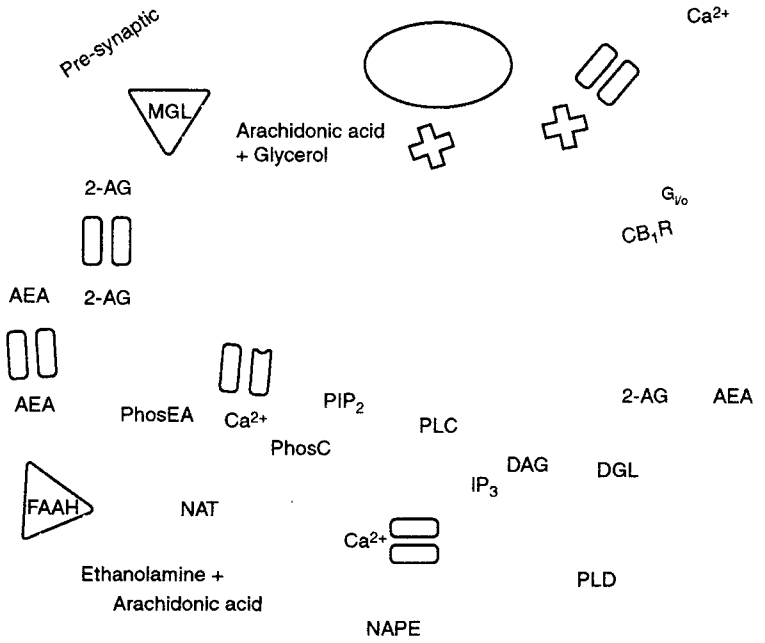


Fig 3 Diagram of a cannabinergic synapse. Pre-synaptic depolarization stimulates post-synaptic endocannabinoid (eCB) synthesis. Retrograde eCBs hyperpolarize the presynaptic terminal, thus reducing further anterograde neurotransmitter release. Calcium ions (Ca^{2+}); phosphatidylinositol 4,5-bisphosphate (PIP_2); phospholipase C (PLC); inositol trisphosphate (IP_3); diacylglycerol (DAG); diacylglycerol lipase (DGL); 2-arachidonoylglycerol (2-AG); phosphatidyl-ethanolamine (PhosEA); phosphatidyl-choline (PhosC); N-acyl transferase (NAT); N-arachidonoyl-phosphatidyl-ethanolamine (NAPE); phospholipase D (PLD); anandamide (AEA); cannabinoid-1 receptor (CB_1R); inhibitory G-protein ($G_{i/o}$); monoacylglycerol lipase (MGL); fatty acid amide hydrolase (FAAH). Adapted with permission from Macmillan Publishers Ltd: British Journal of Pharmacology (*Br J Pharm* **152**:633–48), copyright 2007.

and antagonists. Many sCBs have also been developed with specific receptor affinity and distinct pharmacological profiles. CBR may possess constitutive activity (i.e. low-level G-protein activation in the absence of receptor stimulation), and CB ligands which abolish this are known as inverse agonists.[45] CB_1R also has an allosteric binding site (see Fig. 3), which may permit modulation of endogenous signalling activity. The eCB system may be further manipulated by inhibitors of eCB hydrolysis or inhibitors of the putative CB re-uptake transporter. These ligands and transgenic 'knockout' mice which specifically lack CBR have allowed CB pharmacology to be studied in detail.[22]

Pharmacokinetics

Smoking cannabis causes a rapid elevation in plasma THC concentration. A peak THC concentration is reached within 9 min of smoking a single cigarette. The concentration quickly decreases as a result of rapid tissue distribution. The total amount of drug absorbed depends on the inhalation technique. Obviously, smoking also has attendant health risks. However, absorption and bioavailability of oral preparations are much more variable, partly because of first pass metabolism. Sublingual preparations of CBs have sought to avoid these constraints. Inhaled and transdermal methods of delivery are also being investigated. CBs are highly lipophilic and readily cross the blood-brain barrier. Their metabolites can be detected >5 days after administration. Sixty-five per cent of CB is lost in the faeces, whereas 20% undergoes renal excretion.[23]

Side-effects

Phytocannabinoids differ markedly in their psychoactivity—cannabinol (CBN) is approximately 90% less psychoactive than Δ^9-THC, whereas cannabidiol lacks psychoactivity entirely.[46] The main adverse effects are dysphoria, memory impairment, reduced concentration, disorientation, and motor incoordination.

Tolerance and dependence

There is a controversy as to whether cannabis users become dependent. Previous opinion suggested that tolerance and dependence occur only with heavy use.[47] However, some authors believe that the preponderance of evidence from human research suggests that CB dependence is clinically significant and warrants treatment.[31] Abstinence symptoms resemble those of ethanol or opiate withdrawal, including nausea, vomiting, agitation, confusion, tachycardia, and sweating.[47]

Pain

Pain is a complex psychological perception and there are several points in pain pathways that CBs may exert actions. Mechanical, thermal, and chemical signal transduction occurs via TRP channels, acid-sensing channels, and adenosine receptors on peripheral nociceptors. Small unmyelinated C fibres and larger finely myelinated Aδ fibres synapse in the dorsal horn of the spinal cord where their activity can be influenced by non-nociceptive sensory information.[28] Ascending fibres then transmit impulses to the thalamus and cortex via the contralateral spinothalamic tract and ipsilateral dorsal column visceral pain pathway. However, afferent spinal signals may be enhanced or diminished by supraspinal modulation. The midbrain periaqueductal gray (PAG) receives extensive collaterals from the spinothalamic pathway and projects fibres via the rostral ventromedial medulla (RVM) to the spinal cord dorsal horn. These descending pathways may inhibit or facilitate nociceptive transmission.[60] Further complexity arises from persistent peripheral signalling which results in synaptic plasticity, altered gene transcription, and neuropeptide release.[36] CBRs are found in all of the nociceptive neuroanatomical pathways described. Furthermore, they participate in descending supraspinal pain modulation via the PAG and RVM (see Fig. 4).[59] The principal actions of CB_1R decrease pre-synaptic intracellular calcium concentrations and activate inward-rectifying potassium channels which depress neuronal excitability and reduce transmitter release.[22]

CBs and pain

Animal models are used to investigate distinct pain states induced by a variety of pathophysiological mechanisms. Multiple experiments have provided firm preclinical evidence of CB-mediated analgesia.[60] In 1899, Ernest Dixon observed that dogs which had inhaled cannabis smoke failed to react to pin pricks.[13] The capacity of CBs to profoundly suppress behavioural reactions to acute painful stimuli and neuronal injury was confirmed in the 1960s. However, systemic administration of CBs can produce profound motor effects in experimental animals (i.e. immobility and catalepsy) which can limit interpretation of studies involving a motor response.[60] Further work has, therefore, included electrophysiological and neurochemical analysis of specific neuronal pathways.

