# Medical Marijuana Program

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

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

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

### Section A: Petitioner's Information

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

### Section B: Medical Condition, Medical Treatment or Disease

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

POSTHERPETIC NEURALGIA, PERIPHERAL NEUROPATHY and ALLODYNIA from SHINGLES

### Section C: Background

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

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

SEE ATTACHED PAGES

### Section D: Negative Effects of Current Treatment

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

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

SEE ATTACHED PAGES

## Section E: Negative Effects of Condition or Treatment

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

- Attach additional pages as necessary.

SEE ATTACHED PAGES

## Section F: Conventional Therapies

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

- Attach additional pages as necessary.

SEE ATTACHED PAGES

## Section G: General Evidence of Support for Medical Marijuana Treatment

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

- Attach additional pages as necessary.

SEE ATTACHED PAGES

## Section H: Scientific Evidence of Support for Medical Marijuana Treatment

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

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

SEE ATTACHED PAGES

## Section I: Professional Recommendations for Medical Marijuana Treatment

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

SEE ATTACHED PAGES

| Section J: Submission of Petition |
|---|
| In the event you are unable to answer or provide the required documentation to any of the Sections above (excluding Section D); provide a detailed explanation indicating what you believe is "good cause" for not doing so.<br><br>• Attach additional pages as necessary. |
| |
| |
| |
| |

| I hereby certify that the above information is correct and complete. | |
|---|---|
| My signature below attests that the information provided in this petition is true and that the attached documents are authentic. I formally request that the commissioner present my petition and all supporting evidence to the Board of Physicians for consideration. | |
| Signature: ▶ [redacted] | Date Signed: 11-2-2016 |

# MEDICAL MARIJUANA PROGRAM

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

### Section B: Medical Condition, Medical Treatment or Disease

- **POSTHERPETIC NEURALGIA, PERIPHERAL NEUROPATHY, ALLODYNIA**

### Section C: Background

- Attached Article – Mayo Clinic Postherpetic Neuralgia

### Section D: Negative Effects of Current Treatment

- Attached Article of current accepted treatments – WebMD Treatment of Postherpetic Neuralgia

### Section E: Negative Effects of Condition or Treatment

- The condition is causing constant pain in the dermatomes around the waist. Pain is severe with light touch of clothing and palpation. It interferes with sleep resulting in fatigue, and the chronic nature of it is debilitating. The patient is feeling reduced levels of interest in exercise activities. Fatigue is resulting in weakness making the patient susceptible to falls and accidents. The patient is experiencing depression, reducing interest in social activities.
- Conventional therapies tried were
    - Lidocaine and Capsaicin patches were not effective.
    - Acupuncture was not effective.
    - Neurontin caused overall weakness.
    - Lyrica caused weakness in legs and resulted in a fall.
    - Antidepressant caused insomnia.

### Section F: Conventional Therapies

Attached article – American Academy of Neurology Treatment of Postherpetic Neuralgia

- Indicates that further treatment could include Opioids. However, with the current opioid crisis, this approach is not being considered.

### Section G: General Evidence of Support for Medical Marijuana Treatment

Attached articles –

- Painful Peripheral Neuropathy
- What is postherpetic neuralgia? What causes postherpetic neuralgia?
- A Patients Guide for Using Medical Marijuana for Shingles

- Cannabis Topicals (applied to the skin) – Americans For Safe Access
- Cannabis Topicals Provide Relief for Sore Muscles and Pain
- Topical Use of Cannabis

**Section H: Scientific Evidence of Support for Medical Marijuana Treatment**

Attached articles –

- A double-blind randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment

- Sativex successfully treats neuropathic pain characterized by allodynia: A randomized, double-blind, placebo-controlled clinical trial

- Cannabinoids in the management of difficult to treat pain

**Section I: Professional Recommendations for Medical Marijuana Treatment**

- Attached letter from [redacted]

Section I

STAMFORD HEALTH
Healing. Reimagined.

Affiliate Columbia University College of Physicians and Surgeons
Member NewYork-Presbyterian Healthcare System
A Planetree Hospital

[redacted]
Internal Medicine

November 2, 2016

To whom it may concern,

I am writing this letter at the request of a patient of mine. He has refractory post herpetic neuralgia. He would like the Board of Physicians to consider allowing the use of topical Cannabis to see if it is effective for this disorder.

Sincerely,

[redacted]

[redacted]

C

MAYO CLINIC

Section C

Diseases and Conditions

# Postherpetic neuralgia

By Mayo Clinic Staff

Postherpetic neuralgia (post-hur-PET-ik noo-RAL-juh) is a complication of shingles, which is caused by the chickenpox (herpes zoster) virus. Postherpetic neuralgia affects nerve fibers and skin, causing burning pain that lasts long after the rash and blisters of shingles disappear.

The risk of postherpetic neuralgia increases with age, primarily affecting people older than 60. There's no cure, but treatments can ease symptoms. For most people, postherpetic neuralgia improves over time.

The signs and symptoms of postherpetic neuralgia are generally limited to the area of your skin where the shingles outbreak first occurred — most commonly in a band around your trunk, usually on one side of your body. However postherpetic neuralgia is also common in people whose shingles occurred on the face.

Signs and symptoms may include:

- **Pain that lasts 3 months or longer** after the shingles rash has healed. The associated pain has been described as burning, sharp and jabbing, or deep and aching.
- **Sensitivity to light touch.** People with the condition often can't bear even the touch of clothing on the affected skin (allodynia).
- **Itching and numbness.** Less commonly, postherpetic neuralgia can produce an itchy feeling or numbness.

## When to see a doctor

See a doctor at the first sign of shingles. Often the pain starts before you notice a rash. Your risk of developing postherpetic neuralgia is lessened if you begin taking antiviral medications within 72 hours of developing the shingles rash.

Once you've had chickenpox, the virus remains in your body for the rest of your life. As you age or if your immune system is suppressed, such as from medications or chemotherapy, the virus can reactivate, causing shingles.

Postherpetic neuralgia occurs if your nerve fibers are damaged during an outbreak of shingles. Damaged fibers can't send messages from your skin to your brain as they normally do. Instead, the messages become confused and exaggerated, causing chronic, often excruciating pain that can last months — or even years.

When you have shingles, you might be at greater risk of developing postherpetic neuralgia as a result of:

- **Age.** You're older than 50.
- **Severity of shingles.** You had a severe rash and severe pain.
- **Other illness.** You have a chronic disease, such as diabetes.
- You had shingles on your face or torso.

Depending on how long postherpetic neuralgia lasts and how painful it is, people with the condition can develop:

- Depression
- Fatigue
- Difficulty sleeping
- Lack of appetite
- Difficulty concentrating

You might start by seeing your family doctor. He or she may refer you to a nerve specialist (neurologist) or a doctor who specializes in the treatment of chronic pain.

Here's information to help you get ready for your appointment.

## What you can do

When you make the appointment, ask if there's anything you need to do in advance, such as fasting before a specific test. Make a list of:

- **Your symptoms,** including any that seem unrelated to the reason for your appointment
- **Key personal information,** including major stresses, recent life changes and family medical history
- **All medications, vitamins or other supplements** you take, including the doses
- **Questions to ask** your doctor

Take a family member or friend along, if possible, to help you remember the information you're given.

- What's likely causing my symptoms?
- What else could cause my symptoms?
- What tests do I need?
- Is my condition likely temporary or chronic?
- What's the best course of action?
- What are the alternatives to the primary approach you're suggesting?
- I have other health conditions. How can I best manage them together?
- Are there restrictions I need to follow?
- Should I see a specialist?
- Are there brochures or other printed material I can have? What websites do you recommend?

Don't hesitate to ask other questions.

## What to expect from your doctor

Your doctor is likely to ask you several questions, such as:

- When did your symptoms begin?
- Have your symptoms been continuous or occasional?
- How severe are your symptoms?
- Have you had chickenpox? When?
- What, if anything, seems to improve your symptoms?
- What, if anything, appears to worsen your symptoms?

Your doctor will examine your skin, possibly touching it in places to determine the borders of the affected area.

In most cases, no tests are necessary.

No single treatment relieves postherpetic neuralgia in all people. In many cases, it takes a combination of treatments to reduce the pain.

## Lidocaine skin patches

These are small, bandage-like patches that contain the topical, pain-relieving medication lidocaine. These patches can be cut to fit only the affected area. You apply the patches, available by prescription, directly to painful skin to deliver temporary relief.

## Capsaicin skin patch

A high concentration of an extract of chili peppers (capsaicin) is available as a skin patch to relieve pain. Available only in your doctor's office, the patch is applied by trained personnel after using a numbing medication on the affected area. The process takes at least two hours, but a single application is effective in decreasing pain for some people for up to three months. If effective, the application can be repeated every three months.

## Anticonvulsants

Certain anti-seizure medications, including gabapentin (Neurontin, Gralise) and pregabalin (Lyrica), can lessen the pain of postherpetic neuralgia. These medications stabilize abnormal electrical activity in your nervous system caused by injured nerves. Side effects of these drugs include drowsiness, unclear thinking, unsteadiness and swelling in the feet.

## Antidepressants

Certain antidepressants — such as nortriptyline (Pamelor), duloxetine (Cymbalta) and venlafaxine (Effexor XR) — affect key brain chemicals that play a role in both depression and how your body interprets pain. Doctors often prescribe antidepressants for postherpetic neuralgia in smaller doses than they do for depression alone.

Common side effects of these medications include drowsiness, dry mouth, lightheadedness and weight gain.

## Opioid painkillers

Some people may need prescription-strength pain medications containing tramadol (Ultram, Conzip), oxycodone (Percocet, Roxicet, Xartemis XR) or morphine. Opioids can cause mild dizziness, drowsiness, confusion and constipation. They can also be addictive. Although this risk is generally low, discuss it with your doctor.

Tramadol has been linked to psychological reactions, such as emotional disturbances and suicidal thoughts. Opioid medications should not be combined with alcohol or other drugs and may impair your ability to drive.

## Steroid injections

Steroids are sometimes injected into the spine (intrathecal) for postherpetic neuralgia. However, evidence of effectiveness is inconsistent. A low risk of serious side effects, including meningitis, has been associated with their use.

You may find that the following over-the-counter medications ease the pain of postherpetic neuralgia:

- **Capsaicin.** Capsaicin cream, made from the seeds of hot chili peppers, may relieve pain from postherpetic neuralgia. Capsaicin (Capzasin-P, Zostrix) can cause a burning sensation and irritate your skin, but these side effects usually disappear over time. Because capsaicin cream can

- **Topical analgesics and anesthetics.** Aspirin mixed into an absorbing cream or nonprescription-strength lidocaine cream may reduce skin hypersensitivity.

The herpes zoster vaccine (Zostavax) has been shown to greatly decrease the risk of shingles. The vaccine is approved by the Food and Drug Administration for adults age 50 and older and is recommended for all adults 60 and older who aren't allergic to the vaccine and who don't take immune-suppressing medications.

## References

1. Bajwa ZH, et al. Postherpetic neuralgia. http://www.uptodate.com/home. Accessed Sept. 1, 2015.
2. Tseng HF, et al. Zoster vaccine and the risk of postherpetic neuralgia in patients who developed herpes zoster despite having received the zoster vaccine. Journal of Infectious Diseases. In press. Accessed Sept. 1, 2015.
3. Johnson RW, et al. Postherpetic neuralgia. The New England Journal of Medicine. 2014;371:1526.
4. Dubinsky RM, et al. Practice parameter: Treatment of postherpetic neuralgia. American Academy of Neurology. 2004;63:959.
5. Sampathkumar P, et al. Herpes zoster (shingles) and postherpetic neuralgia. Mayo Clinic Proceedings. 2009;84:274.
6. Important drug warning. U.S. Food and Drug Administration. http://google2.fda.gov/search?q=cache:EKB1SS0qgzQJ:www.fda.gov/downloads/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm213266.pdf+tramadol+suicide+risk&client=FDAgov&8&access=p&oe=UTF-8. Accessed Sept. 3, 2015.

Sept. 16, 2015

Original article: http://www.mayoclinic.org/diseases-conditions/postherpetic-neuralgia/basics/symptoms/con-20023743

D

Section D

WebMD

# How to Treat Nerve Pain After Shingles

For most people, the symptoms of shingles usually fade away along with the rash that may have appeared along one side of their body or face. But for some people, pain persists long after their skin has cleared.

It's called postherpetic neuralgia, and it's a complication of shingles. You might feel intense sensations of tingling, burning, and shooting that don't let up. This could last for 3 months or longer, and you could be sensitive to touch and have trouble wearing clothes.

If you've had shingles and you're hurting weeks or months later, talk to your doctor.

She'll want to know more about your symptoms and come up with a treatment plan. That can include a mix of medications and other things to give you relief.

### What Can I Take to Feel Better?

Your doctor has a host of ways to treat your pain after shingles, including a variety of medications. They include:

Anticonvulsants: These medications were developed to control seizures, but they can also help reduce the pain of postherpetic neuralgia. Examples are:

- Carbamazepine (Carbatrol, Equetro, Epitol, Tegretol)
- Gabapentin (Fanatrex, Neurontin)
- Pregabalin (Lyrica)

Tricyclic antidepressants: These have been shown to help ease the pain of postherpetic neuralgia. They include:

- Amitriptyline (Elavil)
- Desipramine (Norpramin)
- Nortriptyline (Pamelor)

Prescription painkillers: Over-the-counter medicine may be enough for mild cases, but others might need more powerful opioid (narcotic) painkillers, such as:

- Hydrocodone with acetaminophen (Lorcet, Lortab, Norco, Vicodin)
- Long-acting hydrocodone (Zohydro ER, Hysingla ER)
- Hydromorphone (Dilaudid, Exalgo)
- Meperidine (Demerol)

- Oxycodone (OxyContin, OxyFast, Roxicodone)
- Oxycodone and naloxone (Targiniq ER)
- Oxycodone and acetaminophen (Percocet)

Talk to your doctor or pharmacist about side effects of any new prescription or over-the-counter medication.

### Topical Treatments

You might find relief with treatments you put on your skin. You can talk to your doctor about:

Creams: Some of these contain capsaicin, the ingredient in cayenne pepper that gives it a kick. Examples are Capsin and Zostrix. You can buy this over the counter but make sure your doctor knows if you plan on using these.

Patches: Capsaicin is also in Qutenza, which is applied via a patch for one hour every 3 months. You need to visit the doctor's office for this.

Lidoderm is a patch that has a numbing agent called lidocaine. It's applied directly to the painful area of skin. You need a prescription.

### Other Ways to Ease the Pain

Most people with postherpetic neuralgia use medication to control their symptoms. But there are other ways to control the pain, too. They include:

TENS (transcutaneous electrical nerve stimulation): You use a device that shoots tiny electrical currents into the area of pain on the skin. This helps block the pain.

Cold packs: Try a gel-filled one to numb the area unless cooler objects make your neuralgia worse.

Comfortable clothes: Go for looser fits and fabrics such as cotton and silk.

### Can I Prevent It?

The FDA has approved a shingles vaccine. It's called Zostavax. The vaccine is now recommended for everyone 60 and older. For this age group, it reduces the chance of getting shingles by about one half. People from 50 to 59 may want to talk to their doctor about it if they are having ongoing pain or skin issues or have a weakened immune system.

Even in those who get the vaccination and still develop shingles, the painful period is reduced.

Certain medicines can also reduce the severity of shingles and how long it lasts. The main treatment is with antiviral drugs during the early stages of shingles, within 2 to 3 days of symptoms coming on. Medications used include:

- Acyclovir (Zovirax)
- Famciclovir (Famvir)
- Valacyclovir (Valtrex)

AAN Guideline Summary for **PATIENTS**

# TREATMENT OF POSTHERPETIC NEURALGIA

If you have been diagnosed with postherpetic neuralgia, this fact sheet will help you and your doctor discuss possible treatments to decrease your pain and improve your quality of life.

Postherpetic neuralgia affects the nerves and skin. It can be very painful. The pain can ache or burn. It can also feel like an electric shock.

Neurologists from the American Academy of Neurology (AAN), who specialize in diseases of the brain and central nervous system, believe you should know about effective treatment options for postherpetic neuralgia. A group of neurologists reviewed all of the data available and made recommendations. These will help your doctor find the most effective treatments.

## What is the cause?

People develop postherpetic neuralgia after they have experienced a viral infection called herpes zoster. Herpes zoster can cause two conditions that result in small skin blisters—chicken pox and shingles.

Chicken pox is a common childhood herpes virus. It is highly contagious. For some people, their immune system may not have eliminated the virus. The virus remains inactive in the nerve cells. Years later, the virus may reactivate and develop into shingles. Other people may develop shingles after a first exposure to the herpes zoster virus, usually as an adult.

As people get older there is a greater chance they will develop postherpetic neuralgia. It is a continuation of the pain of shingles after the rash has resolved. Age, illness, and stress can trigger the virus to resurface.

The virus affects sensory nerve fibers, causing pain. When the virus reaches the skin it causes a rash with blisters, known as shingles.

Not everyone who gets shingles develops postherpetic neuralgia. It does not develop after chicken pox. The skin lesions of shingles heal in one to three months. But some people still have pain after the skin irritations heal. If the pain lasts longer than three months, you probably have postherpetic neuralgia.

## What are the symptoms?

The pain is often in the same area where the shingles blisters and rash occurred. The pain may include:

- Sharp, burning, or deep aching pain
- Sensitivity to touch and temperature change
- Itching and numbness

Some muscle weakness or paralysis may occur if the nerves cells involved also control muscle movement.

## What are the best treatments?

There's currently no cure. The duration of pain differs from person to person. For most people, the condition improves over time. Researchers found that over half of patients stop feeling pain within one year.

Drugs can help with symptoms. A group of neurologists from the American Academy of Neurology reviewed all of the available data for treatment, including antidepressants, antiepileptic drugs, opioids, medicines used on the skin or as injections, and other treatments. There is not enough data at this time to know for certain the long-term effects of these treatments.

***Antidepressants***

Tricyclic antidepressants are effective and should be used for treatment of postherpetic neuralgia. The drugs —known generically as amitriptyline, nortriptyline, desipramine, and maprotiline—affect brain chemicals

AMERICAN ACADEMY OF NEUROLOGY

that influence both depression and how your body recognizes pain. Side effects include drowsiness, dry mouth, and weight gain. Because these drugs are only given once a day, the drowsiness can be used to help get to sleep and stay asleep. Talk to your doctor or pharmacist about side effects.

***Antiepileptic drugs***

Two drugs used to treat epilepsy also minimize the pain from postherpetic neuralgia. These drugs should be used for treatment. They are gabapentin and pregabalin. As of September 2004, only gabapentin is available in the United States. Side effects of these drugs can include drowsiness and unclear thinking. Talk to your doctor or pharmacist about side effects.

***Opioids***

There is evidence that long-acting oral opioids are effective and should be used for treatment of postherpetic neuralgia. Opioids are narcotics. They are strong pain relievers. Some opioids are natural, which means they come from living sources. Others are synthetic—or man-made. Opioids act on nerve cell receptors in the brain to relieve pain. A weak opioid pain-reliever, tramadol, also showed some benefit in treating postherpetic neuralgia.

People taking opioids may experience side effects such as nausea, mild dizziness, drowsiness, constipation, unclear thinking, and dependency. Talk to your doctor or pharmacist about side effects. Care must be taken to strictly follow the directions on how to take opioid pain relievers. If the long-acting forms of opioids are crushed or allowed to dissolve in the mouth, accidental overdose will occur.

***Topical lidocaine patches***

Lidocaine skin patches are also effective in reducing the pain of postherpetic neuralgia. These are adhesive patches. They contain a pain-relieving drug called lidocaine. The patches are put directly on the affected skin. They can provide relief for hours at a time.

***Aspirin cream and capsaicin***

Aspirin, an anti-inflammatory drug, and capsaicin, which causes degeneration of nerve fibers, in the skin may sometimes be used to relieve the pain and itching from postherpetic neuralgia. Aspirin in ointment or cream is probably effective in reducing the pain of postherpetic neuralgia, but the amount of benefit for aspirin cream and topical capsaicin is below the level that is considered clinically important in treatment of chronic pain.

Other topical pain relievers and antiepileptic drugs, pain relievers that are injected, laser treatments, acupuncture, morphine, and vitamin E were also reviewed. In some cases, it was clear that there was no benefit. In other cases there was not enough information to decide whether there is a benefit.

## Talk to your neurologist

It is important to talk with your doctor about your choices. Together you and your doctor can determine which treatment will provide a decrease in pain and improve quality of life.

This is an evidence-based educational service of the American Academy of Neurology. It is designed to provide members with evidence-based guideline recommendations to assist with decision-making in patient care. It is based on an assessment of current scientific and clinical information, and is not intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on the circumstances involved. Physicians are encouraged to carefully review the full AAN guidelines so they understand all recommendations associated with care of these patients.



AMERICAN ACADEMY OF NEUROLOGY
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**From:** Regina Walsh <qiwalsh@aol.com>
**To:** qiwalsh <qiwalsh@aol.com>
**Date:** Wed, Nov 2, 2016 9:18 pm

AmericansFor SafeAccess
Advancing Legal Medical Marijuana Therapeutics and Research

**Cannabis Topicals (applied to the skin)**

Cannabinoids combined with a penetrating topical cream can enter the skin and body tissues and allow for direct application to affected areas (e.g. allergic skin reactions, post-herpes neuralgia, muscle strain, inflammation, swelling, etc.).

- Cannabinoids in cannabis interact with CB1 and CB2 receptors that are found all over the body, including the skin.
- Both THC and Cannabidiol (CBD) have been found to provide pain relief and reduce inflammation.
- Topical cannabis use does not produce a psychoactive effect, which is different from eating or inhaling the medicine.

Different types of cannabis topicals include:

- Salve: cannabinoids heated into coconut oil combined with bees wax and cooled. Rub directly on skin.
- Cream: cannabinoids heated into shea butter combined with other ingredients and cooled. Rub directly on skin.

Topicals may produce anti-inflammatory and analgesic or pain relief effects.. Research has to date been limited to studies on allergic and post-herpes skin reactions and pain relief. Anecdotal reports on topical treatment efficacy include:

- Certain types of dermatitis (including atopic) and psoriasis

- Balm for lips, fever blisters, herpes
- Superficial wounds, cuts, acne pimples, furuncles, corns, certain nail fungus
- Rheumatism and arthritic pains (up to the 2nd degree of arthritis)
- Torticollis, back pains, muscular pains and cramps, sprains and other contusions
- Phlebitis, venous ulcerations
- Hemorrhoids
- Menstruation pains
- Cold and sore throat, bronchitis
- Asthmatic problems with breathing
- Chronic inflammation of larynx (application in the form of a Priessnitz compress)
- Migraine, head pains, tension headaches
- Pharmaceutical Cannabis or Cannabinoids

Section 6

[redacted]

**Date:** Wed, Nov 2, 2016 9:09 pm

# Cannabis Topicals Provide Relief for Sore Muscles & Pain

April 6, 2016

Topics: Back Pain, Topicals, Pain, Arthritis

Four topic[illegible]

use regularly for aches and pains.

This past winter, I seemed to be sick non-stop. As a result, my normal exercise regime was not an option. So now that I have started back up with early morning boot camp and daily hikes, my muscles have been screaming. After my first few days back at it, I can barely walk, feel hobbled and the aching muscles leave me seriously cranky. Could a cannabis topical balm help relieve my tired sore muscles? The answer is, as you may have guessed, 'Yes'.

**What are Cannabis Balms**

Marijuana topicals can come as a salve, a cream or even an oil. They are meant to be applied to the skin and provide localized relief for pain. Pain may be from nerves, arthritis, inflammation, and general soreness, among other conditions. The benefit of a topical, to many patients, is that a topical can provide pain relief without creating a sense of being high or stoned.

