MMP-054

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.

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1. Petitioner Information

Name: [redacted]
Street Addr
City, State,
Telephone
Email Addr

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

Osteoarthritis

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.

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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.

Osteoarthritis, also called degenerative joint disease, is defined as a disease that occurs when the cartilage breaks down leading to pain, stiffness, and swelling.

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 osteoarthritis 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.

Signatu [redacted]	Date 8/31/16

6.
VOLTAREN
GENERIC NAME : DICLOFENAC
NSAID
"Check with your doctor immediately if any of the following side effects occur:

- Abdominal or stomach burning. Cramping or pain
- belching
- bloody or black, tarry stools
- cloudy urine
- constipation
- decrease in urine output or decrease in urine-concentrating ability
- diarrhea
- dizziness
- feeling of indigestion
- headache
- increased bleeding time
- itching skin or rashloss of appetite
- nausea and vomitingpain in the chest below the brea
- tbone
- pale skin
- severe stomach pain
- swelling
- troubled breathing with exertion
- 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

- Continuing ringing or buzzing or other unexplained noise in the ears
- excess air or gas in the stomach or intestines
- hearing loss
- lack or loss of strength
- passing gas

SITE -- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0045651/#DDIC602207.side_effects_section

CELEBREX
GENERIC NAME. : CELECOXIB
RX NSAID
"Check with your doctor immediately if any of the following side effects occur:"
More common

- Cough
- fever
- skin rash

- sneezing
- sore throat
- swelling of the face, fingers, feet, or lower legs

Less common or rare

- Abnormal growth in the breast
- arm, back, or jaw pain
- bloody or black, tarry stools
- blurred vision
- burning feeling in the chest or stomach
- burning or stinging of the skin
- burning, tingling, numbness, or pain in the hands, arms, feet, or legs
- chest pain or discomfort
- chest tightness or heaviness
- chills
- confusion
- congestion in the chest
- cramps
- diarrhea
- dry mouth
- earache
- fast or irregular heartbeat
- heartburn
- heavy bleeding
- heavy non-menstrual vaginal bleeding
- high blood pressure
- increased hunger
- increased thirst
- increased urination
- loss of appetite
- loss of consciousness
- muscle aches and pains
- nausea
- nerve pain
- painful blisters on the trunk of body
- painful cold sores or blisters on the lips, nose, eyes, or genitals
- pale skin
- redness or swelling in the ear
- sensation of pins and needles
- soreness or redness around the fingernails or toenails
- stabbing pain
- stiff neck
- stomachache
- stomach pain (severe)
- sweating
- tenderness in the stomach area
- troubled breathing with exertion
- unexplained weight loss

- unusual bleeding or bruising
- unusual tiredness or weakness
- unusual weight gain
- vomiting
- vomiting of blood or material that looks like coffee grounds
- weakness
- wheezing

"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

- Back pain
- gas
- headache
- heartburn
- inability to sleep
- pain or burning in the throat
- stuffy or runny nose

Less common

- Anxiety
- bleeding after defecation
- bloody or cloudy urine
- breast pain
- bone deformity
- buzzing or ringing noise in the ears
- change in sense of taste
- constipation
- decrease in height
- decreased appetite
- depression
- difficult, burning, or painful urination
- difficulty with moving or walking
- difficulty with swallowing
- excessive muscle tone, muscle tension, or tightness
- excessive tearing
- feeling of pressure
- hair loss
- hives
- hoarseness
- increased sweating
- infection
- inflammation
- itching, lumps, numbness, pain, rash, redness, scarring, soreness, stinging, swelling, tenderness, tingling, ulceration, or warmth at site
- itching of the vagina or genital area
- joint or muscle pain or stiffness
- large, flat, blue, or purplish patches in the skin
- loss of energy or weakness

- loss of hearing
- muscle pain increased
- muscle stiffness
- nervousness
- numbness or tingling in the fingersor toes
- pain during sexual intercourse
- pain in the back, ribs, arms, or legs
- pounding heartbeat
- puffiness or swelling of the eyelidsor around the eyes, face, lips, or tongue
- redness or swelling in the arms or legs
- sensitivity of the skin to sunlight
- severe sunburn
- sleepiness
- straining while passing stool
- sudden sweating and feelings of warmth
- swelling
- swelling or inflammation of the mouth
- tenderness
- thick, white vaginal discharge with no odor or with a mild odor
- thinning of the hair
- trouble with swallowing
- troubled breathing
- uncomfortable swelling around anus
- unexplained weight loss
- voice changes
- Warmth on the skin
- weakness or heaviness of the legs

SITE -- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0044745/#DDIC601969.side_effects_section

FELDENE
GENERIC NAME : PIROXICAM
RX NSAID
"Check with your doctor immediately if any of the following side effects occur:"
More common

- Bloating
- bloody or black, tarry stools
- burning upper abdominal or stomach pain
- cloudy urine
- constipation
- decrease in urine output or decrease in urine-concentrating ability
- headache
- Heartburn
- indigestion
- itching skin or rash
- loss of appetite
- nausea or vomiting
- pale skin

- severe abdominal or stomach pain, cramping, or burning
- severe and continuing nausea
- swelling
- swelling of the face, fingers, feet, or lower legs
- troubled breathing with exertion
- unusual bleeding or bruising
- unusual tiredness or weakness
- vomiting of blood or material that looks like coffee grounds
- weight changes

Less Common

- Bleeding gums
- blood in the urine
- bloody nose
- blurred vision
- burning feeling in the chest or stomach
- burning, crawling, itching, numbness, prickling, "pins and needles", or tingling feelings
- chest pain
- clay-colored stools
- confusion
- cough or hoarseness
- dark urine
- difficult or labored breathing
- difficult, burning, or painful urination
- difficulty with swallowing
- dilated neck veins
- dizziness
- extreme fatigue
- fainting
- fever or chills
- flushing or redness of the skin
- frequent urge to urinate
- increased sensitivity of the skin to sunlight
- increased thirst
- increased volume of pale, dilute urine
- large, flat, blue, or purplish patches in the skin
- lightheadedness
- lower back or side pain
- nervousness
- noisy breathing
- numbness or tingling in the hands, feet, or lips
- pain or burning in the throat
- peeling of the skin
- pinpoint red or purple spots on the skin
- pounding in the ears
- rapid, shallow breathing
- redness or other discoloration of the skin
- redness, swelling, or soreness of the tongue