Peripheral nociceptor CB_1R expression and activation

Previous data suggested that CB_1R were mainly associated with large myelinated sensory neurons in dorsal root ganglia (DRG) *in vivo*, but that their expression was up-regulated in small diameter neurons in DRG cultures *in vitro* (which model peripheral nerve injury).[2] However, recent work comparing global CB_1R knockout mice with wild-type animals confirms that CB_1R are expressed in a major population of nociceptive neurons in adult DRG.[1]

In a rodent model of inflammatory pain, topical application of the eCB anandamide suppressed both the development and maintenance of carrageenan-evoked thermal hyperalgesia, which was blocked by a CB_1R antagonist

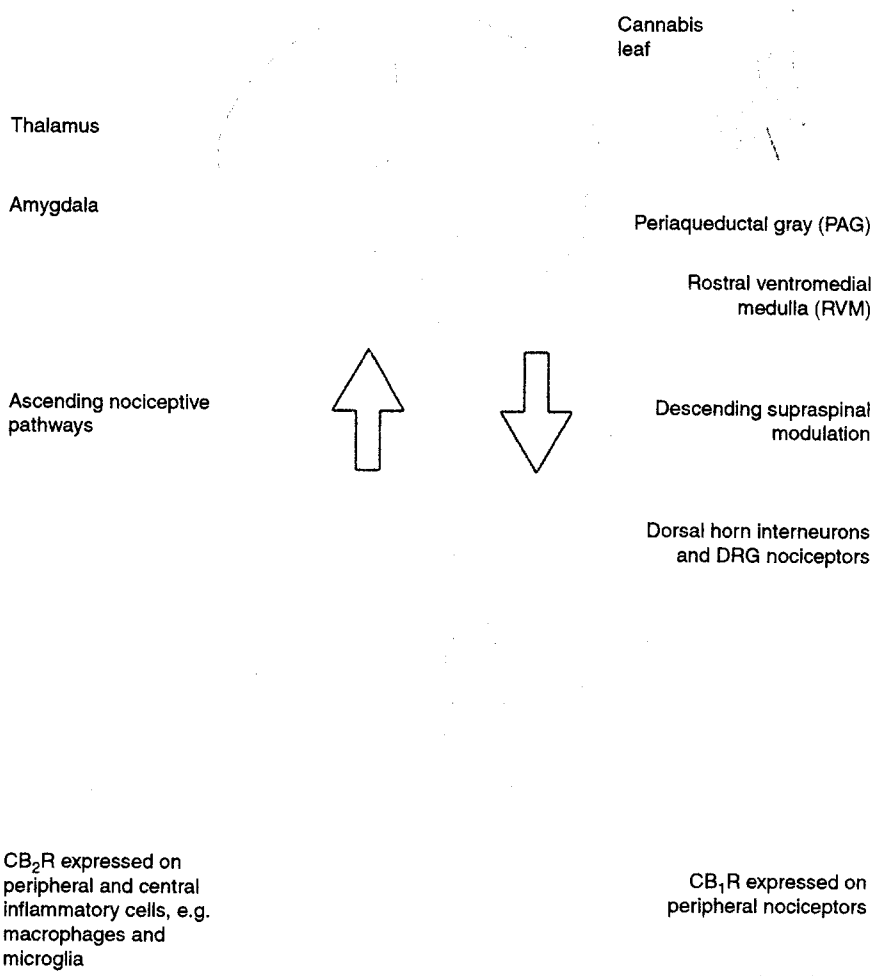


Fig 4 Diagram of the nociceptive pathways in which endocannabinoids and cannabinoid receptors are involved. DRG, Dorsal Root Ganglia; CB_1R, cannabinoid-1 receptor; CB_2R, cannabinoid-2 receptor.

(SR141716A).[49] Intraplantar administration of the CB-agonist WIN55212-2 attenuated mechanical hyperalgesia in this model, and also reduced spinal Fos protein expression which reflected decreased neuronal activity.[38] Co-administration of intraspinal CBs alongside their topical application markedly enhanced this degree of antinociception and also synergized with topical morphine preparations.[62] Methanandamide (a metabolically stable analogue of anandamide) suppressed pain behaviour and prevented the longer term synaptic changes seen after intraplantar formalin injection. Topical administration of the CB agonist HU210 to human skin suppressed capsaicin-evoked thermal hyperalgesia and touch-evoked allodynia.[55] CBs also reduced capsaicin-evoked CGRP release (CECR) both in the periphery and in rat dorsal horn. Peripheral CECR is enhanced in rats with diabetic neuropathy induced by streptozotocin, but this is also attenuated by the CB-agonist CP55940 in a CB_1R-dependent manner.[14] Multiple models of neuropathic pain induced by nerve ligation have demonstrated a role for CB_1R in suppressing hyperalgesia and allodynia.[60] Finally, a targeted CB_1R knockout mouse has been generated which specifically lacks CB_1R on peripheral nervous system nociceptors. These mice have reduced noxious stimuli reaction latencies and response thresholds, suggesting that the CB_1R normally mediates an inhibitory tone on nociceptive activity. Furthermore, the nociceptor-specific loss of CB_1Rs decreased local and systemic

CB-induced analgesia, but did not affect intrathecal CB-mediated pain relief.[1] These experiments offer the opportunity for peripherally mediated CB analgesia, avoiding central side-effects, provided suitable molecules can be identified that do not cross the blood-brain barrier to any significant extent.

Spinal cord CB_1R expression

It is believed that the majority of spinal cord CB_1Rs are found post-synaptically on membranes of intrinsic spinal interneurons. There is differential expression within individual laminae of the dorsal horn. CB_1R immunoreactivity occurs in both excitatory and inhibitory circuits and also co-localizes with μ-opioid receptors on lamina II interneurons. Spinally administered CBs reduce nociception in animal models, and spinal CB_1R up-regulation also occurs after nerve injury, which may enhance the therapeutic effect of CBs in neuropathic pain.[60]

Supraspinal pain circuits

The anti-nociceptive effects of intracerebroventricular CBs are diminished after surgical or pharmacological disruption of the spinal cord. Selective destruction of descending noradrenergic spinal cord projections[18] or administration of an intrathecal α_2-antagonist[30] also reduces the analgesic efficacy of systemic CBs. This implies the involvement of supraspinal descending noradrenergic systems in CB-mediated analgesia. Furthermore, direct injections of CB agonists to specific brain regions have demonstrated the role of CBR in central nocicéption. These areas include the PAG, dorsal raphe nucleus, RVM, amygdale, and thalamus.[60] Analgesia induced by electrical stimulation of the dorsal PAG can be markedly diminished after administration of a selective CB_1R antagonist (SR141716A).[61] This may occur via pre-synaptic inhibition of GABAergic interneurons within the PAG which tonically inhibit descending anti-nociceptive pathways.[60] Metabotropic and ionotropic glutamatergic receptors are also involved.[48] Electrophysiological RVM studies suggest that CBs modulate the activity of intrinsic 'on' and 'off' cells, thus controlling descending pain pathways in a similar manner to morphine.[60] The amygdala has an important role in modulating analgesia. Microinjection of CBs into the basolateral nucleus of the amygdala produces anti-nociception, while bilateral lesions render primates less sensitive to the potent CB agonist WIN55212-2.[32]

