MMP-055

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

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

INSTRUCTIONS

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

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

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

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

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

1. Petition
Name: [redacted]
Street A
City, Sta
Telepho

2. Identify the medical condition or treatment thereof proposed. Please be specific. Do not submit broad categories (such as "mental illness").
Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME)

3. Do you wish to address the Medical Marijuana Review Panel regarding your petition?
- [x] Yes, in Person
- [x] Yes, by Telephone
- [ ] No

4. Do you request that your personally identifiable information or health information remain confidential?
- [ ] Yes
- [x] No

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

RECEIVED
SEP 6 2016
OFFICE OF THE CHIEF OF STAFF

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

Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME) is defined as a disease characterized by profound fatigue, sleep abnormalities, pain, and other symptoms that are made worse by exertion. CFS/ME is a chronic degenerative neuro-immune disease.

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

All of the conventionally perscribed medications for CFS/ME have severe adverse side effects including but not limited to... SEE ATTACHED PAGES

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

SEE ATTACHED PAGES

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

SEE ATTACHED PAGES

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

SEE ATTACHED PAGES

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

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

Signature of Petitioner	Date
[redacted]	8/31/16

6.
PROVIGIL
GENERIC NAME : MODAFINIL
Stimulant

"Check with your doctor immediately if any of the following side effects occur:"

Less common
- Black, tarry stools
- blurred vision or other vision changes
- chest pain
- chills or fever
- clumsiness or unsteadiness
- confusion
- dizziness or fainting
- increased thirst and urination
- mental depression
- problems with memory
- rapidly changing moods
- shortness of breath
- sore throat
- trembling or shaking
- trouble in urinating
- uncontrolled movements of the face, mouth, or tongue
- unusual bleeding or bruising
- unusual tiredness or weakness

SITE -- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0045888/#DDIC600945.side_effects_section

AMANTADINE
GENERIC NAME : AMANTADINE
Dopamine promoter and antiviral

"Check with your doctor immediately if any of the following side effects occur:"
Less common
- Blurred vision
- confusion
- difficult urination
- dizziness or lightheadedness
- fainting
- seeing, hearing, or feeling things that are not there
- swelling of the hands, feet, or lower legs

Rare
- Convulsions (seizures)

- decreased vision or any change in vision
- difficulty in coordination
- fever, chills, or sore throat
- increased blood pressure
- increase in body movements
- irritation and swelling of the eye
- loss of memory
- mental depression
- severe mood or mental changes
- skin rash
- slurred speech
- thoughts of suicide or attempts at suicide
- unexplained shortness of breath

"Check your health care professional if any of the following side effects continue or are bothersome or if you have any questions about them:"

More common

- Agitation, anxiety, or nervousness
- difficulty concentrating
- headachy
- irritability
- loss of appetite
- nausea
- purplish red, net-like, or blotchy spots on the skin
- trouble in sleeping or nightmares

Less common or rare

- Constipation
- decrease in sexual desire
- diarrhea
- drowsiness
- Dryness of the mouth nose and throat
- false sense of well-being
- vomiting
- unusual tiredness or weakness

SITE-- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0045332/#DDIC600083.side_effects_section

VYVANSE
GENERIC NAME :
Lisdexamfetamine
Stimulant

"Lisdexamfetamine has a high risk for abuse. It may be habit-forming if used for a long period of time. Use lisdexamfetamine only as prescribed. Do not share it with others. Abuse of lisdexamfetamine may cause serious heart problems, blood vessel problems, or sudden death."
SITE-- https://www.drugs.com/cdi/lisdexamfetamine.html

"Can cause rapid or irregular heartbeat, delirium, panic, psychosis, and heart failure."
SITE --

http://www.drugfree.org/drug-guide/prescription-stimulants/?utm_source=google&utm_medium=kp&utm_campaign=stimulants

"Check with your doctor immediately if any of the following side effects occur:"

Less Common
- Uncontrolled vocal outbursts or tics (uncontrolled repeated body movements)

SITE -- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0044767/#DDIC602409.side_effects_section

"Call your doctor right away if you notice any of these side effects:"
- Blistering, peeling, red skin rash
- Chest pain that may spread, trouble breathing, nausea, unusual sweating, fainting
- Extreme energy, mood or mental changes, confusion, agitation, unusual behavior
- Fast, pounding, or uneven heartbeat
- Numbness or weakness on one side of your body, sudden or severe headache, problems with vision, speech, or walking
- Seeing, hearing, or feeling things that are not there
- Unexplained sores, coldness, numbness, or color changes on your fingers or toes

"If you notice these less serious side effects, talk with your doctor:"
- Dry mouth
- Feeling anxious, restless, irritable, or nervous
- Loss of appetite, weight loss
- Trouble sleeping
- Vomiting, constipation, diarrhea, or stomach pain

SITE-- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0018936/?report=details#side_effects

CYMBALTA
GENERIC NAME :
Duloxetine delayed-release capsules
SSRI

"Call your doctor right away if you notice any of these side effects:"
- Blistering, peeling, red skin rash
- Confusion, weakness, muscle twitching
- Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
- Decrease in how much or how often you urinate
- Eye pain, vision changes, seeing halos around lights
- Feeling more energetic than usual
- Lightheadedness, dizziness, or fainting
- Restlessness, fever, fast heartbeat, sweating, muscle spasms, diarrhea, seeing or hearing things that are not there
- Unusual moods or behaviors, worsening depression, thoughts about hurting yourself, trouble sleeping
- Unusual bleeding or bruising

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

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

SITE -- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0010059/?report=details#side_effects

NUVIGIL
GENERIC NAMES : ARMODAFINIL
STIMULANT

"Check with your doctor immediately if any of the following side effects occur:"

Less common

- Blistering, burning, crusting, dryness, or flaking of the skin
- burning, crawling, itching, numbness, prickling, "pins and needles", or tingling feelings
- difficult or labored breathing
- fast, irregular, pounding, or racing heartbeat or pulse
- fever
- frequent urination
- headache, severe and throbbing
- increased volume of pale, dilute urine
- itching, scaling, severe redness, soreness, or swelling of the skin
- rash
- shakiness in the legs, arms, hands, or feet
- shortness of breath
- tightness in the chest
- trembling or shaking of the hands or feet
- wheezing

SITE -- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0045631/#DDIC602479.side_effects_section

NEURONTIM, GRALISE, & HORIZANT
GENERIC NAME: GABAPENTIN
ANTICONVULSANT

"Check with your doctor immediately if any of the following side effects occur:"

More Common

- Clumsiness or unsteadiness
- continuous, uncontrolled, back-and-forth, or rolling eye movements
- More Common In Children
- Aggressive behavior or other behavior problems
- anxiety
- concentration problems and change in school performance
- crying
- depression

- false sense of well-being
- hyperactivity or increase in body movements
- rapidly changing moods
- reacting too quickly, too emotional, or overreacting
- restlessness
- suspiciousness or distrust

Less Common

- Black, tarry stools
- chest pain
- chills
- cough
- depression, irritability, or other mood or mental changes
- fever
- loss of memory
- pain or swelling in the arms or legs
- painful or difficult urination
- shortness of breath
- sore throat
- sores, ulcers, or white spots on the lips or in the mouth
- swollen glands
- unusual bleeding or bruising
- unusual tiredness or weakness

"Check with your health care professional if any of the following side effects continue or are bothersome or if you have any questions about them:"

More common

- Blurred vision
- cold or flu-like symptoms
- delusions
- dementia
- hoarseness
- lack or loss of strength
- lower back or side pain
- swelling of the hands, feet, or lower legs
- trembling or shaking

Less common or rare

- Accidental injury
- appetite increased
- back pain
- bloated or full feeling
- body aches or pain
- burning, dry, or itching eyes
- change in vision
- change in walking and balance
- clumsiness or unsteadiness
- congestion
- constipation
- cough producing mucus

- decrease in sexual desire or ability
- difficulty with breathing
- dryness of the mouth or throat
- earache
- excess air or gas in the stomach or intestines
- excessive tearing
- eye discharge
- feeling faint, dizzy, or lightheadedness
- feeling of warmth or heat
- flushed, dry skin
- flushing or redness of the skin, especially on the face and neck
- frequent urination
- fruit-like breath odor
- impaired vision
- incoordination
- increased hunger
- increased sensitivity to pain
- increased sensitivity to touch
- increased thirst
- indigestion
- noise in the ears
- pain, redness, rash, swelling, or bleeding where the skin is rubbed off
- passing gas
- redness or swelling in the ear
- redness, pain, swelling of the eye, eyelid, or inner lining of the eyelid
- runny nose
- sneezing
- sweating
- tender, swollen glands in the neck
- tightness in the chest
- tingling in the hands and feet
- trouble sleeping
- trouble swallowing
- trouble thinking
- twitching
- unexplained weight loss
- voice changes
- vomiting
- weakness or loss of strength
- weight gain

SITE -- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0045606/#DDIC600709.side_effects_section

LYRICA
GENERIC NAME: PREGABALIN
Nerve Pain Medication

"Check with your doctor immediately if any of the following side effects occur:"

Less common

- Difficult or labored breathing
- shortness of breath
- tightness in the chest

Rare

- Blistering, peeling, or loosing of the skin
- chills
- cough
- diarrhea
- difficulty with swallowing
- dizziness
- Fast heartbeat
- hives
- itching
- joint or muscle pain
- puffiness or swelling of the eyelidsor around the eyes, face, lips, or tongue
- red skin lesions, often with a purple center
- red, irritated eyes
- skin rash
- sore throat
- sores, ulcers, or white spots in the mouth or on the lips
- unusual tiredness or weakness

"Check with your health care professional if any of the following side effects continue or are bothersome or if you have any questions about them:"

More common

- Accidental injury
- bloating or swelling of the face, arms, hands, lower legs, or feet
- blurred vision
- burning, tingling, numbness or pain in the hands, arms, feet, or legs
- change in walking and balance
- clumsiness
- confusion
- delusions
- dementia
- difficulty having a bowel movement(stool)
- difficulty with speaking
- double vision
- dry mouth
- fever
- headache
- hoarseness
- increased appetite
- lack of coordination
- loss of memory
- lower back or side pain
- painful or difficult urination
- problems with memory

- rapid weight gain
- seeing double
- sensation of pins and needles
- shakiness and unsteady walk
- sleepiness or unusual drowsiness
- stabbing pain
- swelling
- tingling of the hands or feet
- trembling, or other problems with muscle control or coordination
- unusual weight gain or loss