- severe sunburn
- slow, fast, pounding, or irregular heartbeat or pulse
- sore throat
- sores, ulcers, or white spots on the lips or tongue or inside the mouth
- stomach upset
- swelling or inflammation of the mouth
- swollen glands
- tenderness in the stomach area
- tightness in the chest
- unpleasant breath odor
- unusually warm skin
- weakness or heaviness of the legs
- yellow eyes or skin

Rare

- Anxiety
- back or leg pains
- burning, dry, or itching eyes
- cold sweats
- coma
- cracks in the skin
- diarrhea
- discharge or excessive tearing
- dizziness, faintness, or lightheadedness when getting up from a lying or sitting position
- dry mouth
- flushed, dry skin
- fruit-like breath odor
- general body swelling
- general feeling of discomfort or illness
- high fever
- increased hunger
- increased urination
- inflammation of the joints
- irregular, fast or slow, or shallow breathing
- joint pain
- large, hive-like swelling on the face, eyelids, lips, tongue, throat, hands, legs, feet, or sex organs
- light-colored stools
- loss of heat from the body
- muscle aches and pains
- nightmares
- no blood pressure
- no breathing
- no pulse
- pain or discomfort in the arms, jaw, back, or neck
- pains in the stomach, side, or abdomen, possibly radiating to the back
- pale or blue lips, fingernails, or skin
- puffiness or swelling of the eyelidsor around the eyes, face, lips, or tongue
- red skin lesions, often with a purple center

- red, irritated eyes
- redness, pain, or swelling of the eye, eyelid, or inner lining of the eyelid
- runny nose
- scaly skin
- seeing, hearing, or feeling things that are not there
- seizures
- severe headache
- shakiness
- shivering
- sleepiness
- slurred speech
- sneezing
- sores, welting, or blisters
- stiff neck or back
- stomach pain, continuing
- suddenly sweating
- swollen, painful, or tender lymphglands in the neck, armpit, or groin
- Trouble sleeping

"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

- Acid or sour stomach
- belching
- continuing ringing or buzzing or other unexplained noise in the ears
- excess air or gas in the stomach or intestines
- hearing loss
- passing gas
- stomach discomfort or upset

Less common

- Feeling of constant movement of self or surroundings
- hair loss or thinning of the hair
- lack or loss of strength
- sensation of spinning
- shakiness in the legs, arms, hands, or feet
- trembling or shaking of the hands or feet

Rare

- Change in hearing
- changes in appetite
- inability to sit still
- mood alterations
- need to keep moving
- restlessness

SITE -- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0045586/#DDIC602213.side_effects_section

INDOCIN
GENERIC NAME : INDOMETHACIN

RX NSAID

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

Less Common

- Acid or sour stomach
- belching
- diarrhea
- heartburn
- indigestion
- nausea
- stomach discomfort, upset, or pain
- vomiting

Rare

- Abdominal or stomach cramping, burning or tenderness
- back or leg pains
- bleeding gums
- blistering, peeling, or loosening of the skin
- bloody or black, tarry stools
- blue lips and fingernails
- blurred vision
- breast enlargement and tenderness
- burning, crawling, itching, numbness, prickling, "pins and needles", or tingling feelings
- burning upper abdominal or stomach pain
- canker sores
- change in consciousness
- change in hearing
- chest pain, discomfort, or burning
- clay colored stools
- cloudy or bloody urine
- confusion
- continuing diarrhea
- cough or hoarseness
- coughing that sometimes produces a pink frothy sputum
- cracks in the skin
- dark urine
- decreased appetite
- decreased vision or any change in vision
- depression
- difficult or labored breathing
- difficulty with swallowing
- dilated neck veins
- Dizziness, faintness, or lightheadedness when getting up from a lying or sitting position
- double vision
- dry mouth
- extreme fatigue
- false sense of well-being
- feeling of unreality
- feeling of warmth

- fever with or without chills
- flushed, dry skin
- fruit-like breath odor
- general body swelling
- Greatly decreased frequency of urination or amount of urine
- hair loss
- headache
- heavier menstrual periods
- increased hunger
- increased sweating
- increased thirst
- increased urination
- irregular breathing
- irritation and swelling of the eye
- jerky movements of the head, face, mouth, and neck
- joint pain
- large, flat, blue or purplish patches in the skin
- large, hive-like swelling on the face, eyelids, lips, tongue, throat, hands, legs, feet, or sex organs
- loss of appetite
- loss of balance control
- loss of bladder control
- loss of consciousness
- loss of hearing
- loss of heat from the body
- lower back or side pain
- mask-like face
- mood swings
- muscle aches, pains, or weakness
- muscle spasm or jerking of all extremities
- nervousness
- noisy, rattling breathing
- nosebleeds
- numbness or tingling in the hands, feet, or lips
- pain in the ankles or knees
- pain or discomfort in the upper stomach or throat
- pain with swallowing
- painful or difficult urination
- painful, red lumps under the skin, mostly on the legs
- pale skin
- persistent bleeding or oozing from puncture sites, mouth, or nose
- personality changes
- pinpoint red or purple spots on the skin
- pounding in the ears
- puffiness or swelling of the eyelidsor around the eyes, face, lips, or tongue
- red skin lesions, often with a purple center
- red, irritated eyes
- red, swollen skin

- redness of the face, neck, arms and occasionally, upper chest
- scaly skin
- seeing double
- seeing, hearing, or feeling things that are not there
- seizures
- sense of detachment from self or body
- severe constipation
- severe mental changes
- severe or continuing stomach pain
- shuffling walk
- skin rash, hives or welts, itching
- slow, fast, irregular, pounding, or racing heartbeat or pulse
- slowed movements
- slurred speech
- small red or purple spots on the skin
- sore throat
- sores, ulcers, or white spots on the lips or tongue or inside the mouth
- stiffness of the arms and legs
- sudden loss of consciousness
- swelling of the breasts or breastsoreness in both females and males
- swelling of the face, fingers, feet, ankles or lower legs
- swollen or painful glands
- tightness in the chest
- trembling and shaking of the fingersand hands
- troubled breathing at rest
- troubled breathing with exertion
- unexplained weight loss
- unpleasant breath odor
- unsteadiness or awkwardness
- unusual bleeding or bruising
- unusual tiredness or weakness
- vaginal bleeding
- vomiting of blood or material that looks like coffee grounds
- weakness in the arms, hands, legs, or feet
- weight gain
- yellow eyes or skin