Cannabis infused balms work by being absorbed through the skin and binding to our CB2 receptors, which are found throughout the body. THC and CBD along with other cannabinoids will have an analgesic and anti-inflammatory effect on the body once they come into contact with these receptors. In general, topicals will not get into the blood stream, which is one of the reasons you do not get high. Transdermal patches are another way of medicinal administration and transdermals actually do get into the blood stream, so they are somewhat different to topicals.

**My Top 4 Cannabis Topicals**

Cannabis salves are said to help with sore muscles, back pain, arthritis and many other aches and pains. I have used different balms to help me with acute lower back pain, sore muscles, tendonitis and bursitis in my hips. Many marijuana topicals on the market today carry some of the same ingredients found within drugstore muscle creams, including eucalyptus, camphor, menthol and others. There are a couple of downsides to using topicals; many smell like cannabis and they can often feel greasy due to their carrier oils. Although there is little to no research done on topicals, anecdotally I have found that people who use cannabis topicals seem to uniformly like or love them.

As you may know, there are numerous marijuana balms out on the market, and many that I have yet to try. Here I'm going to tell you about four topicals that I use and like. Each of the balms mentioned below are available for purchase within the state of California.

### Sweet Releaf

I'm going to start with this cannabis salve because I absolutely love it. It has a creamy texture, does not smell like cannabis and provides fast relief from sore muscles. I was barely able to walk after my workout, my quads were so sore, and a colleague at work mentioned this wonder-cream. I happened to have a sample size at home, so I popped it open and with the smallest amount it went straight to work. Within half an hour my pain had decreased significantly. A 1oz jar is $20,which may seem pricey, but a little goes a long way. I am now a huge fan and plan to buy this one in bulk. A testimonial on their site states , "Sweet ReLeaf is the most effective pain relieving cream I have ever used. The smell is pleasant and enchanting and it has a nice body feel. When I have sore muscles I rub it in and the pain and discomfort melts away." I have to say, I back this statement up with my own experience.

### The Original Kind Rub/Menthol Formula

The Kind Rub is a very popular brand I've seen in many dispensaries. I have used this balm for some time and it does work well. When my back hurts after a workout, I put some on and it definitely lessens the pain. That said, the smell of this balm is very powerful, in such a way that you would not want to go on a date after using it. It also has a greenish hue that makes me think of Witch of the West. This salve has a fantastic ingredient list, which includes eucalyptus, rosemary, sage, lavender and chamomile, among other natural herbs. On the product page for this product, Kind says "Great for arthritis, bone and muscle pain, backaches, neck aches, gout, chest congestion, sore feet, dry skin, and much more. Apply to affected the area as often as needed. No THC side effects will be experienced, only the soothing comfort of being free of pain."

### Xternal Balm

Again, this seems to be a popular balm that is carried by many dispensaries. The packaging feels very generic, but I suppose it is about what is inside that matters. That said, I have carried this in my purse for the past few months because I do like to use it. When I have had a really sore muscle it seems to help me. It tends to be on the greasier side of topicals so you need to rub this one in. Their site says it helps combat many conditions and "Xternal Balm is a non-petroleum-jelly topical rub with our proprietary active ingredients. This formula was originally designed for MMA fighters who found it greatly improved recovery time."

### HerbaBuena Body Balm

The folks at Herbabuena offer this balm and I keep it in my bedside table. Herbabuena pays particular attention to the quality of the cannabis they use, and I appreciate this very much. Their balm has a very distinctive smell, it is sort of planty-medicinal which I happen to like. It has a yellowish hue and feels a bit grainy, so you also need to really rub it in before you can put clothes on over it. It says on the jar that it contains 1000mg of THC and a little goes a long way here too. On their site they say, "Our proprietary blend of oils eases all types of muscle and joint pain, and has been reported to be particularly effective as a sports rub and for assisting with arthritis. Starring critically extracted cannabis as well as oils of coconut, jojoba and avocado, cacao butter and beeswax."

If you are new to cannabis and want to learn more, take a look at our Cannabis 101post. HelloMD can help you get your medical marijuana recommendation; it's 100% online, private and efficient.

By [redacted] Co Founder 

Section 6

## Topical Use of Cannabis

### Why use topical?

Cannabis has been used historically to treat a variety of ailments by topical application. Topical medicines are absorbed through the skin to affect a targeted area, as a minimally invasive way to administer, and as a way to reduce side effects. Recent research has confirmed that cannabinoids are effective at reducing pain at peripheral sites.(1) Many medical marijuana patients have found benefit from using topically applied cannabis, as a way to minimize its central nervous system and psychoactive effects. Some patients prepare cannabis in alcohol extracts and apply it as a rub to the affected body part. Others use cannabis oils or balms that they procure at dispensaries or privately prepare.

The skin is one of our largest organs and is capable of absorbing medicine, as well as expelling waste. It makes sense to apply a medicine directly to the site of need. The medicine gets absorbed in the area that is most desirable and will have less of chance to reach areas that are undesirable. Applying a cannabis preparation to the skin does not usually affect brain receptors, and thus has little effect on cognition or memory. It does not produce the "high" effect that has caused so much debate about marijuana as an intoxicant. Skin disorders, in particular, do well with topical cannabis. Eczema, psoriasis, contact dermatitis, pruritis (itching) and even skin infections have been reported to improve with topical cannabis. Marijuana may also be used topically for stopping migraines, headaches or pain.

Cannabis oil has a multitude of uses. It is an excellent pain reliever because it stimulates localized THC and CBD receptors throughout our bodies. It also acts as an anti-inflammatory by stimulating circulation. The massage oil is not only good for a body rub, but has taken pain and swelling away from arthritic joints. Topical alcohol rubs are ideal for arthritic joint pain or sore muscles. Salves may be used anywhere you would use a first-aid ointment. You can use it for cuts and scrapes, infections and dermatitis, eczema, psoriasis and bruises.

### Plant Material – Strain

Cannabis Indica, as opposed to Cannabis Sativa, is best for providing relief for physical symptoms. Some benefits of Indica are – to reduce pain, relax muscles, relieve spasms, reduce inflammation, reduce nausea, relieve headaches and migraines, and as an anti-convulsant.
The active component in Cannabis that is medicinally preferable for use in a topical is a cannabinoid called CBD (cannabidiol). Unlike THC(delta-9 tetrahdrocannabinol), CBD does not induce euphoria, but does have anti-inflammatory, anti-convulsant, anti-psychotic, anti-oxidant, analgesic and neuroprotective properties.(2) Cannabis Indica tends to have a higher concentration of CBD than Cannabis Sativa. There has been a resurgence of interest in high CBD containing strains recognizing that these are preferable for many medicinal uses. Now there are several strains available that have a much higher percentage of CBD.(3) Strain selection allows you to regulate the amount of THC versus CBD, and select the effect you want to obtain.

### Recipes:

#### Topical Cannabis Alcohol

Fill a pint sized mason jar 25% full with dry crushed cannabis. (Most recipes use one part cannabis to 3-4 parts alcohol).Fill to top with alcohol (rubbing alcohol works fine.) Let stand for 2 to 4 weeks in a cool, dark place, shaking occasionally. Strain. Stronger preparations are made by repeating the process. Store in a dark bottle.

#### Topical Cannabis Oil

Use dry crushed cannabis. Add oil (such as hemp oil, or olive oil) so that the plant material is covered with the oil. Keep in a dark cool place for 3 weeks. Shake daily. Filter using a sieve.

**Topical Cannabis Ointment/Lotion**

Dry crushed cannabis is heated in a crock pot or over a double boiler for 45 to 60 minutes with a thick oil or fat, such as olive oil or cocoa butter. Store in a bottle or jar in a cool, dark place for 2-3 months. Filter using a cheese cloth. Reheat with beeswax to thicken for an ointment. Add aloe vera gel to make a lotion.

**Topical Cannabis Salve**

Add beeswax to cannabis infused oil and heat it until all the wax is melted. To test to see if your salve is hard enough, put some on a spoon and set it in a cool place for a few minutes. One pint of oil will need about 1 1/2 ounces of beeswax (5 teaspoons of beeswax are in an ounce).

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Section G

# Painful Peripheral Neuropathy

Painful peripheral neuropathy is a common neurological disorder characterized by numbness, weakness, tingling and pain, often starting in the hands or feet.

## Prevalence and Incidence of Neuropathic Pain and Peripheral Neuropathy

The American Chronic Pain Association estimates that more than 15 million people in the U.S. and Europe have some degree of neuropathic pain. More than two out of every 100 persons are estimated to have peripheral neuropathy; the incidence rises to eight in every 100 people for people aged 55 or older. (1)

## Symptoms of Painful Peripheral Neuropathy

Symptoms and prognosis vary between types of peripheral neuropathy. Generally, there is constant or recurring pain. The pain sensations are variable, and may feel like a stabbing sensation, pins and needles, electric shocks, numbness, or burning or tingling. Symptoms in diabetic polyneuropathy and other generalized neuropathies typically start in the hands or feet and climb towards the trunk. Often the pain is most troublesome at night and can disturb sleep.

The sensations may be more severe or prolonged than would be expected from a particular stimulus. For example, someone who has facial pain from trigeminal neuralgia (tic doloreaux) may find it excruciating to have something brush across a cheek.

Qualitatively the pain may feel different than pain caused by a normal injury. For one reason, neuropathy may affect not only nerves that transmit pain messages, but also non-pain sensory nerves that transmit other tactile sensations, such as vibration or temperature.

Painful peripheral neuropathy may also occur along with damage to motor nerves, or to autonomic nerves that govern basic physiological states, such as blood pressure – both of which cause non-sensory symptoms, such as muscle weakness or lightheadedness.

More than one process may go awry and set the condition in motion. Following an injury or illness, nerve endings may become sensitized and signal pain in the absence of painful stimuli. In some types of neuropathy, a nerve cell outer sheath, the myelin coating, degenerates, which disrupts normal transmission of nerve signals.

## Diagnosis of Peripheral Neuropathy

Diagnosis of painful peripheral neuropathy may require several steps. An exam will involve taking a complete patient history; checking tendon reflexes, muscle tone, motor function and the sense of touch; collecting urine and blood specimens to screen for metabolic or autoimmune disorders; and tests to determine the nature and extent of nerve damage.

Follow-up tests may include an electroencephalogram (EEG) that records electrical activity of the nervous system; a spinal tap to test for breakdown of myelin; brain scans using computed tomography (CT) and/or magnetic resonance imaging (MRI); nerve conduction velocity testing to see how fast electrical signals move; and electromyography, which measures the electrical impulses of muscles at rest and during contraction. A biopsy may also be ordered to inspect the extent of nerve damage.

**Treatments for Peripheral Neuropathy**

Once neuropathy has developed, few types can be fully cured, but early intervention can improve outcomes. Peripheral nerve fibers can slowly regenerate if the nerve cell itself is still alive. Eliminating the underlying cause can prevent future nerve damage. Good nutrition and reasonable exercise can speed healing. Quitting smoking will halt constriction of blood vessels, so that they can deliver more nutrients to help repair injured peripheral nerves.

Mild pain may be relieved by over-the-counter analgesic medication. For patients who have more severe neuropathic pain, neuroactive agents such as anticonvulsants or antidepressants are commonly prescribed; their action on the central nervous system can calm nerve activity. Topical patches that act across the skin – for instance, delivering the anesthetic lidocaine or chili-pepper extract capsaicin – may also provide some relief. Another option is administration of a local anesthetic.

When pain does not respond to those methods, alternatives can include cannabinoids or opiate analgesics. If these measures are ineffective, in a small, select group of patients, opioids may be gradually introduced after carefully considering concerns and side effects. (2) Meanwhile, to relieve the most severe cases of neuropathic pain, nerves may be surgically destroyed, although the results might be only temporary and the procedure can lead to complications.

For some patients, a treatment regimen will also include physical or occupational therapy to rebuild strength and coordination.

**Neuromodulation May Be an Option**

In cases in which drugs are ineffective or side effects intolerable, an option for some patients may be use of an implanted electrical stimulator to interrupt pain signals by producing a mild tingling sensation (paresthesia) in the painful area. Neuromodulation for intractable peripheral neuropathic pain may be carried out through spinal cord stimulation or through peripheral nerve stimulation.

Spinal cord stimulation starts with a trial phase. A permanent implant is generally offered to candidates if the temporary implant reduces pain from 50-70%. For appropriately screened patients, meanwhile, peripheral nerve stimulators can have an 80% to 90% near-term success rate. (3-5)

In patients who eventually develop a tolerance to neurostimulation, a potential future option is delivery of a pain-relief agent to targeted sites in the body using an intrathecal drug delivery system. For instance, ziconotide, a non-opiate drug now often employed to treat complex

regional pain syndrome, has been suggested by specialists as a possibly viable alternative pain-relief agent. (6)

## Many Peripheral Neuropathy Types, Multiple Causes

There are more than 100 different types of peripheral neuropathy, according to the U.S. National Institute of Neurological Disorders and Stroke (NINDS). The condition can either be inherited, or develop due to injury or illness.

Some 30% of peripheral neuropathies occur as a complication of diabetes, and an estimated 26% of patients with diabetes have some degree of diabetic neuropathy, due to prolonged effects of high blood sugar levels. In another 30% of cases, the precise cause of a painful peripheral neuropathy is unclear (or "idiopathic"). Other neuropathy causes include physical injury to a nerve, tumors, exposure to toxins, alcoholism, kidney failure, autoimmune responses, nutritional deficiencies, shingles, HIV infection, and vascular or metabolic disorders. (7)

If only one nerve is affected, the condition is called mononeuropathy. If several nerves are involved, the disorder is called mononeuritis multiplex, and if the condition affects both sides of the body, it is called polyneuropathy. The condition may be general, or located in a particular area, which is called focal peripheral neuropathy.

## Focal or Multifocal Peripheral Neuropathies

Focal or multifocal peripheral neuropathies include:
Carpal tunnel syndrome (caused by pressure on the nerve due to inflammation from repetitive stress), or other so-called "entrapment" syndromes
Radiculopathies, including sciatica (a shooting pain in the arms or legs due to irritation or compression of the nerve root in the spine)
Phantom limb pain and stump pain
Post-traumatic neuralgia
Postherpetic neuralgia (7)

## Generalized Polyneuropathies

Generalized polyneuropathies are more common, and can be present due to:
Diabetes mellitus
Demyelinating conditions (Guillain-Barre Syndrome; chronic inflammatory demyelinating polyneuropathy; Charcot Marie Tooth Disease Type I or II)
Alcoholism
Autoimmune disease (rheumatoid arthritis, lupus)
HIV (caused by the virus itself, by certain drugs used in the treatment of HIV/AIDS or its complications, or as a result of opportunistic infections) (8)
Vitamin B deficiency
Toxin exposure (which may include some chemotherapy drugs or anti-retroviral agents; illicit drug use, such as glue-sniffing; or exposure to heavy metals found in industrial settings such as arsenic, lead, mercury, and thallium) (9)

Irrespective of the type of peripheral neuropathy, most patients will notice some improvement in their symptoms over time, if a holistic treatment approach is maintained, but they will require careful interdisciplinary monitoring and follow-up.

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# What is postherpetic neuralgia? What causes postherpetic neuralgia?

Written by Christian Nordqvist Knowledge center

**Last updated:** Fri 12 September 2014

Neuralgia is severe pain along the course of a nerve. The pain occurs because of a change in neurological structure or function due to irritation or damage of a nerve. **Postherpetic neuralgia** is a painful condition which affects the nerve fibers and skin. Postherpetic neuralgia is a complication of **shingles**.

There are two main types of pain, nociceptive and non-nociceptive pain.

An example of nociceptive pain is what you feel if somebody sticks a needle into your skin; specific pain receptors sense the needle touching your skin and breaking through. Nociceptive pain is when pain receptors sense such things as temperature, touch, vibration, stretch, and chemicals released from damaged cells.

Non-nociceptive pain, or neuropathic pain, comes from within the nervous system itself. The pain is not connected to activation of pain receptor cells in any part of the body. People often refer to it as pinched nerve, or trapped nerve. The nerve itself is sending pain messages either because it is faulty (damaged) or irritated. People with neuralgia have neuropathic pain (non-nociceptive pain).

People with postherpetic neuralgia describe the sensation as one of intense burning or stabbing pain, which often feels as if it is shooting along the course of the affected nerve.

## Description of postherpetic neuralgia

Postherpetic neuralgia is a persistent nerve pain that often occurs as a result of shingles. Shingles is caused by the *herpes varicella-zoster* virus. This virus also causes **chickenpox**. Most of us get chickenpox during childhood, but after we recover the virus remains inactive in our nervous system. Our immune system stops the virus from becoming active.

However, later in life the *herpes varicella-zoster* virus may become reactivated, causing shingles. Shingles is an infection of a nerve and the area of skin around it - usually the nerves of the chest and abdomen on one side of the

body are affected.

If the pain caused by shingles continues after the shingles is over - within two to four weeks - it is known as postherpetic neuralgia.

It is estimated that about one-in-five patients with shingles will go on to have postherpetic neuralgia.

Postherpetic neuralgia is more common as people get older - it is uncommon in children.

# What are the causes of postherpetic neuralgia?

The nerve damage caused by shingles disrupts the proper functioning of the nerve. The faulty nerve becomes confused and sends random, chaotic (uncontrolled) pain signals to the brain, which the patient feels as a throbbing burning pain along the nerve.

Experts believe that shingles results in scar tissue forming next to nerves and pressing on them, causing them to send inaccurate signals, many of which are pain signals to the brain. However, nobody is really sure why some shingles patients go on to develop postherpetic neuralgia.

# What are the symptoms of postherpetic neuralgia?

Symptoms are usually limited to the area of skin where the shingles outbreak first occurred. Symptoms may include:

- Occasional sharp burning, shooting, jabbing pain
- Constant burning, throbbing, or aching pain
- Extreme sensitivity to touch
- Extreme sensitivity to temperature change
- Itching
- Numbness
- Headaches
- In rare cases, if the nerve also controls muscle movement, the patient may experience muscle weakness or paralysis.

Some patients may find the symptoms interfere with their ability to carry out some daily activities, such as bathing or

dressing. Postherpetic neuralgia may also cause fatigue and sleeping difficulties.

# Diagnosing postherpetic neuralgia

As postherpetic neuralgia is a complication of shingles it is easy to diagnose. If the symptoms persist after shingles, or appear after the symptoms of shingles have cleared up, then it is postherpetic neuralgia.

# What is the treatment for postherpetic neuralgia?

Treatment will depend on the type of pain, as well as some aspects of the patient's physical, neurological and mental health.

- **Antidepressants** - these help patients with postherpetic neuralgia not because the patient is depressed, but because they affect key brain chemicals, such as serotonin and norepinephrine, which influence not only depression, but also how the body interprets pain. Dosages for postherpetic neuralgia will tend to be lower than for depression, unless the patient has both depression and postherpetic neuralgia.

  Examples of drugs that inhibit the reuptake of serotonin or norepinephrine are tricyclic antidepressants, such as amitriptyline, desipramine (Norpramin), nortriptyline (Pamelor) and duloxetine (Cymbalta). They will not get rid of the pain, but are said to make it more bearable.

- **Anticonvulsants** - as with trigeminal neuralgia pain, postherpetic pain can be lessened with anticonvulsants because they are effective calming down nerve impulses and stabilize abnormal electrical activity in the nervous system caused by injured nerves. Gabapentin (Neurontin), pregabalin (Lyrica) are examples of commonly prescribed anticonvulsants for this type of pain.

- **Steroids** - a corticosteroid medication is injected into the area around the spinal cord. Injected steroids are effective for postherpetic neuralgia patients with chronic pain (persistent long-term pain). The patient should not receive this medication until the shingles pustular skin rash has completely disappeared.

- **Painkillers** - this may include tramadol (Ultram) or oxycodone (OxyContin). There is a small risk of dependency.

- **TENS (transcutaneous electrical nerve stimulation)** - electrodes are placed over the areas where pain occurs. Small electrical impulses are emitted. The patient turns the TENS device on and off as required. Some patients obtain significant pain relief from TENS, while others don't. Experts are not sure why the electrical impulses relieve pain. Some say that TENS stimulates endorphin release - endorphins are the body's natural painkillers; some people call them natural "feel good" chemicals.

- **Spinal cord or peripheral nerve stimulation** - similar to TENS, but here the devices are implanted under the skin, along the course of peripheral nerves. These devices are a safe, efficient, and effective way to relieve many types of neuropathic pain conditions, including trigeminal neuralgia. As soon as the electrodes are in place, they are switched on to administer a weak electrical current to the nerve. The patient will have a tingling sensation in the area. Experts believe that by stimulating the nonpainful sensory pathway, the electrical impulses trick the brain into turning off or turning right down the painful signals, resulting in pain relief.

  The device is surgically implanted. Before implantation doctors do a trial run using a thin wire electrode - this is to make sure the patient responds well.

  The *spinal cord stimulator* is inserted through the skin into the epidural space over the spinal cord. The *peripheral nerve stimulator* is placed under the skin above a peripheral nerve.

- **Lidocaine skin patches** - these are patches containing lidocaine - a common local anesthetic and antiarrhythmic drug. Lidocaine is also used topically (applied onto the skin) to relieve itching, burning and pain from skin inflammations, injected as a dental anesthetic, and in minor surgery. Although it is not the first line of treatment for neuralgia, it is often effective for relieving pain. The patches can be cut to fit the affected area. Lidocaine patches must not be used on the face.

# Prevention of postherpetic neuralgia

Early shingles treatment - if you see your doctor as soon as any signs or symptoms of shingles appear, your chances of developing neuralgia are reduced. Aggressively treating shingles within two days of the rash appearing helps reduce both the risk of developing subsequent neuralgia or the length and severity if it does.

The only really effective way of preventing postherpetic neuralgia from developing is to protect yourself from shingles and/or chicken pox with the chickenpox (varicella) vaccine and the shingles (varicella-zoster) vaccine.

- **Chickenpox vaccine** - This vaccine (Viravax) is routinely given to children aged 12 to 18 months to prevent chickenpox. Experts recommend it also for adults and older children who have never had chickenpox. The vaccine does not provide 100% immunity, but it does considerably reduce the risk of complications and severity of the disease.

- **Shingles vaccine** - this vaccine (Zostavax) can help protect adults over 60 who have had chickenpox. It does not provide 100% immunity but does considerably reduce the risk of complications and severity of shingles. Experts recommend that people over 60 have this vaccine, regardless of whether or not they have had

**shingles before**. The vaccine is preventative, and is not used to treat people who are infected. The following people should not have the shingles vaccine:

- Those who have had a life-threatening reaction to gelatin, neomycin (an **antibiotic**), or any other shingles vaccine component.
- People who have a weakened immune system
- Patients receiving steroids, **radiotherapy**, and/or **chemotherapy**
- Patients with a history of **bone marrow** or lymphatic **cancer**
- Patients with active, untreated TB (**tuberculosis**)

Doctors say people with a mild cold may take the vaccine, but not those who are moderately or severely ill (they should wait till they are recovered).

Written by Christian Nordqvist

## References

There are no references listed for this article.

## Additional Information

Article last updated on Fri 12 September 2014.

Visit our Pain / Anesthetics category page for the latest news on this subject, or sign up to our newsletter to receive the latest updates on Pain / Anesthetics.