Less common

- Anxiety
- bloated or full feeling
- burning, crawling, itching, numbness, prickling, "pins and needles", or tingling feelings
- Chest pain
- cold sweats
- coma
- cool, pale skin
- cough producing mucus
- decrease or change in vision
- depression
- excess air or gas in the stomach or intestines
- eye disorder
- false or unusual sense of well-being
- general feeling of discomfort or illness
- increased hunger
- joint pain
- loss of appetite
- loss of bladder control
- loss of strength or energy
- muscle aches and pain
- muscle twitching or jerking
- muscle weaknes
- nausea
- nervousness
- nightmares
- noisy breathing
- pain
- passing gas
- rhythmic movement of the muscles
- runny nose
- seizures
- shivering
- slurred speech
- sweating
- trouble sleeping
- twitching

- uncontrolled eye movements
- Vomiting

SITE -- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0046069/#DDIC601627.side_effects_section

PROZAC
GENERIC NAME: FLUOXETINE
SSRI

"Check with your doctor immediately if any of the following side effects occur:"
More common
- Hives, itching, or skin rash
- inability to sit still
- restlessness

Less common
- Chills or fever
- joint or muscle pain

Rare
- Anxiety
- cold sweats
- confusion
- convulsions (seizures)
- cool pale skin
- diarrhea
- difficulty with concentration
- drowsiness
- dryness of the mouth
- excessive hunger
- fast or irregular heartbeat
- headache
- increased sweating
- increased thirst
- lack of energy
- mood or behavior changes
- overactive reflexes
- purple or red spots on the skin
- racing heartbeat
- shakiness or unsteady walk
- shivering or shaking
- talking, feeling, and acting with excitement and activity you cannot control
- trouble with breathing
- unusual or incomplete body or facial movements
- unusual tiredness or weakness

"Check with your health care professional if any of the following side effects continue or are bothersome or if you have any questions about them:"
More common
- Decreased appetite

Less common or rare

- Abnormal dreams
- breast enlargement or pain
- change in sense of taste
- changes in vision
- feeling of warmth or heat
- flushing or redness of the skin, especially on face and neck
- frequent urination
- hair loss
- increased appetite
- increased sensitivity of the skin to sunlight
- menstrual pain
- stomach cramps, gas, or pain
- unusual secretion of milk, in females
- weight loss
- yawning

SITE-- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0045765/#!po=92.4242

CONCERTA
GENERIC NAME: METHYPHENDATE
STIMULANT

"Check with your doctor immediately if any of the following side effects occur:"
More common
- Fast heartbeat

Less common
- Chest pain
- fever
- joint pain
- skin rash or hives

Rare
- Black, tarry stools
- blood in the urine or stools
- blurred vision or other changes in vision
- convulsions
- crusting, dryness, or flaking of the skin
- muscle cramps
- pinpoint red spots on the skin
- scaling, severe redness, soreness, or swelling of the skin
- uncontrolled vocal outbursts or tics (uncontrolled and repeated body movements)
- unusual bleeding or bruising

"Check with your health care professional if any of the following side effects continue or are bothersome or if you have any questions about them:"
More common
- Abdominal or stomach pain
- headache
- loss of appetite
- nervousness

- stuffy nose
- trouble sleeping
- unusually warm skin

Less common

- Anger
- decreased appetite
- dizziness
- drowsiness
- fear
- irritability
- muscle aches
- nausea
- runny nose
- scalp hair loss
- talking, feeling, and acting with excitement
- vomiting

SITE--http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0045263/#DDIC601847.side_effects_section

ELAVIL
GENERIC NAME : AMITRIPTYLINE
Antidepressant and nerve pain medication

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

- Anxiety, restlessness, seeing or hearingthings that are not there
- Chest pain, trouble breathing
- Fast, pounding, or uneven heartbeat
- Feeling more excited or energetic than usual, racing thoughts, trouble sleeping
- Lightheadedness, dizziness, or fainting
- Seizures

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

- Blurred vision, dry mouth, fever
- Change in how much or how often you urinate
- Constipation, diarrhea, nausea, vomiting
- Drowsiness, sleepiness sexual problems

SITE - http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0008944/?report=details#side_effects
NORPRAMIM
GENERIC NAME : DESIPRAMINE
Antidepressant and nerve pain medication

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

- Agitation, irritability, sudden increase in energy, trouble sleeping
- Anxiety, restlessness, fast heartbeat, fever, sweating, muscle spasms or twitching, nausea, vomiting, diarrhea, seeing or hearing things that are not there
- Fast, pounding, or uneven heartbeat
- Fever, cough, chills, sore throat

- Thoughts of hurting yourself or others, worsening depression, unusual behavior
- Vision changes, eye pain

"If you notice these less serious side effects, talk with your doctor:"
- Dry mouth constipation tiredness

SITE -- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0009853/?report=details#side_effects
PAMELOR
GENERIC NAME : NORTRIPTYLINE
Antidepressant and nerve pain medication

"Call your doctor right away if you notice any of these side effects:"
- Anxiety, restlessness, fever, sweating, muscle spasms, twitching, nausea, vomiting, diarrhea, seeing or hearing things that are not there
- Change in how much or how often you urinate, problems urinating
- Chest pain or fast, pounding, or uneven heartbeat
- Eye pain, vision changes, seeing halos around lights
- Seizures or tremors
- Thoughts of hurting yourself or others, unusual behavior

SITE -- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0011451/?report=details#side_effects
SAVELLA
GENERIC NAME : MILNACIPRAN
Antidepressant and nerve pain medication

"Check with your doctor immediately if any of the following side effects occur:"

More Common
- Blurred vision
- body aches or pain
- chills
- cough
- difficulty with breathing
- dizziness
- ear congestion
- fast, irregular, pounding, or racing heartbeat or pulse
- fear or nervousness
- fever
- headache
- increased sweating
- loss of voice
- nasal congestion
- pounding in the ears
- runny nose
- slow or fast heartbeat
- sneezing
- sore throat

- unusual tiredness or weakness

Less Common

- Back pain
- burning, crawling, itching, numbness, prickling, "pins and needles", or tingling feelings
- chest pain or discomfort
- chills
- decrease in frequency of urination
- decrease in urine volume
- difficult or painful urination
- difficulty in passing urine(dribbling)
- frequent urination
- groin pain
- muscle aches
- pain or burning with urination
- shakiness in the legs, arms, hands, or feet
- swollen, tender prostate
- tightness in the chest

Rare

- Bladder pain
- bloating or swelling of the face, arms, hands, lower legs, or feet
- bloody or cloudy urine
- bruise
- discouragement
- fall
- feeling sad or empty
- frequent urge to urinate
- full or bloated feeling
- heartburn
- increased or decreased weight
- irritability
- lack of appetite
- loss of interest or pleasure
- lower back or side paipressure in the stomach
- rapid weight gain
- swelling of the abdominal or stomach are
- tingling of the hands or feet
- tiredness
- trouble concentrating
- trouble sleeping
- unusual weight gain or loss
- vomiting

"Check with your health care professional if any of the following side effects continue or are bothersome or if you have any questions about them:"

More common

- Feeling of warmth
- headache, severe and throbbing
- redness of the face, neck, arms, and occasionally, upper chest

- sudden sweating

Less common

- Abdominal or stomach pain
- Change or problems and with discharge of semen
- decreased appetite
- decreased interest in sexual intercourse
- inability to have or keep an erection
- loss in sexual ability, desire, drive, or performance
- not able to ejaculate semen
- rash
- swelling of the testes
- irritability
- loss of taste
- night sweats
- passing gas
- sleepiness or unusual drowsiness
- stomach discomfort, upset, or pain

RARE

- Acid or sour stomach
- belching
- bloated
- change in taste
- excess air or gas in the stomach or intestines
- full feeling
- heartburn
- indigestion
- irritability
- loss of taste
- night sweats
- passing gas
- sleepiness or unusual drowsiness
- stomach discomfort, upset, or pain

SITE- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0044734/#DDIC602849.side_effects_section

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

- Hallucinations

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

- Constipation Lightheadedness
- Nausea or vomiting
- Sleepiness

SITE -- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0009704/?report=details#side_effects
OXYCONTIN
GENERIC NAME : OXYCODONE
NARCOTIC

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

- Blue lips, fingernails, or skin
- Extreme dizziness or weakness, shallow breathing, slow or uneven heartbeat, sweating, cold or clammy skin, seizures
- Lightheadedness, dizziness, fainting
- Severe constipation, stomach pain, or vomiting
- Trouble breathing or slow breathing

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

- Headache
- Mild constipation, nausea, or vomiting
- Mild sleepiness or tiredness

SITE -- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0011542/?report=details#side_effects

VICODIN
GENERIC NAME: HYDROCODONE
Narcotic

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

- Peeling, red skin rash
- Change in how much or how often you urinate
- Dark urine or pale stools, loss of appetite, stomach pain, yellow skin or eyes
- Extreme weakness, shallow breathing, slow heartbeat, sweating, cold or clammy skin
- Lightheadedness, dizziness, fainting
- Unusual bleeding or bruising

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

- Constipation, nausea, vomiting
- Tiredness or sleepiness

SITE -- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0010590/?report=details#side_effects

It is extremely important to note that for some CFS/ME patients their muscle, joint, and/or neuropathic/nerve pain is so severe that it requires the use of prescription narcotic pain relievers such as codeine, OxyContin, and hydrocodone, as noted above. The use of prescription narcotic painkillers is extremely dangerous.

Prescriptions for painkillers have climbed 300% in the past decade causing 46 deaths per day which equals almost 17,000 Americans dying each year from overdose. Also, for every one death more than 30 Americans go to the ER for opioid/painkiller complications totaling more than 510,000.

One of the most dangerous factors of using prescription opioids is the fact that tolerance builds extremely quickly. Patients may start out on a very low dose that numbs their pain; but within just a few months of taking the prescription exactly as ordered they are taking very dangerous, deadly overdose levels to have the same pain numbing effects.

In as short as a few months to 1+ year a patient may be taking 5 to 10 fold more prescription opioids for them to work causing a profound chance for addiction, overdose and/or death.

While some patients with more severe pain take prescription narcotics others only take over the counter drugs such as acetaminophen (Tylenol and its generics). Many people believe that acetaminophen is a safe alternative to taking perception narcotics. However, over 80,000 Americans visit ERs due to taking too much acetaminophen. Acetaminophen is now the leading cause of liver failure in this country.