CB_2R-mediated anti-nociception

The current analgesic potential of CB agonists in humans is limited by unwanted psychoactivity which is mediated by neuronal CB_1R.[22] However, certain selective CB_2R agonists have also been shown to have anti-nociceptive properties.[17] CB_2R are mainly found outside the CNS in cells of immune origin including mast cells, monocytes, and lymphocytes. The brain's resident immune cells (microglia) express CB_2R under pathological conditions, but CNS neurons apparently do not. Targeted CB_2R activation may therefore avoid centrally mediated psychoactivity. A variety of selective CB_2R agonists have been developed which exhibit anti-inflammatory and peripheral anti-hyperalgesic properties in multiple models of persistent nociception. These include HU308, AM1241, and JWH-133 whose effects are antagonized by specific CB_2R antagonists. AM1241 can stimulate the release of β-endorphin from skin keratinocytes, which suggests that μ-opioid receptors may be involved in its mechanism of action.[17] The CB_2R agonist JWH015 reduced postoperative hypersensitivity after paw incision by decreasing microglial and astrocytic activation in the spinal cord.[53] The peripheral immune cell CB_2R stimulation may down-regulate inflammation by suppressing the release of inflammatory mediators which would otherwise cause nociceptor sensitization.

Endocannabinoids

The anti-nociceptive properties of eCBs have been established in a number of experiments. Anandamide plays an important role in PAG-controlled analgesia. PAG-extracellular fluid collected by midbrain microdialysis after formalin hindpaw injection reveals elevated anandamide concentrations when assessed by liquid chromatography/mass spectrometry. Studies of metabolically stable anandamide analogues and the effects of anandamide in FAAH knockout mice suggest that anandamide-mediated anti-nociception can occur at other sites within the CNS and periphery. FAAH is also localized within the amygdala, which suggests that eCBs may influence its nociceptive activity.[60]

Cyclooxygenase

Prostanoids are metabolites of arachidonic acid that include pro-inflammatory prostaglandins that potentiate the ability of bradykinin to sensitize afferent C-fibres.[47] Anandamide and 2-AG are metabolized by cyclooxgenase-2 (COX-2) to these derivatives which bind prostaglandin receptors with nanomolar affinity (e.g. PGE_2 ethanolamide). The up-regulation of COX-2 during inflammation may therefore diminish eCB tone. However, COX-2 inhibitors may partly suppress pain by preventing the conversion of anti-nociceptive eCBs to pro-nociceptive prostanoids.[27 60]

Clinical practice

Multiple sclerosis

We have investigated the therapeutic potential of cannabis in MS. The CAMS study was a large randomized placebo-controlled trial which examined whether CBs were beneficial in the treatment of MS symptoms.[63] A total of

667 patients from 33 centres in the UK were randomized to receive either synthetic Δ^9-THC (dronabinol) or a cannabis-plant extract, containing both Δ^9-THC and cannabidiol (Cannador). The first 15 week phase of the trial showed no effect on the primary outcome measure of muscle spasticity as assessed by the Ashworth score. However, there was a positive effect on patient-reported measures of spasticity, pain levels, quality of sleep, and decreased spasms in both treatment groups. Furthermore, those patients receiving Δ^9-THC experienced significant improvements in the Ashworth score over 12 months. This group also appeared to accrue less disability at 12 months which may suggest a benefit of Δ^9-THC on disease progression.[3 64] We are currently investigating this in our Cannabis Use in Progressive Inflammatory brain Disease (CUPID) trial.

Clinical trials of CBs as analgesics

When James Lind sailed into Plymouth Sound on board HMS *Salisbury* in 1747, the results of his citrus fruit trial for the treatment of scurvy were remarkable. Inclusion criteria were putrid gums, spots, lassitude, and knee weakness. Criticism could be made of the small study size (12 scorbutic seamen), open-label design, and somewhat dubious comparative treatment arms (which included seawater and sulphuric acid). However, the primary outcome measure of functional recovery was robust and the results in the orange-and-lemon patient group were impressive: the first sailor returned to regular service, while the second was sufficiently recovered to act as research assistant (n=2, number needed to treat=1).[57] Unfortunately, although many clinical trials of CB analgesia have suffered similar design flaws to Lind's research, their results have been much more equivocal.

Early studies evaluated oral THC or sCBs in cancer-related, postoperative, or neuropathic pain.[50] A randomized, controlled crossover trial in 10 patients with cancer pain showed that 15 and 20 mg doses of oral THC were superior to placebo, but caused marked sedation.[41] A follow-up confirmed these sedative effects, but showed that a lower dose of THC 10 mg was suitable for mild pain only.[42] I.m. injections of the sCB levonantradol in a randomized, double-blind trial of 56 patients with severe postoperative or trauma pain showed benefit compared with placebo but there was no apparent dose–effect relationship.[26] Two single patient studies showed that THC 5 mg was only equianalgesic with codeine 50 mg in spinal cord ependymoma, but significantly improved spasticity;[34] and while THC was no better than placebo in a patient with familial Mediterranean fever, the amount of morphine required for breakthrough pain was significantly lowered.[19] A meta-analysis of these trials concluded that CBs were no more effective than codeine in controlling pain and the authors did not advocate their widespread introduction into clinical practice.[8] However, the total patient number in all 9 trials was only 222 and included diverse pain syndromes. Furthermore, studies lacking strict inclusion criteria may underestimate treatment efficacy in distinct patient subgroups. For example, a recent randomized crossover controlled trial compared the effectiveness of dihydrocodeine with the sCB nabilone.[15] Ninety-six patients with chronic neuropathic pain received an incremental dose of either dihydrocodeine or nabilone over a 6 week period before crossover. The final mean visual analogue score was 6.0 mm greater in the nabilone group and so the authors concluded that dihydrocodeine was more efficacious. However, the study was criticized because of patient drop out, and because allodynia and sympathetic dysfunction were over-represented in this patient population.[9] These signs are mechanistically distinct from the dysaesthesia which occurs in many central pain syndromes, but the study design was not powered to determine benefit in the latter patient group where the evidence base for CB use is strongest (see below). The effects of Δ^9-THC have been assessed using experimental pain conditions in healthy human individuals. Twelve Swiss cannabis-naïve volunteers were subjected to heat, cold, pressure and repeated transcutaneous electrical stimulation after receiving single oral doses of Δ^9-THC (20 mg), morphine (30 mg) and a THC-morphine combination.[39] Δ^9-THC did not significantly reduce pain in any paradigm, but did have a slight additive effect with morphine in the electrical stimulation test. This partially corroborates animal work which suggests that CBs are more potent against chronic pain states than against acute discomfort caused by noxious stimuli in uninjured tissue.[44] Studies assessing the use of CBs in postoperative analgesia have been mixed. Two trials using Δ^9-THC failed to demonstrate a benefit,[4 7] while a third which used a cannabis plant extract (Cannador) reported significant dose-related improvements in rescue analgesia requirements.[20]