"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

- Mild headache

Less common

- Continuing ringing or buzzing or other unexplained noise in the ears
- difficulty having a bowel movement(stool)
- discouragement
- feeling sad or empty
- general feeling of discomfort or illness
- hearing loss

- irritability
- loss of interest or pleasure
- sleepiness
- trouble with concentrating

Rare

- Anxiety
- bloated or full feeling
- changes in patterns and rhythms of speech
- excess air or gas in the stomach or intestines
- feeling of constant movement of self or surroundings
- involuntary muscle movements
- lightheadedness
- passing gas
- sensation of spinning
- tiredness
- trouble sleeping
- trouble with speaking

SITE -- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0045364/#DDIC602195.side_effects_section

MOBIC
GENERIC NAME : MELOXICAM
RX NSAID
"Check with your doctor immediately if any of the following side effects occur:"
Less Common

- Arm, back, or jaw pain
- bleeding gums
- bloating
- blood in the urine
- blurred vision
- burning upper abdominal or stomach pain
- canker sores
- chest tightness or heaviness
- chills
- cloudy urine
- cough
- cramping
- dark urine
- decreased frequency or amount of urine
- difficult or labored breathing
- dilated neck veins
- dizziness
- dizziness, faintness, or lightheadedness when getting up suddenly from a lying or sitting position
- general tiredness and weakness
- headache
- hives or welts
- increased blood pressure
- increased sensitivity of the skin to sunlight

- increased thirst
- irregular breathing
- itching, redness, or other discoloration of the skin
- large, hive-like swelling on the face, eyelids, lips, tongue, throat, hands, legs, feet, or sex organs
- light-colored stools
- loss of appetite
- lower side or back pain
- noisy breathing
- pain or discomfort in the arms, jaw, back, or neck
- painful or difficult urination
- pains in the stomach, side, or abdomen, possibly radiating to the back
- pinpoint red or purple spots on the skin
- pounding in the ears
- redness, soreness, or itching skin
- seizures
- severe and continuing nausea
- severe sunburn
- shakiness in the legs, arms, hands, or feet
- skin blisters
- sore throat
- sores, ulcers, or white spots on the lips or tongue or inside the mouth
- sores, welting, or blisters
- stomach bloating, burning, cramping, tenderness, or pain
- sweating
- swelling or puffiness of the face
- swollen glands
- trembling or shaking of the hands or feet
- trouble breathing
- unusual bleeding or bruising
- upper right abdominal or stomachpain
- watery or bloody diarrhea
- weight gain or loss
- yellow eyes or skin

Rare

- Area rash
- blistering, peeling, or loosening of the skin
- bloody or black, tarry stools
- clay-colored stools
- cold, clammy skin
- continuing vomiting
- cough or hoarseness
- cracks in the skin
- difficulty with swallowing
- fast, weak pulse
- fever with or without chillgreatly decreased frequency of urination or amount of urine
- joint or muscle pain
- lightheadedness

- loss of heat from the body
- puffiness or swelling of the eyelidsor around the eyes, face, lips, or tongue
- red skin lesions, often with a purple center
- red, irritated eyes
- red, swollen skin
- scaly skin
- severe stomach pain
- tightness in the chest
- unpleasant breath odor
- unusual tiredness or weakness
- vomiting of blood or material that looks like coffee grounds

"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

- Diarrhea
- gas
- heartburn
- indigestion

Less common or rare

- Abdominal or stomach pain
- abnormal dreaming
- anxiety
- appetite increased
- bad, unusual, or unpleasant after taste
- belching
- bloated or full feeling
- burning feeling in the chest or stomach
- burning, crawling, itching, numbness, prickling, "pins and needles", or tingling feelings
- burning, dry, or itching eyes
- change in taste
- changes in vision
- confusion
- constipation
- continuing ringing or buzzing or other unexplained noise in the ears
- decreased urination
- discharge
- discouragement
- dry mouth
- excess air or gas in the stomach
- excessive tearing
- feeling of constant movement of self or surroundings
- feeling sad or empty
- general feeling of discomfort or illness
- hair loss
- hearing loss
- hot flushes
- irritability

- loss of interest or pleasure
- nausea or vomiting
- nervousness
- pain or burning in the throat
- rapid breathing
- redness, pain, or swelling of the eye, eyelid, or inner lining of the eyelid
- sensation of spinning
- sleepiness
- stomach upset
- sunken eyes
- tenderness in the stomach area
- thinning of the hair
- thirst
- tiredness
- trouble concentrating
- trouble sleeping
- wrinkled skin

SITE -- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0046213/#DDIC601497.side_effects_section

LODINE
GENERIC NAME : ETODOLAC
RX NSAID
"Check with your doctor immediately if any of the following side effects occur:"
More common

- Abdominal or stomach bloating, burning, cramping or pain
- belching
- bloody or black, tarry stools
- blurred vision
- body aches or pain
- cloudy urine
- congestion
- constipation
- cough or hoarseness
- decrease in urine output or decrease in urine-concentrating ability
- diarrhea
- dizziness
- dryness or soreness of throat
- feeling of indigestion
- fever or chills
- headache
- increased bleeding time
- itching skin
- loss of appetite
- lower back or side pain
- nausea and vomiting
- nervousness
- pain in the chest below the breastbone

- painful or difficult urination
- pale skin
- pounding in the ears
- rash
- runny nose
- severe stomach pain
- slow or fast heartbeat
- swelling
- tender, swollen glands in neck
- trouble in swallowing
- troubled breathing with exertion
- unusual bleeding or bruising
- unusual tiredness or weakness
- voice changes
- vomiting of blood or material that looks like coffee grounds
- weight loss

"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

- Bloated, full feeling
- continuing ringing or buzzing or other unexplained noise in ears
- excess air or gas in stomach or intestines
- hearing loss
- lack or loss of strength
- passing gas
- sneezing
- stuffy nose

SITE-- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0045443/#DDIC602209.side_effects_section

TYLENOL

GENERIC NAME : ACETAMINOPHEN

ANALGESIC

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

- Bloody or black, tarry stools
- Dark urine or pale stools, nausea, vomiting, loss of appetite, severe stomach pain, yellow skin or eyes
- Fever or a sore throat that lasts longer than 3 days, or pain that lasts longer than 5 days
- Lightheadedness, fainting, sweating, or weakness
- Unusual bleeding or bruising
- Vomiting blood or material that looks like coffee grounds

"Do not drink alcohol while you are using this medicine. Acetaminophen can damage your liver, and alcohol can increase this risk. Do not take acetaminophen without asking your doctor if you have 3 or more drinks of alcohol every day."