7. CFS causes severe suffering and severely impairs the patients ability to carry on activities of daily living. The U.S. FDA has been quoted as stating "We consider [ME/CFS] to be in the category of serious or life threatening diseases." Every aspect of a patients life is affected by CFS from their ability to work to manage their home life to spend time with friends and family. The fatigue that they suffer from is unrelenting no matter how much rest is obtained. Symptoms of CFS are usually exasperated from exertion in what is called post-exertion mayliese.

CFS has many debilitating symptoms. The hallmark symptom of CFS is the all encompassing, unrelenting fatigue. The fatigue level will be different in patients ranging from a patient needing to lower their work load to needing to quit their job to along with not working to not be able to keep up with normal household chores to being bedridden. The fatigue can completely rob someone of their livelihood. The level of fatigue that a patient experiences can and most likely will fluctuate. Some patients will have severe fatigue that slightly improves over time without a full recovery. Other patients will have levels of fatigue that will improve at times and remiss at others. There are patients who will have all diff levels of fatigue at different times during their illness.3.1

Patients with CFS often have muscle pain, joint pain and/or neuropathic/nerve pain. The pain is often felt deep in their body. Pain can be felt in any muscle and/or joint and in any amount and or combination of muscles or joints ranging from either one muscle and/or joint in pain to pain throughout all muscles and joints. It can be all levels of pain including mild to moderate to severe. The levels in pain will fluctuate with no set amount of time for any level to stay at; meaning some patients will have moderate pain for years then periods of severe and mild intersplaced. Other patients will have severe pain for awhile then periods of no pain but still fatigue. Other patients will have other combinations of pain level and amount of time for pain levels. All patients will have their own different and distinct pain symptoms.

Swollen and tender lymp nodes are common. The swollen and tender lymp nodes are because CFS causes widespread inflammation. Information may be anywhere in the body causing symptoms such as headache, sore throat, any joint pain, deep bone, muscle pain or nerve pain. Inflamation may be in the brain causing "brain fog", forgetfulness. confusion, impaired memory and concentration, and other cognitive difficulties.

Inflamation may be in other organs causing things like blurred vision, stuffy or runny nose, stomach ailments.

Inflamation is very common among CFS patients and causes them severe suffering that limits their daily activities.

8. There are no prescription medications to alleviate suffering that does not also cause suffering in and of itself. All of the conventionally prescribed medications have many adverse side effects that cause the patient to suffer and while certain other medications can be prescribed to help alleviate the side effects; those medications also can cause their own side effects.

That is especially true in the case of prescription painkillers.

There are a few non prescription medical therapies that are used with limited success. Most non prescription therapies have little benefit to helping in the long run and do not lead to a patient being cured of their CFS. The therapies are cathartic such as stress management techniques, meditation, deep breathing exercises, and graded exercise therapy if the patient is physically able to perform the motions.

9. The use of medical marijuana in CFS/ME patients is extremely beneficial in many ways. Medical marijuana alleviates the suffering caused by CFS and also the suffering patients get from adverse effects of their treatments.

Medical marijuana can provide some patients with energy deepening on which strain of marijuana is consumed. Sativa-dominant strains provide energetic benefits among many other therapeutic benefits.

Medical marijuana is extremely beneficial in treating the symptoms of muscle, joint, and neuropathic/nerve pain. Medical marijuana is a medically, scientifically and anecdotally proven treatment for all kinds of pain whether it be a muscular pain and/or joint/bone pain, nerve pain or any other kind of pain. One of marijuana's main components is Tetrahydrocannabinol (THC). THC affects the endocannabinoid system. The endocannabinoid system is made up of cannabinoids called anandamide and 2-AG (2-arachidonoyl glycerol)—which also act on CB receptors. Cannabinoids regulate how cells communicate—how they send, receive, or process messages.

The reason that marijuana helps pain is the fact some of the active pharmacological components of Narijuana mimic an internal chemical harm reduction system in our bodies,Endocannabinoid System (ECS), that keeps outlet health and well being in balence. The ECS is controlled by chemicals that the body produces itself called endocannabinoids. Our endocannabinoids keep the most critical biological functions in balance such as pain, the immune system, sleep, appetite and more. When the body looses that sense of balance it moves into a state of stress and then the endocannabinoids get to work fixing the problem. The pharmaceutically active components in marijuana mimic endocannabinoids so they are effective in helping restore the body and mange crises. The endocannabinoid system controls pain and inflammation. Narijuana works with the endocannabinoid system to reduce pain by keeping the system in balance. Muscle and joint pain is reduced in patients taking medical marijuana sometimes completely. Marijuana has 20x the anti-inflammatory power of aspirin and 2x the anti-inflammatory power of hydrocortisone so if the pain is caused by inflammation then medical marijuana is very effective in treating it.

Marijuana is also very effective at significantly reding neuropathic pain. Both THC and CBD activate the two main cannabinoid receptors, CB1&CB2, in the endocannabinoid system. CB1 & CB2 regulate the release of neurotransmitter and the CNS immune cells to manage pain levels.

Medical marijuana is extremely beneficial in treating all aspects of the inflammatory symptoms present in patients. Whether those inflammatory symptoms are muscle, joint, bone, and/or nerve pain or headaches, "brain fog" and/or other cognitive issues, or stomach ailments, or any other symptom caused As stated above marijuana has 20x the anti-inflammatory power of aspirin and 2x the anti-inflammatory power of hydrocortisone.

Medical marijuana works to reduce inflammation and curtailing the pain associated with infla. because of its two major cannabinoids; tetrahydrocannabidiol (THC) and cannabidiol (CBD).

Both THC & CBD reduce inflammation in CFS/ME patients. Also along with helping CFS/ME THC has been proven to reduce the development of atherosclerosis, a chronic inflammation disease that is a major

risk factor for strokes and heart attacks. THC also has been proven to lower the inflammation caused by the flu. Those two findings show that THC is beneficial in helping CFS/ME because as stated above one of the symptoms of CFS/ME is inflammation of the brain. THC has been proven to reduce the development of atherosclerosis which is a chronic inflammation disease that in part targets the brain (strokes); so it will also reduce inflammation in the brain from CFS/ME. Another way the finding shows that THC is beneficial in helping CFS/ME is again as stated above a symptom of CFS/ME is autoimmune; dealing with the immune system. The flu virus attacks the immune system so if THC is beneficial in helping heal from the flu, it also is beneficial in the whole immune system.

CBD has been proven to reduce joint inflammation. Joint inflammation may be one of the causes of joint pain for CFS/ME.

Medical marijuana is such a strong anti-inflammatory that the cannabinoids in it may be beneficial in certain types of cancers triggered by inflammation.

THC & CBD decrease the production and release of pro-inflammatory cytokines and decrease the activation of the LPS-induced STAT1 transcription factor, a key factor in some of the pro-inflammatory process. CBD, also reduces the activity of the NF-kappaB pathway, which is a primary pathway regulating pro-inflammatory genes, and it upregulates the activation of the STAT3 transcription factor, which induces anti-inflammatory events. CBD assists in reducing inflammation by suppressing fatty acid amidohydrolase activity, which then results in an increased concentration of the anti-inflammatory endocannabinoid, anandamide.

Widespread inflammatory pain is common with CFS/ME. Medical marijuana has been proven as helpful in pain management. Cannabis' cannabinoids act upon th the cannabinoid receptors, CB1 & CB2. CB1 & CB2 are involved the lessening of pain associated with infla. Studied have shown that CBD is effective in reducing neuropathic/nerve pain because it reduces the inflammation causing sciatic nerve constriction.

http://www.ncbi.nlm.nih.gov/pubmed/22448949

http://www.ncbi.nlm.nih.gov/m/pubmed/25635955/

http://www.ncbi.nlm.nih.gov/m/pubmed/18035205/

http://www.ncbi.nlm.nih.gov/m/pubmed/26385201/

http://www.ncbi.nlm.nih.gov/m/pubmed/26015168/

http://www.ncbi.nlm.nih.gov/m/pubmed/25635955/

http://www.ncbi.nlm.nih.gov/m/pubmed/25160710/

http://www.ncbi.nlm.nih.gov/m/pubmed/26325482/

https://www.researchgate.net/publication/264988433_Neuropathic_orofacial_pain_Cannabinoids_as_a_t

herapeutic_avenue

http://www.ncbi.nlm.nih.gov/m/pubmed/18035205/

http://www.jpain.org/article/S1526-5900(15)00601-X/abstract

http://www.ncbi.nlm.nih.gov/m/pubmed/24117398/

http://www.ncbi.nlm.nih.gov/m/pubmed/12185373/

http://www.ncbi.nlm.nih.gov/m/pubmed/25846617/

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2628209/

http://www.ncbi.nlm.nih.gov/m/pubmed/19910459/

http://www.ncbi.nlm.nih.gov/m/pubmed/18073275/

http://www.ncbi.nlm.nih.gov/m/pubmed/10367294/

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2664885/

http://www.ncbi.nlm.nih.gov/m/pubmed/18073275/

http://www.ncbi.nlm.nih.gov/m/pubmed/25703248/

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2664885/

http://www.ncbi.nlm.nih.gov/m/pubmed/11972997/

http://www.ncbi.nlm.nih.gov/m/pubmed/14963641/

http://www.ncbi.nlm.nih.gov/m/pubmed/17157290/

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3728280/

http://www.ncbi.nlm.nih.gov/books/NBK6154/

PubMed Search term

The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review.

Review article

Boychuk DG, et al. J Oral Facial Pain Headache. 2015.
Show full citation

Abstract

AIMS: To carry out a systematic review to assess the effectiveness of cannabis extracts and cannabinoids in the management of chronic nonmalignant neuropathic pain.

METHODS: Electronic database searches were performed using Medline, PubMed, Embase, all evidence-based medicine reviews, and Web of Science, through communication with the Canadian Consortium for the Investigation of Cannabinoids (CCIC), and by searching printed indices from 1950. Terms used were marijuana, marihuana, cannabis, cannabinoids, nabilone, delta-9-tetrahydrocannabinol, cannabidiol, ajulemic acid, dronabinol, pain, chronic, disease, and neuropathic. Randomized placebo-controlled trials (RCTs) involving cannabis and cannabinoids for the treatment of chronic nonmalignant pain were selected. Outcomes considered were reduction in pain intensity and adverse events.

RESULTS: Of the 24 studies that examined chronic neuropathic pain, 11 studies were excluded. The 13 included studies were rated using the Jadad Scale to measure bias in pain research. Evaluation of these studies suggested that cannabinoids may provide effective analgesia in chronic neuropathic pain conditions that are refractory to other treatments.