However, other studies have been more encouraging. A randomized, double-blind, placebo-controlled trial of 24 patients with central neuropathic pain because of MS showed that dronabinol 10 mg day^{-1} reduced pain by an average of 21%.[58] The number needed to treat for a pain reduction of 50% from baseline (on the numerical rating scale—NRS) was 3.5. A further crossover study comprising a total of 24 patients—18 of whom had MS—found that pain levels were significantly lowered when either dronabinol or an equal ratio of dronabinol to cannabidiol was used.[40] A placebo-controlled crossover trial using a metabolite of dronabinol (Δ^9-THC-11-oic acid) showed that neuropathic pain measured by visual analogue scores was significantly improved, while adverse psychoactive side-effects were absent.[29]

Sativex is derived from extracts of selected strains of cannabis plants which produce high and reproducible yields of Δ^9-THC and cannabidiol (CBD). It is administered as a sublingual spray and each 100 μl actuation delivers 2.7 mg of THC and 2.5 mg of CBD. The

non-psychoactive CBD may compete with THC for CB_1R binding sites and thus diminish negative psychotropic effects. CBD may also reduce nociceptive neurotransmission by antagonizing TRPV1 receptors. It is manufactured in the UK by GW Pharmaceuticals and was licensed in Canada in 2005 as an adjunct for central neuropathic pain in MS. Sativex has been used to investigate the efficacy of cannabis-based medicinal extracts in the treatment of neuropathic pain caused by brachial plexus avulsion.[5] This condition is believed to represent an excellent human model of central neuropathic pain as a result of the relative homogeneity of the anatomical lesions, pain characteristics, and patient characteristics. The randomized, double-blind crossover trial involved 48 patients with intractable symptoms who received three consecutive 2 week courses of an oromucosal spray containing either placebo, Sativex, or THC. The primary outcome measure was mean pain severity score during the last 7 days of treatment. The treatment effect was not as large as originally hypothesized, but both the primary outcome measure and sleep measures showed statistically significant improvements. The medications were reported to be generally well tolerated. A double-blind placebo-controlled trial studied 66 MS patients with central neuropathic pain who were randomized to receive either placebo or Sativex while maintaining their existing analgesia.[51] A total of 64 patients completed the 5 week trial, which demonstrated a greater reduction in mean pain intensity in the active treatment group. An uncontrolled, open-label 2 yr extension to this study was undertaken in which other analgesia was varied as required.[52] The primary end-point was the number, frequency, and type of patient-reported adverse events. Secondary end-points included changes from the original baseline in an 11-point NRS (NRS-11) neuropathic pain score. Forty-four per cent of the original patients completed the 2 yr follow-up, and maintained their pain-score improvement. A high number of patients experienced a mild or moderate adverse event (92%) which mainly included nausea and dizziness. Twenty-five per cent of patients withdrew from the study because of these. Some temporary buccal mucosal changes also occurred in 14% of patients. A recent press release by GW Pharmaceuticals reported the preliminary results of a 14 week randomized placebo-controlled trial of Sativex in 339 MS patients with neuropathic pain. Fifty per cent of Sativex recipients reached the primary end-point of a 30% or greater improvement in pain scores. However, this was not statistically significant because a high response rate (45%) occurred in the placebo group. Finally, a recent meta-analysis assessed the effect of Sativex, cannabidiol, and dronabinol in neuropathic and MS-related pain.[24] The authors acknowledged that the total patient number was relatively small, but concluded that CBs were effective in treating neuropathic pain in MS. Most of these studies suffer from similar methodological problems of identifying hard outcome measures when there is a potential bias introduced by unblinding because of side-effects. In addition, placebo responses in such studies can be high, and make interpretation of results difficult. These issues have yet to be resolved, and in many respects we have not made much progress in trial design since the days of James Lind.

Current CB prescription

Nabilone is licensed in the UK for the treatment of chemotherapy-induced nausea and vomiting as is dronabinol (Marinol) in the USA. Sativex can be prescribed on a named-patient basis for neuropathic pain but availability may be dependent on funding.

Summary

Preclinical evidence demonstrates the importance of CBRs in nociceptive neurotransmission. CBs acting via neuronal pre-synaptic CB_1R inhibit neurotransmitter release. Exogenous CBs are potent analgesics in animal models, whereas eCBs may mediate a physiological anti-nociceptive 'tone'. Microglial activation and peripheral inflammation may be down-regulated via CB_2R. CB synergism with opioid analgesics could reduce opioid requirements. sCBs may avoid CB_1R-mediated psychoactivity by using combinations of CB_2R agonists and peripheral CB_1R agonists which do not cross the blood-brain barrier. Many clinical trials of CB-mediated analgesia have provided negative or equivocal results. The strongest evidence of their benefit is for central neuropathic pain in MS. However, CBs play a fundamental physiological role in nociception. Advances in cannabis research have ensured a future for these analgesic molecules which have been used since antiquity.

Funding

The CUPID trial is funded by the Medical Research Council. Laboratory CB_2R research is funded by the South West Regional Development Agency.

References

1 Agarwal N, Pacher P, Tegeder I, *et al.* Cannabinoids mediate analgesia largely via peripheral type 1 cannabinoid receptors in nociceptors. *Nat Neurosci* 2007; **10**: 870–9

2 Ahluwalia J, Urban L, Capogna M, Bevan S, Nagy I. Cannabinoid 1 receptors are expressed in nociceptive primary sensory neurons. *Neuroscience* 2000; **100**: 685–8

3 Baker D, Jackson SJ, Pryce G. Cannabinoid control of neuroinflammation related to multiple sclerosis. *Br J Pharm* 2007; **152**: 649–54

4 Beaulieu P. Effects of nabilone, a synthetic cannabinoid, on postoperative pain. *Can J Anesth* 2006; **53**: 769–75

5 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 randomized control trial. *Pain* 2004; **112**: 299–306

6 Booth M. *Cannabis*. New York: Bantam Books, 2003

7 Buggy DJ, Toogood L, Maric S, Sharpe P, Lambert DG, Rowbotham DJ. Lack of analgesic efficacy of oral δ-9-tetrahydrocannabinol in postoperative pain. *Pain* 2003; **106**: 169–72

8 Campbell FA, Tramèr MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *Br Med J* 2001; **323**: 13–6

9 Cohen SP. Cannabinoids for chronic pain. *Br Med J* 2008; **336**: 167–8

10 Culpeper N. *The English Physitian: or An Astrologo-Physical Discourse of the Vulgar Herbs of this Nation*. London: Peter Cole, 1652.

11 Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 1992; **258**: 1946–9

12 Di Marzo V. A brief history of cannabinoid and endocannabinoids pharmacology as inspired by the work of British scientists. *Trends Pharmacol Sci* 2006; **27**: 134–40

13 Dixon WE. The pharmacology of cannabis indica. *Br Med J* 1899; **2**: 1354–7

14 Ellington HC, Cotter MA, Cameron NE, Ross RA. The effect of cannabinoids on capsaicin-evoked calcitonin gene-related peptide (CGRP) release from the isolated paw skin of diabetic and non-diabetic rats. *Neuropharmacology* 2002; **42**: 966–75

15 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: randomized, crossover, double blind study. *Br Med J* 2008; **336**: 199–201

16 Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. *J Am Chem Soc* 1964; **86**: 1646–1647.