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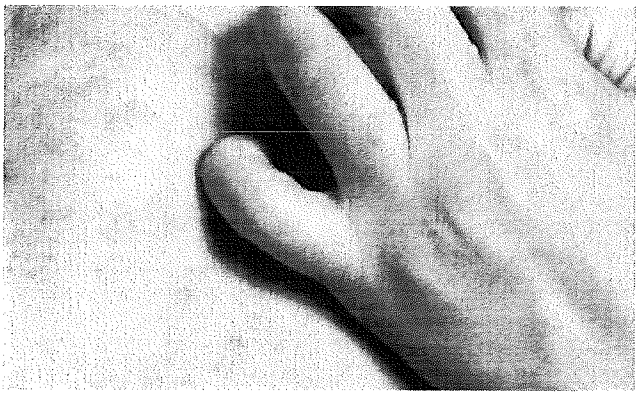
Section G



# A Patients Guide for Using Medical Marijuana for Shingles

April 28, 2015 Shingles



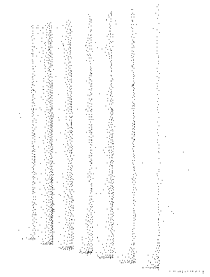
Shingles is a painful condition that originates from the same virus that causes chickenpox, called varicella zoster. For reasons that are poorly understood, decades after contracting chickenpox, the virus can "wake up" in some individuals, causing shingles. Unlike chickenpox, shingles is not contagious, but it does cause painful symptoms such as headache, sensitivity to light, rashes, blistering, and trouble thinking clearly. There is no cure for shingles, but there are treatments that can reduce the pain and symptoms associated with it, including medical marijuana.

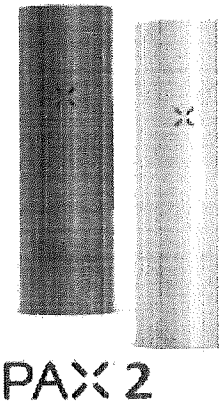


## How Medical Marijuana Helps Patients with Shingles

Shingles causes pain in part by attacking nerve cells. Traditional painkillers like morphine do not work well since shingles damages the receptors that would ordinarily allow traditional painkillers to provide relief. However, the receptors for cannabis and cannabinoids are located throughout the body and are not attacked by the shingles virus allowing medical marijuana to provide pain relief to shingles patients. Medical marijuana can also reduce inflammation, one of the major symptoms of shingles. Several studies have investigated the actions that allow medical marijuana to provide these types of relief:

- The natural endocannabinoid system present in the human body, which cannabinoids in medical marijuana can activate, has neuro-protective functions that can fight nerve inflammation and damage. By activating the CB1 receptor in the body, cannabinoids from medical marijuana can encourage these neuro-protective actions (Regulatory Role of Cannabinoid Receptor 1 in Stress-Induced Excitotoxicity and Neuroinflammation, Silvia, Z., et al.)
- Painkillers such as morphine can have a detrimental effect on the body's ability to fight against pain on its own. Chronic or long term use of opioid painkillers has been shown to interfere with the action of the body's natural endocannabinoids, especially once tolerance to opioids has developed (Chronic Morphine Modulates the Contents of Endocannabinoid, 2-Arachidonoyl Glycerol, Viganò, D., et al.)
- There are two known cannabinoid receptors in the body, CB1 and CB2. CB1 is more frequently found in the nervous system, particularly in the cerebellum and basal



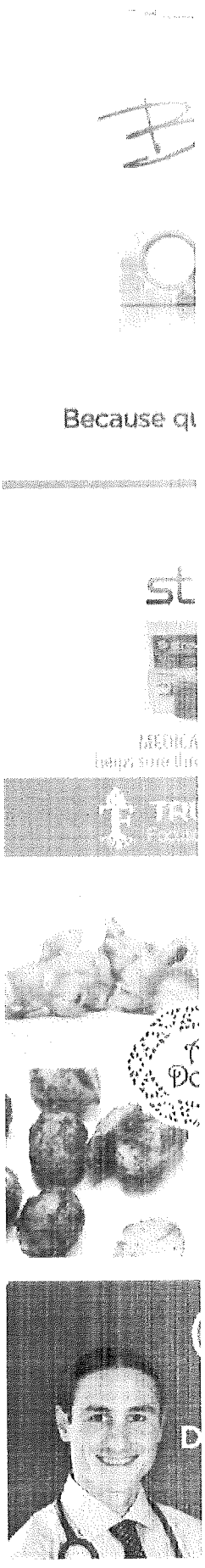




ganglia [where the pain caused by shingles primarily originates]. Activating the CB1 receptor causes significant reduction in neuroinflammation (Inflammation and aging: can endocannabinoids help, Marchalant, Y., et al.)

Medical marijuana can help relieve the symptoms of pain caused by shingles as well as potentially reduce inflammation and protect nerve cells no matter how patients choose to take their medication. This means that shingles patients have many options of how to medicate using medical marijuana according to what feels most comfortable. These options include:

- Vaporizing medical marijuana using vaporizer equipment to inhale medical marijuana's cannabinoids as steam
- Smoking medical marijuana through more traditional means, such as pipes or cigarettes
- Ingesting medical marijuana prepared in food, liquids or tinctures

As research continues, scientists are learning more about how medical marijuana can help shingles patients, as well as coming closer to a cure for this painful disease. Many patients with shingles have found relief through cannabis, which is approved for chronic pain in most medical marijuana states. Speak with your doctor to find out if medical marijuana might be right for you.

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# Cannabinoids in the management of difficult to treat pain

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## Abstract

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This article reviews recent research on cannabinoid analgesia via the endocannabinoid system and non-receptor mechanisms, as well as randomized clinical trials employing cannabinoids in pain treatment. Tetrahydrocannabinol (THC, Marinol®) and nabilone (Cesamet®) are currently approved in the United States and other countries, but not for pain indications. Other synthetic cannabinoids, such as ajulemic acid, are in development. Crude herbal cannabis remains illegal in most jurisdictions but is also under investigation. Sativex®, a cannabis derived oromucosal spray containing equal proportions of THC (partial $CB_1$ receptor agonist ) and cannabidiol (CBD, a non-euphoriant, anti-inflammatory analgesic with $CB_1$ receptor antagonist and endocannabinoid modulating effects) was approved in Canada in 2005 for treatment of central neuropathic pain in multiple sclerosis, and in 2007 for intractable cancer pain. Numerous randomized clinical trials have demonstrated safety and efficacy for Sativex in central and peripheral neuropathic pain, rheumatoid arthritis and cancer pain. An Investigational New Drug application to conduct advanced clinical trials for cancer pain was approved by the US FDA in January 2006. Cannabinoid analgesics have generally been well tolerated in clinical trials with acceptable adverse event profiles. Their adjunctive addition to the pharmacological armamentarium for treatment of pain shows great promise.

**Keywords:** cannabinoids, tetrahydrocannabinol, cannabidiol, analgesia, pain management, multiple sclerosis

## Introduction

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Chronic pain represents an emerging public health issue of massive proportions, particularly in view of aging populations in industrialized nations. Associated facts and figures are daunting: In Europe, chronic musculoskeletal pain of a disabling nature affects over one in four elderly people (Frondini et al 2007), while figures from Australia note that older half of older people suffer persistent pain, and up to 80% in nursing home populations (Gibson 2007). Responses to an ABC News poll in the USA indicated that 19% of adults (38 million) have chronic pain, and 6% (or 12 million) have utilized cannabis in attempts to treat it (ABC News et al 2005).

Particular difficulties face the clinician managing intractable patients afflicted with cancer-associated pain, neuropathic pain, and central pain states (eg, pain associated with multiple sclerosis) that are often inadequately treated with available opiates, antidepressants and anticonvulsant drugs. Physicians are seeking new approaches to treatment of these conditions but many remain concerned about increasing governmental scrutiny of their prescribing practices (Fishman 2006), prescription drug abuse or diversion. The entry of cannabinoid medicines to the pharmacopoeia offers a novel approach to the issue of chronic pain management, offering new hope to many, but also stoking the flames of controversy among politicians and the public alike.

This article will attempt to present information concerning cannabinoid mechanisms of analgesia, review randomized clinical trials (RCTs) of available and emerging cannabinoid agents, and address the many thorny issues that have arisen with clinical usage of herbal cannabis itself ("medical marijuana"). An effort will be made to place the issues in context and suggest rational approaches that may mitigate concerns and indicate how standardized pharmaceutical cannabinoids may offer a welcome addition to the pharmacotherapeutic armamentarium in chronic pain treatment.

## Cannabinoids and analgesic mechanisms

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Cannabinoids are divided into three groups. The first are naturally occurring 21-carbon terpenophenolic compounds found to date solely in plants of the *Cannabis* genus, currently termed phytocannabinoids (Pate 1994). The best known analgesic of these is $\Delta^9$-tetrahydrocannabinol (henceforth, THC)(Figure 1), first isolated and synthesized in 1964 (Gaoni and Mechoulam 1964). In plant preparations and whole extracts, its activity is complemented by other "minor" phytocannabinoids such as cannabidiol (CBD) (Figure 1), cannabis terpenoids and flavonoids, as will be discussed subsequently.

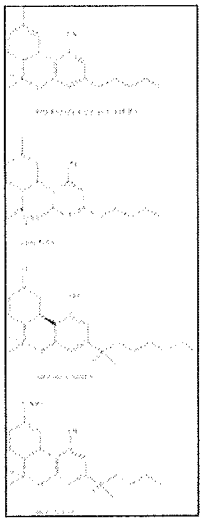

Figure 1
Molecular structures of four cannabinoids employed in pain treatment.

Long before mechanisms of cannabinoid analgesia were understood, structure activity relationships were investigated and a number of synthetic cannabinoids have been developed and utilized in clinical trials, notably nabilone (Cesamet®, Valeant Pharmaceuticals), and ajulemic acid (CT3, IP-751, Indevus Pharmaceuticals) ( Figure 1).

In 1988, the first cannabinoid receptor was identified ($CB_1$) (Howlett et al 1988) and in 1993, a second was described ($CB_2$) (Munro et al 1993). Both are 7-domain G-protein coupled receptors affecting cyclic-AMP, but

$CB_1$ is more pervasive throughout the body, with particular predilection to nociceptive areas of the central nervous system and spinal cord (Herkenham et al 1990; Hohmann et al 1999), as well as the peripheral nervous system (Fox et al 2001; Dogrul et al 2003) wherein synergy of activity between peripheral and central cannabinoid receptor function has been demonstrated (Dogrul et al 2003). $CB_2$, while commonly reported as confined to lymphoid and immune tissues, is also proving to be an important mediator for suppressing both pain and inflammatory processes (Mackie 2006). Following the description of cannabinoid receptors, endogenous ligands for these were discovered: anandamide (arachidonylethanolamide, AEA) in 1992 in porcine brain (Devane et al 1992), and 2-arachidonylglycerol (2-AG) in 1995 in canine gut tissue (Mechoulam et al 1995) ( Figure 1). These endocannabinoids both act as retrograde messengers on G-protein coupled receptors, are synthesized on demand, and are especially active on glutamatergic and GABA-ergic synapses. Together, the cannabinoid receptors, their endogenous ligands ("endocannabinoids") and metabolizing enzymes comprise the endocannabinoid system (ECS) (Di Marzo et al 1998), whose functions have been prosaically termed to be "relax, eat, sleep, forget and protect" (p. 528). The endocannabinoid system parallels and interacts at many points with the other major endogenous pain control systems: endorphin/enkephalin, vanilloid/transient receptor potential (TRPV), and inflammatory. Interestingly, our first knowledge of each pain system has derived from investigation of natural origin analgesic plants, respectively: cannabis (*Cannabis sativa*, *C. indica*) (THC, CBD and others), opium poppy (*Papaver somniferun*) (morphine, codeine), chile peppers (eg, *Capsicum annuum*, *C. frutescens*, *C. chinense*) (capsaicin) and willow bark (*Salix* spp.) (salicylic acid, leading to acetylsalicylic acid, or aspirin). Interestingly, THC along with AEA and 2-AG, are all partial agonists at the $CB_1$ receptor. Notably, no endocannabinoid has ever been administered to humans, possibly due to issues of patentability and lack of commercial feasibility (Raphael Mechoulam, pers comm 2007). For an excellent comprehensive review of the endocannabinoid system, see Pacher et al (2006), while Walker and Huang have provided a key review of antinociceptive effects of cannabinoids in models of acute and persistent pain (Walker and Huang 2002).

A clinical endocannabinoid deficiency has been postulated to be operative in certain treatment-resistant conditions (Russo 2004), and has received recent support in findings that anandamide levels are reduced over controls in migraineurs (Sarchielli et al 2006), that a subset of fibromyalgia patients reported significant decreased pain after THC treatment (Schley et al 2006), and the active role of the ECS in intestinal pain and motility in irritable bowel syndrome (Massa and Monory 2006) wherein anecdotal efficacy of cannabinoid treatments have also been claimed.

The endocannabinoid system is tonically active in control of pain, as demonstrated by the ability of SR141716A (rimonabant), a $CB_1$ antagonist, to produce hyperalgesia upon administration to mice (Richardson et al 1997). As mentioned above, the ECS is active throughout the neuraxis, including integrative functions in the periacqueductal gray (Walker et al 1999a; Walker et al 1999b), and in the ventroposterolateral nucleus of the thalamus, in which cannabinoids proved to be 10-fold more potent than morphine in wide dynamic range neurons mediating pain (Martin et al 1996). The ECS also mediates central stress-induced analgesia (Hohmann et al 2005), and is active in nociceptive spinal areas (Hohmann et al 1995; Richardson et al 1998a) including mechanisms of wind-up (Strangman and Walker 1999) and N-methyl-D-aspartate (NMDA) receptors (Richardson et al 1998b). It was recently demonstrated that cannabinoid agonists suppress the maintenance of vincristine-induced allodynia through activation of $CB_1$ and $CB_2$ receptors in the spinal cord (Rahn et al 2007). The ECS is also active peripherally (Richardson et al 1998c) where $CB_1$ stimulation reduces pain, inflammation and hyperalgesia. These mechanisms were also proven to include mediation of contact dermatitis via $CB_1$ and

$CB_2$ with benefits of THC noted systemically and locally on inflammation and itch (Karsak et al 2007). Recent experiments in mice have even suggested the paramount importance of peripheral over central $CB_1$ receptors in nociception of pain (Agarwal et al 2007).

Cannabinoid agonists produce many effects beyond those mediated directly on receptors, including anti-inflammatory effects and interactions with various other neurotransmitter systems (previously reviewed (Russo 2006a). Briefly stated, THC effects in serotonergic systems are widespread, including its ability to decrease 5-hydroxytryptamine (5-HT) release from platelets (Volfe et al 1985), increase its cerebral production and decrease synaptosomal uptake (Spadone 1991). THC may affect many mechanisms of the trigeminovascular system in migraine (Akerman et al 2003; Akerman et al 2004; Akerman et al 2007; Russo 1998; Russo 2001). Dopaminergic blocking actions of THC (Müller-Vahl et al 1999) may also contribute to analgesic benefits.

The glutamatergic system is integral to development and maintenance of neuropathic pain, and is responsible for generating secondary and tertiary hyperalgesia in migraine and fibromyalgia via NMDA mechanisms (Nicolodi et al 1998). Thus, it is important to note that cannabinoids presynaptically inhibit glutamate release (Shen et al 1996), THC produces 30%–40% reduction in NMDA responses, and THC is a neuroprotective antioxidant (Hampson et al 1998). Additionally, cannabinoids reduce hyperalgesia via inhibition of calcitonin gene-related peptide (Richardson et al 1998a). As for Substance P mechanisms, cannabinoids block capsaicin-induced hyperalgesia (Li et al 1999), and THC will do so at sub-psychoactive doses in experimental animals (Ko and Woods 1999). Among the noteworthy interactions with opiates and the endorphin/enkephalin system, THC has been shown to stimulate beta-endorphin production (Manzanares et al 1998), may allow opiate sparing in clinical application (Cichewicz et al 1999), prevents development of tolerance to and withdrawal from opiates (Cichewicz and Welch 2003), and rekindles opiate analgesia after a prior dosage has worn off (Cichewicz and McCarthy 2003). These are all promising attributes for an adjunctive agent in treatment of clinical chronic pain states.

The anti-inflammatory contributions of THC are also extensive, including inhibition of PGE-2 synthesis (Burstein et al 1973), decreased platelet aggregation (Schaefer et al 1979), and stimulation of lipooxygenase (Fimiani et al 1999). THC has twenty times the anti-inflammatory potency of aspirin and twice that of hydrocortisone (Evans 1991), but in contrast to all nonsteroidal anti-inflammatory drugs (NSAIDs), demonstrates no cyclo-oxygenase (COX) inhibition at physiological concentrations (Stott et al 2005a).

Cannabidiol, a non-euphoriant phytocannabinoid common in certain strains, shares neuroprotective effects with THC, inhibits glutamate neurotoxicity, and displays antioxidant activity greater than ascorbic acid (vitamin C) or tocopherol (vitamin E) (Hampson et al 1998). While THC has no activity at vanilloid receptors, CBD, like AEA, is a $TRPV_1$ agonist that inhibits fatty acid amidohydrolase (FAAH), AEA's hydrolytic enzyme, and also weakly inhibits AEA reuptake (Bisogno et al 2001). These activities reinforce the conception of CBD as an endocannabinoid modulator, the first clinically available (Russo and Guy 2006). CBD additionally affects THC function by inhibiting first pass hepatic metabolism to the possibly more psychoactive 11-hydroxy-THC, prolonging its half-life, and reducing associated intoxication, panic, anxiety and tachycardia (Russo and Guy 2006). Additionally, CBD is able to inhibit tumor necrosis factor-alpha (TNF-α) in its own right in a rodent model of rheumatoid arthritis (Malfait et al 2000). At a time when great concern is accruing in relation to NSAIDs in relation to COX-1 inhibition (gastrointestinal ulcers and bleeding) and COX-2 inhibition (myocardial infarction and cerebrovascular accidents), CBD, like THC, inhibits neither enzyme at pharmacologically relevant doses (Stott et al 2005a). A new explanation of inflammatory and analgesic effects of CBD has recently come to

light with the discovery that it is able to promote signaling of the adenosine receptor A2A by inhibiting the adenosine transporter (Carrier et al 2006).

Other "minor phytocannabinoids" in cannabis may also contribute relevant activity (McPartland and Russo 2001). Cannabichromene (CBC) is the third most prevalent cannabinoid in cannabis, and is also anti-inflammatory (Wirth et al 1980), and analgesic, if weaker than THC (Davis and Hatoum 1983). Cannabigerol (CBG) displays sub-micromolar affinity for $CB_1$ and $CB_2$ (Gauson et al 2007). It also exhibits GABA uptake inhibition to a greater extent than THC or CBD (Banerjee et al 1975), suggesting possible utilization as a muscle relaxant in spasticity. Furthermore, CBG has more potent analgesic, anti-erythema and lipooxygenase blocking activity than THC (Evans 1991), mechanisms that merit further investigation. It requires emphasis that drug stains of North American (ElSohly et al 2000; Mehmedic et al 2005), and European (King et al 2005) cannabis display relatively high concentrations of THC, but are virtually lacking in CBD or other phytocannabinoid content.

Cannabis terpenoids also display numerous attributes that may be germane to pain treatment (McPartland and Russo 2001). Myrcene is analgesic, and such activity, in contrast to cannabinoids, is blocked by naloxone (Rao et al 1990), suggesting an opioid-like mechanism. It also blocks inflammation via PGE-2 (Lorenzetti et al 1991). The cannabis sesquiterpenoid β-caryophyllene shows increasing promise in this regard. It is anti-inflammatory comparable to phenylbutazone via PGE-1 (Basile et al 1988), but simultaneously acts as a gastric cytoprotective (Tambe et al 1996). The analgesic attributes of β-caryophyllene are increasingly credible with the discovery that it is a selective $CB_2$ agonist (Gertsch et al 2007), with possibly broad clinical applications. α-Pinene also inhibits PGE-1 (Gil et al 1989), while linalool displays local anesthetic effects (Re et al 2000).

Cannabis flavonoids in whole cannabis extracts may also contribute useful activity (McPartland and Russo 2001). Apigenin inhibits TNF-α (Gerritsen et al 1995), a mechanism germane to multiple sclerosis and rheumatoid arthritis. Cannflavin A, a flavone unique to cannabis, inhibits PGE-2 thirty times more potently than aspirin (Barrett et al 1986), but has not been subsequently investigated.

Finally, β-sitosterol, a phytosterol found in cannabis, reduced topical inflammation 65% and chronic edema 41% in skin models (Gomez et al 1999).

## Available cannabinoid analgesic agents and those in development

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Very few randomized controlled trials (RCTs) have been conducted using smoked cannabis (Campbell et al 2001) despite many anecdotal claims (Grinspoon and Bakalar 1997). One such study documented slight weight gain in HIV/AIDS subjects with no significant immunological sequelae (Abrams et al 2003). A recent brief trial of smoked cannabis (3.56% THC cigarettes 3 times daily) in HIV-associated neuropathy showed positive results on daily pain, hyperalgesia and 30% pain reduction (vs 15% in placebo) in 50 subjects over a treatment course of only 5 days (Abrams et al 2007) (Table 1). This short clinical trial also demonstrated prominent adverse events associated with intoxication. In Canada, 21 subjects with chronic pain sequentially smoked single inhalations of 25 mg of cannabis (0, 2.5, 6.0, 9.5% THC) via a pipe three times a day for 5 days to assess effects on pain (Ware et al 2007) with results the authors termed "modest": no changes were observed in acute neuropathic pain scores, and a very low number of subjects noted 30% pain relief at the end of the study (Table 1). Even after political and legal considerations, it remains extremely unlikely that crude cannabis could ever be approved by the FDA as a prescription medicine as outlined in the FDA Botanical Guidance document (Food and Drug Administration

2004; Russo 2006b), due to a lack of rigorous standardization of the drug, an absence of Phase III clinical trials, and pulmonary sequelae (bronchial irritation and cough) associated with smoking (Tashkin 2005). Although cannabis vaporizers reduce potentially carcinogenic polyaromatic hydrocarbons, they have not been totally eliminated by this technology (Gieringer et al 2004; Hazekamp et al 2006).

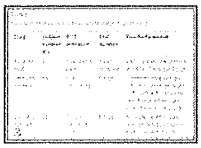

Table 1
Results RCTs of cannabinoids in treatment of pain syndromes ()

Oral dronabinol (THC) is marketed in synthetic form as Marinol® (Solvay Pharmaceuticals) in various countries, and was approved in the USA for nausea associated with chemotherapy in 1985, and in 1992 for appetite stimulation in HIV/AIDS. Oral dronabinol's expense, variability of action, and attendant intoxication and dysphoria have limited its adoption by clinicians (Calhoun et al 1998). Two open label studies in France of oral dronabinol for chronic neuropathic pain in 7 subjects (Clermont-Gnamien et al 2002) and 8 subjects (Attal et al 2004), respectively, failed to show significant benefit on pain or other parameters, and showed adverse event frequently requiring discontinuation with doses averaging 15–16.6 mg THC. Dronabinol did demonstrate positive results in a clinical trial of multiple sclerosis pain in two measures (Svendsen et al 2004), but negative results in post-operative pain (Buggy et al 2003) (Table 1). Another uncontrolled case report in three subjects noted relief of intractable pruritus associated with cholestatic jaundice employing oral dronabinol (Neff et al 2002). Some authors have noted patient preference for whole cannabis preparations over oral THC (Joy et al 1999), and the contribution of other components beyond THC to therapeutic benefits (McPartland and Russo 2001). Inhaled THC leads to peak plasma concentration within 3–10 minutes, followed by a rapid fall while levels of intoxication are still rising, and with systemic bioavailability of 10%–35% (Grotenhermen 2004). THC absorption orally is slow and erratic with peak serum levels in 45–120 minutes or longer. Systemic bioavailability is also quite low due to rapid hepatic metabolism on first pass to 11-hydroxy-THC. A rectal suppository of THC-hemisuccinate is under investigation (Broom et al 2001), as are transdermal delivery techniques (Challapalli and Stinchcomb 2002). The terminal half-life of THC is quite prolonged due to storage in body lipids (Grotenhermen 2004).