Similar articles

Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials.
Review article
Lynch ME, et al. Br J Clin Pharmacol. 2011.

Efficacy and adverse effects of medical marijuana for chronic noncancer pain: Systematic review of randomized controlled trials.
Review article
Deshpande A, et al. Can Fam Physician. 2015.

Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain.
Iskedjian M, et al. Curr Med Res Opin. 2007.

[Efficacy, tolerability and safety of cannabinoids for chronic neuropathic pain: A systematic review of randomized controlled studies].
Petzke F, et al. Schmerz. 2016.

Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review.
Review article
Campbell FA, et al. BMJ. 2001.

See all

[redacted] / Chronic Fatigue Syndrome

CONCLUSION: Cannabis-based medicinal extracts used in different populations of chronic nonmalignant neuropathic pain patients may provide effective analgesia in conditions that are refractory to other treatments. Further high-quality studies are needed to assess the impact of the duration of the treatment as well as the best form of drug delivery.

PMID: 25635955 [PubMed - indexed for MEDLINE]

Comment in

J Oral Facial Pain Headache. 2015 Winter;29(1):5-6.

BJP BRITISH JOURNAL OF PHARMACOLOGY | BPS BRITISH PHARMACOLOGICAL SOCIETY

Br J Pharmacol. 2014 Feb; 171(3): 636–645. PMCID: PMC3969077
Published online 2014 Jan 13. doi: 10.1111/bph.12439

Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT_{1A} receptors without diminishing nervous system function or chemotherapy efficacy

Sara Jane Ward,[1] Sean D McAllister,[2] Rumi Kawamura,[2] Ryuchi Murase,[2] Harshini Neelakantan,[3] and Ellen A Walker[3]

[1]Center for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA, USA
[2]Cancer Research, California Pacific Medical Center Research Institute, San Francisco, CA, USA
[3]Pharmaceutical Sciences, Temple University School of Pharmacy, Philadelphia, PA, USA

Correspondence Sara Jane Ward, Center for Substance Abuse Research, Temple University School of Medicine, 3500 N Broad St, Philadelphia, PA 19140, USA. E-mail: saraward@temple.edu

Received 2013 Mar 10; Revised 2013 Aug 12; Accepted 2013 Oct 4.

Abstract

Go to:

Background and Purpose

Paclitaxel (PAC) is associated with chemotherapy-induced neuropathic pain (CIPN) that can lead to the cessation of treatment in cancer patients even in the absence of alternate therapies. We previously reported that chronic administration of the non-psychoactive cannabinoid cannabidiol (CBD) prevents PAC-induced mechanical and thermal sensitivity in mice. Hence, we sought to determine receptor mechanisms by which CBD inhibits CIPN and whether CBD negatively effects nervous system function or chemotherapy efficacy.

Experimental Approach

The ability of acute CBD pretreatment to prevent PAC-induced mechanical sensitivity was assessed, as was the effect of CBD on place conditioning and on an operant-conditioned learning and memory task. The potential interaction of CBD and PAC on breast cancer cell viability was determined using the MTT assay.

Key Results

PAC-induced mechanical sensitivity was prevented by administration of CBD (2.5 – 10 $mg \cdot kg^{-1}$) in female C57Bl/6 mice. This effect was reversed by co-administration of the 5-HT_{1A} antagonist WAY 100635, but not the CB_1 antagonist SR141716 or the CB_2 antagonist SR144528. CBD produced no conditioned rewarding effects and did not affect conditioned learning and memory. Also, CBD + PAC combinations produce additive to synergistic inhibition of breast cancer cell viability.

Conclusions and Implications

Our data suggest that CBD is protective against PAC-induced neurotoxicity mediated in part by the 5-HT_{1A}

receptor system. Furthermore, CBD treatment was devoid of conditioned rewarding effects or cognitive impairment and did not attenuate PAC-induced inhibition of breast cancer cell viability. Hence, adjunct treatment with CBD during PAC chemotherapy may be safe and effective in the prevention or attenuation of CIPN.

Keywords: cannabidiol, paclitaxel, chemotherapy-induced neuropathic pain, CIPN, 5-HT_{1A}, breast cancer, cannabinoid, mechanical sensitivity

Introduction

Go to:

Chemotherapy-induced peripheral neuropathy (CIPN) is a serious dose-limiting side effect associated with several commonly used chemotherapeutic agents, including taxanes, platinum agents and vinca alkaloids. CIPN occurs in 30–40% of patients but incidences can approach 75% with certain regimens. Common peripheral sensory symptoms include paresthesias and dysesthesias, pain, numbness and tingling, and sensitivity to touch and temperature. Motor symptoms include weakness and gait and balance disturbances (Visovsky *et al.*, 2007). In most cases, CIPN is only partially reversible with cessation of treatment and in the worst cases damage can be permanent. To date, no one drug or drug class is considered to be safe and effective for treatment of CIPN (Lynch *et al.*, 2004), making the identification of alternative effective analgesics a crucial medical need.

The exact mechanism of CIPN has not been fully elucidated and can differ across classes of chemotherapeutic agents. In general, these agents can affect cellular microtubules, disrupt mitochondrial function or impair DNA synthesis. Such assaults on peripheral nerves can lead to sensitization and spontaneous activity of these fibres (Xiao and Bennett, 2008), alteration of voltage-gated sodium and transient receptor potential vanilloid (TRPV) channel activity and expression (Adelsberger *et al.*, 2000; Gauchan *et al.*, 2009), dorsal column ascending fibre pathology (Cavaletti *et al.*, 1995), and infiltration of activated microglia and release of pro-inflammatory cytokines (Hu and McLachlan, 2002), ultimately leading to ascending pain pathway sensitization (Peters *et al.*, 2007). Functional changes to the descending inhibitory pain pathway can also result, altering noradrenaline and 5-HT signalling and further amplifying the effects of central sensitization (Baron *et al.*, 2010).

Cannabinoids suppress neuropathic pain induced by traumatic nerve injury, toxic insults and metabolic changes (for review, see Guindon and Hohmann, 2008). The mixed CB_1/CB_2 agonist WIN55,212-2 suppresses neuropathic nociception induced by the chemotherapeutic agent paclitaxel (PAC) through a CB_1-specific mechanism (Pascual *et al.*, 2005). WIN55,212-2 also suppresses vincristine-induced neuropathy through activation of both CB_1 and CB_2 receptors (Rahn *et al.*, 2007). Activation of CB_2 receptors partially attenuates vincristine-induced neuropathy (Rahn *et al.*, 2007) and fully attenuates PAC-induced neuropathy (Rahn *et al.*, 2008; Deng *et al.*, 2012) in rats. In humans, several studies have demonstrated anti-neuropathic effects of whole cannabis, Δ^9-tetrahydrocannabinol (THC), or its synthetic analogues nabilone or dronabinol (Pinsger *et al.*, 2006; Skrabek *et al.*, 2008; Ware *et al.*, 2010). However, several reports describe these effects as modest, while others have reported negative results (Wade *et al.*, 2004; Johnson *et al.*, 2010). Importantly, patients in the vast majority of studies also report several adverse events such as dizziness, dryness, sedation, disorientation and decreased concentration, and while these were not categorized as serious they probably limit the tolerability and compliance with such treatments.

One of the more successful cannabis-based pharmaceuticals for the treatment of pain is the buccal spray Sativex [1:1 formulation of THC and the phytocannabinoid cannabidiol (CBD)], approved in the EU and Canada for treatment of multiple sclerosis spasticity, with an additional license in Canada for use in multiple sclerosis-associated neuropathic pain and cancer pain. Sativex has recently entered directly into US late-stage trials because of its promising therapeutic uses, and has shown pain-relieving effects in two recent clinical trials: one for cancer pain (Johnson *et al.*, 2010) and one for neuropathic pain associated with multiple sclerosis (Langford *et al.*, 2013). However, the psychoactive side effects of Sativex mediated by THC may limit its broader utility in the clinic. For

example, THC and Sativex have been determined to produce similar subjective and physiological effects (Johnson *et al.*, 2010; Karschner *et al.*, 2011). However, mounting preclinical evidence now demonstrates that CBD alone has anti-neuropathic effects (Costa *et al.*, 2007; Toth *et al.*, 2010; Xiong *et al.*, 2012; see Fernández-Ruiz *et al.*, 2013 for review). To date, no clinical trials have yet commenced to study the efficacy of the non-psychoactive CBD as a monotherapy for the treatment of neuropathic pain. We have recently reported that 14 days of administration of CBD prevents the onset of PAC-induced mechanical and thermal sensitivity in a female mouse model of CIPN (Ward *et al.*, 2011).

In the present set of experiments, we aimed to determine whether sub-chronic dosing regimen of CBD would prevent PAC-induced mechanical sensitivity while also determining whether this effect is mediated by activation of 5-HT_{1A} receptors. CBD binds to the 5-HT_{1A} receptor as an agonist with micromolar affinity (Russo *et al.*, 2005), and research has demonstrated potent anti-neuropathic effects with 5-HT_{1A} agonists (e.g. Colpaert, 2006). Indeed, intra-periaqueductal grey injection of CBD produces dose-dependent antinociception that is blocked by co-administration of the 5-HT_{1A} antagonist WAY100635 (Maione *et al.*, 2011). Lastly, we also sought to determine whether treatment with CBD would have any effects on conditioned reward, learning and memory, and the inhibitory activity of PAC on breast cancer cell viability.

Methods

Go to:

Animals. Female C57Bl/6 mice weighing 16–20 g (Taconic Farms, Cranbury, NJ, USA; Jackson Labs, Chicago, IL, USA) were acclimatized to the temperature- and humidity-controlled vivarium and housed in groups of four for at least 5 days before initiation of behavioural studies. Artificial lighting provided a reverse 12 h light/dark cycle (lights off 10:00 h). The animals had free access to dietary food and water except where noted. The total number of animals used was 240 and the procedures used were as humane as possible and complied with the guidelines of the Temple University Institutional Animal Care and Use Committee. All studies involving animals are reported in accordance with the ARRIVE guidelines for reporting experiments involving animals (Kilkenny *et al.*, 2010; McGrath *et al.*, 2010).