17 Guindon J, Hohmann AG. Cannabinoid CB_2 receptors: a therapeutic target for the treatment of inflammatory and neuropathic pain. *Br J Pharm* 2008; **153**: 319–34

18 Gutierrez T, Nackley AG, Neely MH, Freeman KG, Edwards GL, Hohmann AG. Effects of neurotoxic destruction of descending noradrenergic pathways on cannabinoid antinociception in models of acute and tonic nociception. *Brain Res* 2003; **987**: 176–85

19 Holdcroft A, Smith M, Jacklin A, *et al.* Pain relief with oral cannabinoids in familial Mediterranean fever. *Anaesthesia* 1997; **5**: 483–6

20 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**: 1040–6

21 House of Lords Science and Technology Committee. *Cannabis*. The Stationery Office, 1998; HL Paper 151

22 Howlett AC, Barth F, Bonner TI, *et al.* International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol Rev* 2002; **54**: 161–202

23 Huestis MA. Pharmacokinetics and metabolism of plant cannabinoids, Δ^9-tetrahydrocannabinol, cannabidiol and cannabinol. *Handb Exp Pharmacol* 2005; **168**: 657–90

24 Iskedjian M, Bereza B, Gordon A, Piwko C, Einarson TR. Meta-analysis of cannabis based treatments for neuropathic and multiple-sclerosis-related pain. *Curr Med Res Opin* 2007; **23**: 17–24

25 Iversen L. *The Science of Marijuana*. New York: Oxford University Press, 2000

26 Jain AK, Ryan JR, McMahon FG, Smith G. Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. *J Clin Pharmacol* 1981; **21**: 320S–326S

27 Jhaveri MD, Richardson D, Chapman V. Endocannabinoid metabolism and uptake: novel targets for neuropathic and inflammatory pain. *Br J Pharm* 2007; **152**: 624–32

28 Kandel E, Schwartz J, Jessell T. *Principles of Neural Science*. New York: McGraw-Hill, 2000

29 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**: 1757–62

30 Lichtman AH, Martin BR. Cannabinoid-induced antinociception is mediated by a spinal alpha 2-noradrenergic mechanism. *Brain Res* 1991; **559**: 309–14

31 Lichtman AH, Martin BR. Cannabinoid tolerance and dependence. *Handb Exp Pharmacol* 2005; **168**: 691–717

32 Manning BH, Merin NM, Meng ID, Amaral DG. Reduction in opioid- and cannabinoid-induced antinociception in rhesus monkeys after bilateral lesions of the amygdaloid complex. *J Neurosci* 2001; **21**: 8238–46

33 Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* 1990; **346**: 561–4

34 Maurer M, Henn V, Dittrich A, Hoffman A. Delta-9-THC shows antispastic and analgesic effects in a single case double blind trial. *Eur Arch Psychiatry Clin Neurosci* 1990; **240**: 1–4

35 Mechoulam R, Shvo Y. The structure of cannabidiol. *Tetrahedron* 1963; **19**: 2073–8

36 Melzack R, Wall P. *The Challenge of Pain*, 2nd Edn. London: Penguin, 1996

37 Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 1993; **365**: 61–5

38 Nackley AG, Suplita RL, II, Hohmann AG. A peripheral cannabinoid mechanism suppresses spinal fos protein expression and pain behavior in a rat model of inflammation. *Neuroscience* 2003; **117**: 659–70

39 Naef M, Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Zbinden A, Brenneisen R. The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions. *Pain* 2003; **105**: 79–88

40 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**: 440–552

41 Noyes R, Brunk SF, Baram DA, Canter A. Analgesic effects of delta-9-THC. *J Clin Pharm* 1975; **15**: 139–43

42 Noyes R, Brunk SF, Avery DH, Canter A. The analgesic properties of delta-9-THC and codeine. *Clin Pharmacol Ther* 1975; **18**: 84–9

43 O'Shaughnessy WB. On the cannabis indica or Indian hemp. *Pharmacol J* 1843; **2**: 594

44 Pertwee R. Cannabinoid receptors and pain. *Prog Neurobiol* 2001; **63**: 569–611

45 Pertwee R. Pharmacological actions of cannabinoids. *Handb Exp Pharmacol* 2005; **168**: 1–51

46 Pertwee R. Cannabinoid pharmacology: the first 66 years. *Br J Pharm* 2006; **147**: S161–S171

47 Rang HP, Dale MM. *Pharmacology*, 2nd Edn. Edinburgh: Churchill Livingstone, 1991

48 Rea K, Roche M, Finn DP. Supraspinal modulation of pain by cannabinoids: the role of GABA and glutamate. *Br J Pharm* 2007; **152**: 633–48

49 Richardson JD, Kilo S, Hargreaves KM. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. *Pain* 1998; **75**: 111–9

50 Robson P. Human studies of cannabinoids and medicinal cannabis. *Handb Exp Pharmacol* 2005; **168**: 717–56

51 Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 2005; **65**: 812–9

52 Rog DJ, Nurmikko TJ, Young CA. Oromucosal Δ^9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. *Clin Ther* 2007; **29**: 2068–79

53 Romero-Sandoval A, Eisenach JC. Spinal cannabinoid receptor type 2 activation reduces hypersensitivity and spinal cord glial ctivation after paw incision. *Anesthesiology* 2007; **106**: 787–94

54 Royal Pharmaceutical Society of Great Britain. *Report on Cannabis*. 1998

55 Rukwied R, Watkinson A, McGlone F, Dvorak M. Cannabinoid agonists attenuate capsaicin-induced responses in human skin. *Pain* 2003; **102**: 283–8

56 Ryberg E, Larsson N, Sjögren S, *et al*. The orphan receptor GPR55 is a novel cannabinoid receptor. *Br J Pharmacol* 2007; **152**: 984–6

57 Sutton G. Putrid gums and 'Dead Men's Cloaths': James Lind aboard the Salisbury. *J R Soc Med* 2003; **96**: 605–8

58 Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *Br Med J* 2004; **329**: 253–60

59 Vaughan CW. Stressed-out endogenous cannabinoids relieve pain. *Trends Pharmacol Sci* 2006; **27**: 69–71

60 Walker JM, Hohmann AG. Cannabinoid mechanisms of pain suppression. *Handb Exp Pharmacol* 2005; **168**: 509–54

61 Walker JM, Huang SM, Strangman NM, Tsou K, Sañudo-Peña MC. Pain modulation by release of the endogenous cannabinoid anandamide. *Proc Natl Acad Sci USA* 1999; **96**: 12198–203

62 Yesilyurt O, Dogrul A, Gul H, *et al*. Topical cannabinoid enhances topical morphine antinociception. *Pain* 2003; **105**: 303–8

63 Zajicek JP, Fox P, Sanders HP, *et al*. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomized placebo-controlled trial. *Lancet* 2003; **362**: 1517–26

64 Zajicek JP, Sanders HP, Wright DE, *et al*. Cannabinoids in Multiple Sclerosis (CAMS) study, safety and efficacy data for up to 12 months follow-up. *J Neurol Neurosurg Psychiatry* 2005; **76**: 1664–9

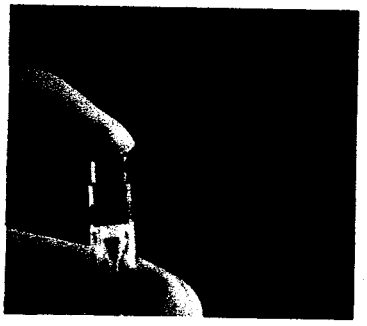
Study: Cannabis Effectively Treats Neuropathic Pain

Posted on **March 13, 2014** by **UnitedPatientsGroup.com**

144

A new study from researchers at the University of Glasgow in the UK shows what many medical cannabis patients have already discovered: Cannabis oil helps with neuropathy.