Nabilone (Cesamet) (Figure 1), is a synthetic dimethylheptyl analogue of THC (British Medical Association 1997) that displays greater potency and prolonged half-life. Serum levels peak in 1–4 hours (Lemberger et al 1982). It was also primarily developed as an anti-emetic in chemotherapy, and was recently re-approved for this indication in the USA. Prior case reports have noted analgesic effects in case reports in neuropathic pain (Notcutt et al 1997) and other pain disorders (Berlach et al 2006). Sedation and dysphoria were prominent sequelae. An RCT of nabilone in 41 post-operative subjects actually documented exacerbation of pain scores after thrice daily dosing (Beaulieu 2006) (Table 1). An abstract of a study of 82 cancer patients on nabilone claimed improvement in pain levels after varying periods of follow-up compared to patients treated without this agent (Maida 2007). However, 17 subjects dropped out, and the study was neither randomized nor controlled, and therefore is not included in Table 1.

Ajulemic acid (CT3, IP-751) (Figure 1), another synthetic dimethylheptyl analogue, was employed in a Phase II RCT in 21 subjects with improvement in peripheral neuropathic pain (Karst et al 2003) (Table 1). Part of its analgesic activity may relate to binding to intracellular peroxisome proliferator-activator receptor gamma (Liu et

al 2003). Peak plasma concentrations have generally been attained in 1–2 hours, but with delays up to 4–5 hours is some subjects (Karst et al 2003). Debate surrounds the degree of psychoactivity associated with the drug (Dyson et al 2005). Current research is confined to the indication of interstitial cystitis.

Cannador® (IKF-Berlin) is a cannabis extract administered in oral capsules, with differing figures as to THC:CBD ratios (reviewed in (Russo and Guy 2006)), generally approximately 2:1. Two pharmacokinetic studies on possibly related material have been reported (Nadulski et al 2005a; Nadulski et al 2005b). In a Phase III RCT employing Cannador in spasticity in multiple sclerosis (MS) (CAMS) (Zajicek et al 2003) (Table 1), no improvement was noted in the Ashworth Scale, but benefit was observed in spasm-associated pain on subjective measures. Both Marinol and Cannador produced reductions in pain scores in long-term follow-up (Zajicek et al 2005). Cannador was assayed in postherpetic neuralgia in 65 subjects with no observed benefit (Ernst et al 2005) (Table 1), and in 30 post-operative pain subjects (CANPOP) without opiates, with slight benefits, but prominent psychoactive sequelae (Holdcroft et al 2006) (Table 1).

Sativex® (GW Pharmaceuticals) is an oromucosal whole cannabis-based spray combining a $CB_1$ partial agonist (THC) with a cannabinoid system modulator (CBD), minor cannabinoids and terpenoids plus ethanol and propylene glycol excipients and peppermint flavoring (McPartland and Russo 2001; Russo and Guy 2006). It was approved by Health Canada in June 2005 for prescription for central neuropathic pain in multiple sclerosis, and in August 2007, it was additionally approved for treatment of cancer pain unresponsive to optimized opioid therapy. Sativex is a highly standardized pharmaceutical product derived from two *Cannabis sativa* chemovars following Good Agricultural Practice (GAP) (de Meijer 2004), yielding Tetranabinex® (predominantly-THC extract) and Nabidiolex® (predominantly-CBD extract) in a 1:1 ratio. Each 100 μL pump-action oromucosal Sativex spray actuation provides 2.7 mg of THC and 2.5 mg of CBD. Pharmacokinetic data are available, and indicate plasma half lives of 85 minutes for THC, 130 minutes for 11-hydroxy-THC and 100 minutes for CBD (Guy and Robson 2003). Sativex effects commence in 15–40 minutes, an interval that permits symptomatic dose titration. A very favorable adverse event profile has been observed in over 2500 patient years of exposure in over 2000 experimental subjects. Patients most often ascertain an individual stable dosage within 7–10 days that provides therapeutic relief without unwanted psychotropic effects (often in the range of 8–10 sprays per day). In all RCTs, Sativex was adjunctively added to optimal drug regimens in subjects with intractable symptoms, those often termed "untreatable." Sativex is also available by named patient prescription in the UK and the Catalonia region of Spain. An Investigational New Drug (IND) application to study Sativex in advanced clinical trials in the USA was approved by the FDA in January 2006 in patients with intractable cancer pain.

The clinical trials performed with Sativex have recently been assessed in two independent review articles (Barnes 2006; Pérez 2006). In a Phase II clinical trial in 20 patients with neurogenic symptoms (Wade et al 2003), Tetranabinex, Nabidiolex, and Sativex were tested in a double-blind RCT vs placebo (Table 1). Significant improvement was seen with both Tetranabinex and Sativex on pain (especially neuropathic), but post-hoc analysis showed symptom control was best with Sativex ($p < 0.0001$), with less intoxication than with THC-predominant extract.

In a Phase II double-blind crossover study of intractable chronic pain (Notcutt et al 2004) in 24 subjects, visual analogue scales (VAS) were 5.9 for placebo, 5.45 for Nabidiolex, 4.63 for Tetranabinex and 4.4 for Sativex extracts ($p < 0.001$). Sativex produced best results for pain in MS subjects ($p < 0.0042$) (Table 1).

In a Phase III study of pain associated due to brachial plexus avulsion (N = 48) (Berman et al 2004), fairly

comparable benefits were noted in Box Scale-11 pain scores with Tetranabinex and Sativex extracts (Table 1).

In a controlled double-blind RCT of central neuropathic pain, 66 MS subjects showed mean Numerical Rating Scale (NRS) analgesia favoring Sativex over placebo (Rog et al 2005) (Table 1).

In a Phase III double-blind, placebo-controlled trial (N = 125) of peripheral neuropathic pain with allodynia (Nurmikko et al 2007), Sativex produced highly statistically significant improvements in pain levels, dynamic and punctate allodynia (Table 1).

In a SAFEX study of Phase III double-blind RCT in 160 subjects with various symptoms of MS (Wade et al 2004), 137 patients elected to continue on Sativex after the initial study (Wade et al 2006). Rapid declines were noted in the first twelve weeks in pain VAS (N = 47) with slower sustained improvements for more than one year. During that time, there was no escalation of dose indicating an absence of tolerance to the preparation. Similarly, no withdrawal effects were noted in a subset of patients who voluntarily stopped the medicine abruptly. Upon resumption, benefits resumed at the prior established dosages.

In a Phase II double-blind, randomized, placebo-controlled, 5-week study of 56 rheumatoid arthritis patients with Sativex (Blake et al 2006), employed nocturnal treatment only to a maximum of 6 sprays per evening (16.2 mg THC + 15 mg CBD). In the final treatment week, morning pain on movement, morning pain at rest, DAS-28 measure of disease activity, and SF-MPQ pain at present all favored Sativex over placebo (Table 1).

Results of a Phase III study (N = 177) comparing Sativex, THC-predominant extract and placebo in intractable pain due to cancer unresponsive to opiates (Johnson and Potts 2005) demonstrated that Sativex produced highly statistically significant improvements in analgesia (Table 1), while the THC-predominant extract failed to produce statistical demarcation from placebo, suggesting the presence of CBD in the Sativex preparation was crucial to attain significant pain relief.

In a study of spinal injury pain, NRS of pain were not statistically different from placebo, probably due to the short duration of the trial, but secondary endpoints were clearly positive (Table 1). Finally, in an RCT of intractable lower urinary tract symptoms in MS, accompanying pain in affected patients was prominently alleviated (Table 1).

Highly statistically significant improvements have been observed in sleep parameters in virtually all RCTs performed with Sativex in chronic pain conditions leading to reduced "symptomatic insomnia" due to symptom reduction rather than sedative effects (Russo et al 2007).

Common adverse events (AE) of Sativex acutely in RCTs have included complaints of bad taste, oral stinging, dry mouth, dizziness, nausea or fatigue, but do not generally necessitate discontinuation, and prove less common over time. While there have been no head-to-head comparative RCTs of Sativex with other cannabinoid agents, certain contrasts can be drawn. Sativex (Rog et al 2005) and Marinol (Svendsen et al 2004) have both been examined in treatment of central neuropathic pain in MS, with comparable results (Table 1). However, adverse events were comparable or greater with Marinol than with Sativex employing THC dosages some 2.5 times higher due to the presence of accompanying CBD (Russo 2006b; Russo and Guy 2006).

Similarly, while Sativex and smoked cannabis have not been employed in the same clinical trial, comparisons of side effect profiles can be made on the basis of SAFEX studies of Sativex for over a year and up to several years in MS and other types of neuropathic pain (Russo 2006b; Wade et al 2006), and government-approved research

programs employing standardized herbal cannabis from Canada for chronic pain (Lynch et al 2006) and the Netherlands for general conditions (Janse et al 2004; Gorter et al 2005) over a period of several months or more. As is evident in Figure 2 (Figure 2), all adverse events are more frequently reported with herbal cannabis, except for nausea and dizziness, both early and usually transiently reported with Sativex (see (Russo 2006b) for additional discussion).

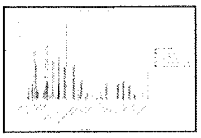

Figure 2
Comparison of adverse events (AE) encountered with long term therapeutic use of herbal cannabis in the Netherlands (Janse et al 2004; Gorter et al 2005) and Canada (Lynch et al 2006), vs that observed in safety-extension (SAFEX) studies of Sativex oromucosal ...

## Practical issues with cannabinoid medicines

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Phytocannabinoids are lipid soluble with slow and erratic oral absorption. While cannabis users claim that the smoking of cannabis allows easy dose titration as a function of rapid onset, high serum levels in a short interval inevitably result. This quick onset is desirable for recreational purposes, wherein intoxication is the ultimate goal, but aside from paroxysmal disorders (eg, episodic trigeminal neuralgia or cluster headache attack), such rapid onset of activity is not usually necessary for therapeutic purposes in chronic pain states. As more thoroughly reviewed elsewhere (Russo 2006b), cannabis smoking produces peak levels of serum THC above 140 ng/mL (Grotenhermen 2003; Huestis et al 1992), while comparable amounts of THC in Sativex administered oromucosally remained below 2 ng/mL (Guy and Robson 2003).

The vast majority of subjects in Sativex clinical trials do not experience psychotropic effects outside of initial dose titration intervals (Figure 2) and most often report subjective intoxication levels on visual analogue scales that are indistinguishable from placebo, in the single digits out of 100 (Wade et al 2006). Thus, it is now longer tenable to claim that psychoactive effects are a necessary prerequisite to symptom relief in the therapeutic setting with a standardized intermediate onset cannabis-based preparation. Intoxication has remained a persistent issue in Marinol usage (Calhoun et al 1998), in contrast.

Recent controversies have arisen in relation to non-steroidal anti-inflammatory drugs (NSAID), with concerns that COX-1 agents may provoke gastrointestinal ulceration and bleeding, and COX-2 drugs may increase incidents of myocardial infarction and cerebrovascular accidents (Fitzgerald 2004; Topol 2004). In contrast, neither THC nor CBD produce significant COX inhibition at normal dosage levels (Stott et al 2005a).

Frequent questions have been raised as to whether psychoactive drugs may be adequately blinded (masked) in randomized clinical trials. Internal review and outside analysis have confirmed that blinding in Sativex spasticity studies has been effective (Clark and Altman 2006; Wright 2005). Sativex and its placebo are prepared to appear identical in taste and color. About half of clinical trial subjects reported previous cannabis exposure, but results of two studies (Rog et al 2005; Nurmikko et al 2007) support the fact that cannabis-experienced and naïve patients were identical in observed efficacy and adverse event reporting

Great public concern attends recreational cannabis usage and risks of dependency. The addictive potential of a drug is assessed on the basis of five elements: intoxication, reinforcement, tolerance, withdrawal and dependency. Drug abuse liability (DAL) is also assessed by examining a drug's rates of abuse and diversion. US

Congress placed cannabis in Schedule I of the Controlled Substances Act in 1970, with drugs categorized as addictive, dangerous, possessing severe abuse potential and no recognized medical value. Marinol was placed in Schedule II, the category for drugs with high abuse potential and liability to produce dependency, but certain recognized medical uses, after its FDA approval in 1985. Marinol was reassigned to Schedule III in 1999, a category denoting a lesser potential for abuse or lower dependency risk after documentation that little abuse or diversion (Calhoun et al 1998) had occurred. Nabilone was placed and has remained in Schedule II since 1985.

The degree to which a drug is reinforcing is determined partly by the by the rate of its delivery to the brain (Samaha and Robinson 2005). Sativex has effect onset in 15–40 minutes, peaking in a few hours, quite a bit slower than drugs of high abuse potential. It has been claimed that inclusion of CBD diminishes psychoactive effects of THC, and may lower potential drug abuse liability of the preparation (see Russo (2006b)) for discussion). Prior studies from Sativex clinical trials do not support the presence reinforcement or euphoria as problems in administration (Wade et al 2006).

Certain facets of acute cannabinoid exposure, including tachycardia, hypothermia, orthostatic hypotension, dry mouth, ocular injection, intraocular pressure decreases, etc. are subject to rapid tachyphylaxis upon continued administration (Jones et al 1976). No dose tolerance to the therapeutic effects of Sativex has been observed in clinical trials in over 1500 patient-years of administration. Additionally, therapeutic efficacy has been sustained for several years in a wide variety of symptoms; SAFEX studies in MS and peripheral neuropathic pain, confirm that Sativex doses remain stable or even decreased after prolonged usage (Wade et al 2006), with maintenance of therapeutic benefit and even continued improvement.

Debate continues as to the existence of a clinically significant cannabis withdrawal syndrome with proponents (Budney et al 2004), and questioners (Smith 2002). While withdrawal effects have been reported in recreational cannabis smokers (Solowij et al 2002), 24 volunteers with MS who abruptly stopped Sativex after more than a year of continuous usage displayed no withdrawal symptoms meeting Budney's criteria. While symptoms recurred after 7–10 days of abstinence from Sativex, prior levels of symptom control were readily re-established upon re-titration of the agent (Wade et al 2006).

Overall, Sativex appears to pose less risk of dependency than smoked cannabis based on its slower onset, lower dosage utilized in therapy, almost total absence of intoxication in regular usage, and minimal withdrawal symptomatology even after chronic administration. No known abuse or diversion incidents have been reported with Sativex to date (as of November 2007). Sativex is expected to be placed in Schedule IV of the Misuse of Drugs Act in the United Kingdom once approved.

Cognitive effects of cannabis have been reviewed (Russo et al 2002; Fride and Russo 2006), but less study has occurred in therapeutic contexts. Effects of chronic heavy recreational cannabis usage on memory abate without sequelae after a few weeks of abstinence (Pope et al 2001). Studies of components of the Halstead-Reitan battery with Sativex in neuropathic pain with allodynia have revealed no changes vs placebo (Nurmikko et al 2007), and in central neuropathic pain in MS (Rog et al 2005), 4 of 5 tests showed no significant differences. While the Selective Reminding Test did not change significantly on Sativex, placebo patients displayed unexpected improvement.

Slight improvements were observed in Hospital Anxiety and Depression Scales depression and anxiety scores were noted with Sativex in MS patients with central neuropathic pain (Rog et al 2005), although not quite statistically significant. No long-term mood disorders have been associated with Sativex administration.

Debate continues with regard to the relationship between cannabis usage and schizophrenia (reviewed (Fride and Russo 2006)). An etiological relationship is not supported by epidemiological data (Degenhardt et al 2003), but if present, should bear relation to dose and length of high exposure. It is likely that lower serum levels of Sativex in therapeutic usage, in conjunction with anti-psychotic properties of CBD (Zuardi and Guimaraes 1997), would minimize risks. Children and adolescents have been excluded from Sativex RCTs to date. SAFEX studies of Sativex have yielded few incidents of thought disorder, paranoia or related complaints.

Adverse effects of cannabinoids on immune function have been observed in experimental animals at doses 50–100 times the psychoactive level (Cabral 2001). In four patients using herbal cannabis therapeutically for over 20 years, no abnormalities were observed in leukocyte, CD4 or CD8 cell counts (Russo et al 2002). Investigation of MS patients on Cannador revealed no major immune changes (Katona et al 2005), and similarly, none occurred with smoked cannabis in a short-term study of HIV patients (Abrams et al 2003). Hematological measures have been normal in all Sativex RCTs without clinical signs of immune dysfunction.

Concerns are frequently noted with new drug-drug interactions, but few have resulted in Sativex RCTs despite its adjunctive use with opiates, many other psychoactive analgesic, antidepressant and anticonvulsant drugs (Russo 2006a), possibly due to CBD ability to counteract sedative effects of THC (Nicholson et al 2004). No effects of THC extract, CBD extract or Sativex were observed in a study of effects on the hepatic cytochrome P450 complex (Stott et al 2005b). On additional study, at 314 ng/ml cannabinoid concentration, Sativex and components produced no significant induction on human CYP450 (Stott et al 2007). Thus, Sativex should be safe to use in conjunction with other drugs metabolized via this pathway.

The Marinol patient monograph cautions that patients should not drive, operate machinery or engage in hazardous activities until accustomed to the drug's effects (http://www.solvaypharmaceuticals-us.com/static/wma/pdf/1/3/1/9/Marinol5000124ERev52003.pdf). The Sativex product monograph in Canada (http://www.bayerhealth.ca/display.cfm?Object_ID=272&Article_ID=121&expandMenu_ID=53&prevSubItem=5_52) suggests that patients taking it should not drive automobiles. Given that THC is the most active component affecting such abilities, and the low serum levels produced in Sativex therapy (vide supra), it would be logical that that patients may be able to safely engage in such activities after early dose titration and according to individual circumstances, much as suggested for oral dronabinol. This is particularly the case in view of a report by an expert panel (Grotenhermen et al 2005) that comprehensively analyzed cannabinoids and driving. It suggested scientific standards such as roadside sobriety tests, and THC serum levels of 7–10 ng/mL or less, as reasonable approaches to determine relative impairment. No studies have demonstrated significant problems in relation to cannabis affecting driving skills at plasma levels below 5 ng/mL of THC. Prior studies document that 4 rapid oromucosal sprays of Sativex (greater than the average single dose employed in therapy) produced serum levels well below this threshold (Russo 2006b). Sativex is now well established as a cannabinoid agent with minimal psychotropic effect.

Cannabinoids may offer significant "side benefits" beyond analgesia. These include anti-emetic effects, well established with THC, but additionally demonstrated for CBD (Pertwee 2005), the ability of THC and CBD to produce apoptosis in malignant cells and inhibit cancer-induced angiogenesis (Kogan 2005; Ligresti et al 2006), as well as the neuroprotective antioxidant properties of the two substances (Hampson et al 1998), and improvements in symptomatic insomnia (Russo et al 2007).

The degree to which cannabinoid analgesics will be adopted into adjunctive pain management practices currently

remains to be determined. Data on Sativex use in Canada for the last reported 6-month period (January-July 2007) indicated that 81% of prescriptions issued for patients in that interval were refills (data on file, from Brogan Inc Rx Dynamics), thus indicating in some degree an acceptance of, and a desire to, continue such treatment. Given their multi-modality effects upon various nociceptive pathways, their adjunctive side benefits, the efficacy and safety profiles to date of specific preparations in advanced clinical trials, and the complementary mechanisms and advantages of their combination with opioid therapy, the future for cannabinoid therapeutics appears very bright, indeed.

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Section H

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# Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial

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**Abstract**

Cannabinoids are known to have analgesic properties. We evaluated the effect of oro-mucosal sativex, (THC: CBD), an endocannabinoid system modulator, on pain and allodynia, in 125 patients with neuropathic pain of peripheral origin in a five-week, randomised, double-blind, placebo-controlled, parallel design trial. Patients remained on their existing stable analgesia. A self-titrating regimen was used to optimise drug administration. Sixty-three patients were randomised to receive sativex and 62 placebo. The mean reduction in pain intensity scores (primary outcome measure) was greater in patients receiving sativex than placebo (mean adjusted scores −1.48 points vs. −0.52 points on a 0–10 Numerical Rating Scale ($p = 0.004$; 95% CI: −1.59, −0.32). Improvements in Neuropathic Pain Scale composite score ($p = 0.007$), sleep NRS ($p = 0.001$), dynamic allodynia ($p = 0.042$), punctate allodynia ($p = 0.021$), Pain Disability Index ($p = 0.003$) and Patient's Global Impression of Change ($p < 0.001$) were similarly greater on sativex vs. placebo. Sedative and gastrointestinal side effects were reported more commonly by patients on active medication. Of all participants, 18% on sativex and 3% on placebo withdrew during the study. An open-label extension study showed that the initial pain relief was maintained without dose escalation or toxicity for 52 weeks.


*Keywords:* Sativex; Cannabinoid; Peripheral neuropathic pain; Allodynia

## 1. Introduction

The treatment of chronic neuropathic pain is mainly pharmacological, with antidepressants, antiepileptic drugs, opioids and topical local anaesthetics constituting the first-line therapy [2]. Despite differences in their mechanism of action, these agents appear similar in analgesic efficacy and tolerability. There is a well-recognised need for better pain relief than is currently available. This study reports the effect of the administration of a highly standardised THC:CBD endocannabinoid system modulator, sativex (Sativex®), on the severity of pain and allodynia, and associated sleep disturbance, mental distress and disability in patients with peripheral

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neuropathic pain. Identification of cannabinoid receptors [20] and encouraging results from preclinical and clinical studies [15,16] and change in the political and scientific scene in some countries, notably Canada, have led to revived interest in cannabinoids as a therapeutic modality. Two controlled trials on central pain associated with MS found short-term efficacy from them [26,30], whereas two other studies in which pain was not a primary outcome measure gave conflicting results [33,40]. Neuropathic pain of peripheral or mixed peripheral and central origin was reported to respond to ajulemic acid, sativex or smoked cannabis; however, treatment arms in these studies were short, between 5 and 14 days [1,6,19].

Sativex is derived from extracts of selected strains of cannabis plants (*Cannabis sativa*) which produce high and reproducible yields of the principal active cannabinoids, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). It is administered as a spray for sublingual and oro-pharyngeal administration. Each 100 μl spray delivers 2.7 mg of THC and 2.5 mg of CBD.

Cannabinoids are thought to work via two types of receptors, CB1 and CB2. CB1 is widely distributed in the peripheral and central nervous system, acting as a presynaptic modulator of neurotransmitter release. The main target for the effects of THC, CB1, occurs at many sites critical for nociception. CB2 is also activated by THC but in normal circumstances is found in immune cells only. However, in clinical pain the role of the CB2 receptor may be different because following tissue injury it is shown to be expressed in central nervous system microglia and dorsal root ganglion cells following tissue injury [28] CBD appears to have limited affinity for either cannabinoid receptor, but in higher doses may potentiate the effects of THC [32] and mediate non-cannabinoid effects by activating the TRPV1 receptor [8]. Combining the two in the same preparation is thought to lead not only to increased analgesic effect but may also result in antagonism of adverse effects [27].

## 2. Methods

### 2.1. Study design

This was a 5-week multi-centre (5 centres in UK, 1 in Belgium), randomised, double-blind, placebo-controlled parallel group study. Patients were screened to determine eligibility and completed baseline diary assessments of daily pain intensity and sleep disturbance scores in the 7–10 days prior to first treatment assignment. After eligibility was confirmed, patients were assigned to the next sequential randomisation number within each centre. The randomisation schedule had a 1:1 treatment allocation ratio with randomly permuted blocks stratified by centre and was generated using a computer based pseudo-random number algorithm. The randomisation schedule was held by the sponsor with a copy in patient-specific sealed envelopes sent to the pharmacy in each centre. Once the patient's eligibility was confirmed, they were assigned to the next sequential randomisation number within each centre. The placebo medication was identical in composition, appearance, odour and taste with the study medication but without cannabis extract. That the smell and taste of the cannabinoid preparation might lead to unblinding was averted by disguising them with addition of peppermint oil to both preparations. All medication was provided in identical amber vials, packaged and labelled by the sponsor.

### 2.2. Study patients

Patients had to have a current history of unilateral peripheral neuropathic pain and allodynia. Further enrolment criteria are shown in Table 1. Concomitant analgesia was maintained at a stable dosage regimen for the duration of the study. The decision to recruit was based on the patient's history. No tests for drugs of abuse potential were carried out. Ethical approval was granted by the Local Ethics Committees of the participating centres. In one centre the approval was conditional on patients not driving during the trial.