Drugs. PAC solution [Teva Parenteral Medicines: dissolved in 1:1 mixture of alcohol and cremophor (CRM)] was obtained from Temple University Hospital Cancer Center (Philadelphia, PA, USA). For cell viability studies in breast cancer cell lines, PAC was obtained from Sigma (St. Louis, MO, USA). CBD, morphine sulfate, and the CB_1 (SR141716A) and CB_2 receptor (SR144528) antagonist were provided by the National Institute on Drug Abuse drug supply program (Bethesda, MD, USA). WAY100635 was purchased from RBI. PAC was diluted in 0.9% saline. CBD was dissolved in a 1:1 mixture of ethanol and CRM (Sigma-Aldrich, St. Louis, MO, USA) and diluted with saline to a final ratio of 1:1:18 (ethanol : CRM : saline). Morphine and WAY100635 were dissolved in 0.9% saline. All injections were given i.p. in a volume of 10 $\mu L \cdot g^{-1}$ of body weight.

Mechanical allodynia

In the first set of experiments, mechanical allodynia was assessed in five groups of mice ($n = 8$ per group) using von Frey monofilaments of varying forces (0.07–4.0 g) applied to the mid-plantar surface of the right hind paw, with each application held in c-shape for 6 s using the up-down method of Dixon (1980). Mice were placed in individual Plexiglas compartments (Med Associates, St. Albans, VT, USA) on top of a wire grid floor suspended 20 cm above the laboratory bench top and acclimatized to the environment for 15 min before each test session. Baseline sensitivity to the monofilaments was assessed 1 day before the start of drug administration and continued weekly for 10 weeks. On experimental days 1, 3, 5 and 7, mice received the following two i.p. injections, spaced 15 min apart: group 1 – CRM vehicle, CRM vehicle; group 2 – CRM vehicle, 4.0 $mg \cdot kg^{-1}$ PAC; group 3 – CRM vehicle, 8.0 $mg \cdot kg^{-1}$ PAC; group 4 – 2.5 $mg \cdot kg^{-1}$ CBD, 8.0 $mg \cdot kg^{-1}$ PAC; 5.0 $mg \cdot kg^{-1}$ CBD, 8.0 $mg \cdot kg^{-1}$ PAC. Mechanical allodynia was not assessed on injection days. PAC and CBD doses were based on significant findings

from Ward *et al.* (2011).

In the second set of experiments, mechanical allodynia was assessed in an identical manner to that described above. Four groups of mice were treated on experimental days 1, 3, 5 and 7 with three i.p. injections spaced 15 min apart: group 1 – saline, CRM vehicle, CRM vehicle; group 2 – saline, CRM vehicle, 8.0 $mg{\cdot}kg^{-1}$ PAC; group 3 – saline, 5.0 $mg{\cdot}kg^{-1}$ CBD, 8.0 $mg{\cdot}kg^{-1}$ PAC; group 4 – 1.0 $mg{\cdot}kg^{-1}$ WAY100635, 5.0 $mg{\cdot}kg^{-1}$ CBD, 8.0 $mg{\cdot}kg^{-1}$ PAC. Dose of WAY100635 was based on several studies investigating blockade of $5\text{-}HT_{1A}$ agonist-mediated behavioural pharmacological effects (e.g. Hagiwara *et al.*, 2008).

In the third set of experiments, mechanical allodynia was assessed 1 day before the start of drug administration and on day 15 following the first injections. Five groups of mice were treated on experimental days 1, 3, 5 and 7 with three i.p. injections spaced 15 min apart: group 1 – saline, CRM vehicle, CRM vehicle; group 2 – saline, CRM vehicle, 8.0 $mg{\cdot}kg^{-1}$ PAC; group 3 – saline, 5.0 $mg{\cdot}kg^{-1}$ CBD, 8.0 $mg{\cdot}kg^{-1}$ PAC; group 4 – 3.0 $mg{\cdot}kg^{-1}$ SR141716, 5.0 $mg{\cdot}kg^{-1}$ CBD, 8.0 $mg{\cdot}kg^{-1}$ PAC; group 5 – 3.0 $mg{\cdot}kg^{-1}$ SR144528, 5.0 $mg{\cdot}kg^{-1}$ CBD, 8.0 $mg{\cdot}kg^{-1}$ PAC. Doses of SR141716 and SR144528 were based on several studies investigating blockade of CB_1 and CB_2 agonist-mediated effects respectively (Rahn *et al.*, 2007; 2008,).

Place conditioning

The conditioned rewarding effects of CBD and morphine were assessed using a standard mouse place conditioning procedure and Med Associates mouse three compartment place conditioning chambers (MED-CPP-3013). Mice received vehicle or morphine (2.5–10 $mg{\cdot}kg^{-1}$, i.p.; 15 min pretreatment) or vehicle or CBD (2.5–10 $mg{\cdot}kg^{-1}$, i.p.; 30 min pretreatment) on alternate days for 30 min conditioning sessions for 6 successive days. Vehicle injections were paired with the black compartment and the drug injections with the white compartment of the conditioned place preference (CPP) apparatus. On day 7, test sessions were conducted where mice in a drug-free state had 30 min free access to all chambers following an initial 5 min acclimation in the central grey compartment. The time spent in the drug- and vehicle-paired compartments was recorded on the test day and the data are presented as time spent in the drug-paired compartment.

Autoshaping

The effect of CBD (2.0–20 $mg{\cdot}kg^{-1}$, i.p.) on acquisition and retention of a conditioned learning task was assessed using a modified autoshaping procedure and Med Associates mouse operant conditioning chambers (ENV 307W) as described in Foley *et al.* (2008). Briefly, mice were weighed and food-restricted for 24 h before the experimental session. On the acquisition day, mice were placed inside a standard mouse experimental chamber, and the availability of a sweet liquid reinforcer (50% vanilla Ensure in tap water; Abbott Laboratories, Columbus, OH, USA) under a variable interval schedule was signalled by a tone. The mouse was reinforced with the vanilla Ensure if it made a nose-poke response into a centre dipper receptacle during an 8 s period following the tone. Each acquisition session lasted for 2 h or until 20 reinforced nose pokes were recorded. For the retention test, mice were placed back into the chambers 24 h following the acquisition session under the same conditions. In the present experiment, mice were pretreated with vehicle or CBD 30 min before the acquisition session.

Cell culture and treatments

The mouse and human breast cancer cell lines used were 4T1 (obtained from ATCC) and MDA-MB231-luc-D3H2LN (obtained from Caliper; Jenkins *et al.*, 2005) cells respectively. Cell lines were maintained at 37°C and 5% CO_2. In all experiments, the different cell populations were first cultured in RPMI media containing 10% FBS. Cells were then seeded into 96-well plates in 10% FBS and on the first day of treatment the media was replaced with vehicle control or drug in RPMI and 0.1% FBS as previously reported (McAllister *et al.*, 2005). The

media with the appropriate compounds were replaced every 24 h.

MTT assay

Assays were performed as previously described (McAllister *et al.*, 2007). Cell viability (%) was calculated as the MTT absorbance of the treated cells/control cells × 100.

Pharmacological and statistical analyses

IC_{50} values were calculated using CompuSyn (Paramus, NJ, USA). To test for synergism, the combination index (CI) was also calculated using Compusyn where CI <1, = 1 and >1 indicates synergism, additive effect and antagonism, respectively, as previously described (Chou *et al.*, 1993; Chou, 2006) and as previously published by our group (Marcu *et al.*, 2010). Based on the classic isobologram for mutually exclusive effects relative to the end point of measurement, the CI value for x % inhibition is calculated as: $CI = (D)_1/(Dx)1 + (D)_2/(Dx)_2$.

$(D)_1$ PAC; $(D)_2$ represents CBD; $(Dx)_1$ and $(Dx)_2$ are the doses for x% growth that can be obtained using the IC_F equation described above. $(D)_1$ and $(D)_2$ are the concentrations in the combination which also inhibit cell growth by x % (Chou *et al.*, 1993).

Results

Go to:

Mechanical allodynia

Treatment with either 4.0 or 8.0 $mg \cdot kg^{-1}$ PAC on alternating days for a total of four injections produced mechanical sensitivity in female C57Bl/6 mice. Peak sensitivity was achieved by week 2 post-treatment and lasted for the full 10 weeks of the study for the 8.0 $mg \cdot kg^{-1}$ PAC dose. Co-administration of either 2.5 or 5.0 $mg \cdot kg^{-1}$ CBD 15 min prior to each PAC injection prevented PAC-induced mechanical sensitivity. Two-way ANOVA revealed significant main effects of treatment [$F(4, 310) = 27.71$, $P < 0.0001$] and time [$F(9, 310) = 5.001$, $P < 0.001$] and no significant interaction ($F < 1.0$). Bonferroni post-tests revealed a significant increase in sensitivity in both the 4.0 and 8.0 $mg \cdot kg^{-1}$ PAC groups compared with Veh/Veh. In contrast, the PAC groups pretreated with either 2.5 or 5.0 $mg \cdot kg^{-1}$ CBD were not significantly different from Veh/Veh in their mechanical sensitivity (Figure 1).

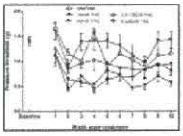


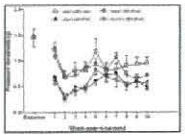
Figure 1

Effect of CBD pretreatment (2.5, 5.0 $mg \cdot kg^{-1}$, i.p.) on PAC-induced mechanical allodynia in female C57Bl/6 mice. Baseline sensitivity to von Frey filaments was assessed on the day before drug administration and continued weekly ...

Additional administration of the $5\text{-}HT_{1A}$ antagonist WAY 100635 (1.0 $mg \cdot kg^{-1}$) before PAC and CBD treatment attenuated the reversal of PAC-induced mechanical sensitivity by CBD. Two-way ANOVA revealed significant effects of treatment [$F(3, 280) = 24.66$, $P < 0.0001$] and time [$F(9, 280) = 5.058$, $P < 0.001$] and no significant interaction ($F < 1.0$). Bonferroni post-test revealed a significant increase in the sensitivity of the PAC group and the WAY/CBD/PAC groups compared with Veh/Veh/Veh. In contrast, the Veh/CBD/PAC group did not differ significantly from the Veh/Veh/Veh group on mechanical sensitivity (Figure 2).

Figure 2

Effect of WAY100635 pretreatment (1.0 $mg \cdot kg^{-1}$, i.p.) on CBD prevention of PAC-induced mechanical allodynia in female C57Bl/6 mice. Baseline sensitivity to von Frey filaments was



assessed on the day before drug administration and ...