Over 80,000 Americans visit ERs due to taking too much acetaminophen. Acetaminophen is now the leading cause of liver failure in this country.

SITE-- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0008785/?report=details#side_effects

ULTRAM
GENERIC NAME: TRAMADOL
NARCOTIC
"Check with your doctor immediately if any of the following side effects occur:"
Less Common Or Rare

- Abdominal or stomach fullness
- abnormal or decreased touchsensation
- blisters under the skin
- bloating
- blood in the urine
- blood pressure increased
- blurred vision
- change in walking and balance
- chest pain or discomfort
- chills
- convulsions (seizures)
- darkened urine
- difficult urination
- dizziness or lightheadedness when getting up from a lying or sitting position
- fainting
- fast heartbeat
- frequent urge to urinate
- gaseous abdominal or stomach pain
- heart rate increased
- indigestion
- irregular heartbeat
- loss of memory
- numbness and tingling of the face, fingers, or toes
- numbness, tingling, pain, or weakness in the hands or feet
- pain in the arms, legs, or lower back, especially pain in the calves or heels upon exertion
- pain or discomfort in the arms, jaw, back, or neck
- pains in the stomach, side or abdomen, possibly radiating to the back
- pale bluish-colored or cold hands or feet
- recurrent fever
- seeing, hearing, or feeling things that are not there
- severe cramping
- severe nausea
- severe redness, swelling, and itching of the skin
- shortness of breath
- sweats
- trembling and shaking of the handsor feet
- trouble performing routine tasks
- weak or absent pulses in the legs
- yellow eyes or skin

"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
- agitation
- anxiety
- constipation
- cough
- diarrhea
- discouragement
- drowsiness
- dry mouth
- feeling of warmth
- feeling sad or empty
- feeling unusually cold
- fever
- general feeling of discomfort or illness
- headache
- heartburn
- irritability
- itching of the skin
- joint pain
- loss of appetite
- loss of interest or pleasure
- loss of strength or weakness
- muscle aches and pains
- nausea
- nervousness
- redness of the face, neck, arms, and occasionally, upper chest
- restlessness
- runny nose
- shivering
- skin rash
- sleepiness or unusual drowsiness
- sore throat
- stuffy nose
- sweating
- tiredness
- trouble concentrating
- unusual feeling of excitement
- weakness

Less Common Or Rare

- Abnormal dreams
- appetite decreased
- back pain
- bladder pain
- blistering, crusting, irritation, itching, or reddening of the skin
- bloody or cloudy urine
- body aches or pain

- change in hearing
- clamminess
- cold flu-like symptoms
- confusion
- cough producing mucus
- cracked, dry, or scaly skin
- decreased interest in sexual intercourse
- difficult, burning, or painful urination
- difficulty with moving
- disturbance in attention
- ear congestion
- ear drainage
- earache or pain in ear
- excessive gas
- fall
- false or unusual sense of well-being
- feeling hot
- feeling jittery
- flushing or redness of the skin
- general feeling of bodily discomfort
- goosebumps
- headache, severe and throbbing
- hoarseness
- hot flashes
- inability to have or keep an erection
- itching, pain, redness, swelling, tenderness, or warmth on the skin
- joint sprain
- joint stiffness
- joint swelling
- loss in sexual ability, desire, drive, or performance
- loss of voice
- lower back or side pain
- muscle aching or cramping
- muscle injury
- muscle pain or stiffness
- muscle spasms or twitching
- nasal congestion
- neck pain
- night sweats
- pain
- pain in the limbs
- pain or tenderness around the eyesand cheekbones
- pain, swelling, or redness in the joints
- skin discoloration
- swelling
- swelling of the hands, ankles, feet, or lower legs
- tightness of the chest

- trouble in holding or releasing urine
- trouble with sleeping
- troubled breathing
- weight increased or decreased

"After you stop using this medicine, it may still produce some side effects that need attention. During this period of time, check with your doctor immediately if you notice the following side effects:"

- Gooseflesh
- high blood pressure
- increased sweating
- increased yawning
- shivering or trembling
- unusually large pupils

SITE -- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0044659/#DDIC601787.side_effects_section

PERCOCET
GENERIC NAME : ACETAMINOPHEN/OXYCODONE
NARCOTIC

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

- Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
- Extreme weakness, shallow breathing, uneven heartbeat, seizures, sweating, or cold or clammy skin
- Lightheadedness, dizziness, or fainting
- Trouble breathing

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

- Mild lightheadedness, sleepiness, or drowsiness
- Mild nausea or vomiting
- Headache

SITE -- http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0011543/?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 : ACETAMINOPHEN/HYDROCODONE
NARCOTIC

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

- Blistering, 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

ZOHYDRO ER
GENERIC NAME : HYDROCODONE
NARCOTIC
"Severity: Major
If any of the following side effects occur while taking hydrocodone, check with your doctor immediately:"
Less common:

- Bloating or swelling of the face, arms, hands, lower legs, or feet
- body aches or pain
- chills
- cough
- depression
- difficult or labored breathing
- ear congestion
- fear or nervousness
- fever
- headache
- loss of voice
- nasal congestion
- rapid weight gain
- runny nose
- sneezing
- sore throat
- tightness in the chest
- tingling of the hands or feet
- unusual tiredness or weakness
- unusual weight gain or loss

"check with them if any of the following side effects continue, or if you are concerned about them:"
More common:

- Difficulty having a bowel movement (stool)
- nausea

Less common:

- Abdominal or stomach pain or discomfort
- back pain
- bladder pain

- bloody or cloudy urine
- difficult, burning, or painful urination
- dry mouth
- frequent urge to urinate
- heartburn
- itching skin
- lower back or side pain
- muscle spasms
- vomiting

SITE -- https://www.drugs.com/sfx/zohydro-er-side-effects.html

Some osteoarthritis 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

Other patients may try to avoid taking prescription medications and take ibuprofen and other NSAIDS instead; raising their risk of having a heart attack or stroke.