THC/CBD spray was administered to 128 patients, and a placebo was given to 118 people in the control group. The patients who used the cannabis spray reported improved sleep and significant improvement in pain levels. Overall, the treatment showed a statistically significant change in comparison to thecontrol group.



"These findings demonstrate that, in a meaningful proportion of otherwise treatment- resistant patients, clinically important improvements in pain, sleep quality and SGIC (Subject Global Impression of Change) of the severity of their condition are obtained with THC/CBD spray," the researchers concluded. "THC/CBD spray was well tolerated and no new safety concerns were identified."

This study focused on patients with allodynia, but cannabis has been shown to help with neuropathic pain associated other ailments, too. Here are just a few of the studies on the effect of cannabis on neuropathic pain:

- A 2011 study of the effects of smoked cannabis on HIV neuropathy found statistically significant improvement in pain, as well as mood and daily functioning.
- According to a 2010 study, post-traumatic and postsurgical neuropathic pain can be effectively treated by smoking cannabis.
- In 2011, researchers found that vaporized cannabis, even in low doses, helped with general and peripheral neuropathy in patients who didn't find relief from traditional treatment.
- A 2004 study found a clinically relevant analgesic effect from THC pills on neuropathy associated with multiple sclerosis.

It's clear from these studies that cannabis, however it's administered, can significantly improve the lives of people suffering neuropathy, whatever the cause. It's clear that we need wider access to medical cannabis, so everyone who suffers neuropathic pain can find the relief that only cannabis provides.

State of Connecticut

SENATOR LEONARD A. FASANO
SENATE REPUBLICAN PRESIDENT PRO TEMPORE
34TH DISTRICT

LEGISLATIVE OFFICE BUILDING
300 CAPITOL AVENUE, SUITE 3400
HARTFORD, CONNECTICUT 06106-1591
www.SenatorFasano.com

HARTFORD: (860) 240-8800
TOLL FREE: (800) 842-1421
FAX: (860) 240-8306
Len.Fasano@cga.ct.gov

January 8th, 2019

Connecticut Department of Consumer Protection
Medical Marijuana Program
450 Columbus Blvd.
Suite 901
Hartford, CT 06103

To Whom It May Concern:

This petition was sent to the office of Senator Fasano, I am forwarding it to the DCP on behalf of the constituent, Mr. [redacted].

Thank you,

Tara Frilling
Legislative Aide to Senator Len Fasano

FROM THE OCTOBER 2015 ISSUE

The Woman With Knives in Her Neck

When traditional painkillers fail, is medical marijuana the answer?

By David Casarett | Thursday, August 27, 2015

RELATED TAGS: PERSONAL HEALTH, VACCINES & DRUGS

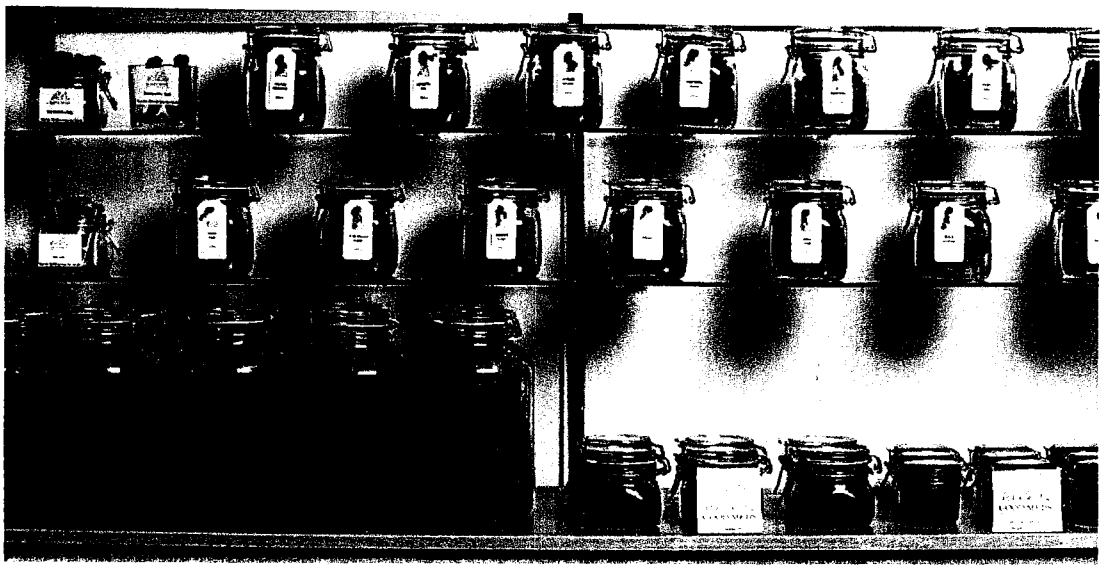
Stuart Briers

There's no such thing as a "typical" medical marijuana patient. The marijuana clinics that I've visited have encompassed a wide swath of society, and the people I've met are living proof of the diversity of this population. Nevertheless, my first thought when I meet Rachel in this particular clinic waiting room is that she doesn't belong here.

Rachel is in her early 40s, blond and wearing a crisply tailored deep-blue suit that looks like it's made of expensive silk. Just for comparison, the guy sitting next to her is a skinny, unshaven lad wearing baggy shorts, a tank top and flip-flops. He looks like he's heading to the beach, while Rachel looks like she's taking a well-earned break from a board meeting. Later I find out she's the co-owner of a large chain of boutiques.

Rachel tells me that her experience with medical marijuana began about a year ago, when she was at the site of a new store. A piece of construction equipment fell on her, fracturing her cervical spine and initially leaving her paralyzed. After a month in the hospital, her spine was stabilized, and she was able to walk again.

But she was far from well because pieces of her spine damaged some of the nerves that emerge from the



Good Meds medical cannabis center in Lakewood, Colo., lines its shelves with medical marijuana. Centers like this one are a resource for patients who need an alternative when typical pain relievers don't work for them.

Matthew Staver/The Washington Post/Getty Images

"They hit me when I move the wrong way, but I can't avoid them. They just . . . happen."

Those attacks were so severe, and so unpredictable, they scared her away from regular exercise. Eventually she avoided walking her corgi, Max, or even doing the dishes because she was afraid that the wrong move would bring on another lightning strike. The drugs her doctors prescribed didn't help much, and opioids like morphine made her feel "drugged." So she turned to marijuana.

Rachel tells me that once she started using it, two things happened. First, as she'd hoped, the bouts of pain became less severe. Then as her pain improved a little, she became less afraid of the next episode. She began to exercise more. She took Max for long walks. And then she started seeing her trainer again for light aerobic workouts. Soon it seemed that the spells of pain became less frequent.