Conversely, additional administration of either the CB_1 antagonist SR141716 (3.0 $mg \cdot kg^{-1}$) or the CB_2 antagonist SR144528 (3.0 $mg \cdot kg^{-1}$) had no effect on the reversal of PAC-induced mechanical sensitivity by CBD as measured on day 15 post-initiation of treatment. One-way ANOVA revealed a significant effect of treatment [$F(8, 79) = 7.647$, $P < 0.05$]. Dunnett's multiple comparison test determined that only the Veh/Veh/PAC, WAY/CBD/PAC, SR1/Veh/PAC and SR2/Veh/PAC groups were statistically different from the Veh/Veh/Veh control group ($P < 0.05$), showing significant mechanical allodynia (Figure 3). Furthermore, the ability of WAY to block CBD's anti-allodynic effect could not be attributed to the effect of WAY alone on PAC-induced mechanical sensitivity, as WAY itself did not potentiate the effect of PAC alone (WAY/Veh/PAC).

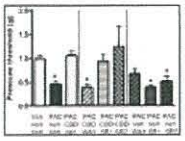


Figure 3

Effect of CB_1 (SR141716; SR1) or CB_2 (SR144528; SR2) receptor antagonism on CBD prevention of PAC-induced mechanical allodynia in female C57Bl/6 mice. Sensitivity to von Frey filaments was assessed on day 15 post-treatment. Mice received the following ...

Place conditioning and autoshaping

There was no effect of CBD on time spent in the white, CBD-paired compartment compared with CRM vehicle control, although there was a trend towards a decrease in the time spent in the CBD-paired compartment at the highest dose tested. One-way ANOVA revealed no significant effect of treatment [$F(3, 31) = 2.477$, n.s.]. By comparison, morphine treatment significantly increased the time spent in the white, morphine-paired compartment compared with saline vehicle control [$F(3, 30) = 15.66$, $P < 0.0001$] (Figure 4). Furthermore, CBD treatment had no effect on the time to earn 10 reinforcers during the acquisition [$F(3, 32) < 1$] or retention [$F(3, 25) = 1.692$, n.s.] sessions (Figure 5).

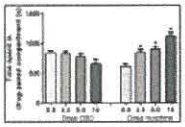


Figure 4

Ability of CBD (2.5–10 $mg \cdot kg^{-1}$, i.p.) or morphine (2.5–10 $mg \cdot kg^{-1}$, i.p.) to produce place conditioning in female C57Bl/6 mice. Mice received vehicle or morphine (2.5–10 mg·kg ...

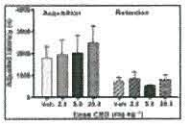


Figure 5

Effect of CBD administration (2.5–20 $mg \cdot kg^{-1}$, i.p.) on acquisition and retention of a conditioned food reward task. Nose-poke responses are reinforced when made within 8 s following a tone signalling availability ...

CBD enhances PAC inhibition of breast cancer cell viability

Multiple studies now show that CBD can act as a direct antitumor agent against aggressive cancers (Massi *et al.*, 2013). Therefore, there is the potential for CBD to produce synergistic, additive or antagonist effects when combined with PAC. We studied these potential interactions by evaluating the effects of the drugs alone and in combination on breast cancer cell viability. 4T1 and luciferase-labelled MDA-MB231-luc-D3H2LN (LN 231) cells were treated for 2 days with a range of concentrations of either PAC or CBD and the ability of the drugs to inhibit cell viability was assessed using the MTT assay (Figure 6A). In this assay, CBD was more potent than PAC

at inhibiting cell viability and CBD acted as a full agonist whereas PAC acted as a partial agonist. PAC could not fully inhibit cell viability even up to concentration of 50 μM. PAC began to precipitate out of solution in the MTT assay at the higher concentration range which precluded us from further concentrating the drug. The average values from the concentration response curves which were then used to derive medium-effect plot parameters including the dose-reduction index were calculated (Table 1). Using the calculated IC_{50} values, various dose ratios of CBD and PAC were combined in both 4T1 and LN 231 cells and viability was evaluated (Figure 6B and C). The use of higher dose ratios was limited by the solubility of PAC; however, this did not affect the calculation of a CI. As shown in Figure 6D, the combination of CBD and PAC led to an additive and synergistic inhibition of cell viability in 4T1 and LN 231 cells respectively.

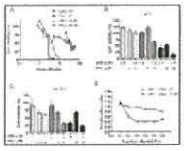


Figure 6

Treatments combining CBD and PAC produce additive to synergistic inhibition of breast cancer cell viability. Cell viability was measured using the MTT assay. (A) 4T1 and MDA-MB231-luc-D3H2LN (LN 231) cells were treated for 2 days with vehicle, CBD or ...

Table 1

Calculated median-effect plot parameters and DRI for drugs and drug combinations

Discussion

Go to:

We had previously reported that a 14 day dosing regimen of CBD (5.0 and 10 $mg{\cdot}kg^{-1}$) prevented the onset of PAC-induced mechanical and thermal sensitivity (Ward *et al.*, 2011). In the present study, we determined that both 2.5 and 5 $mg{\cdot}kg^{-1}$ CBD treatment, administered only before each of the four PAC injections of a standard dosing regimen for inducing CIPN in rodents, also prevents the development of PAC-induced mechanical sensitivity in female C57Bl/6 mice. The present study further demonstrated that 5-HT_{1A} receptors are partially involved in the neuroprotective effect of CBD in this model, in that co-administration of the 5-HT_{1A} antagonist blocked the preventive effect of CBD on PAC-induced mechanical sensitivity. In contrast, neither the CB_1 antagonist SR141716 nor the CB_2 antagonist SR144528 affected the efficacy of CBD, suggesting its neuroprotective effect was not mediated by activation of CB_1 or CB_2 receptors. Furthermore, treatment with the antagonists alone did not further exacerbate PAC-induced mechanical sensitivity. In addition, CBD did not produce conditioned rewarding effects using the place conditioning procedure, nor did it produce deficits in acquisition or retention of an operant learning task using the autoshaping procedure. Lastly, CBD did not attenuate the anti-neoplastic effect of PAC on breast cancer cells in culture. Indeed, at optimal concentrations, CBD + PAC combinations produce additive to synergistic inhibition of breast cancer cell viability.

Cannabinoids represent a promising pharmacotherapeutic strategy for treatment of neuropathic pain considering that available alternatives are not always successful in the clinic. A putative role for cannabinoids in the amelioration of established PAC-induced CIPN has recently been demonstrated. Pascual *et al.* (2005) showed that the non-selective cannabinoid agonist WIN 55,212-2 reduced an established thermal hyperalgesia and tactile allodynia 22 days post-PAC treatment in rats, and that this effect was blocked by the CB_1 antagonist SR141716, suggesting the involvement of the CB_1 receptor; the potential participation of the CB_2 receptor in mediating this effect, however, was not investigated. The anti-neuropathic efficacy of non-selective CB agonist therapies, including the THC : CBD combination Sativex, appears promising; nonetheless, unwanted side effects, mainly the production of psychoactivity produced through activation of CB_1 receptors, remain a hindrance to their wider use (Johnson *et al.*, 2010; Karschner *et al.*, 2011; but see Langford *et al.*, 2013). The efficacy and safety of CB_2

selective agents in humans for treatment of neuropathic pain remain to be determined. Activation of CB_2 receptors has been shown to suppress established chemotherapy-induced CIPN in rats (Naguib *et al.*, 2008; Rahn *et al.*, 2008; Deng *et al.*, 2012). In the study of Rahn *et al*, CB_2 agonist administration was most effective at 30 min post-injection, with mechanical sensitivity re-emerging 60 min following agonist administration, suggesting that repeated administration would be necessary to treat the CIPN symptoms in the long term.

Based on growing preclinical literature, the myriad of CBD's pharmacological effects, from anti-neuropathic to anxiolytic and antipsychotic, may be mediated through either CB receptor-dependent and independent mechanisms or combinations thereof (Izzo *et al.*, 2009). It is important from both a basic science mechanistic as well as drug discovery perspective to identify which of these are necessary and/or sufficient for CBD's anti-neuropathic effects specifically. In the present study, we demonstrated that activation of $5\text{-}HT_{1A}$ receptors is necessary for the protective effect of CBD against PAC-induced neuropathic pain, in that pretreatment with WAY100635 blocked this effect. CBD acts as a direct agonist at $5\text{-}HT_{1A}$ receptors (Russo *et al.*, 2005; Alves *et al.*, 2010), and activation of the $5\text{-}HT_{1A}$ receptor in the rostroventromedial medulla plays an important role in modulating the descending inhibitory pain pathway (Colpaert, 2006; Viisanen and Pertovaara, 2010). Importantly, 5-hydroxytryptaminergic drugs presently represent one of the only drug classes showing efficacy in the treatment of neuropathic pain in human clinical trials (Finnerup *et al.*, 2010). $5\text{-}HT_{1A}$ agonism has also been shown to be neuroprotective via attenuation of microglial activation and oxidative stress (Collier *et al.*, 2011a,b2011b), two immune alterations relevant to CIPN. Results from the present study failed to show a role for CB_1 or CB_2 receptor activation in CBD's anti-neuropathic effect. Although CBD has no appreciable affinity for CB_1 or CB_2 receptors, some evidence suggests that it can act as an indirect CB agonist via enhancement of eCB levels (Bisogno *et al.*, 2001; Campos *et al.*, 2013). However, our results are in agreement with the previous report by Comelli *et al.* (2008) demonstrating that CBD's anti-hyperalgesic effect did not involve CB_1 and CB_2 receptors. Others have shown that neither CB_1 nor CB_2 receptor activation was involved in CBD's neuroprotective (Sagredo *et al.*, 2007; 2011,) or anti-inflammatory (Costa *et al.*, 2004) effects in other rodent models, whereas CBD-induced tail flick analgesia was blocked by co-administration of the CB_1 antagonist SR141716 (Maione *et al.*, 2011). CB_1 receptor involvement in the pharmacological effects of CBD on non-nociceptive behaviours has also been reported (Casarotto *et al.*, 2010; Do Monte *et al.*, 2013). Additionally, CBD binds with moderate affinity to TRPV1 (vanilloid) receptors and important nociceptive modulators, and anti-neuropathic effects of CBD have been shown to depend upon TRPV1 activation (Comelli *et al.*, 2008), while acute antinociceptive effects have not (Maione *et al.*, 2011). Taken together with these other findings, our results suggest that specific pharmacological effects of CBD, such as its activity at $5\text{-}HT_{1A}$ and TRPV1 receptors, mediate CBD's anti-neuropathic effects, while its activity at other targets, including CB receptors, may be more important for other actions.