It is extremely important to note that for some patients with osteoarthritis pain is so severe that it requires the use of prescription narcotic painkillers 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. Osteoarthritis 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.

7. Osteoarthritis causes severe suffering and severely impairs the patient's ability to carry on activities of daily living. Osteoarthritis causes severe pain in the and around the joints of a patient due to the wearing down of cartilage. Along with severe and chronic pain osteoarthritis also causes stiffness and swelling.

The pain that a patient with osteoarthritis has can vary in level from moderate to severe to debilitating. The pain can be so bad it can make a person have to quit their job, stop driving, and not be able to partake in activities that were once easy and enjoyable. The pain, stiffness a and swelling can be so severe that patients can not climb stairs even in their home, carry groceries, and/or even walk without the assistance of a cane or walker. Some patients may have such severe pain, stiffness and swelling that they may require a wheelchair at times.

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 osteoarthritis. The therapies can be cathartic such as stress management techniques, meditation and yoga. Some patients do find limited benefit from accupuncture. However it is usually not enough to completely eradicate or heavily eradicate their pain.

9. Medical marijuana is a medically, scientifically and anecdotally prover treatment for osteoarthritis. Medical marijuana is extremely beneficial in helping alleviate pain. Two cannabinoids found in cannabis, tetrahydrocannabinol (THC) and cannabidiol (CBD), are very effective at lowering pain levels associated with acute pain conditions, chronic pain conditions, spasticity, neuropathic/nerve pain, headaches, and migraines; among others.

THC and CBD help in pain management and treatment because they activate the two main cannabinoid receptors, CB1 and CB2, of the body's endocannabinoid system. CB1 and CB2 regulate the release of neurotransmitter and central nervous system immune cells to manage the patient's pain levels.

There are a vast amount of studies supporting medical marijuana's effectiveness in managing and treating pain.

Medical marijuana has demonstrated the ability to significantly lower pain levels in patients suffering from neuropathic/nerve pain along with nociceptive pain. Nociceptive pain is pain that is that from tissue damage and is usually sharp, aching and/or throbbing. Medical marijuana has even shown it can help manage pain that has not been helped by other treatments.

Studies have found that using medical marijuana for the management of pain is a safe practice. After a year of using marijuana regularly patients with chronic pain were found to be at no greater a risk of serious adverse effects than those who don't uses marijuana.

Preclinical studies support the idea that the endocannabinoid system is involved in alleviating osteoarthritis pain in patients. In an animal trial, cannabidiol (CBD), was shown to effectively block the progression of arthritis. Researchers also found that CBD protected joints against severe damage. They then concluded that CBD offers a potent anti-arthritic effect. Other studies done have shown that synthetic cannabinoids offer strong anti-inflammatory and immunosuppressive properties and they reduce joint damage in mice with osteoarthritis.

The pain that a patient feels can be either neuropathic/nerve or nociceptive (sharp, throbbing, aching). CBD and tetrahydrocannabinol (THC) activate the CB1 and CB2 receptors of the endocannabinoid system. CB1 & CB2 regulate the release of neurotransmitter and central nervous system immune cells to manage both neuropathic/nerve pain and nociceptive pain levels. The activation of the CB1 receptor has been specifically found to reduce pain sensitivity in the osteoarthritic knee joints of rats. In another animal study, it was found that activating CB2 receptors reduces pain and the inflammation associated with osteoarthritis.

It's also important to note that maintaining healthy bones helps reduce the risk of osteoarthritis. Studies have shown that cannabis and its cannabinoids help modulate bone growth and its maintenance. When activating the CB1 and CB2 receptors, cannabinoids help to manage proper bone formation.

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Cannabinoid receptors and the regulation of bone mass

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Abstract

Go to:

A functional endocannabinoid system is present in several mammalian organs and tissues. Recently, endocannabinoids and their receptors have been reported in the skeleton. Osteoblasts, the bone forming cells, and osteoclasts, the bone resorbing cells, produce the endocannabinoids anandamide and 2-arachidonoylglycerol and express CB2 cannabinoid receptors. Although CB2 has been implicated in pathological processes in the central nervous system and peripheral tissues, the skeleton appears as the main system physiologically regulated by CB2. CB2-deficient mice show a markedly accelerated age-related bone loss and the *CNR2* gene (encoding CB2) in women is associated with low bone mineral density. The activation of CB2 attenuates ovariectomy-induced bone loss in mice by restraining bone resorption and enhancing bone formation. Hence synthetic CB2 ligands, which are stable and orally available, provide a basis for developing novel anti-osteoporotic therapies. Activation of CB1 in sympathetic nerve terminals in bone inhibits norepinephrine release, thus balancing the tonic sympathetic restrain of bone formation. Low levels of CB1 were also reported in osteoclasts. CB1-null mice display a skeletal phenotype that is dependent on the mouse strain, gender and specific mutation of the CB1 encoding gene, *CNR1*.

Keywords: endocannabinoids, bone formation, bone mass, bone mineral density, bone remodelling, bone resorption, CB1 cannabinoid receptors, CB2 cannabinoid receptors, single-nucleotide polymorphism, osteoporosis

Introduction

Go to:

In humans and other vertebrates alike, bone structure undergoes substantial temporal changes throughout life. These changes comprise: (i) a rapid skeletal growth phase accompanied by accrual of peak bone mass; (ii) a steady-state phase whereby bone mass remains constant; (iii) age-related bone loss (Segev *et al.*, 2006). These changes are the consequence of a continuous process of resorption/formation of the mineralized matrix referred to as bone remodelling (Figure 1). Imbalanced bone remodelling leads to bone mass accrual (positive imbalance) or bone loss (negative imbalance) (Karsenty, 2001). The remodelling process occurs concomittantly in multiple foci, which in humans encompass approximately 5% of trabecular, endosteal and osteonal surfaces (Parfitt, 1982). The remodelling cycle in individual foci (Figure 1) consists of a relatively rapid (that is a few weeks) resorption of pre-existing mineralized matrix by a bone-specific haematopoietic cell type, the osteoclast, derived from monocytes (Roodman, 1999). It is then followed by a slower (that is a few months) stage of bone formation by

[redacted] Osteoarthritis

another bone-specific cell type, the osteoblast (Parfitt, 1982), which belongs to the stromal cell system of bone marrow (Bab *et al.*, 1986). Different foci are usually at different phases of the cycle and the net effect on bone mass reflects the overall balance between bone resorption and formation. The significance of balanced bone remodelling is demonstrated by osteoporosis, the most common degenerative disease in developed societies, which results from a net increase in bone resorption, bone loss, weakening of the skeleton and increased fracture risk, primarily in females but also in males.