### 2.3. Study medication and procedures

Initial dosing was under clinical supervision at the study site. A pre-dose 100 mm "Intoxication" (0 = no intoxication and 100 = extreme intoxication) Visual Analogue Scale (VAS) was obtained and vital signs were checked. A maximum of 8 sprays were administered over 2 h with Intoxication VAS and vital signs checked at regular intervals. If, following any dose, patients scored higher than 25 mm, or there were clinical concerns, e.g. the patients showing dysphoria or cardiovascular changes, subsequent doses were omitted [6,7].

After satisfactory completion of initial dosing, patients began home dose titration and were allowed a maximum dose of 8 sprays per 3-hour interval and a maximum of 48 sprays per 24 h. At the next visit (after 7–10 days) titration, compliance and adverse events were reviewed, and patients advised on how to optimise dosing for the rest of the study period. Those patients who satisfactorily completed the trial were offered the opportunity to participate in a common open-label extension study of sativex.

All used and unused study medication containers were returned at each visit to the research centre. Patients were withdrawn from the study if there were indications of misuse, including failure to record dosage accurately. Periodic telephone monitoring was undertaken at pre-arranged times during home dosing to check the patient's condition and to answer any queries. Throughout the study, allowable concomitant medications or treatments were continued to provide adequate background analgesia at a constant dose. Any medication, other than the study medication taken during the study, was recorded.

Patients kept a diary from the screening visit until end of treatment in which they recorded daily their pain and sleep scores (on the appropriate NRS), as well as adverse events and the number of sprays used.

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Table 1
Enrolment criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| Unilateral peripheral neuropathic pain and allodynia | Cannabinoid use (cannabis, Marinol® (synthetic THC) or nabilone (synthetic cannabinoid analogue)) at least 7 days before randomisation. Subjects were required to abstain from use of cannabis during the study |
| Age 18 or over, male or female | Schizophrenia, psychosis, or other major psychiatric condition beyond depression with underlying condition |
| A history of at least 6 months duration of pain due to a clinically identifiable nerve lesion | Concomitant severe non-neuropathic pain or the presence of cancer related neuropathic pain or from diabetes mellitus |
| Demonstrate mechanical allodynia and impaired sensation within the territory of affected nerve(s) on clinical examination | Known history of alcohol or substance abuse |
| Patients with complex regional pain syndrome (CRPS) were eligible if they showed evidence of peripheral nerve lesion (diagnosed as CRPS type II) | Severe cardiovascular condition, poorly controlled hypertension, epilepsy, pregnancy, lactation, significant hepatic or renal impairment |
| A baseline severity score of at least 4 on the numerical rating scale for spontaneous pain for at least 4 of 7 days in the baseline week | Scheduled surgery or anaesthesia |
| A stable medication regimen of analgesics for at least 2 weeks prior to study entry | Terminal illness or subjects inappropriate for placebo therapies |
| Female patients of child bearing potential and male patients whose partner was of child bearing potential had to agree to use effective contraception | Known hypersensitivity to cannabinoids |
| Willing for his or her name to be notified to the UK Home Office | Participation within a trial in the last 12 weeks |

### 2.4. Testing for allodynia

Tests for allodynia were carried out at baseline and end of study. The investigator recorded the most painful area within the affected territory. Mechanical dynamic allodynia was assessed by stroking the skin over the affected area five times with a standardised brush, designed specifically for sensory testing (Senselab Brush-05, Somedic, Horby, Sweden) at $\geqslant 5$ s intervals, and recording the pain severity on a 0–10 point scale. All strokes were of the same length, minimum 2 cm. Each dynamic allodynia score was calculated as the average of the five strokes.

Punctate allodynia was measured using an in-house built pressure algometer comprising a strain gauge connected to a metal filament with a diameter of 1 mm and blunt tip at baseline and end of study. The filament was manually directed against the skin at an angle of 90° and a steadily increasing pressure applied until the patient verbally indicated that they perceived pain (punctate pressure pain threshold). A contralateral mirror image site was used as control to identify any systemic effect from the trial drugs, as well as to introduce the method to the patient before performing the test on the allodynic site. This control site was checked for evidence of local injury, scar, rash or neurological deficit. During each session the normal contralateral side was tested first. Once the patient indicated that the sensation of pressure had turned into pain, the algometer was removed and the pressure reading (in grams) recorded. The same method was used for allodynic sites.

In addition, patients were asked to verbally rate the intensity of the pain elicited, choosing a number between 0 (no pain) and 10 (most intense pain imaginable). The investigators were aware of the previous punctate allodynia threshold and could use it as guidance. Because some investigators expressed concern at using a rigid threshold as a targe for the second measurement, it was agreed that they could exercise discretion in applying the force needed to reproduce approximately the same pain as at baseline. The patients' verbal pain score and pressure used were recorded. Each punctate pain provocation test was done only once during a single visit.

### 2.5. Outcome measures

The primary outcome measure was a change from baseline on a numerical rating scale (NRS) of mean intensity of global neuropathic pain, where 0 = "No Pain" and 10 = "Worst Possible Pain". Secondary measures included the composite score calculated from the Neuropathic Pain Scale (NPS) [10], tests for mechanical allodynia, a four-step verbal rating scale for sleep disturbance (see below), the Pain Disability Index (PDI) [31], the Patient Global Impression of Change (PGIC) of both pain and allodynia, and the General Health Questionnaire (GHQ-12) [5]. Possible cognitive decline was assessed using the Brief Repeatable Battery of Neuropsychological tests (BRB-N) [7]. Information regarding the frequency of administration of the medication was recorded by the subjects in their diary. Adverse events were collected at each clinic visit, and haematology, clinical chemistry and ECG monitored at the beginning and end of the study.

### 2.6. Statistical analysis

The sample size calculation was based on an expected SD of 1.8 for the pain intensity score, estimated from several studies on peripheral neuropathic pain. To detect a difference between treatment groups of 1.0 on a 0–10 (11-point) NRS with 80% power and a 5% level of significance, 52 evaluable subjects per group were required. A dropout rate of 15% was anticipated, bringing the total number of patients needed to 120.

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The primary analysis for the primary and secondary endpoints was performed on the intention-to-treat (ITT) population. The neuropathic pain intensity NRS score at baseline was defined as the mean of all diary entries from Day −7 to Day −1 and, for the end of treatment score, the mean of all diary entries during the last 7 days in the study, or the last 3 days in the event of withdrawal. The NRS scores were summarised by treatment group for baseline, each week and end of treatment. The change in NRS pain scores was compared between treatment groups using analysis of covariance, the model including treatment and trial centre as factors and baseline pain severity as a covariate. From this analysis the adjusted treatment means, treatment difference and 95% Confidence Interval (95% CI) for the treatment difference were calculated.

The total scores for all questionnaires (NPS, PDI, GHQ-12), as well as 0–10 NRS ratings of punctate and mechanical allodynia, were obtained at baseline and end of the 5-week trial. Sleep disturbance was measured by asking the subjects to indicate the number of times they woke in previous nights due to symptoms on a four category scale where 1 = none, 2 = once, 3 = twice, 4 = more than twice. The scores for this "Sleep Disturbance NRS" were obtained at baseline and weekly thereafter until the end of trial. Statistical comparisons were performed in the same way as the primary outcome measure. The PGIC was compared between treatments using Fisher's Exact Test.

## 3. Results

A total of 141 patients were assessed for eligibility, 16 (11%) of whom failed to meet the eligibility criteria. Sixty-three subjects were randomised to sativex and 62 to placebo (Fig. 1). At all participating centres, the randomisation led to a complete balance between treatment allocations. Baseline demographic details for both groups are shown in Table 2. The treatment groups were well matched for age, duration of neuropathic pain, distribution of diagnostic pain subgroups, height, weight and for history of previous cannabis use. The diagnosis was based on existing clinical, imaging and neurophysiological

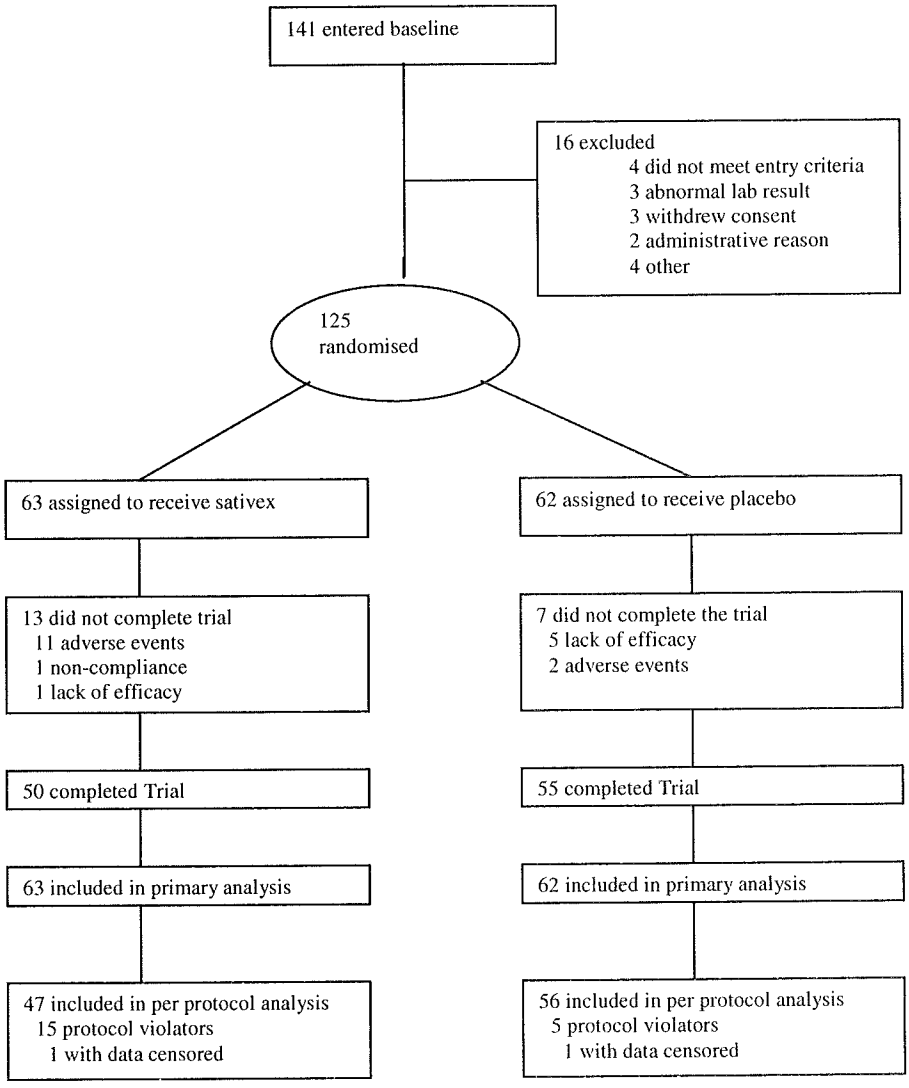


Fig. 1. Study flow.

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Table 2
Patient characteristics

| | Sativex ($N = 63$) | Placebo ($N = 62$) |
|---|---|---|
| Age, yr mean (SD) | 52.4 (15.8) | 54.3 (15.2) |
| Women, *N* (%) | 35 (55.6) | 39 (62.9) |
| White, *N* (%) | 61 (97) | 60 (97) |
| Weight, kg mean (SD) | | |
| Men | 79.9 (16.7) | 86.8 (16.7) |
| Women | 72.0 (18.2) | 72.7 (17.3) |
| Duration of pain, yr mean (SD) | 6.4 (5.7) | 6.2 (6.4) |
| Underlying diagnosis | | |
| Subjects (%) | | |
| Postherpetic neuralgia | 10 (16) | 7 (11) |
| Peripheral neuropathy | 13 (21) | 12 (19) |
| Upper limb | 2 | 1 |
| Lower limb | 5 | 4 |
| Face/neck/trunk | 6 | 7 |
| Focal nerve lesion | 26 (41) | 28 (45) |
| Upper limb | 8 | 7 |
| Lower Limb | 10 | 11 |
| Face/neck/trunk | 8 | 10 |
| Radiculopathy | 7 (11) | 6 (10) |
| CRPS type II | 7 (11) | 8 (13) |
| Other | 0 (0) | 1 (2) |
| Prior cannabis use *N* (%) | 13 (21) | 12 (19) |
| Concomitant medication | | |
| Subjects *N* (%) | | |
| Antiepileptic | 21 (33) | 21 (34) |
| Tricyclic | 16 (25) | 21 (34) |
| Opioid | 40 (63) | 46 (74) |
| Strong[a] | 7 (11) | 8 (13) |
| Weak[b] | 33 (52) | 38 (61) |
| Analgesic, non-opioid | 10 (16) | 6 (10) |
| Anti-inflammatory | 10 (16) | 15 (24) |
| Pain NRS, mean (SD) | 7.3 (1.4) | 7.2 (1.5) |
| NPS composite score, mean (SD) | 61.1 (13.0) | 62.4 (13.7) |
| Dynamic allodynia NRS, mean (SD) | 5.4 (2.7) | 5.0 (3.4) |
| Punctate allodynia NRS, mean (SD) | 7.3 (1.8) | 7.4 (2.1) |
| Punctate allodynia, pressure g, mean (SD) | 68.8 (47.7) | 83.0 (77.4) |
| Pain Disability Index ( PDI) mean (SD) | 40.9 (14.7) | 42.1 (13.4) |
| Sleep disturbance NRS, mean (SD) | 3.0 (0.8) | 3.0 (0.9) |
| GHQ-12, mean (SD) | 17.2 (7.3) | 17.6 (6.5) |

[a] Morphine, methadone, oxycodone, pethidine.
[b] Tramadol, codeine, dihydrocodeine, dextropropoxyphene.

data. Aetiologies varied from post-infectious to traumatic, vascular and idiopathic. In nearly one-half of patients the cause was posttraumatic and involved a single nerve or nerve branch (focal nerve lesion) while in one-fifth the lesion was at cervical, brachial or lumbosacral plexus level or involved several nerves (peripheral neuropathy); in this group the original cause was either inflammation or diffuse trauma and remained frequently unknown. The locations of focal nerve lesions and peripheral neuropathics were similar across the two groups (Table 2). The background use of concomitant analgesic medication was high in both groups. The most frequently reported medication was opioids, being taken by 74% of the placebo group and 63% of the sativex group. Other frequently used background medications were tricyclic antidepressants, antiepileptic drugs, and NSAIDs (Table 2).

Thirteen sativex patients (21%) failed to complete the study; 11 withdrew because of side effects, 1 due to patient non-compliance and one due to lack of efficacy. Seven patients (11%) on placebo failed to complete the study, 2 because of adverse effects and 5 because of lack of effect. All randomised patients were included in the ITT analysis. For the per-protocol (PP) analysis, there were 47 patients on sativex and 56 on placebo. Protocol violations were due to failure to meet the stringent time window set for the final visits (12 patients on sativex, 2 on placebo), use of prohibited medication (6 on sativex, two of whom also failed to meet the final visit time window, and 2 on placebo) or violation of inclusion/exclusion criteria (0 on sativex, 2 on placebo). One patient in each group had their data censored because of use of prohibited medication after Day 26.

### 3.1. Primary outcome measure

At baseline, the mean intensity of reported pain scores (SD) on NRS was in the severe range with no difference between the sativex and placebo groups 7.3 (1.4) and 7.2 (1.5), respectively (Table 2). At the end of treatment, the sativex group demonstrated an adjusted mean change in NRS score of −1.48 points (a 22% reduction) while the change for the placebo group was −0.52 points (an 8% reduction) (Fig. 2). The estimated treatment

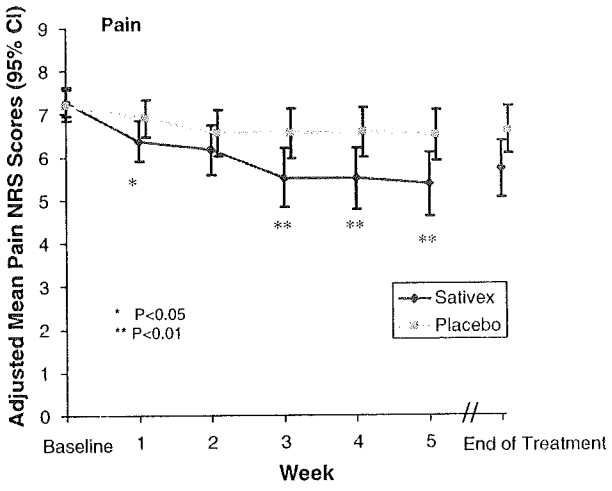


Fig. 2. Reduction of global neuropathic pain NRS scores in the two groups during the trial. First-week: home-titration; subsequent four weeks: maintenance therapy. Weekly mean pain scores were obtained from pain diaries. End-point scores were obtained from diary entries during the last 7 days, or last 3 days in case of withdrawal, for the ITT analysis. Error bars represent 95% confidence intervals.

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difference of −0.96 points was statistically significant in favour of sativex ($p = 0.004$; 95% CI: −1.59, −0.32). The improvement in pain over placebo was evident from the second week after self-titration and was maintained until the end of the study (Fig. 2). On sativex, 26% of patients had at least a 30% reduction in pain score and 20% of patients had at least a 50% reduction in pain score, compared with 15% and 8% of patients on placebo; the NNT (50%) and NNT (30%) calculated from these figures were 8.5 and 8.6, respectively. Analysis of the PP population also showed a significant treatment difference of −1.42 points in favour of sativex ($p < 0.001$; 95% CI: −2.10, −0.74).

### 3.2. Secondary outcome measures

All questionnaire-based measures of pain and pain-related co-morbidity improved significantly more in patients randomised to sativex than placebo (Table 3). NPS composite score in the sativex group decreased significantly more than in the placebo group. Sleep disturbance also decreased early on and improvement was maintained until the end of the study (Fig. 3). Of the seven functional areas assessed in the PDI, only sexual activity failed to show a substantial improvement on sativex (Table 3).

### 3.3. Allodynia

#### 3.3.1. Dynamic mechanical allodynia

All patients recruited into the study showed dynamic allodynia. There was no difference in detected mean (SD) allodynia pain scores between the two groups at baseline (5.4 (2.7) vs. 5.0 (3.4)). At the end of treatment, the mean reduction of dynamic allodynia was 20% in the sativex group, and 5% in the placebo group, with an estimated mean treatment difference of −0.82 ($p = 0.042$; 95% CI: −1.6, −0.03)) in favour of sativex. NNT for 30% reduction in the allodynia score was 9.2 and for 50% reduction 7.5.

#### 3.3.2. Punctate allodynia

At baseline, all randomised patients except one on sativex showed punctate allodynia with clearly reduced thresholds in the affected area vs. contralateral control

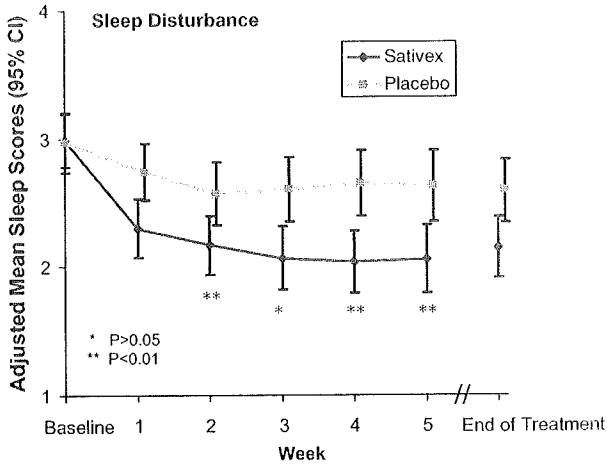


Fig. 3. Reduction is sleep disturbance scores in the two groups during the trial. For details, see text, and legend for Fig. 2.

(mean (SD) difference between the contralateral site and allodynic site: 127 (78) g). The severity of the allodynia within the affected area was comparable between both sativex and placebo groups for pressure needed to elicit pain (68.8 (47.7) g vs. 83.0 (77.4) g) and for the level of pain generated by the stimulus itself (7.3 (1.7) vs. 7.4 (2.1)). At the end of study, there was no evidence of a change in the punctate pain threshold at the contralateral control site, irrespective of whether the patients were on sativex or placebo (treatment difference 11.1 g in favour of placebo; $p = 0.3$). At the allodynic site, the placebo group reported unchanged punctate pain pressure thresholds at end of study (83.0 (77.4) g vs. 85.8 (68.9) g) with no change in pain levels (7.4 (2.1) and 7.2 (2.2)). In the sativex group, the threshold levels increased from 68.8 (47.7) g to 86.2 (73.2) g but not significantly compared to the placebo group ($p = 0.14$). Despite this increase of applied punctate pressure there was a notable decrease in the allodynia pain scores (baseline: 7.3 (1.7) vs. end of treatment: 6.2 (2.6)). The estimated treatment difference of −0.87 was in favour of sativex ($p = 0.021$; 95% CI: −1.62, −0.13), giving an NNT (30%) of 5.9 and NNT (50%) of 13.4.

Inspection of punctate allodynia data revealed that in some cases the pressure applied with the algometer to the allodynic site had changed considerably between

Table 3
Summary of the results of the secondary efficacy end-points (ITT analysis)

| Secondary outcomes | Sativex | Placebo | Estimated mean difference (95% CI)[a] | $p$-Value |
|---|---|---|---|---|
| NPS composite score | −10.07 | −2.04 | −8.03 (−13.83, −2.23) | 0.007 |
| Sleep disturbance NRS | −0.79 | −0.36 | −0.43 (−0.67, −0.19) | 0.001 |
| Pain Disability Index (PDI) | −5.61 | 0.24 | −5.85 (−9.62, −2.09) | 0.003 |
| Dynamic allodynia NRS | −1.18 | −0.37 | −0.82 (−1.60, −0.03) | 0.042 |
| Punctate allodynia NRS | −1.09 | −0.21 | −0.87 (−1.62, −0.13) | 0.021 |
| GHQ-12 | −3.09 | −2.34 | −0.75 (−2.84, 1.35) | 0.483 |
| PGIC (all neuropathic pain) | 51.61 | 19.35 | 32.26 (16.40, 48.12) | <0.001 |
| PGIC (pain at allodynic site) | 46.77 | 17.74 | 29.03 (13.79, 44.67) | 0.001 |

[a] All treatment comparisons in favour of sativex.

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pre-treatment and post-treatment. When a sensitivity analysis was carried out in patients in whom the investigators applied a similar degree of force (<5% greater) to the allodynic area on the second testing occasion (44 patients on sativex and 45 on placebo), there was a significantly larger reduction of allodynia pain in the sativex group than the placebo group leading to a treatment difference of −0.94 ($p = 0.046$; 95% CI: −1.85, −0.02) in line with the ITT analysis.

When all subjects were analysed together, there was a strong correlation between the intensity of punctate allodynia, dynamic allodynia and spontaneous pain at baseline and end of study, with similar strong correlations between the three parameters for change in scores (punctate allodynia vs. dynamic allodynia, $r = 0.526$, $p < 0.001$; punctate allodynia vs. pain $r = 0.369$; $p < 0.001$; dynamic allodynia vs. pain, $r = 0.436$, $p < 0.001$). Inspection of sativex and placebo groups separately showed that similar significant correlations were present, except for change in dynamic allodynia in the placebo group ($r = 0.065$, $p = 0.61$).

Results of the secondary efficacy end-points are summarised in Table 3. Thirty-two (51.6%) patients taking sativex compared to 12 (19.3%) taking placebo considered their primary condition to be very much, much or minimally improved ($p < 0.001$, Fisher's exact test). The odds ratio for achieving a better response on sativex than placebo, calculated from a logistic regression of the data, was 3.55 (95% CI: −7.61, −1.72) in favour of sativex. There was no difference between groups in the GHQ-12 score.