A novel strategy investigated in the present study is that of assessing the ability of CB-based pharmacotherapy to prevent the development of PAC-induced mechanical sensitivity as opposed to acutely reversing it. Other studies have demonstrated the ability of agents from other drug classes, including anticonvulsants (Xiao *et al.*, 2007), antidepressants (Xiao *et al.*, 2008) and opioids (Rahn *et al.*, 2008), to reduce CIPN symptoms in rodents, but to date no one drug or drug class is considered to be effective for reversal of CIPN (Lynch *et al.*, 2004). CIPN represents a neuropathic pain state with the unique possibility of aiming to prevent its onset with effective adjunctive treatment, as opposed to only attempting to reverse its symptoms following its onset. However, such investigations into prevention of PAC-induced CIPN in rodents are few. Interestingly, CBD has also recently been reported to protect against the onset of type I diabetic peripheral neuropathic pain (Toth *et al.*, 2010), hepatic ischaemia/reperfusion injury (Mukhopadhyay *et al.*, 2011), and retinal inflammation and degeneration (El-Remessy *et al.*, 2008) in rodent models. While clinical trials are ongoing investigating the anti-inflammatory effects of CBD as a monotherapy in disease states such as inflammatory bowel disease and graft versus host disease, its efficacy at preventing the onset of neuropathic pain in humans remains to be determined.

CBD represents a significant improvement in CB-based pharmacotherapy, in that CBD represents a cannabinoid that is regarded as being devoid of psychoactive euphoric effects. Surprisingly, however, a few preclinical studies to date have investigated CBD in reward models (e.g. Parker *et al.*, 2004). Here we demonstrated across a wider range of doses that CBD does not produce a CPP in C57Bl/6 mice using parameters that readily detect the conditioned rewarding properties of the same doses of morphine (Figure 4). CBD does, however, bind to several brain receptors and its anxiolytic and antipsychotic actions have been well characterized in animals and more recently in humans, so it is worth investigating whether CBD produces other CNS effects that would be considered adverse. An important pharmacological effect of CB receptor activation in addition to euphoria that has been extensively studied is disruption of learning and memory processes (see Lichtman *et al.*, 2002 for review). In the present study, we demonstrated that CBD across a wide range of doses did not impair acquisition or retention of an instrumental learning task. Interestingly, others have reported that CBD actually enhances certain types of learning, specifically extinction (Bitencourt *et al.*, 2008) and reconsolidation (Stern *et al.*, 2012). Determination of the effect of a putative anti-CIPN pharmacotherapy on learning and memory is important because cancer chemotherapeutics themselves are associated with a form of cognitive impairment in many cancer patients also known as 'chemofog' or 'chemobrain' (Argyriou *et al.*, 2011). CB agonists are likely to exacerbate these effects, while in contrast CBD should not affect cognition, and may therefore prove to be a more tolerable alternative as an adjuvant chemotherapy agent. In fact, as oxidative stress is a leading hypothesis regarding the mechanism underlying chemotherapy-associated cognitive impairment, the ability of CBD to reverse this phenomenon should also be investigated.

Finally, CBD has direct antitumor activity in multiple types of cancer (Massi *et al.*, 2013). We determined that at optimal concentrations, CBD in combination with PAC produces additive to synergistic inhibition of breast cancer cell viability. Our results in breast cancer cells are in agreement with a recent investigation demonstrating CBD could enhance the activity of first-line agents targeting prostate cancer in culture and *in vivo* (Aviello *et al.*, 2011). The doses that prevent PAC-induced allodynia in our model overlap with doses of CBD that attenuate breast cancer metastasis *in vivo* (McAllister *et al.*, 2011). This integrated approach to using CBD to prevent CIPN while directly and indirectly targeting tumour progression makes it a potential valuable therapeutic for the treatment of cancer patients undergoing treatments with first-line agents.

In summary, our data suggest that CBD is protective against PAC-induced neurotoxicity and that this effect is in part mediated by the 5-HT_{1A} receptor system. Furthermore, CBD treatment is devoid of other nervous system effects such as conditioned reward or cognitive impairment. CBD also did not attenuate the efficacy of PAC in inhibiting breast cancer cell viability. Taken together, adjunct treatment with CBD during PAC chemotherapy treatment may be safe and effective in the prevention or attenuation of CIPN.

Acknowledgments

Go to:

We acknowledge Khristina Pavlenko and Mak Sarich.

Glossary

Go to:

CB	cannabinoid
CBD	cannabidiol
CI	combination index
CIPN	chemotherapy-induced peripheral neuropathy

CPP	conditioned place preference
CRM	cremophor
PAC	paclitaxel
THC	tetrahydrocannabinol
TRPV	transient receptor potential vanilloid

Conflict of interest

Go to:

There are no conflicts of interest present.

References

Go to:

Adelsberger H, Quasthoff S, Grosskreutz J, Lepier A, Eckel F, Lersch C. The chemotherapeutic oxaliplatin alters voltage-gated Na(+) channel kinetics on rat sensory neurons. Eur J Pharmacol. 2000;406:25–32. [PubMed]

Alves FH, Crestani CC, Gomes FV, Guimarães FS, Correa FM, Resstel LB. Cannabidiol injected into the bed nucleus of the stria terminalis modulates baroreflex activity through 5-HT1A receptors. Pharmacol Res. 2010;62:228–236. [PubMed]

Argyriou AA, Assimakopoulos K, Iconomou G, Giannakopoulou F, Kalofonos HP. Either called 'chemobrain' or 'chemofog,' the long-term chemotherapy-induced cognitive decline in cancer survivors is real. J Pain Symptom Manage. 41:126–139. [PubMed]

Aviello G, Romano B, Borrelli F, Capasso R, Gallo L, Piscitelli F, et al. Chemopreventive effect of the non-psychotropic phytocannabinoid cannabidiol on experimental colon cancer. J Mol Med (Berl) 2011-2012;90:925–934. [PubMed]

Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol. 2010;9:807–819. [PubMed]

Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol. 2001;134:845–852. [PMC free article] [PubMed]

Bitencourt RM, Pamplona FA, Takahashi RN. Facilitation of contextual fear memory extinction and anti-anxiogenic effects of AM404 and cannabidiol in conditioned rats. Eur Neuropsychopharmacol. 2008;18:849–859. [PubMed]

Campos AC, Ortega Z, Palazuelos J, Fogaça MV, Aguiar DC, Díaz-Alonso J. The anxiolytic effect of cannabidiol on chronically stressed mice depends on hippocampal neurogenesis: involvement of the endocannabinoid system. Int J Neuropsychopharmacol. 2013;16:1407–1419. [PubMed]

Casarotto PC, Gomes FV, Resstel LB, Guimarães FS. Cannabidiol inhibitory effect on marble-burying behaviour: involvement of CB1 receptors. Behav Pharmacol. 2010;21:353–358. [PubMed]

Cavaletti G, Tredici G, Braga M, Tazzari S. Experimental peripheral neuropathy induced in adult rats by repeated intraperitoneal administration of taxol. Exp Neurol. 1995;133:64–72. [PubMed]

Chou TC. Theoretical basis, experimental design, and computerized simulation of synergism and antagonism in drug combination studies. Pharmacol Rev. 2006;58:621–681. [PubMed]

Chou TC, Tan QH, Sirotnak FM. Quantitation of the synergistic interaction of edatrexate and cisplatin in vitro. Cancer Chemother Pharmacol. 1993;31:259–264. [PubMed]

Collier RJ, Wang Y, Smith SS, Martin E, Ornberg R, Rhoades K. Complement deposition and microglial activation in the outer retina in light-induced retinopathy: inhibition by a 5-HT1A agonist. Invest Ophthalmol Vis Sci.

2011a;52:8108–8116. [PubMed]

Collier RJ, Patel Y, Martin EA, Dembinska O, Hellberg M, Krueger DS. Agonists at the serotonin receptor (5-HT(1A)) protect the retina from severe photo-oxidative stress. Invest Ophthalmol Vis Sci. 2011b;52:2118–2126. [PubMed]

Colpaert FC. 5-HT(1A) receptor activation: new molecular and neuroadaptive mechanisms of pain relief. Curr Opin Investig Drugs. 2006;7:40–47. [PubMed]

Comelli F, Giagnoni G, Bettoni I, Colleoni M, Costa B. Antihyperalgesic effect of a Cannabis sativa extract in a rat model of neuropathic pain: mechanisms involved. Phytother Res. 2008;22:1017–1024. [PubMed]

Costa B, Giagnoni G, Franke C, Trovato AE, Colleoni M. Vanilloid TRPV1 receptor mediates the antihyperalgesic effect of the nonpsychoactive cannabinoid, cannabidiol, in a rat model of acute inflammation. Br J Pharmacol. 2004;143:247–250. [PMC free article] [PubMed]

Costa B, Trovato AE, Comelli F, Giagnoni G, Colleoni M. The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. Eur J Pharmacol. 2007;556:75–83. [PubMed]

Deng L, Guindon J, Vemuri VK, Thakur GA, White FA, Makriyannis A, et al. The maintenance of cisplatin- and paclitaxel-induced mechanical and cold allodynia is suppressed by cannabinoid CB2 receptor activation and independent of CXCR4 signaling in models of chemotherapy-induced peripheral neuropathy. Mol Pain. 2012;8:71. [PMC free article] [PubMed]

Dixon WJ. Efficient analysis of experimental observations. Annu Rev Pharmacol Toxicol. 1980;20:441–462. [PubMed]

Do Monte FH, Souza RR, Bitencourt RM, Kroon JA, Takahashi RN. Infusion of cannabidiol into infralimbic cortex facilitates fear extinction via CB1 receptors. Behav Brain Res. 2013;250:23–27. [PubMed]

El-Remessy AB, Tang Y, Zhu G, Matragoon S, Khalifa Y, Liu EK, et al. Neuroprotective effects of cannabidiol in endotoxin-induced uveitis: critical role of p38 MAPK activation. Mol Vis. 2008;14:2190–2203. [PMC free article] [PubMed] Retracted

Fernández-Ruiz J, Sagredo O, Pazos MR, García C, Pertwee R, Mechoulam R, et al. Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid? Br J Clin Pharmacol. 2013;75:323–333. [PMC free article] [PubMed]

Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain. 2010;150:573–581. [PubMed]