Figure 1

Model of regulation of bone remodelling by the skeletal endocannabinoid system. Shown is remodelling focus consisting of resorption lacuna carved by osteoclasts and being refilled by osteoblasts, which secrete osteoid (unmineralized bone matrix) and control ...

The coordinated occurrence of multiple remodelling sites is suggestive of a complex hierarchical regulation consisting of local, autocrine/paracrine and systemic endocrine (Manolagas, 2000). Indeed, studies in genetically modified mice have demonstrated paracrine control of osteoclast formation and activity by factors such as receptor activator of NF-κB ligand, osteoprotegerin, macrophage colony-stimulating factor and interleukin 6, which are derived from neighbouring stromal cells, including osteoblasts and their precursors (Poli *et al.*, 1994; Simonet *et al.*, 1997; Bucay *et al.*, 1998; Lacey *et al.*, 1998; Kong *et al.*, 1999; Suda *et al.*, 2001). Locally, osteoblasts are regulated mainly by bone morphogenetic proteins (Yoshida *et al.*, 2000). Systemically, it is well established that depletion of gonadal hormones in females and males favours bone loss in mammals, including humans (Most *et al.*, 1997; Alexander *et al.*, 2001; Gabet *et al.*, 2005). In addition, parathyroid hormone (Potts and Juppner, 1998; Gunther *et al.*, 2000), calcitonin (Nicholson *et al.*, 1986), insulin-like growth factor I (Yakar *et al.*, 2002) and the osteogenic growth peptide (Bab and Chorev, 2002) are involved in the control of bone formation. More recently, it has been reported that bone remodelling is also subject to a hierarchically superior central control by hypothalamic leptin and neuropeptide Y signalling (Ducy *et al.*, 2000; Baldock *et al.*, 2002) as well as downstream sympathetic signalling through osteoblastic β2 adrenergic receptors (Takeda *et al.*, 2002). Lately, it has been suggested that imbalances in bone remodelling, previously attributed to excessive thyroid activity and oestrogen depletion, may result from the interaction between the pituitary-derived thyroid-stimulating hormone and follicular-stimulating hormone and receptors expressed in bone cells (Abe *et al.*, 2003; Sun *et al.*, 2006).

The actions of cannabinoids and endocannabinoids are mediated mainly by G protein-coupled cannabinoid receptors type 1 (CB1) and type 2 (CB2) (Howlett, 2002). CB1 and CB2 share 44% overall identity (68% identity for the transmembrane domains). CB1 is perhaps the most abundantly expressed G protein-coupled receptor in the CNS. It is also present in peripheral neurons and the gonads and to some extent in several other peripheral tissues. CB2 is expressed in the immune system, cirrhotic liver, arteriosclerotic plaques, inflamed gastrointestinal mucosa and brain inflammation (Sugiura *et al.*, 2002; Julien *et al.*, 2005; Steffens *et al.*, 2005; Wright *et al.*, 2005). That CB1 and CB2 are not functionally identical is demonstrated by the presence of cannabinoid agonists and antagonist with distinct binding specificities to either receptor (Hanus *et al.*, 1999; Shire *et al.*, 1999). Both receptors signal via the G(i/o) subclass of G proteins, inhibiting stimulated adenylyl cyclase activity. Further downstream, the CBs induce the activation of p42/44 mitogen-activated protein kinase (Wartmann *et al.*, 1995; Melck *et al.*, 1999; Liu *et al.*, 2000), p38 mitogen-activated protein kinase (Derkinderen *et al.*, 2001), c-Jun N-terminal kinase (Rueda *et al.*, 2000; Derkinderen *et al.*, 2001), AP-1 (Liu *et al.*, 2000), the neural form of focal adhesion kinase (Derkinderen *et al.*, 1996), PKB (Gomez del Pulgar *et al.*, 2000) and Ca^{2+} transients (Mombouli *et al.*, 1999).

The main CB1 and CB2 endogenous ligands are *N*-arachidonoylethanolamine (AEA or anandamide) and

2-arachidonoylglycerol (2-AG) (Devane *et al.*, 1992; Mechoulam *et al.*, 1995). Anandamide is present in a variety of tissues such as the brain, kidney, liver, spleen, testis, uterus and blood in picomoles per gram concentrations, with the highest levels reported in the CNS. The low anandamide concentrations have been attributed to low substrate (arachidonic acid esterified at the 1-position) levels for this pathway (Hansen *et al.*, 2000) and/or the short anandamide half-life *in vivo* ($t_{1/2}$<5 min) (Willoughby *et al.*, 1997). Anandamide is biosynthesized through *N*-acyl phosphatidylethanolamine phospholipase D-dependent and -independent pathways (Simon and Cravatt, 2006). The main anandamide-degrading enzyme is fatty acid amide hydrolase, a membrane-associated serine hydrolase enriched in the brain and liver (Cravatt *et al.*, 2001). In general, the tissue distribution of 2AG is similar to that of anandamide; however, its concentration is 300–1000 higher (ng g^{-1} range). 2AG production has been demonstrated in the CNS as well as in platelets and macrophages, especially in response to stimulation by inflammatory agents such as lipopolysaccharide (Varga *et al.*, 1998; Di Marzo *et al.*, 1999). 2AG is generated from arachidonic acid-enriched membrane phospholipids, such as inositol phospholipids, through the combined actions of phospholipase C and diacylglycerol lipases (DAGLα and DAGLβ) (Stella *et al.*, 1997; Bisogno *et al.*, 2003). It has been proposed that like other monoacylglycerols, 2AG is metabolized by a monoacylglycerol lipase (Konrad *et al.*, 1994).

A couple of striking observations led us to assess the occurrence and role of a skeletal endocannabinoid system. One is that, bone formation and bone mass, as well as the central production of at least one major endocannabinoid, 2-AG, are subject to negative control by leptin (Di Marzo *et al.*, 2001). The second observation is that traumatic brain injury enhances both bone formation (Orzel and Rudd, 1985; Wildburger *et al.*, 1998) and central 2-AG production (Panikashvili *et al.*, 2001).