She uses a marijuana-based oil in a vape pen. These devices are like e-cigarettes, except that they deliver tetrahydrocannabinol (THC) and cannabidiol (CBD) instead of nicotine. Rachel tells me she uses her vape pen "all day."

How many times in a typical day?

Rachel thinks carefully. "A dozen."

I'm not sure what my expression reveals, but it causes her to re-evaluate her estimate — though not in the direction I expected.

"Maybe two dozen?"

I'm having trouble imagining the effects of 24 doses of THC, the ingredient in marijuana that produces the "high" feeling for which it's so well known. I'm also wondering how that regimen might affect a daily routine that involves managing a chain of clothing stores. But Rachel seems bemused by my questions.

"Well, we opened two new stores in the last three months. I must be doing something right."

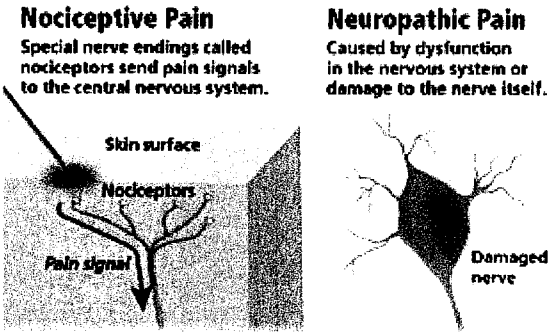
two decades ago, when he was in a pain fellowship in San Francisco, many of his patients got marijuana through a buyer's club in Oakland. They told him it was the only treatment that worked.

"That," he says, "really grabbed my attention."

Then he says something that grabs my attention.

"Those people all had neuropathic pain, like Rachel did."

What he means is that they had a very specific type of pain. Neuropathic pain isn't caused by a direct injury, like arthritis or a broken bone, that stimulates normal pain nerves — that's nociceptive pain. Instead, neuropathic pain is caused by the nerves themselves.



Alila Medical Media/Shutterstock and Alison Mackey/Discover

To understand neuropathic pain, it helps to think about the way that electronic devices like pagers and cell phones work. When I was a resident, two of us had to carry a "code pager" at all times. This was the pager that would go off if someone had a cardiac arrest anywhere in the hospital. Because these devices were so important, they were designed to withstand the apocalypse. To make them especially dependable, these pagers operated on local emergency radio channels that were bulletproof, but filled with static. So every once in a while, a pager would spring to life, emitting an unintelligible squawk and three beeps that would send a confused resident scrambling for the door, until it became apparent that it was just a false alarm.

That's how neuropathic pain happens. An injury to a nerve creates static, but pain nerves don't know how to interpret static any more than those pagers knew how to interpret it. Instead, nerves that carry pain signals interpret static just like they interpret any signal: as pain. Just as those emergency pagers interpreted static as an emergency and let loose a blood-curdling squawk, nerves that carry pain assume that static represents a painful stimulus, and that's what they tell the brain.

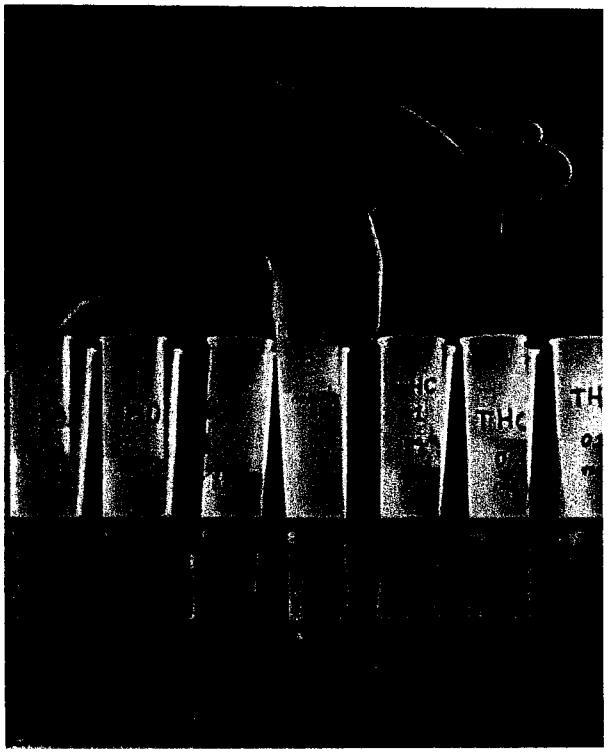
Wilsey is particularly interested in Rachel's story because he thinks that if marijuana can treat pain, it's probably most effective against neuropathic pain. And he believes it is effective. In fact, he tells me about several studies that he and others have done, finding that people like Rachel report much better pain relief.

How does marijuana relieve pain? This is where things get interesting, because what Wilsey tells me is not what I expected.

"You've got your glial cells," he says. "They're the predominant cell type in the brain."

I'm confused by this because glial cells are known primarily as the brain's immune cells. They help to scavenge and clean up debris, but they aren't involved in thinking or movement, as neurons are.

So how could glial cells be involved in treating pain? I admit somewhat sheepishly that I've always



CBD and THC, two of the main active ingredients in marijuana, are gaining the attention of researchers because of their pain-relieving potential.

Mauro Fermariello/Science Source

I love this analogy, but I learn that it's not true. Wilsey explains that glial cells aren't just structural, and they're not just immune cells. They may have a big role in pain management. For instance, we know that they have receptors that bind to THC.

He's not sure yet how those glial cells are involved in pain, or how marijuana might act on them to provide pain relief. One theory is that glial cells have some sort of modulating effect on neurons. That is, they might reduce neuronal activity, in much the same way that my fellow residents and I would turn down the volume on those code pagers as far as we could. That adjustment wouldn't eliminate random beeps, but it did make them less startling. Perhaps those glial cells work through cytokines, which are molecules that coordinate the body's response to inflammation, but we don't really know. Whatever the mechanism, Wilsey is convinced that these glial cells are much more than bubble wrap.

If Wilsey is less interested in neurons than he is in glial cells, he's also less interested in THC than he is in the lesser-known cannabinoid CBD.

THC and CBD have a fascinating relationship that's a little like the one between Don Quixote and Sancho Panza in Cervantes' picaresque tale. The Don was a loopy aristocrat with odd delusions of chivalry and a skewed perception of reality that led him — among other adventures — to imagine that a windmill was a giant against which he was honor-bound to battle. Sancho, on the other hand, was the humble servant and the practical, common-sense squire. He did his best to keep his master on the straight and narrow path, or at least to prevent him from doing too much harm to himself, or to windmills.

You can think of THC as the Don Quixote of marijuana's cannabinoids. Its receptors are scattered all over the brain, in the cortex, in the cerebellum and in the reward centers, among other places. So it can make you goofy, confused, high and even paranoid. All those are the quixotic effects of THC, and it's because of those effects that THC is the cannabinoid everyone notices, just as Don Quixote got top billing.