Foley JJ, Raffa RB, Walker EA. Effects of chemotherapeutic agents 5-fluorouracil and methotrexate alone and combined in a mouse model of learning and memory. Psychopharmacology (Berl) 2008;199:527–538. [PMC free article] [PubMed]

Gauchan P, Andoh T, Ikeda K, Fujita M, Sasaki A, Kato A, et al. Mechanical allodynia induced by paclitaxel, oxaliplatin and vincristine: different effectiveness of gabapentin and different expression of voltage-dependent calcium channel alpha(2)delta-1 subunit. Biol Pharm Bull. 2009;32:732–734. [PubMed]

Guindon J, Hohmann AG. Cannabinoid CB2 receptors: a therapeutic target for the treatment of inflammatory and neuropathic pain. Br J Pharmacol. 2008;153:319–334. [PMC free article] [PubMed]

Hagiwara H, Fujita Y, Ishima T, Kunitachi S, Shirayama Y, Iyo M, et al. Phencyclidine-induced cognitive deficits in mice are improved by subsequent subchronic administration of the antipsychotic drug perospirone: role of serotonin 5-HT1A receptors. Eur Neuropsychopharmacol. 2008;8:448–454. [PubMed]

Hu P, McLachlan EM. Macrophage and lymphocyte invasion of dorsal root ganglia after peripheral nerve lesions in the rat. Neuroscience. 2002;112:23–38. [PubMed]

Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. Trends Pharmacol Sci. 2009;30:515–527. [PubMed]

Jenkins DE, Hornig YS, Oei Y, Dusich J, Purchio T. Bioluminescent human breast cancer cell lines that permit rapid and sensitive in vivo detection of mammary tumors and multiple metastases in immune deficient mice.

Breast Cancer Res. 2005;7:R444–R454. [PMC free article] [PubMed]

Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC : CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manage. 2010;39:167–179. [PubMed]

Karschner EL, Darwin WD, McMahon RP, Liu F, Wright S, Goodwin RS, et al. Subjective and physiological effects after controlled Sativex and oral THC administration. Clin Pharmacol Ther. 2011;89:400–407. [PMC free article] [PubMed]

Kilkenny C, Browne W, Cuthill IC, Emerson M, Altman DG. Animal research: reporting *in vivo* experiments: the ARRIVE guidelines. Br J Pharmacol. 2010;160:1577–1579. [PMC free article] [PubMed]

Langford RM, Mares J, Novotna A, Vachova M, Novakova I, Notcutt W. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol. 2013;260:984–997. [PubMed]

Lichtman AH, Varvel SA, Martin BR. Endocannabinoids in cognition and dependence. Prostaglandins Leukot Essent Fatty Acids. 2002;66:269–285. [PubMed]

Lynch JJ, 3rd, Wade CL, Zhong CM, Mikusa JP, Honore P. Attenuation of mechanical allodynia by clinically utilized drugs in a rat chemotherapy-induced neuropathic pain model. Pain. 2004;110:56–63. [PubMed]

McAllister SD, Chan C, Taft RJ, Luu T, Abood ME, Moore DH, et al. Cannabinoids selectively inhibit proliferation and induce death of cultured human glioblastoma multiforme cells. J Neurooncol. 2005;74:31–40. [PubMed]

McAllister SD, Christian RT, Horowitz MP, Garcia A, Desprez PY. Cannabidiol as a novel inhibitor of Id-1 gene expression in aggressive breast cancer cells. Mol Cancer Ther. 2007;6:2921–2927. [PubMed]

McAllister SD, Murase R, Christian RT, Lau D, Zielinski AJ, Allison J, et al. Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis. Breast Cancer Res Treat. 2011;129:37–47. [PMC free article] [PubMed]

McGrath J, Drummond G, McLachlan E, Kilkenny C, Wainwright C. Guidelines for reporting experiments involving animals: the ARRIVE guidelines. Br J Pharmacol. 2010;160:1573–1576. [PMC free article] [PubMed]

Maione S, Piscitelli F, Gatta L, Vita D, De Petrocellis L, Palazzo E, et al. Non-psychoactive cannabinoids modulate the descending pathway of antinociception in anaesthetized rats through several mechanisms of action. Br J Pharmacol. 2011;162:584–596. [PMC free article] [PubMed]

Marcu JP, Christian RT, Lau D, Zielinski AJ, Horowitz MP, Lee J, et al. Cannabidiol enhances the inhibitory effects of delta9-tetrahydrocannabinol on human glioblastoma cell proliferation and survival. Mol Cancer Ther. 2010;9:180–189. [PMC free article] [PubMed]

Massi P, Solinas M, Cinquina V, Parolaro D. Cannabidiol as potential anticancer drug. Br J Clin Pharmacol. 2013;75:303–312. [PMC free article] [PubMed]

Mukhopadhyay P, Rajesh M, Horváth B, Bátkai S, Park O, Tanchian G, et al. Cannabidiol protects against hepatic ischemia/reperfusion injury by attenuating inflammatory signaling and response, oxidative/nitrative stress, and cell death. Free Radic Biol Med. 2011;50:1368–1381. [PMC free article] [PubMed]

Naguib M, Diaz P, Xu JJ, Astruc-Diaz F, Craig S, Vivas-Mejia P, et al. MDA7: a novel selective agonist for CB2 receptors that prevents allodynia in rat neuropathic pain models. Br J Pharmacol. 2008;155:1104–1116. [PMC free article] [PubMed]

Parker LA, Burton P, Sorge RE, Yakiwchuk C, Mechoulam R. Effect of low doses of delta9-tetrahydrocannabinol and cannabidiol on the extinction of cocaine-induced and amphetamine-induced conditioned place preference learning in rats. Psychopharmacology (Berl) 2004;175:360–366. [PubMed]

Pascual D, Goicoechea C, Suardíaz M, Martín MI. A cannabinoid agonist, WIN 55,212-2, reduces neuropathic

nociception induced by paclitaxel in rats. Pain. 2005;118:23–34. [PubMed]

Peters CM, Jimenez-Andrade JM, Jonas BM, Sevcik MA, Koewler NJ, Ghilardi JR, et al. Intravenous paclitaxel administration in the rat induces a peripheral sensory neuropathy characterized by macrophage infiltration and injury to sensory neurons and their supporting cells. Exp Neurol. 2007;203:42–54. [PubMed]

Pinsger M, Schimetta W, Volc D, Hiermann E, Riederer F, Pölz W. Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain–a randomized controlled trial. Wien Klin Wochenschr. 2006;118:327–335. [PubMed]

Rahn EJ, Makriyannis A, Hohmann AG. Activation of cannabinoid CB1 and CB2 receptors suppresses neuropathic nociception evoked by the chemotherapeutic agent vincristine in rats. Br J Pharmacol. 2007;152:765–777. [PMC free article] [PubMed]

Rahn EJ, Zvonok AM, Thakur GA, Khanolkar AD, Makriyannis A, Hohmann AG. Selective activation of cannabinoid CB2 receptors suppresses neuropathic nociception induced by treatment with the chemotherapeutic agent paclitaxel in rats. J Pharmacol Exp Ther. 2008;327:584–591. [PMC free article] [PubMed]

Russo EB, Burnett A, Hall B, Parker KK. Agonistic properties of cannabidiol at 5-HT1a receptors. Neurochem Res. 2005;30:1037–1043. [PubMed]

Sagredo O, Ramos JA, Decio A, Mechoulam R, Fernández-Ruiz J. Cannabidiol reduced the striatal atrophy caused 3-nitropropionic acid in vivo by mechanisms independent of the activation of cannabinoid, vanilloid TRPV1 and adenosine A2A receptors. Eur J Neurosci. 2007;26:843–851. [PubMed]

Sagredo O, Pazos MR, Satta V, Ramos JA, Pertwee RG, Fernández-Ruiz J. Neuroprotective effects of phytocannabinoid-based medicines in experimental models of Huntington's disease. J Neurosci Res. 2011;89:1509–1518. [PubMed]

Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. J Pain. 2008;9:164–173. [PubMed]

Stern CA, Gazarini L, Takahashi RN, Guimarães FS, Bertoglio LJ. On disruption of fear memory by reconsolidation blockade: evidence from cannabidiol treatment. Neuropsychopharmacology. 2012;37:2132–2142. [PMC free article] [PubMed]

Toth CC, Jedrzejewski NM, Ellis CL, Frey WH., 2nd Cannabinoid-mediated modulation of neuropathic pain and microglial accumulation in a model of murine type I diabetic peripheral neuropathic pain. Mol Pain. 2010;6:16. [PMC free article] [PubMed]

Viisanen H, Pertovaara A. Roles of the rostroventromedial medulla and the spinal 5-HT(1A) receptor in descending antinociception induced by motor cortex stimulation in the neuropathic rat. Neurosci Lett. 2010;476:133–137. [PubMed]

Visovsky C, Collins M, Abbott L, Aschenbrenner J, Hart C. Putting evidence into practice: evidence-based interventions for chemotherapy-induced peripheral neuropathy. Clin J Oncol Nurs. 2007;11:901–913. [PubMed]

Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. Mult Scler. 2004;10:434–441. [PubMed]

Ward SJ, Ramirez MD, Neelakantan H, Walker EA. Cannabidiol prevents the development of cold and mechanical allodynia in paclitaxel-treated female C57Bl6 mice. Anesth Analg. 2011;113:947–950. [PMC free article] [PubMed]

Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ. 2010;182:E694–E701. [PMC free article] [PubMed]

Xiao W, Boroujerdi A, Bennett GJ, Luo ZD. Chemotherapy-evoked painful peripheral neuropathy: analgesic effects of gabapentin and effects on expression of the alpha-2-delta type-1 calcium channel subunit. Neuroscience. 2007;144:714–720. [PMC free article] [PubMed]

Xiao W, Naso L, Bennett GJ. Experimental studies of potential analgesics for the treatment of chemotherapy-evoked painful peripheral neuropathies. Pain Med. 2008;9:505–517. [PubMed]

Xiao WH, Bennett GJ. C-fiber spontaneous discharge evoked by chronic inflammation is suppressed by a long-term infusion of lidocaine yielding nanogram per milliliter plasma levels. Pain. 2008;137:218–228. [PubMed]

Xiong W, Cui T, Cheng K, Yang F, Chen SR, Willenbring D, et al. Cannabinoids suppress inflammatory and neuropathic pain by targeting α3 glycine receptors. J Exp Med. 2012;209:1121–1134. [PMC free article] [PubMed]