Cannabinoid receptors in bone

Go to:

Osteoblast progenitors, such as mouse bone marrow-derived stromal cells and MC3T3 E1 preosteoblasts (Sudo *et al.*, 1983; Jorgensen *et al.*, 2004), exhibit very low levels, if any, of CB1. CB2 expression in these cells is also very low (Bab, 2005; Ofek *et al.*, 2006). However, when the cells are grown for 5–28 days in medium that promotes osteoblast differentiation (Bellows *et al.*, 1986), CB2 mRNA expression increases progressively in parallel to the expression of osteoblastic marker genes such as tissue non-specific alkaline phosphatase (*TNSALP*) (Zhou *et al.*, 1994), parathyroid hormone receptor 1 (*PTHRc1*) (Zhang *et al.*, 1995) and the osteoblastic master regulatory gene, *RUNX2* (Araujo *et al.*, 2004). In osteoclasts, CB1 is expressed at low levels. By contrast, CB2 mRNA transcripts in these cells are present in high abundance (Bab, 2005; Idris *et al.*, 2005; Ofek *et al.*, 2006; Scutt and Williamson, 2007). *In vivo*, CB2 protein is present in trabecular osteoblasts and their decedents, the osteocytes (Lian *et al.*, 2004), as well as in osteoclasts (Ofek *et al.*, 2006). CB1 is highly expressed in skeletal sympathetic nerve terminals (Tam *et al.*, 2006).

Cannabinoid receptor activation and bone cell differentiation and activity

Go to:

Activation of CB2 has different effects in early osteoblast progenitors and in more mature osteoblastic cells. In the early precursors, represented by bone marrow-derived, partially differentiated osteoblastic cells that show limited CB2 expression, the specific CB2 agonist HU-308 (Hanus *et al.*, 1999) but not the specific CB1 agonist noladin ether (Hanus *et al.*, 2001), triggers a G_i protein-mediated mitogenic effect and consequent expansion of the preosteoblastic pool (Bab, 2005). *Ex vivo* osteoblastic colony formation by bone marrow stromal $cb2^{-/-}$ cells is markedly diminished, whereas colony-forming unit osteoblastic formation by wild-type cells is stimulated by HU-308 (Ofek *et al.*, 2006; Scutt and Williamson, 2007). In mature osteoblastic cells, represented by the MC3T3 E1 cell line, the same ligand stimulates osteoblast-differentiated functions such as alkaline phosphatase activity and matrix mineralization (Bab, 2005; Ofek *et al.*, 2006). Thus, CB2 signalling is involved in several regulatory pro-osteogenic processes along the osteoblast lineage (Figure 1).

In bone marrow-derived osteoclastogenic cultures and in the RAW 264.7 cell line, we showed that CB2 activation inhibits osteoclast formation by restraining mitogenesis at the monocytic stage, prior to incubation with receptor activator of NF-κB ligand. It also suppresses osteoclast formation by repressing receptor activator of NF-κB ligand expression in osteoblasts and osteoblast progenitors (Figure 1; Ofek *et al.*, 2006). Likewise, it has been recently shown that the cannabinoid receptor agonist ajulemic acid also suppresses osteoclastogenesis (George *et al.*, 2007). By contrast, another study reported the stimulation of osteoclast formation and bone resorption by cannabinoid receptor agonists and their inhibition by antagonists (Idris *et al.*, 2005). These allegedly paradoxical results could occur because of variations in experimental conditions, or more probably, from opposite, cell type-dependent specificities of some cannabinoid ligands.

Presence and biosynthesis of endocannabinoids in the skeleton

Go to:

Anandamide and 2-AG are present in bone at levels nearly as high as the brain levels of these endocannabinoids (Figure 1; Tam *et al.*, 2007 and unpublished results). Both ligands are produced by osteoblastic cells in culture. In addition, DAGLα and DAGLβ, enzymes critically involved in the 2-AG biosynthesis, are expressed in osteoblasts, osteocytes and bone-lining cells. DAGLβ expression was also found in osteoclasts. Although both 2-AG and anandamide are perceived as non-selective agonists of CB1 and CB2, our findings in bone and bone cell cultures suggest that 2-AG activates CB1 in the sympathetic nerve terminals, whereas anandamide affects bone cells directly by binding to CB2 (Figure 1).

Skeletal phenotype of cannabinoid receptor-deficient mice

Go to:

We used cannabinoid receptor mutant mice to assess the physiologic role of CB1 and CB2 in the control of bone mass. In the case of CB1, the skeletal phenotype depends on the mouse strain and/or the construct used for gene mutation. In one CB1-deficient line, backcrossed to CD1 mice ($CD1^{CB1-/-}$), the N-terminal 233 codons of the *CNR1* gene were ablated (Ledent *et al.*, 1999). The effect of this mutation shows a clear gender disparity. Females have normal trabecular bone with a slight cortical expansion, whereas male $CD1^{CB1-/-}$ mice exhibit high bone mass (Tam *et al.*, 2006). Sexually mature $CD1^{CB1-/-}$ mice of either gender display normal bone formation and resorption parameters, suggesting that the male phenotype is acquired early in life, during the developmental phase when peak bone mass is determined. A similar male phenotype was reported in an independent study (Idris *et al.*, 2005) in which these mice were further backcrossed to Biozzi ABH mice (Amor *et al.*, 2005). In the second line, backcrossed to C57BL/6J mice ($C57^{CB1-/-}$), almost the entire protein-encoding sequence was removed (Zimmer *et al.*, 1999). Both male and female $C57^{CB1-/-}$ have a low bone mass phenotype accompanied by increased osteoclast counts and decreased bone formation rate (Tam *et al.*, 2006). Our recent findings suggest that CB1 controls osteoblast function by negatively regulating norepinephrine release from sympathetic nerve terminals in the immediate vicinity of these cells. Norepinephrine suppresses bone formation by binding to osteoblastic β2 adrenergic receptor (Takeda *et al.*, 2002); this suppression is alleviated by activation of sympathetic CB1 (Figure 1; Tam *et al.*, 2007).