### 3.4. Dosing pattern

The mean (SD) number of sprays taken during the first week of dose titration for sativex and placebo was 7.3 (3.5) and 10.9 (3.9), respectively. From the second week onwards, the dose frequency remained stable in both treatment groups, with no tendency to increasing dose over the duration of the study. The number of sprays used daily in the placebo group was higher than in the sativex group (Table 4). Over the study period, patients randomised to sativex used a mean (SD) of 10.9 (6.8) sprays daily compared with 19.0 (8.3) by patients on placebo.

### 3.5. Adverse events and withdrawals

Fifty-seven (91%) patients in the sativex group experienced at least one adverse event (AE) during the course of the study compared with 48 (77%) patients in the placebo group. The most frequent AEs were central nervous system related or gastrointestinal. Most were observed at onset of treatment, and in the majority described as mild. However, 6 (10%) patients on sativex reported several gastrointestinal AEs (nausea, vomiting diarrhoea, constipation) with none on placebo reporting the same. Severe symptoms suggesting involvement of the nervous system were reported with sativex in 7 (11%) and placebo 5 (8%) cases. All reported gastrointestinal AEs combined irrespective of their severity were more common in the sativex group (31/63 (49%) than in the placebo group (20/62 (32%), $p = 0.003$, Fisher's exact test), whereas the nervous system AEs (33/63 vs. 23/62, $p > 0.10$) were not. One case of severe psychiatric AE was recorded on both groups (with sativex, emotional stress associated with paranoid thinking and with placebo, confusion) and 6 further mild-to-moderate ones in the sativex group as opposed to 3 in the placebo group; these were mainly mood related. AEs seen in 3 or more subjects are shown in Table 5 for all AEs and for those considered possibly related to treatment.

In the sativex group, 11 (18%) patients withdrew due to an AE compared with 2 (3%) in the placebo group. There was one transient ischaemic attack in the sativex group rated as a serious adverse event (SAE) and

Table 4
Summary of exposure to study medicine (number of sprays per day based on patient diary entries)

| | | Sativex ($N = 63$) | Number of patients remaining | Placebo ($N = 62$) | Number of patients remaining |
|---|---|---|---|---|---|
| Week 1 | Mean (SD) | 7.31 (3.54) | 62 | 10.94 (3.90) | 62 |
| | Median (range) | 6.64 (1.3–14.7) | | 11.14 (3.0–21.3) | |
| Week 2 | Mean (SD) | 12.46 (8.07) | 58 | 20.08 (9.79) | 61 |
| | Median (range) | 10.86 (1.6–42.7) | | 19.71 (2.3–47.9) | |
| Week 3 | Mean (SD) | 13.32 (8.30) | 55 | 21.10 (10.79) | 60 |
| | Median (range) | 11.43 (1.7–37.4) | | 20.07 (1.7–48.0) | |
| Week 4 | Mean (SD) | 12.86 (8.63) | 53 | 22.23 (11.51) | 57 |
| | Median (range) | 10.86 (2.0–39.0) | | 20.43 (1.7–48.1) | |
| Week 5 | Mean (SD) | 13.63 (8.65) | 48 | 22.26 (11.68) | 54 |
| | Median (range) | 12.64 (1.1–37.7) | | 19.93 (2.9–50.6) | |
| Overall | Mean (SD) | 10.89 (6.81) | | 19.02 (8.32) | |
| | Median (range) | 9.81 (1.3–31.4) | | 17.91 (2.4–41.5) | |

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Table 5
Treatment emergent adverse events (AEs) experienced by 3 or more subjects (~ 5%) receiving sativex compared with placebo and the % of subject who withdrew due to these AEs

| Adverse event | Number (%) of patients experiencing AEs | | Number (%) of patients who withdrew due to AE | |
|---|---|---|---|---|
| | Sativex ($N = 63$) | Placebo ($N = 62$) | Sativex ($N = 63$) | Placebo ($N = 62$) |
| Dizziness | 18 (28.6) | 9 (14.5) | 2 (3.2) | 0 |
| Nausea | 14 (22.2) | 7 (11.3) | 1 (1.6) | 0 |
| Fatigue | 13 (20.6) | 5 (8.1) | 0 | 0 |
| Dry mouth | 11 (17.5) | 3 (4.8) | 0 | 0 |
| Vomiting | 8 (12.7) | 3 (4.8) | 2 (3.2) | 0 |
| Feeling drunk | 6 (9.5) | 1 (1.6) | 1 (1.6) | 0 |
| Headache | 6 (9.5) | 9 (14.5) | 0 | 0 |
| Diarrhoea | 4 (6.3) | 0 | 2 (3.2) | 0 |
| Nasopharyngitis | 4 (6.3) | 2 (3.2) | 0 | 0 |
| Anorexia | 4 (6.3) | 0 | 1 (1.6) | 0 |
| Somnolence | 4 (6.3) | 1 (1.6) | 0 | 1 (1.6) |
| Abdominal pain upper | 3 (4.8) | 1 (1.6) | 0 | 0 |
| Disturbance in attention | 3 (4.8) | 0 | 0 | 0 |
| Memory impairment | 3 (4.8) | 0 | 0 | 0 |

considered unrelated to study treatment. Oral discomfort, other than dryness of mouth, occurred in 8 (13%) patients taking sativex and 11 (18%) taking placebo and was usually reported as mild. One patient on sativex had transient mucosal ulcerations but leukoplakia was not observed. No significant haematological or biochemical abnormalities were encountered in laboratory parameters.

The Brief Repeatable Battery of Neuropsychological Tests (BRB-N) was given to 85 patients (43 randomised to sativex and 42 to placebo). No difference was seen between groups assessed for cognitive function with this method at the beginning and end of treatment (Table 6).

Intoxication scores (SD) remained low throughout the study, peaking after the self-titration week at 8.0 (15.4) for sativex and 3.0 (7.9) for placebo on a 0–100 scale, respectively. Five patients on sativex and 2 patients on placebo scored more than 40/100 during the maintenance period.

### 3.6. Long-term use of sativex

At the end of their 5-week trial period, each patient was offered the chance to enter an open-label extension study. Of the 125 subjects eligible, a total 89 (71%) of the patients accepted the offer. They subsequently underwent re-titration of sativex from zero, in a way identical to that used in the randomisation phase. Patients were reviewed initially at 4 weeks thereafter every 8 weeks.

The duration of participation in the extension trial ranged from 1 to 871 days. By study closure, 56 (63%) patients had been withdrawn; 18 patients due to adverse effects, 16 due to lack of efficacy, 15 due to withdrawal of consent, 7 for other reasons. The mean (SD) duration of the participation of withdrawn patients was 135 (147) days. An LOCF analysis involving 76 patients carried out at 52 weeks demonstrated a mean decrease of pain NRS from the baseline of 7.3 (1.4) to 5.9 (2.4), i.e., similar to that seen in the randomised trial. The daily number of sprays did not increase appreciably during this period (N (SD) 10.2 (6.0) at the end of the re-titration vs. 12.2 (7.6) at 52 weeks). Two episodes of serious adverse effects were reported (urticaria with eyelid oedema and an event of somnolence, dysarthria and weakness) both leading to withdrawal of the patient in question from the study.

## 4. Discussion

This study demonstrates that sativex is effective in the relief of peripheral neuropathic pain when given in addition to existing medication. Greater than 30% improvement in pain intensity, generally considered as clinically meaningful [9], was reported by 26% of subjects receiving sativex, compared with 15% of patients taking

Table 6
Psychomotor function during the trial shown as adjusted mean change from baseline in the BRB-N for each treatment group

| Test | Sativex | $N$ | Placebo | $N$ | Difference | $p$-Value |
|---|---|---|---|---|---|---|
| Selective reminding | 0.55 | 43 | 0.52 | 42 | 0.02 | 0.92 |
| 10/36 Spatial recall | 0.85 | 43 | 0.31 | 42 | 0.53 | 0.21 |
| Symbol digit modalities | 1.48 | 43 | 3.63 | 42 | −2.15 | 0.16 |
| Paced serial addition | 7.67 | 33 | 6.38 | 34 | 1.28 | 0.66 |
| Word list generation | 2.35 | 42 | 2.44 | 42 | −0.08 | 0.96 |

No difference between groups (positive difference denotes better function on sativex and negative on placebo).

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placebo. At recruitment, all our patients were either non-responders to several conventional neuropathic analgesics, or were in severe pain despite taking appropriate therapy. Considering the refractory nature of their pain, and that patients remained on their existing analgesia, the improvement of the ongoing pain in those on the active drug is encouraging. Further evidence for the efficacy of sativex comes from improvement in mechanical dynamic and punctate allodynia pain, sleep and disability demonstrated in this study. Reduction in systematically measured mechanical allodynia is not commonly reported in controlled trials on neuropathic pain [17] and usually only seen in single dose studies or following other than oral administration, and failure is common. [3,21,23,29,34–36]. Because to date there are no reliable data converting reduction in allodynia scores to clinically meaningful improvement, the NNT values presented should be interpreted with caution.

In comparison with pain relief reported from other cannabis-related clinical trials, sativex in our group of patients demonstrated a greater difference over placebo (0.96, 95% CI −1.59, −0.32) than in patients with plexus avulsion (treatment difference −0.58, 95% CI −0.98, −0.18) but somewhat less than in patients with central pain due to MS (−1.25; 95% CI −2.11, 0.39) [6,26]. The treatment difference reported for dronabinol in MS patients deprived of concomitant analgesic medication was 0.6 (95% CI −1.8, 0) while that for smoked cannabis in painful HIV neuropathy was approximately the same as in the present study (as extrapolated from the reported median 18% treatment difference in pain relief from mean baseline scores of 53 and 54/100) [1,30]. Differences in patient populations, numbers of withdrawals, concomitant medications, trial designs and trial durations probably explain a great deal of these varying results. Interestingly, the two other cannabinoid trials in which evoked pain was assessed, albeit in a limited fashion, also report some benefit in line with the present study [1,30].

Our reason for maintaining existing analgesia was based on both ethical and clinical considerations. A number of treatments that have shown efficacy in peripheral neuropathic pain are in widespread use in accordance with existing guidelines [2]. Depriving a patient from such therapies during a placebo-controlled trial could not be ethically justified. Clinical practice is also moving toward combination therapies due to the realisation that in chronic neuropathic pain multiple mechanisms are the norm [12,39].

The lack of GHQ-12 to show any change during the present study is in line with virtually all other cannabinoid trials in which the psychosocial domain was explored, irrespective of the measure used (GHQ-30, [40]; GHQ-28, [33]; SF-36, [30]; GHQ-12, [6]; HADS, [26]; POMS, [1]). GHQ-12 is a well-validated measure of anxiety, depression and social dysfunction [37] and shows adequate sensitivity to change in longitudinal studies in manifest depression [11]. The role of the endocannabinoid system in the regulation of anxiety and mood disorders still remains unclear, and both CB1 agonists and antagonists have been shown to possess either anxiolytic or anxiogenic effects as well as variable effects on mood [38]. It is possible that GHQ-12 cannot detect modest changes in a population such as ours scoring just above the mean of the general population [24]. Alternatively, the above paradoxical effects of THC, or the ability of CBD to block some of the psychomimetic effects of THC, may explain the lack of change in this measure.

The self-titration schedule used in this study was chosen for several reasons. Previous studies [6,26] indicated that individual subjects have a variable threshold to the known pharmacodynamic effects of sativex. A self-titration regimen permitted individual patients to optimise their dose on the basis of their own efficacy and tolerability response. Both experimental and human volunteer studies suggest that tolerance to some of the side effects of cannabis occurs within days of its repeated administration [14,18,22]. A self-titration regimen allows for this to occur, further optimising the therapeutic response. There appears to be substantial between-patient variability in the pharmacokinetics of THC and other cannabinoids [13,14] and in such circumstances the implementation of a fixed-dose regimen is likely to yield suboptimal results.

The mean number of sprays taken daily by the sativex group remained stable during the course of the study despite patients having the freedom to determine their own dosing, indicating that tolerance did not develop at least over the 4-week stable treatment period of this study. The dose titration regimen used was usually successful in providing the optimal therapeutic level for individual patients. This conclusion is endorsed by the observation that those patients who took part in the open-label extension study did not increase the number of daily sprays during the first 52 weeks of open-label treatment while apparently maintaining the initial analgesic effect.

While the therapeutic effects of cannabis have often been attributed to THC, the second major constituent of the trial medication, CBD has been shown to have effects which may be additive to those of THC in pain relief in animal models, and also to have the potential to ameliorate some of the psychoactive effects of THC [27]. This interaction between the two components may permit subjects to tolerate mean daily doses of more than 27 mg THC. This dose is in excess of those used in other controlled studies of THC, and may account for the observed efficacy [14].

The adverse events reported by the patients were mostly gastrointestinal, central nervous system related or topical. While reported gastrointestinal AEs were more common in the sativex group, central nervous sys-

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tem AEs were not; and, importantly, objective measurement of psychomotor performance did not vary across the two groups. In general, the number of patients who withdrew is similar to those reported in well-known large trials of other drugs used in neuropathic pain [4,25]. That PCIG scores favoured sativex over placebo suggests that subjective pain relief, reduced disability and improved sleep overrode the negative impact of AEs.

There was no formal assessment of whether unblinding might have taken place. The psychotrophic effects of cannabis are well known to the public, and 20% of the participants in the present trial had previous exposure to cannabis. A post-hoc analysis found that previous use of cannabis was not predictive of the change in mean pain scores. Classical psychotrophic effects of cannabis were reported by relatively few patients. The intoxication scores were marginally higher in the sativex group, and psychometric tests (BRB-N) remained unchanged during the trial. It is therefore unlikely that a significant number of those on sativex would have correctly guessed they were on active medication unless they deliberately overdosed. From returned trial medication it was concluded that such practice did not take place. Patients taking placebo may have concluded that they were taking inactive substance, given that they used a relatively high number of sprays. However, the majority of patients took less than the highest allowable dosage. Also, only 5 (8%) of the placebo group withdrew for lack of efficacy, suggesting that no significant unblinding took place.

We conclude that the results from this study indicate that sativex has a positive broad spectrum therapeutic effect in neuropathic pain, when used in addition to existing analgesic medication. The emergence of a highly standardised, uniform preparation of THC:CBD should allow for further studies which better define the role for cannabinoids in the treatment of neuropathic pain syndromes.

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GW Pharma acted as the sponsor of the study, provided the medication, participated in the study design, co-ordinated the study between centres and carried out the first set of analyses. The analyses were verified by an independent statistician. The principal investigator had full access to all the data and carried out further confirmatory analyses. All authors contributed to the study design, collection of the data and interpretation of the results. The editorial content of this paper is of the authors, as is the final decision to submit for publication.

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ORIGINAL ARTICLE

# A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment

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Sativex, a THC/CBD fixed dose combination oromucosal spray, does not have an INN. Nabiximols is the FDA US Adopted Name (USAN)

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**Conflicts of interest**
M. Serpell, S. Ratcliffe, J. Hovorka, M. Schofield and E. Ehler were all investigators in this study and received investigator fees from GW accordingly for their participation in the study. GW medical writers L. Taylor and H. Lauder undertook the initial compilation and quality control review of the manuscript. Together with the other authors, the target journal was then agreed and all authors reviewed and contributed to the content of the manuscript, and agreed upon the final submitted version. All Intellectual Property Rights arising out of the current clinical study are vest in or exclusively licensed to GW.

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## Abstract

**Background:** Peripheral neuropathic pain (PNP) associated with allodynia poses a significant clinical challenge. The efficacy of $\Delta^9$-tetrahydrocannabinol/cannabidiol (THC/CBD) oromucosal spray, a novel cannabinoid formulation, was investigated in this 15-week randomized, double-blind, placebo-controlled parallel group study.

**Methods:** In total, 303 patients with PNP associated with allodynia were screened; 128 were randomized to THC/CBD spray and 118 to placebo, in addition to their current analgesic therapy. The co-primary efficacy endpoints were the 30% responder rate in PNP 0–10 numerical rating scale (NRS) score and the mean change from baseline to the end of treatment in this score. Various key secondary measures of pain and functioning were also investigated.

**Results:** At the 30% responder level, there were statistically significant treatment differences in favour of THC/CBD spray in the full analysis (intention-to-treat) dataset [$p = 0.034$; 95% confidence interval (CI): 1.05–3.70]. There was also a reduction in mean PNP 0–10 NRS scores in both treatment groups that was numerically higher in the THC/CBD spray group, but which failed to reach statistical significance. Secondary measures of sleep quality 0–10 NRS score ($p = 0.0072$) and Subject Global Impression of Change (SGIC) ($p = 0.023$) also demonstrated statistically significant treatment differences in favour of THC/CBD spray treatment.

**Conclusions:** These findings demonstrate that, in a meaningful proportion of otherwise treatment-resistant patients, clinically important improvements in pain, sleep quality and SGIC of the severity of their condition are obtained with THC/CBD spray. THC/CBD spray was well tolerated and no new safety concerns were identified.

**What's already known about this topic?**

- Neuropathic pain is a debilitating form of chronic pain and can be difficult to treat, with only approximately half of sufferers achieving partial relief, often requiring the use of novel analgesics due to the ineffectiveness of conventional pharmacotherapies.
- Cannabinoids, including $\Delta^9$-tetrahydrocannabinol/cannabidiol (THC/CBD) spray, have demonstrated efficacy in addressing this unmet need. A previous randomized controlled trial in neuropathic pain patients demonstrated positive effects in pain and allodynia at 5 weeks.

**What does this study add?**

- The study demonstrates that THC/CBD spray can provide clinically relevant improvements in pain, sleep quality and patient global impression of the change in their condition in a meaningful proportion of usually treatment-resistant patients.
- This supports the hypothesis that THC/CBD could be a useful candidate for peripheral neuropathic pain treatment, demonstrating efficacy in a few key outcomes over a much longer period of time (15 weeks compared to 5 weeks).

## 1. Introduction

Neuropathic pain is a chronic, debilitating and widespread condition with an estimated prevalence of over 1% (Backonja and Serra, 2004). Two recent population-based studies in Europe estimated the prevalence of chronic neuropathic pain, or pain with neuropathic characteristics, to be 8% and 7%, respectively (Torrance et al., 2006; Bouhassira et al., 2008). Neuropathic pain can be triggered by a variety of diseases and conditions, but the mechanisms that establish and maintain it are specific to the characteristics of the damage and/or dysfunction of the nervous system. Allodynic pain, characterized as pain evoked by a normally non-nociceptive stimulus (such as temperature), is a subgroup of peripheral neuropathic pain (PNP) and can be very difficult to treat.

A mechanistic approach to neuropathic pain is currently believed to represent the optimal means of symptom management (Jensen et al., 2001; Woolf and Max, 2001). However, there is little clinical proof that this approach is the most effective strategy. Existing therapies for PNP include tricyclic and related antidepressants, anti-epileptic agents and opioids (Attal et al., 2006). However, these therapies may have only a limited effect on PNP, and the side-effect problems associated with each are well known.

The endocannabinoid system modulator, $\Delta^9$-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray, is formulated from plant-based extracts prepared from genetically distinct chemotypes of *Cannabis sativa* L. and contains an approximately 1:1 ratio of THC : CBD, plus smaller amounts of other compounds, including minor cannabinoids and terpenes (Russo, 2011). It was recently licensed for use in various European countries for the relief of spasticity in multiple sclerosis (MS) (MHRA Public Assessment Report, 2010), as well as outside the European Union (in Canada, Israel, New Zealand). THC/CBD spray is also licensed for use in Canada for the treatment of central neuropathic pain (CNP) in MS patients.

Cannabinoids are thought to act primarily via specific receptors, designated cannabinoid receptor-1 ($CB_1$) and cannabinoid receptor-2 ($CB_2$). $CB_1$ receptors are predominantly distributed throughout the nervous systems, while $CB_2$ receptors are primarily located in the periphery, especially the immune system (Howlett et al., 2002).

Cannabinoids are postulated to offer a new therapeutic approach to neuropathic pain treatment. Previous studies using synthetic THC and a synthetic metabolite of THC demonstrated effects in patients on CNP (Svendsen et al., 2004) and PNP associated with allodynia (Karst et al., 2003), respectively. Furthermore, in a previous randomized controlled trial (RCT) (Rog et al., 2005) and in an open-label extension study (Rog et al., 2007), GW has shown that THC/CBD spray has pain relieving effects in neuropathic pain associated with MS and in difficult to treat pain following brachial plexus avulsion (Berman et al., 2004). In addition, a previous 5-week GW study of THC/CBD spray in the treatment of PNP concluded that THC/CBD spray is an effective treatment, which provided a rapid clinically relevant improvement (Nurmikko et al., 2007).

The objectives of this study were to investigate the therapeutic benefits of 15-week THC/CBD spray treatment on PNP associated with allodynia, as well as associated sleep disturbance and patient quality of life.

## 2. Methods

### 2.1 Study design

This was a 15-week (1-week baseline and 14-week treatment period), multi-centre, double-blind, randomized, placebo-controlled, parallel group study to evaluate the efficacy of THC/CBD spray in patients with PNP associated with

allodynia. The study took place at 21 centres in the United Kingdom (UK), seven centres in Czech Republic, six centres in Romania, four centres in Belgium and one centre in Canada. The study was approved by the relevant Institution Review Board or Ethical Committee in each country and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All patients provided written informed consent to take part in the study.

All visits took place at study centres. Following eligibility screening, patients completed a 7-day baseline period. Patients were then assessed, randomized and received dose introduction. Visits occurred at the end of weeks 2, 6, 10 and at the end of the study (treatment week 14) or earlier if they withdrew. A follow-up visit occurred 28 days after study completion or withdrawal. Patients were then given the opportunity to enrol in an open-label extension study. Results from the open-label extension study will not be presented in this report.

At each visit, the following information was recorded: adverse events (AEs), vital signs, intoxication 0–10 numerical rating scale (NRS), sleep quality 0–10 NRS, PNP 0–10 NRS, neuropathic pain scale (NPS), use of rescue analgesia, any changes in current medical conditions, dose of regular maintenance analgesic, changes in concomitant medication, current dose of study medication and medication compliance. Clinical laboratory sampling (haematology, biochemistry and urinalysis) was carried out at screening and at the end of treatment.

## 2.2 Inclusion and exclusion criteria

### 2.2.1 Inclusion criteria

Eligible patients were aged 18 or older, had mechanical allodynia within the territory of the affected nerve(s) (confirmed by either a positive response to stroking the allodynic area with a SENSELAB™ Brush 05 (Somedic AB, Hörby, Sweden) or to force applied by a 5.07 g Semmes-Weinstein monofilament), at least a 6-month history of PNP, and were receiving the appropriate treatment for their PNP. Eligible patients had at least one of the following underlying conditions, which caused their PNP: post-herpetic neuralgia, peripheral neuropathy, focal nerve lesion, radiculopathy or Complex Regional Pain Syndrome (CRPS) type 2. Patients also had a sum score of at least 24 on a pain 0–10 NRS for more than 6 days (baseline days 2–7) during the baseline period (average 0–10 NRS score of 4/10), and pain that was not wholly relieved by their current therapy. In addition, their analgesic regimen was stable for at least 2 weeks preceding study entry and they were willing for the responsible authorities (i.e., primary care consultant or physician) to be notified of their participation in the study.