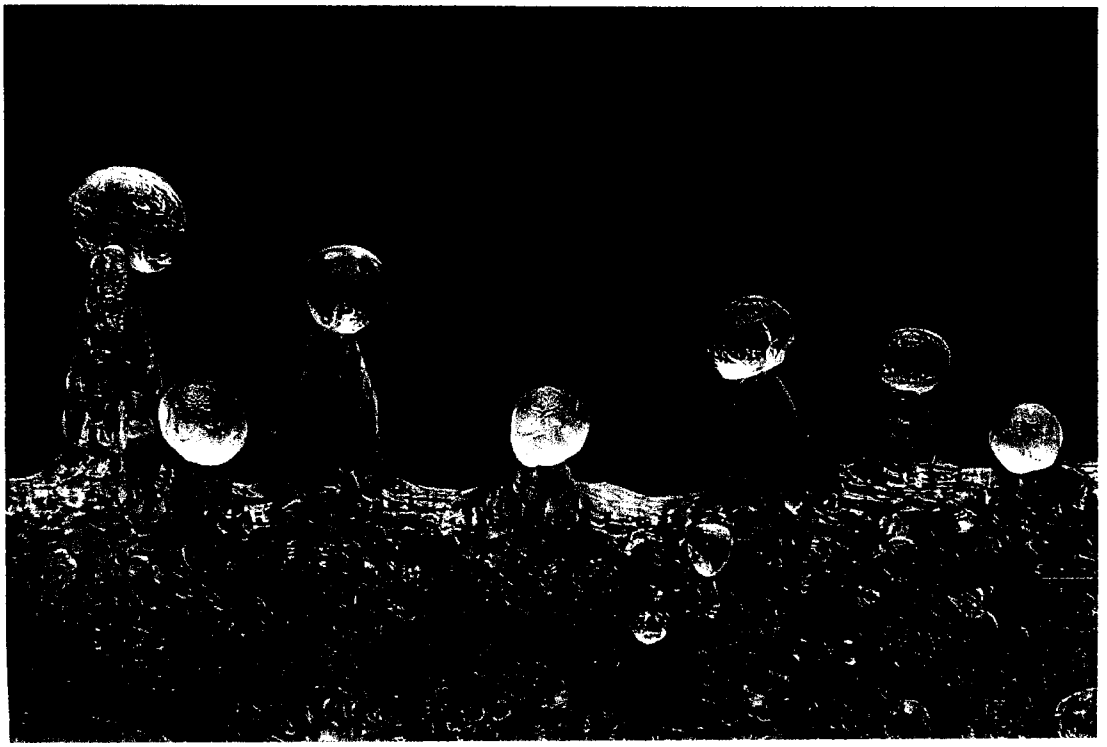
CBD, on the other hand, is more like Sancho Panza. Its most notable characteristic is what it *doesn't* do. Specifically, it doesn't produce any of the psychoactive effects of THC. It doesn't make you feel high or paranoid, and it doesn't make you hallucinate. Like Sancho, CBD does whatever it does quietly, and almost invisibly.

But just as Sancho is as important — in his own way — to the tale as his master is, it's possible that CBD might be more valuable than we thought. And maybe THC isn't as necessary as we'd assumed.

effects.

Neuropathic pain is Wilsey's specialty, but I wonder what he thinks about nociceptive pain. Remember, that's the more common kind of pain you have with arthritis or if you pull a muscle or break a leg. It's also the kind of pain that I often see in my patients with advanced cancer.

Wilsey shrugs. "We're not really sure, but there's reason to think there might not be much benefit."



A close-up of glandular trichomes on the leaves of a cannabis plant, like the one pictured at left. Trichomes protect the plant, but they also secrete numerous compounds, including cannabinoids such as THC.

Antonio Romero/Science Source

As evidence, he tells me about studies that have used a common laboratory test of pain. You expose volunteers' skin to a piece of metal heated to a temperature most of us would agree is uncomfortable (about 113 degrees Fahrenheit). That's their "pain threshold." Then you see whether a drug lets them tolerate a higher temperature without squirming. Wilsey says that marijuana doesn't seem to increase pain thresholds as much as some other drugs, such as morphine.

Wilsey says we don't know much about the effect of cannabinoids in regular nociceptive pain because there just haven't been many studies. Most of the research has been on neuropathic pain because that kind of pain can be very difficult to treat. Rachel had visited multiple specialists and received countless drugs. Those drugs didn't work, or caused unacceptable side effects, or both, so she was ready to try anything.

On the other hand, patients with more common nociceptive pain have numerous treatment options. There's acetaminophen (Tylenol), which has been around for decades because it works, as well as non-steroidals like ibuprofen (Motrin) and opioids like morphine. They all work well, so there's little pressure to come up with another drug to treat nociceptive pain.

As Wilsey says goodbye, I'm thinking that maybe Rachel was onto something. There's research evidence

cause nausea and dizziness, especially at first. They cause constipation, too, often requiring the use of laxatives every day. And they can make you sleepy, forgetful and sometimes confused.

Could marijuana help someone to reduce the dose of opioids, or stop them altogether?

To answer that question, I seek out Jonathan Gavrin, a physician who has given more opioids to patients in a day than most doctors give in a year. Like Wilsey, he's an anesthesiologist. But he's also a palliative care physician who knows a lot about pain management. Gavrin is wiry and compact, with short hair and narrow rectangular glasses. He looks a little like a younger, fitter Kevin Spacey.

When I tell him about Rachel and her desire to avoid opioids, he nods energetically: "Oh, sure. I know that's true." Gavrin proceeds to tell me about his bad experiences with opioids and other drugs after he underwent a knee replacement a couple of years ago.

"They made me sick. Really sick. Hated it." He pauses. "No euphoria, though. They didn't make me feel good. Just crappy." He laughs, "I got ripped off."

So if marijuana could reduce the need for opioids? "That would be great. We don't want our patients drowning in a pharmacological soup," Gavrin says.

Yet we do inflict this on patients, all the time. We add drugs on top of drugs, and Rachel was by no means the only victim of a doctor's prescription pad. I tell Gavrin this.

He laughs again. "Well, of course. We desperately want to make people feel better. So we do everything we can to help. That's why we've developed such a drug culture. It's hard to see people suffer, so we reach for a prescription pad. Maybe we get lucky with the first drug, but sometimes not, and we add, and add."

CapturedNuance/iStock

get what Rachel wanted: comfort without the side effects of opioids.

Marijuana's promise of pain relief is impressive in its own right, but when you add in the possibility of avoiding other drugs, and their side effects, it starts to look very appealing. Of course, marijuana has side effects of its own, ranging from a dry mouth and rapid heart rate to confusion and paranoia. But Rachel figured out a way to avoid those, through small frequent doses.

And that opportunity to tweak and customize and improve your treatment through trial and error might be the single most impressive promise of medical marijuana. Instead of taking pills that she was given, Rachel much preferred to find her own way, experimenting on herself until she found a regimen that worked for her. Although it was the end result of better pain management that she was looking for, her newfound control over her own health and the satisfaction of solving problems for herself was an unexpected but welcome bonus.

And could marijuana help other people reduce or avoid prescription medications?

"That," Gavrin says, "would be cool."

From Stoned by David Casarett, published July 14, 2015, by Current, an imprint of Penguin Publishing Group, a division of Penguin Random House LLC.