Cannabinoid receptor type 2-deficient animals have a gender-independent skeletal phenotype. During their first 2–3 months of life, $CNR2^{-/-}$ mice accrue a normal peak trabecular bone mass (Bab *et al.*, 2007), but later display a markedly enhanced age-related bone loss; their trabecular bone volume density at 1 year of age is approximately half compared with wild-type controls (Ofek *et al.*, 2006). Reminiscent of human postmenopausal osteoporosis (Brown *et al.*, 1984), the $CNR2^{-/-}$ mice have a high bone turnover with increases in both bone resorption and formation, which are at a net negative balance (Ofek *et al.*, 2006). Because healthy CB2 mutant mice are otherwise normal, it appears that the main physiologic involvement of CB2 is associated with maintaining bone remodelling at balance.

Prevention and reversal of bone loss by CB2 agonist

Go to:

Unlike CB1, CB2 is not associated with the cannabinoid psychoactive effects. Therefore, CB2-specific ligands could offer an opportunity to prevent and/or rescue bone loss while avoiding the psychological side effects of cannabinoids. Indeed, the specific, non-psychoactive CB2 agonist, HU-308 (Hanus *et al.*, 1999), attenuates bone loss induced by oestrogen depletion in ovariectomized (OVXed) animals using either 'preventive' (Ofek *et al.*, 2006) or 'rescue' (unpublished data) protocols. In the preventive approach, HU-308 administration commenced immediately after ovariectomy. To assess reversal of bone loss, the drug was given beginning 6 weeks post-ovariectomy to allow for bone loss to occur. Treatment consisted of daily i.p. injections for 4–6 weeks. The attenuation of bone mass reflected both inhibition of bone resorption and stimulation of bone formation (Bab, 2005). Hence, CB2 agonists may become an orally available, combined antiresorptive and anabolic therapy for osteoporosis.

CB2 and osteoporosis in humans

Go to:

The findings in mice prompted us to determine if cannabinoid receptors also contribute to the regulation of bone mass in humans. We therefore studied polymorphisms in the human *CNR1* locus, encoding the CB1 receptor, and the *CNR2* locus, encoding the CB2 receptor, in a case–control sample of osteoporotic patients collected by Professor de Vernejoul at the Hôpital Lariboisière in Paris (Karsak *et al.*, 2005). The study comprised 68 postmenopausal osteoporotic women with an average bone mineral density (BMD, measured by dual-energy X-ray absorptiometry) T-score of -3.062 ± 0.799 at the lumbar spine and 220 age-matched healthy controls.

The *CNR1* locus is located on chromosome 5q15. It encompasses a single coding exon that is preceded by several non-coding 5′ exons, indicating a complex transcriptional regulation of this gene by different promoters (McCaw *et al.*, 2004; Zhang *et al.*, 2004). Analysis of four single-nucleotide polymorphisms (SNPs) spanning nearly 20 kb around the CB1-coding exon revealed no significant association with the osteoporosis phenotype, suggesting that the *CNR1* locus does not play a major role in this sample.

The *CNR2* locus is located on chromosome 1p36. This genomic region and its mouse orthologue on chromosome 4 have been previously linked to BMD and osteoporosis in several independent association analyses (Devoto *et al.*, 1998, 2001, 2005). However, these analyses did not consider *CNR2* as a potential candidate gene. Like *CNR1*, the *CNR2* gene also consists of a single coding exon, which is preceded by non-coding upstream exon. We analysed a total of 26 SNPs spanning approximately 300 kb around the CNR2 locus (genomic position 23750771–24039933). Several of these SNPs showed a significant association with the disease phenotype, suggesting that *CNR2* polymorphisms are important genetic risk factors for osteoporosis. The most significant *P*-values for allele and genotype associations were observed with SNPs located within the CB2-coding region (0.0014 and 0.00073 respectively). Furthermore, when BMD at the lumbar spine was analysed as a quantitative trait, highly significant differences were found in BMD between individuals carrying different SNPs in the CB2-coding region. Hence, we sequenced the CB2-coding exon in all 388 patients and controls thus identifying two missense variants, Gln63Arg and His316Tyr, with the Arg63 variant being more common in the osteoporotic patients than in the healthy controls (Karsak *et al.*, 2005). Taken together, these findings suggest that a common variant of the CB2 receptor contributes to the aetiology of osteoporosis in humans.

Recently, several candidate quantitative trait loci in BMD, including *CNR2*, were analysed in a cohort of 1110 Japanese women and 1128 Japanese men, 40–79 years of age (Yamada *et al.*, 2007). This cohort was randomly recruited to a prospective study on ageing. For the *CNR2* locus, they studied a single SNP (rs2501431, A → G), which had shown the strongest association in our French sample ($P=0.0007$). BMD, as measured by peripheral quantitative computed tomography or dual-energy X-ray absorptiometry, was always lower in women with the AA genotype compared with the AG and GG genotypes. Together, these studies strongly suggest that *CNR2* is the

susceptibility gene for low BMD and osteoporosis on chromosome 1p36.

Conclusions

Go to:

Our recent studies in mice and humans suggest an important role for the endocannabinoid system in the regulation of skeletal remodelling and the consequent implications on bone mass and biomechanical function. Although the CB1 cannabinoid receptor has been identified in sympathetic terminals innervating the skeleton, its role in controlling bone turnover remains to be elucidated. The CB2 cannabinoid receptor is expressed in bone cells. Its bone anabolic action, including some of the mechanisms involved, has been reported in some detail, and is also inferred from the human genetic studies. These studies portray polymorphisms in *CNR2*, the gene encoding CB2, as important genetic risk factors for osteoporosis. Taken together, the reports on cannabinoid receptors in mice and humans pave the way for the development of (i) cannabinoid drugs to combat osteoporosis, and (ii) diagnostic measures to identify osteoporosis-susceptible polymorphisms in *CNR2*.

Abbreviations

Go to:

2-AG	2-arachidonoylglycerol
BMD	bone mineral density
CB1	cannabinoid receptor type 1
CB2	cannabinoid receptor type 2
DAGL	diacylglycerol lipase
SNP	single-nucleotide polymorphism

Notes

Go to:

Conflict of interest

The authors are inventors on patent applications related to the use of cannabinoid receptor ligands in skeletal therapy and diagnosis of osteoporosis. Rights in this intellectual property and those pertinent to HU-308 are assigned to; Yissum Research Development Company of the Hebrew University of Jerusalem.

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