### 2.2.2 Exclusion criteria

Patients with severe pain from other concomitant conditions were excluded, as were those with a history of significant psychiatric, renal, hepatic, cardiovascular or convulsive disorders, or with a known hypersensitivity to the study medication. Those with CRPS type 1, cancer-related PNP or pain resulting from diabetes mellitus were excluded. Patients receiving a prohibited medication [including cannabis or cannabinoid-based medications (in the last year), any analgesics taken on a 'PRN' (when required) basis, the introduction of any new analgesic medication, or any alteration to the dosage of the patient's concomitant analgesic medication (other than the rescue analgesia provided), or all paracetamol-containing medications (stopped on the day the patient entered the baseline period)], who were unwilling to abstain for the study duration were also excluded, as were those with a known history of alcohol or substance abuse. Women of child-bearing potential or their partners were excluded unless willing to ensure effective contraception was used throughout the study, as were those who had received an investigational medicinal product within 12 weeks of screening. Pregnant or lactating women and those planning a pregnancy were excluded. Patients with any physical abnormality at screening (i.e., any abnormalities that, in the opinion of the investigator, would prevent the patient from safely participating in the study), or those intending to travel or donate blood during the study were also ineligible to take part.

## 2.3 Study medication and procedures

A pump action oromucosal spray was used to deliver study medication. Each 100 μL spray of THC/CBD delivered 2.7 mg of THC and 2.5 mg of CBD to the oral mucosa, and each spray of placebo delivered the excipients plus colorants. Both THC/CBD spray and placebo contained peppermint oil to blind the smell and taste. Patients self-administered the medication to their optimal dose, but were restricted to a maximum of eight sprays in a 3-h period up to a maximum of 24 sprays per 24-h period. Initially, patients began at a maximum of one spray per 4-h period. Thereafter patients were advised to self-titrate their medication to symptom relief or maximum dose, but increases were limited to a maximum of 50% of the previous day's dose.

### 2.3.1 Concomitant medications

As would be expected in this group of patients, many were receiving concomitant medications for analgesia and were allowed to continue their concomitant analgesic medication, with the exception of paracetamol (acetaminophen), provided that a stable dose was maintained throughout the study. Patients were not permitted to take analgesics on a 'PRN' (when required) basis, and the introduction of any new analgesic medication or any alteration to the dosage of the patients' concomitant analgesic medication (other than the rescue analgesia provided) was prohibited during the study. The rescue analgesia provided contained paracetamol Ph Eur 500 mg. The maximum single dose was two 500 mg tablets, and the maximum total daily dose was 4 g (i.e., 8

tablets per day). A single dose was not to be taken more frequently than every 4 h, with no more than four doses in any 24-h period.

## 2.4 Study endpoints

### 2.4.1 Primary efficacy endpoints

In this study, a 0–10 NRS was used as the primary measure of pain severity. The efficacy endpoints for analysis were the proportion of patients showing a 30% or more improvement from baseline to the end of treatment in PNP 0–10 NRS score, and the mean change in PNP 0–10 NRS score from baseline to the end of treatment. End of treatment PNP 0–10 NRS scores were the average of all scores during the last 7 days of the evaluable treatment period.

The PNP 0–10 NRS was recorded daily by patients in their diary books. Each patient was instructed to complete their PNP 0–10 NRS score by reviewing their day's pain at the end of every day. Patients were asked, 'On a scale of "0 to 10", please indicate the average level of your nerve pain over the last 24 h', with the anchors: 0 = 'no pain', 10 = 'worst possible pain'. The assessment reviewed the entire day's pain, and therefore, the perception of pain was less likely to be influenced directly by sleep, compared with an assessment made on waking. Patients were instructed to relate 'no pain' to the time prior to their onset of their PNP associated with allodynia.

### 2.4.2 Secondary efficacy endpoints

Secondary endpoints included the mean changes from baseline to the end of treatment in the following scores: NPS, sleep quality 0–10 NRS, Subject Global Impression of Change (SGIC), Brief Pain Inventory (short form) (BPI-SF), dynamic and punctate allodynia tests, quality of life (EQ-5D) health questionnaire, as well as the proportion of patients showing a 50% or more improvement in PNP 0–10 NRS score, and the use of rescue analgesia.

#### 2.4.2.1 NPS

The NPS (neuropathic pain scale PDF) was collected weekly in the patient diaries during the whole length of the study. The variable for analysis was the change in mean NPS score from baseline (mean of two assessments during the baseline period) to the end of the study (mean of last two assessments during the evaluable period).

The NPS consists of 10 individual items. Nine of these provide a total of ten 0–10 NRS responses and there is a multi-part free text question. The NPS score to be used for the analysis was the sum of the ten 0–10 NRS responses. If up to three individual items were missing, then an NPS score was imputed by multiplying the mean of the completed items by 10. If more than three individual items were missing, then the whole score was missing.

#### 2.4.2.2 Sleep quality 0–10 NRS

Sleep quality was assessed at all study visits on a 0–10 NRS, with the main variable for analysis being the change from baseline to the end of treatment in sleep quality 0–10 NRS score. The sleep quality 0–10 NRS was completed at the same time each day, i.e., bedtime in the evening. The patient was asked 'on a scale of "0 to 10", please indicate how your pain disrupted your sleep last night', with the anchors: 0 = 'did not disrupt sleep' and 10 = 'completely disrupted (unable to sleep at all)'.

#### 2.4.2.3 SGIC

At baseline, patients wrote a brief description of their pain caused by peripheral neuropathy, which was used at the end of treatment to aid their memory regarding their symptoms at the start of the study. The SGIC was completed at the end of treatment. A 7-point Likert-type scale was used to evaluate the patients' perception of their condition, and patients were asked, 'Please assess the status of your pain due to peripheral neuropathy since entry into the study using the scale below', with the anchors: 'very much improved', 'much improved', 'slightly improved', 'no change', 'slightly worse', 'much worse' or 'very much worse'.

#### 2.4.2.4 BPI-SF

The BPI-SF (Cleeland and Ryan, 1994) was performed twice, once at baseline and once at the end of treatment, with the change in score between these time points being the variable for analysis. The BPI-SF consists of nine questions, each of which consists of a single response apart from question 9, which is sub-divided into seven parts (9A–9G). Questions 3–6 ask patients to rate pain on a 0–10 scale over the prior week (where 0 = 'no pain' and 10 = 'pain as bad as you can imagine'). Severity is measured as worst pain, least pain, average pain and pain right now. The severity composite score was calculated as the arithmetic mean of the four severity items (range 0–10). The minimum value is zero and maximum is 10.

The BPI-SF also records the degree to which pain interferes with activities on a 0–10 scale (where 0 = 'does not interfere at all' and 10 = 'pain completely interferes with activity'). As such, a higher score represents a poorer outcome.

Two composite scores were calculated from the BPI-SF:
(1) The pain severity composite score: the arithmetic mean of the four pain scores (questions 3–6) and represents the pain intensity.
(2) The pain interference composite score: the arithmetic mean of the seven interference items (questions 9A–9G) and represents the effect of pain.

#### 2.4.2.5 Dynamic allodynia test

The dynamic allodynia test was performed twice, once at baseline and once at the end of treatment, with the change in score between these time points being the variable for analy-

sis. At each time point, dynamic allodynia was assessed by stroking the skin over the affected area five times with a SENSELAB Brush 05, designed specifically for sensory testing at 5-s intervals, and recording the pain severity on a 0–10 NRS, where 0 = 'no pain' and 10 = 'most pain imaginable'. All strokes were of the same length, minimum 2 cm. The mean of the five scores for the identified allodynic area only was calculated to define the dynamic allodynia pain score.

#### 2.4.2.6 Punctate allodynia test

The punctate allodynia test was performed twice, once at baseline and once at the end of treatment, with the change in score between these time points being the variable for analysis. Punctate allodynia was measured using an in-house built pressure algometer comprising a strain gauge connected to a metal filament with a diameter of 1 mm and blunt tip at baseline and end of study. The filament was manually directed against the skin at an angle of 90° and a steadily increasing pressure was applied until the patient verbally indicated that they perceived pain (punctate pressure pain threshold). Patients were asked to verbally rate the intensity of the pain elicited, choosing a number between 0 = 'no pain' and 10 = 'most intense pain imaginable'. The average of the ascending pain threshold forces, as available, for the identified allodynic area only was calculated to define the punctate allodynia pain threshold force.

#### 2.4.2.7 EQ-5D questionnaire

The EQ-5D questionnaire (The Euroqol Group, 1990) was completed twice during the study, once at baseline and once at the end of treatment.

The EQ-5D questionnaire provided two outcomes:

(1) A weighted health state index visual analogue scale (VAS).

(2) A self-rated health status VAS.

The self-rated health status VAS anchors were: 0 = 'worst health state imaginable' to 100 = 'best health state imaginable'. The weighted health state index used the same VAS as above but was calculated for each assessment without imputation to account for missing values, i.e., if one or more individual items were missing, then the whole index was missing.

The change from baseline to the end of treatment was calculated for both VASs.

#### 2.4.2.8 Use of rescue analgesia

Use of breakthrough medication was recorded daily during the study as the number of paracetamol tablets taken. The change in mean daily quantities of tablets used was calculated from baseline to the last 7 days of treatment.

### 2.4.3 Safety endpoints

The safety endpoints were the incidence of AEs and serious adverse events (SAEs), clinical laboratory sampling pre- and post-treatment, vital signs, oral examination and intoxication 0–10 NRS.

### 2.4.4 Sample size

Based upon previous GW studies, it was believed that this study would result in a difference in the primary endpoint between THC/CBD spray and placebo patients of at least 0.9 points on the PNP 0–10 NRS. Also based on previous GW studies and the literature, it was estimated that the standard deviation of the changes from baseline in the primary endpoint would be approximately 2.1 points (Rowbotham et al., 1998; Rice et al., 2001; Serpell and Neuropathic Pain Study Group, 2002; Boureau et al., 2003). Taking this into account, for a significance level of 5% and 80% power, we would need a total of 174 evaluable patients (87 in each group) to detect a difference of 0.9 points in the PNP 0–10 NRS. Allowing for 20% of randomized patients to be unevaluable, then 218 patients (109 in each group) would need to be randomized.

## 2.5 Method of assigning patients to treatment groups and blinding

Patients were randomized to receive either THC/CBD spray or placebo. Randomization was carried out using a predetermined computer-generated randomization code, produced by the GW Biometrics Department, in which treatment allocation was made using permuted blocks of four. Study medication was pre-packed by the GW Clinical Trial Supplies Department and dispatched to the investigator centres labelled with patient numbers. The randomization scheme involved patient numbers being assigned sequentially by the investigator staff.

Study medication was provided in 5.5-mL type I amber glass vials labelled with the GW name, study code, patient number, visit number and the expiry date. The investigator staff, pharmacy and GW Clinical Department held sealed code break envelopes for each patient. Since THC/CBD spray is a plant-based extract in alcoholic solution with a distinctive smell, taste and colour, both THC/CBD spray and placebo contained peppermint oil to blind the smell and taste. The placebo also contained quinoline and sunset yellow, to match the colour of the plant extract. As such, participants, investigators are caregivers were all blinded to the treatment allocation.

## 2.6 Statistical methods

All randomized patients who received at least one dose of test treatment and had on-treatment efficacy data were included in the intention-to-treat (ITT) analysis set. The per protocol (PP) analysis set included those with evaluable data for the primary parameter with no protocol deviations, which were considered to affect the comparison between treatments for this endpoint. All summaries and statistical analyses were performed using SAS Version 9.1 (SAS Insti-

tute Inc., Cary, NC, USA). Statistical comparisons of efficacy data between treatments used two-sided statistical tests at the 5% significance level. PNP 0–10 NRS scores were evaluated by analysis of covariance (ANCOVA), with baseline values as covariate and treatment group and centre group as main effect. These tests were performed at the 10% significance level as a possible indicator of an interactive effect. An additional analysis was performed on the PNP 0–10 NRS dataset to assess the time course of the treatment effect using repeated measures. A multivariate linear model was used with a separate unstructured covariance matrix in each treatment arm. The mean (fixed effects structure) incorporated full treatment-by-(categorical) time interaction. Baseline was included as a covariate, together with baseline-by-time interaction. Grouped centre was included as a categorical covariate. The fitted model was also used to produce a final time point comparison.

Changes from baseline to the end of treatment were compared between treatment groups using ANCOVA for the following secondary endpoints: NPS, dynamic allodynia pain score, punctate allodynia pain score, BPI-SF, sleep quality 0–10 NRS and EQ-5D. Models included treatment and centre group as factors and baseline mean usage as a covariate.

The change from baseline in mean daily quantity of rescue analgesia usage was analysed in a fashion similar to the PNP 0–10 NRS.

In the SGIC outcome, the two treatment groups were compared using ordinal logistic regression and the proportional odds model, incorporating centre group.

### 2.7 Amendments during trial

The following inclusion criterion was removed: 'Subject has at least moderate PNP, which is defined as the total of the two NPS scores before randomization being at least 80'. After ethics approval had been granted for the study, the Committee for Medicinal Products for Human Use (CHMP) Guideline on Clinical Investigation of Medicinal Products Intended for the Treatment of Neuropathic Pain were finalized and issued (CPMP guideline, 2004). The CHMP guidance notes clearly recommended that the 0–10 NRS should be used as the primary efficacy endpoint. Therefore, to have an entry criterion of the two NPS scores before randomization being at least 80 in addition to the minimum 0–10 NRS pain scores was considered futile. The NPS was still collected as a secondary outcome measure and analysed and reported accordingly.

## 3. Results

The study took place between 27 September 2005 and 18 October 2006. In total, 303 patients were recruited and 246 were randomized and analysed at 39 study centres. Of these, 128 received THC/CBD spray, 118 received placebo and 57 were withdrawn before randomization. A total of 173 patients completed the study, 21 ceased treatment but remained in the study, and 52 withdrew. Six patients (one taking placebo and five taking THC/CBD spray) were not included in the analysis as they had no on-treatment efficacy data. A summary of the flow of the trial can be found in Fig. 1. The mean duration of the underlying neuropathic condition in these patients was similar between treatment groups at approximately 6 years with the minima and maxima also being similar at 0.6–38.1 years for THC/CBD spray and 0.4–39.3 years for placebo groups, respectively. The duration of their treatment-resistant neuropathic pain was also similar and no notable differences in the proportions of patients with each type of underlying condition were seen between treatment groups, the most common of which was focal nerve lesions for both groups. These and other study population demographics are displayed in Table 1. Overall, the mean daily dose of THC/CBD spray was 8.9 sprays and for placebo was 14.2 sprays, and the median duration of treatment was 78.2 days for THC/CBD spray and 86.4 days for placebo.

### 3.1 Concomitant medication

The majority of patients (90% overall) continued to take analgesics during the study. The most commonly reported classes of analgesic were non-selective monoamine reuptake inhibitors (tricyclic antidepressants) taken by 26% of patients, anti-epileptics (pregabalin) taken by 20% of patients and other anti-epileptics (gabapentin) taken by 23% of patients. In addition, 19% and 18% of patients, respectively, took natural opium alkaloids (such as dihydrocodeine) and other opioids (mostly tramadol). The most commonly reported classes of non-analgesic concomitant medication were proton pump inhibitors (18%), HMG Co-A reductase inhibitors (statins, 15%), angiotensin-converting enzyme inhibitors (14%) and beta blocking agents (13%).

### 3.2 Primary endpoint: 30% responder analysis and change from baseline to the end of treatment in PNP 0–10 NRS

A total of 34 patients (28%) receiving THC/CBD spray were classified as responders at the 30% level compared with 19 patients (16%) on placebo. Responder analysis at this level showed a statistically significant treatment difference in the evaluable period for the ITT population with an odds ratio of 1.97 ($p = 0.034$; 95% CI: 1.05–3.70), in favour of THC/CBD spray treatment (Table 2). This finding was supported by the PP analysis set, in which 27 (36%) of patients in the THC/CBD spray treatment group achieved at least a

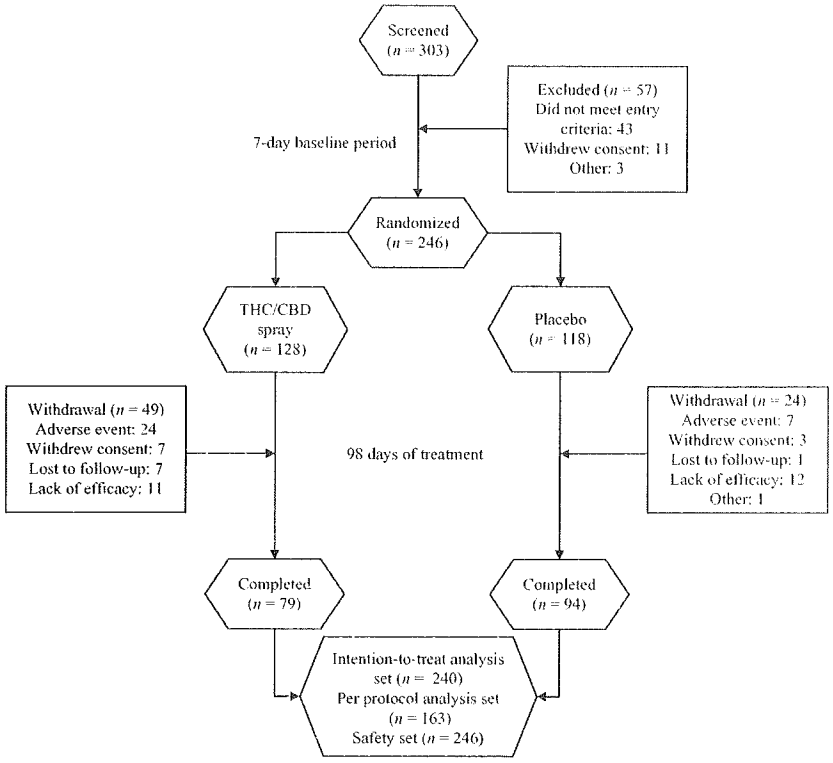


**Figure 1** Breakdown of patients enrolled in the study.

30% improvement in 0–10 NRS pain scores compared with 18 (20%) in the placebo treatment group, with an odds ratio of 2.27 ($p = 0.021$; 95% CI: 1.12–4.57) (Table 2). For 30% responders, the proportion of responders was observed to increase much more quickly in relation to the dose of THC/CBD spray compared with placebo, as illustrated in Fig. 2. At a point of around 14–15 sprays per day, the response rate in

**Table 1** Demographics and baseline characteristics for all patients who took part in the study.

| | THC/CBD spray (*n* = 128) | Placebo (*n* = 118) | Total (*n* = 246) |
|---|---|---|---|
| | No. of patients (%) | | |
| Gender | | | |
| Male | 43 (34) | 53 (45) | 96 (39) |
| Female | 85 (66) | 65 (55) | 150 (61) |
| Ethnic origin | | | |
| White/Caucasian | 127 (99) | 116 (98) | 243 (99) |
| Black/African American | 0 | 2 (2) | 2 (1) |
| Other | 1 (1) | 0 | 1 (< 0.5) |
| Previous cannabis use in the last year | 13 (10) | 12 (10) | 25 (10) |
| Type of underlying condition causing neuropathic pain | | | |
| Post-herpetic neuralgia | 34 (27) | 30 (25) | 64 (26) |
| Peripheral neuropathy | 35 (27) | 25 (21) | 60 (24) |
| Focal nerve lesion | 44 (34) | 52 (44) | 96 (39) |
| Complex regional pain syndrome-II | 17 (13) | 14 (12) | 31 (13) |
| | Mean (SD) | | |
| Age (years) | 57.6 (14.4) | 57.0 (14.1) | 57.3 (14.2) |
| Body mass index (kg/m$^2$) | 28.4 (6.5) | 27.3 (4. 9) | 27.9 (5.8) |
| Duration of neuropathic condition (years) | 6.3 (6.7) | 6.3 (6.4) | 6.3 (6.6) |
| Duration of peripheral neuropathic condition (years) | 5.7 (6.3) | 5.2 (5.4) | 5.5 (5.9) |

CBD, cannabidiol; THC, $\Delta^9$-tetrahydrocannabinol.

**Table 2** Summary of the analysis of all primary and secondary efficacy endpoints (ITT and PP analysis sets). Treatment differences between THC/CBD spray and placebo are presented using change from baseline to the end of treatment data for each endpoint, unless otherwise stated.

| Endpoint | ITT analysis set | | | PP analysis set | | |
|---|---|---|---|---|---|---|
| Primary endpoints | | | | | | |
| | Odds ratio | 95% CI | *p*-value | Odds ratio | 95% CI | *p*-value |
| 30% responder analysis (PNP 0–10 NRS) | 1.970 | 1.049 to 3.702 | 0.034 | 2.266 | 1.124 to 4.568 | 0.021 |
| | Treatment difference (SE) | 95% CI | *p*-value | Treatment difference (SE) | 95% CI | *p*-value |
| PNP 0–10 NRS | −0.34 (0.230) | −0.79 to 0.11 | 0.139 | −0.48 (0.303) | −1.08 to 0.12 | 0.116 |
| Secondary endpoints | | | | | | |
| | Treatment difference (SE) | 95% CI | *p*-value | Treatment difference (SE) | 95% CI | *p*-value |
| NPS | −2.86 (2.211) | −7.22 to 1.50 | 0.198 | −5.26 (2.873) | −10.94 to 0.41 | 0.069 |
| Sleep quality 0–10 NRS | −0.83 (0.306) | −1.43 to −0.23 | 0.007 | −0.91 (0.369) | −1.63 to −0.18 | 0.015 |
| BPI-SF (pain severity composite score) | −0.25 (0.236) | −0.72 to 0.21 | 0.288 | −0.27 (0.291) | −0.85 to 0.30 | 0.349 |
| BPI-SF (average pain) | −0.34 (0.237) | −0.81 to 0.12 | 0.148 | −0.47 (0.299) | −1.06 to 0.13 | 0.122 |
| BPI-SF (worst pain) | −0.30 (0.265) | −0.82 to 0.22 | 0.255 | −0.39 (0.322) | −1.02 to 0.25 | 0.234 |
| BPI-SF (pain interference composite score) | −0.32 (0.241) | −0.80 to 0.15 | 0.183 | −0.39 (0.304) | −0.99 to 0.21 | 0.204 |
| Dynamic allodynia test | 0.08 (0.305) | −0.52 to 0.68 | 0.795 | −0.27 (0.359) | −0.98 to 0.44 | 0.460 |
| Punctate allodynia test | −0.14 (0.118) | −0.37 to 0.09 | 0.233 | −0.06 (0.150) | −0.35 to 0.24 | 0.701 |
| EQ-5D (weighted health status index VAS) | −0.01 (0.024) | −0.06 to 0.04 | 0.617 | – | – | – |
| EQ-5D (self-rated health status VAS) | −0.75 (2.459) | −5.60 to 4.09 | 0.760 | – | – | – |
| Use of rescue analgesia | −0.38 (0.237) | −0.85 to 0.09 | 0.112 | 0.40 (0.316) | −1.02 to 0.23 | 0.211 |
| | Odds ratio | 95% CI | *p*-value | Odds ratio | 95% CI | *p*-value |
| 50% responder analysis (PNP 0–10 NRS) | 1.699 | 0.645 to 4.476 | 0.280 | 2.045 | 0.750 to 5.576 | 0.157 |
| SGIC (end of treatment only) | 1.762 | 1.080 to 2.876 | 0.023 | 2.988 | 1.661 to 5.378 | 0.0003 |

BPI-SF, Brief Pain Inventory (short form); CBD, cannabidiol; CI, confidence interval; ITT, intention-to-treat; NRS, numerical rating scale; PNP, peripheral neuropathic pain; PP, per protocol; SGIC, Subject Global Impression of Change; THC, Δ⁹-tetrahydrocannabinol; VAS, visual analogue scale.

patients receiving THC/CBD spray slowed, while for those taking placebo, the proportion of responders was still increasing maximally.

In the co-primary endpoint of change from baseline to the end of treatment in PNP 0–10 NRS score, for the ITT and PP datasets, the adjusted mean reduction in PNP 0–10 NRS score gave respective estimated treatment differences of −0.34 points ($p = 0.14$; 95% CI: −0.79 to 0.11 points) and −0.48 points ($p = 0.12$; 95% CI: −1.08 to 0.12 points), in favour of a benefit with

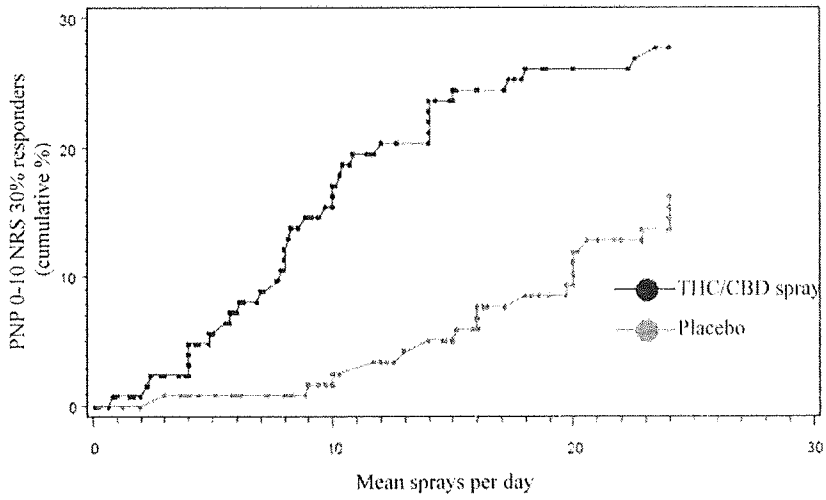


**Figure 2** Cumulative percentage of responders at the 30% level by mean sprays.

**Table 3** Sleep quality ratings by study visit, ITT and PP datasets.

| | Adjusted mean change from baseline | | | |
|---|---|---|---|---|
| | THC/CBD spray ($n$ = 122) | Placebo ($n$ = 117) | Treatment difference (THC/CBD spray vs. placebo) | Lower and upper limits 95% CI |
| Time point | ITT | | | |
| Visit 3 (day 15) | −1.44 | −0.73 | −0.70 | −1.22, −0.19 |
| Visit 4 (day 43) | −1.45 | −0.74 | −0.71 | −1.31, −0.11 |
| Visit 5 (day 71) | −1.39 | −0.66 | −0.74 | −1.34, −0.13 |
| Visit 6 (day 99) | −1.47 | −0.69 | −0.78 | −1.36, −0.21 |
| Final visit (day 127) | −1.57 | −0.74 | −0.83 | −1.43, −0.23 |
| | PP | | | |
| | ($n$ = 73) | ($n$ = 89) | | |
| Visit 3 (day 15) | −1.46 | −0.81 | −0.65 | −1.30, −0.01 |
| Visit 4 (day 43) | −1.62 | −0.83 | −0.78 | −1.58, 0.01 |
| Visit 5 (day 71) | −1.52 | −0.71 | −0.81 | −1.58, −0.03 |
| Visit 6 (day 99) | −1.49 | −0.58 | −0.91 | −1.63, −0.18 |
| Final visit (day 127) | −1.49 | −0.58 | −0.91 | −1.63, −0.18 |

CBD, cannabidiol; CI, confidence interval; ITT, intention-to-treat; PP, per protocol; THC, $\Delta^9$-tetrahydrocannabinol.

THC/CBD spray treatment. However, these failed to reach statistical significance.

### 3.3 Secondary efficacy analysis

At the 50% responder level in the PNP 0–10 NRS score analysis, the treatment difference was also in favour of the THC/CBD spray treatment group in both the ITT and the PP populations, but did not reach statistical significance in either population (Table 2).

For the ITT complete period, the adjusted mean sleep quality 0–10 NRS score decreased (improved) by 1.57 points from a mean baseline score of 5.4 points in the THC/CBD spray group, compared with an adjusted decrease of 0.74 points from a baseline of 5.8 points in the placebo group. The estimated treatment difference was −0.83 points, in favour of THC/CBD spray, a highly statistically significant result compared with placebo ($p = 0.0072$; 95% CI: −1.43 to −0.23 points) (Table 3). In the PP population, the treatment difference was slightly greater, in favour of THC/CBD spray, and was also statistically significant compared with placebo (−0.91 points, $p = 0.015$; 95% CI: −1.63 to −0.18 points) (Table 3).

In the secondary efficacy analysis of SGIC, there was a statistically significant treatment difference in favour of THC/CBD spray in the ITT dataset, compared with placebo (odds ratio: 1.76; $p = 0.023$; 95% CI: 1.08–2.88) that was mirrored in the PP population, with the odds ratio in favour of THC/CBD spray increasing to 2.99 compared with placebo ($p = 0.0003$; 95% CI: 1.66, 5.38). The proportion of patients selecting each category is presented in Fig. 3.

Decreases (improvements) in favour of the THC/CBD spray group were also observed in the following parameters: NPS total score, mean number of tablets of rescue medication administered, BPI-SF scores (pain severity composite score, average pain, worst pain and pain interference composite score) and EQ-5D questionnaire scores (both weighted health status index VAS and self-rated health status VAS). These results applied to both ITT and PP population analysis sets, but none reached statistical significance (Table 2). The dynamic allodynia test score increased (improved) in the ITT analysis set but was not in favour of active treatment in the PP analysis set (Table 2).

Interestingly, there was an apparent treatment by centre interaction in the changes from baseline to the end of treatment in sleep quality 0–10 NRS ($p = 0.016$) and BPI-SF scores ($p = 0.079$) (in the domain of 'pain interference composite'), with an apparent treatment effect in the UK but not elsewhere (data not shown).

### 3.4 Safety and tolerability

All AEs experienced by patients with an incidence of 3% or greater during this study are displayed in Table 4. The most common system organ classes (SOCs) affected for treatment-related AEs were 'nervous system disorders', 'gastrointestinal disorders', 'general disorders and administration site conditions', 'infections and infestations' and 'psychiatric disorders'. 'Psychiatric disorders' were experienced by 36 (28%) patients receiving THC/CBD spray versus only 11 (9%) receiving placebo. By preferred term, dissociation [nine (7%) THC/CBD spray patients affected vs.

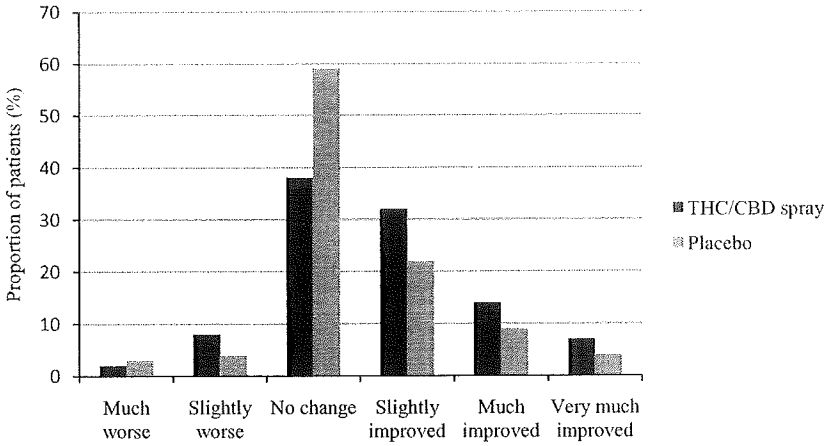


**Figure 3** Subject global impression of change, intention-to-treat complete period.

no placebo patients] and disorientation [eight (6%) THC/CBD spray patients affected vs. no placebo patients] were the most commonly reported AEs in this SOC (Table 4). Additionally, other SOCs were more commonly affected in the THC/CBD spray versus placebo arms, notably 'nervous system disorders', 'gastrointestinal disorders' and 'general disorders and administration site conditions' (Table 4).

The majority of treatment-emergent AEs were mild to moderate in severity across both treatment groups. Ten patients (8%) receiving THC/CBD spray experienced SAEs, none of which was considered to be treatment-related. Six patients (5%) receiving placebo experienced a treatment-emergent SAE, one of which was considered related to treatment. A total of 33 patients stopped receiving study medication due to AEs, 25 in the THC/CBD spray arm and 8 in the placebo group. No obvious trends were shown for biochemistry, haematology or urinalysis, and no mean changes in blood pressure and pulse rate were observed from baseline to final visit. Furthermore, no patients died during the course of this study.

## 4. Discussion

Neuropathic pain is one of the most difficult types of pain to treat (The Committee for Medicinal Products for Human Use (CHMP), 2004), with fewer than half of treated patients receiving meaningful benefit from any pharmacological drug (Attal et al., 2006). The current study patients represented an especially resistant treatment group as they had not responded adequately to existing therapies, had a mean pain 0–10 NRS score of 4 or above, despite the majority currently taking analgesics for their neuropathic pain, and had a median duration of neuropathic pain of more than 3 years. In the face of such prolonged neuropathic pain, a new therapy faces enormous challenges to modify significantly the changes established within the nervous system. Despite these limiting factors, this study confirms the results previously reported, showing THC/CBD spray to produce a clinically relevant improvement (30% or more) in mean daily pain in a significantly greater proportion of patients than placebo when administered in addition to existing medication (Nurmikko et al., 2007). Furthermore, since the evidence base is considered to be poor for medicines currently licensed for the treatment of evoked neuropathic phenomena, these findings suggest that THC/CBD spray is a promising new candidate for treating mixed neuropathic pain characterized by allodynia (Rowbotham et al., 1998). An additional advantage of THC/CBD oromucosal spray is the simple handling and fast action of the medicament.

A greater than 30% improvement in pain intensity, considered to signify a clinically meaningful improvement (Rasmussen et al., 2004), was reported by 28% of patients receiving THC/CBD spray compared with 16% of patients taking placebo. This finding was statistically significant in favour of THC/CBD spray and, considering the patient population in the study, is encouraging. The co-primary analysis of the mean change from baseline to the end of treatment in PNP 0–10 NRS score also showed a treatment difference in favour of THC/CBD spray, but this did not reach statistical significance.

The importance of sleep in chronic pain states has been well established (Casarett et al., 2001; Turk and Dworkin, 2004), and improved sleep is considered a significant treatment objective by patients (Dworkin et al., 2005), especially as neuropathic pain tends to be worse at night (Stacey et al., 2010). Here, we demonstrate a statistically significant improvement in sleep with THC/CBD spray treatment, a finding that sup-

**Table 4** Number of patients with at least one all-causality or treatment-related AE with an incidence of 3% or greater by primary system organ class and preferred term (as medically encoded using the Medical Dictionary for Regulatory Activities [MedDRA] version 8.1).

| | All-causality | | Treatment-related | |
|---|---|---|---|---|
| System organ class<br>Preferred term | THC/CBD spray ($n$ = 128) | Placebo ($n$ = 118) | THC/CBD spray ($n$ = 128) | Placebo ($n$ = 118) |
| | No. of patients (%) | | No. of patients (%) | |
| Total subjects with at least one AE | 109 (85) | 83 (70) | 97 (76) | 56 (47) |
| Nervous system disorders | 79 (62) | 34 (29) | 73 (57) | 20 (17) |
| Dizziness | 52 (41) | 12 (10) | 50 (39) | 11 (9) |
| Dysgeusia | 14 (11) | 2 (2) | 14 (11) | 2 (2) |
| Headache | 13 (10) | 9 (8) | 8 (6) | 7 (6) |
| Disturbance in attention | 8 (6) | 2 (2) | 8 (6) | 1 (1) |
| Neuropathy peripheral | 6 (5) | 4 (3) | 3 (2) | 0 |
| Tremor | 6 (5) | 0 | 4 (3) | 0 |
| Somnolence | 5 (4) | 2 (2) | 5 (4) | 2 (2) |
| Balance disorder | 4 (3) | 2 (2) | 4 (3) | 2 (2) |
| Memory impairment | 4 (3) | 2 (2) | 4 (3) | 2 (2) |
| Sedation | 4 (3) | 0 | 4 (3) | 0 |
| Gastrointestinal disorders | 60 (47) | 43 (36) | 48 (38) | 30 (25) |
| Nausea | 23 (18) | 14 (12) | 22 (17) | 9 (8) |
| Vomiting | 13 (10) | 7 (6) | 6 (5) | 3 (3) |
| Diarrhoea | 12 (9) | 6 (5) | 8 (6) | 2 (2) |
| Dry mouth | 11 (9) | 4 (3) | 11 (9) | 4 (3) |
| Abdominal pain upper | 6 (5) | 1 (1) | 4 (3) | 0 |
| Dyspepsia | 6 (5) | 4 (3) | 1 (1) | 3 (3) |
| Constipation | 4 (3) | 2 (2) | 2 (2) | 0 |
| Mouth ulceration | 4 (3) | 6 (5) | 4 (3) | 6 (5) |
| Oral pain | 4 (3) | 3 (3) | 4 (3) | 3 (3) |
| General disorders and administration site conditions | 45 (35) | 30 (25) | 38 (30) | 23 (19) |
| Fatigue | 20 (16) | 8 (7) | 19 (15) | 5 (4) |
| Feeling drunk | 8 (6) | 3 (3) | 8 (6) | 3 (3) |
| Application site pain | 7 (5) | 2 (2) | 7 (5) | 2 (2) |
| Psychiatric disorders | 36 (28) | 11 (9) | 30 (23) | 4 (3) |
| Dissociation | 9 (7) | 0 | 9 (7) | 0 |
| Disorientation | 8 (6) | 0 | 8 (6) | 0 |
| Depression | 6 (5) | 0 | 3 (2) | 0 |
| Anxiety | 4 (3) | 1 (1) | 3 (2) | 1 (1) |
| Panic attack | 4 (3) | 1 (1) | 3 (2) | 0 |
| Infections and infestations | 35 (27) | 26 (22) | 1 (1) | 3 (3) |
| Nasopharyngitis | 9 (7) | 8 (7) | 1 (1) | 1 (1) |
| Gastroenteritis | 4 (3) | 1 (1) | 0 | 0 |
| Lower Respiratory Tract Infection | 4 (3) | 3 (3) | 0 | 0 |
| Metabolism and nutrition disorders | 15 (12) | 6 (5) | 10 (8) | 5 (4) |
| Increased appetite | 6 (5) | 1 (1) | 6 (5) | 1 (1) |
| Anorexia | 4 (3) | 1 (1) | 1 (1) | 1 (1) |
| Respiratory, thoracic and mediastinal disorders | 15 (12) | 16 (14) | 7 (5) | 5 (4) |
| Pharyngolaryngeal pain | 7 (5) | 5 (4) | 2 (2) | 5 (4) |
| Dyspnoea | 4 (3) | 3 (3) | 1 (1) | 0 |
| Musculoskeletal and connective tissue disorders | 11 (9) | 8 (7) | 2 (2) | 1 (1) |
| Injury, poisoning and procedural complications | 9 (7) | 6 (5) | 2 (2) | 0 |
| Skin and subcutaneous tissue disorders | 9 (7) | 9 (8) | 2 (2) | 2 (2) |
| Rash | 5 (4) | 4 (3) | 1 (1) | 0 |
| Eye disorders | 7 (5) | 6 (5) | 5 (4) | 3 (3) |
| Ear and labyrinth disorders | 6 (5) | 1 (1) | 5 (4) | 1 (1) |
| Vertigo | 5 (4) | 0 | 5 (4) | 0 |
| Vascular disorders | 4 (3) | 5 (4) | 3 (2) | 2 (2) |
| Investigations | 3 (2) | 3 (3) | 2 (2) | 2 (2) |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | 3 (2) | 1 (1) | 0 | 0 |
| Renal and urinary disorders | 3 (2) | 2 (2) | 0 | 1 (1) |
| Cardiac disorders | 2 (2) | 2 (2) | 1 (1) | 0 |
| Reproductive system and breast disorders | 2 (2) | 1 (1) | 0 | 0 |
| Immune system disorders | 1 (1) | 0 | 0 | 0 |
| Blood and lymphatic system disorders | 0 | 2 (2) | 0 | 0 |

AE, adverse effect; CBD, cannabidiol; THC, $\Delta^9$-tetrahydrocannabinol.

ports the consistent improvements in sleep seen in other clinical studies of this drug (Rog et al., 2005, 2007; Attal et al., 2006; Nurmikko et al., 2007). This provides further evidence for the efficacy of THC/CBD spray. Additionally, these improved sleep quality findings are also consistent with recent studies with smoked cannabis (Ware et al., 2010) and synthetic THC (Toth et al., 2012).

Analysis of the SGIC parameter evolution in the current study demonstrated a statistically significant treatment difference in favour of THC/CBD spray, with the most pronounced difference observed in the 'No Change' category, selected by a relatively high proportion of patients in the placebo group. The SGIC tool is considered the 'gold standard' measure of patient outcome in chronic pain trials (Dworkin et al., 2005). Based on this, our findings suggest that overall, patients can achieve important changes in quality of life with THC/CBD spray treatment.

Interestingly, other cannabinoid trials in which evoked pain was assessed reported some similar benefits to the current study (Svendsen et al., 2004; Abrams et al., 2007; Ware et al., 2010; Toth et al., 2012). Two RCTs that evaluated the effects of smoked cannabis on post-traumatic, post-surgical neuropathic pain (Ware et al., 2010) or HIV-associated sensory pain (Abrams et al., 2007) both demonstrated benefits in levels of pain intensity with active treatment. A further two trials that investigated different synthetic forms of THC, dronabinol (Svendsen et al., 2004) and nabilone (Toth et al., 2012) in the treatment of evoked pain, again demonstrated benefits in levels of pain intensity, as well as improvements in the quality of life and overall patient status, which is similar to the current study.

All other secondary endpoints that directly measured pain intensity showed improvements from baseline to the end of treatment, with treatment differences in favour of THC/CBD spray compared with placebo treatment, with only one exception. The punctate allodynia test score was found to improve with THC/CBD spray treatment, but the treatment difference was in favour of placebo. The analysis of rescue analgesia use also showed a tendency for reduced use in the THC/CBD spray treatment group compared with placebo, which could have impacted the pain questionnaire outcomes.

Throughout this study, existing analgesia was maintained based on ethical and clinical considerations. A variety of treatments for neuropathic pain have demonstrated efficacy and are in widespread use based on existing guidelines (Attal et al., 2006). To deprive a patient of these treatments during a placebo-controlled trial would not be ethical. Moreover, the use of combination treatments in clinical practice is becoming more commonplace due to the understanding that multiple pain mechanisms contribute to neuropathic pain (Woolf, 2004; Wade et al., 2010). Adding THC/CBD spray to a mixture of pain treatments, which work by different mechanisms, should not impede the activity of THC/CBD spray. However, if the other treatments are providing partial pain relief, this could reduce the magnitude of benefit derived from THC/CBD spray. The patients recruited for this trial were often very resistant to pharmacological therapy, so to show a 30% improvement in pain intensity in a proportion of patients was a clinically significant achievement.

The self-titration regimen used was chosen for a number of reasons, including the variable threshold of individual patients to the pharmacodynamic effects of THC/CBD spray (Rog et al., 2005; Attal et al., 2006). Having a self-titration schedule allowed patients to optimize their dose based on their own efficacy and tolerability.

In terms of safety, THC/CBD spray was well tolerated in this study, with low levels of intoxication experienced, and no evidence of tolerance developing, since there was a stable dose pattern following initial titration. The most common treatment-emergent, treatment-related events were dizziness, nausea, fatigue and dysgeusia (distortion of sense of taste). These AEs have been observed in other clinical studies with THC/CBD spray and are recognized as having a possible causal relationship to the study medication (Rog et al., 2005; Nurmikko et al., 2007; Wade et al., 2010). The increased incidence of AEs in certain SOCs with THC/CBD spray treatment compared with placebo (i.e., 'psychiatric disorders', 'nervous system disorders', 'gastrointestinal disorders' and 'general disorders and administration site conditions') have also been previously reported in other clinical trials with THC/CBD spray (Rog et al., 2005; Nurmikko et al., 2007; Wade et al., 2010). Psychiatric events such as dissociation and disorientation are known to be common in clinical trials with THC/CBD spray and are representative of a cannabis 'high' (Wade, 2012). A review of 805 THC/CBD spray patients versus 741 placebo patients found that 4% taking THC/CBD spray versus 0.5% taking placebo experienced disorientation, while 1.7% taking THC/CBD spray versus 0.1% taking placebo experienced dissociation (Wade, 2012). While the incidence of these two specific AEs was higher in this study, this may have been due to the titration regimen adopted. Indeed, a slower up-titration administration regimen for THC/CBD spray (over a 10-day period) was associated with a

lower number of AEs in later studies (Collin et al., 2010; Novotna et al., 2011). In clinical trials of THC/CBD spray using a slow up-titration schedule, the incidence of psychiatric AEs is reduced from 15% to 8% compared with the original more aggressive regimen adopted in this study (Wade, 2012).

A total of 10 SAEs were experienced by patients receiving THC/CBD spray; however, none was considered to be treatment-related. There were no consistent patterns of difference between THC/CBD spray and placebo for haematology, biochemistry and urinalysis parameters. Furthermore, changes in vital signs for pulse rate and systolic blood pressure were unremarkable compared with baseline.

### 4.1 Study limitations

The presence of a substantial proportion of non-responders in this study suggests that the analysis of mean changes may not be the most appropriate means of identifying whether the medication has a clinically useful effect, since the lack of improvement in the non-responders would dilute the improvement seen in responders. In clinical practice, non-responders to treatment would be unlikely to remain on a non-effective drug and would therefore not contribute to understanding the utility of the medicine in the population of patients for whom it is suitable. This dilemma has been discussed by McQuay et al. (2008).

Another potential study limitation was the inclusion of multiple aetiologies of PNP leading to considerable clinical trial heterogeneity. The issue of clinical trial heterogeneity in patients with neuropathic pain has been well-documented, and several other controlled trials of promising new therapeutic candidates have been negative (Baron et al., 2012). By contrast, a variety of neuropathic pain studies in heterogeneous populations such as the current study have reported positive results in terms of pain scores (Serpell, 2002; Rowbotham et al., 2003), including studies in which vaporized cannabis (Wilsey et al., 2013) and cannabis cigarettes (Wilsey et al., 2008) were used, although slightly different pain scales were adopted than those used in the current study. Several clinical trials and post-hoc analyses have shown greater efficacy of the study drug when patients are sub-grouped based on baseline sensory symptoms and/or pain thresholds (Edwards et al., 2006; Simpson et al., 2010; Campbell et al., 2012). As such, future studies that incorporate sensory profiling may reveal specific subgroups of patients in which THC/CBD spray is efficacious.

A potential drawback of the maximum dose of 24 daily sprays adopted in this study was the potential for a 'placebo effect', which may have diminished the positive results seen with THC/CBD spray. While the treatment difference in favour of THC/CBD spray increased with increasing daily doses of study medication, this effect appeared to drop off at a dose of around 14–15 sprays per day. At a similar dose, however, the proportion of responders in the placebo treatment group was still increasing markedly with increasing numbers of daily sprays. This suggests that patients who took higher mean daily doses of placebo perceived a benefit in the subjective pain severity score. The consequence of this effect is an apparent decrease in the true treatment advantage of THC/CBD spray over placebo, observed at lower daily doses. These findings suggest that future studies would benefit from a reduction in the current dose ceiling of 24 sprays per day, thus allowing comparison of the two treatment groups at similar mean doses.

## 5. Conclusions

In conclusion, this study has shown that in a meaningful proportion of otherwise treatment-resistant patients, clinically important improvements in their pain, sleep quality and global impression of change in the severity of their condition were obtained by taking THC/CBD spray. There is also a possibility that these results may have been more strongly in favour of THC/CBD spray if the upper dose level had been capped to below 24 sprays daily, and a slower titration regimen had been adopted in an attempt to improve the overall tolerability and its effect of early withdrawals and, secondarily, to reduce the placebo response. Reassuringly, there was no evidence of tolerance developing and few patients reported experiencing severe AEs. Taken together, these finding are encouraging and suggest that treatment of PNP associated with allodynia with THC/CBD spray could bring significant benefit to patients.

#### Author contributions

All authors made a substantial contribution to the acquisition and interpretation of the data, critically reviewed the article and approved the final version for publication.

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