

MMP-017

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

INSTRUCTIONS

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


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

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

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

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

1. Petitioner Information

Name: Joel Meer MD
Street Address: 
City, State, Zip Code: _____
Telephone Number: _____
Email Address: _____

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

Chronic non cancer pain

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

- Yes, in Person
 Yes, by Telephone
 No

at the discretion of the review panel

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

- Yes
 No

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

RECEIVED

AUG 26 2016

**OFFICE OF THE
CHIEF OF STAFF**

MEDICINAL MARIJUANA PETITION
(Continued)

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

for # 5 to # 10

see my letter of 08-24-16

& See attached reference articles

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

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

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

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

MEDICINAL MARIJUANA PETITION
(Continued)

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

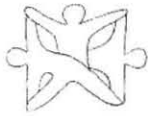


I certify, under penalty of perjury, that I am 18 years of age or older; that the information provided in this petition is true and accurate to the best of my knowledge; and that the attached documents are authentic.

Signature of Petitioner

Date

05-25-16



Joel Meer, MD

Board Certified Physical Medicine & Rehabilitation

August 24, 2016

New Jersey Department of Health
Office of Commissioner
Medical Marijuana Program

Dear Program Representatives:

I am a New Jersey based physician writing in support of the addition of chronic pain and PTSD as qualifying conditions.

I am board certified in Physical Medicine & Rehabilitation. I did my residency in New Jersey at the nationally acclaimed Kessler Institute. My career, spanning 26 years, includes a 22-year stint as the Chairman of the Department of Physical Medicine and Rehabilitation at Newark Beth Israel Medical Center (RWJ-Barnabas Health).

Throughout my career, I have been treating acute and chronic pain of traumatic or non-traumatic etiologies. As people that treat chronic pain know, one often tries everything available and is left wanting for more tools in an attempt to provide the best care a physician is capable of giving. I have known for a long time that cannabis has a valid role to play in the management of chronic pain. It has also been apparent that many chronic pain patients carry concurrent mental health diagnoses including severe anxiety, PTSD, and depression.

When New Jersey developed the MMP, I was initially happy, until I realized that the 30% to 50% of my patients, who could benefit from medical cannabis, were not going to be eligible because chronic pain was an excluded diagnosis. There is a history of traditional herbal medicine dating back over 2000 years in China and India documenting cannabis as a treatment for chronic pain, among other uses. The validity and truth of these systems is evident to people with open eyes and open minds. Consider acupuncture: non-western, non-allopathic, yet an effective tool for treating/healing.

Though not as plentiful as we would wish, there is a growing body of scientific study supporting the use of cannabis in the above contexts (see reference articles included). This, together with the long history of traditional use, and an acceptable side effect profile (compared with many common pharmacological medications which we prescribe daily) make it reasonable and appropriate for you to include chronic pain and PTSD as qualifying conditions.

Sincerely,



Joel Meer, MD

RECEIVED

AUG 26 2016

OFFICE OF THE
CHIEF OF STAFF

Cannabinoids for the Treatment of Chronic Non-Cancer Pain: An Updated Systematic Review of Randomized Controlled Trials

Journal of Neuroimmune Pharmacology
June 2015, Volume 10, Issue 2, pp 293–301

M. E. Lynch, Mark A. Ware

INVITED REVIEW

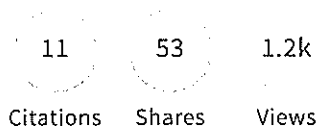
First Online: 22 March 2015

DOI (Digital Object Identifier): 10.1007/s11481-015-9600-6

Cite this article as:

Lynch, M.E. & Ware, M.A. J Neuroimmune Pharmacol (2015) 10: 293.

doi:10.1007/s11481-015-9600-6



Abstract

An updated systematic review of randomized controlled trials examining cannabinoids in the treatment of chronic non-cancer pain was conducted according to PRISMA guidelines for systematic reviews reporting on health care outcomes. Eleven trials published since our last review met inclusion criteria. The quality of the trials was excellent. Seven of the trials demonstrated a significant analgesic effect. Several trials also demonstrated improvement in secondary outcomes (e.g., sleep, muscle stiffness and spasticity). Adverse effects most frequently reported such as fatigue and dizziness were mild to moderate in severity and generally well tolerated. This review adds further support that currently available cannabinoids are safe, modestly effective analgesics that provide a reasonable therapeutic option in the management of chronic non-cancer pain.

Keywords

Cannabinoids Chronic non-cancer pain Neuropathic pain Systematic review Marijuana

References

Blyth FM, March LM, Brnabic AJ, Jorm LR, Williamson M, Cousins MJ (2001) Chronic pain in Australia: a prevalence study. *Pain* 89:127–134

[PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=110661681) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=110661681)

[CrossRef](http://dx.doi.org/10.1016/S0304-3960(01)03773-0) ([http://dx.doi.org/10.1016/S0304-3960\(01\)03773-0](http://dx.doi.org/10.1016/S0304-3960(01)03773-0))

Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D (2006) Survey of chronic pain in Europe: prevalence, impact on daily life and treatment. *Eur J Pain* 10:287–333

[PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=160959341) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=160959341)

[CrossRef](http://dx.doi.org/10.1016/j.ejpain.2005.06.009) (<http://dx.doi.org/10.1016/j.ejpain.2005.06.009>)

Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcotte TD, Bentley BA, Gouaux B (2012) Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. *CMAJ* 184:1143–1150

[PubMedCentral](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3394820) (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3394820>)

[PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=225863341) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=225863341)

[CrossRef](http://dx.doi.org/10.1503/cmaj.110837) (<http://dx.doi.org/10.1503/cmaj.110837>)

Cravatt BF, Demarest K, Patricelli PM, Bracey MH, Giang DK, Martin BR, Lichtman AH (2001) Supersensitivity to anandamide and enhanced endogenous cannabinoid signaling in mice lacking fatty acid amide hydrolase. *Proc Natl Acad Sci* 98:9371–9376

[PubMedCentral](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC57427) (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC57427>)

[PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=114709001) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=114709001)

[CrossRef](http://dx.doi.org/10.1073/pnas.1611916981) (<http://dx.doi.org/10.1073/pnas.1611916981>)

Finnerup NB, Sindrup SH, Jensen TS (2010) The evidence for pharmacological treatment of neuropathic pain. *Pain* 150:573–581

[PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=207752131) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=207752131)

[CrossRef](http://dx.doi.org/10.1016/j.pain.2010.06.010) (<http://dx.doi.org/10.1016/j.pain.2010.06.010>)

Huggins JP, Smart TS, Langman S, Taylor L, Young T (2012) An efficient randomised, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-04457845, which modulates endocannabinoids but fails to induce effective analgesia in patients with pain due to osteoarthritis of the knee. *Pain* 153:1837–1846

[PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=227275001) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=227275001)

[CrossRef](http://dx.doi.org/10.1016/j.pain.2012.04.020) (<http://dx.doi.org/10.1016/j.pain.2012.04.020>)

Kahan M, Srivastava A, Spithoff S, Bromley L (2014) Prescribing smoked cannabis for chronic noncancer pain: preliminary recommendations. *Can Fam Physician* 60:1083–1090

[PubMedCentral](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4264803) (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4264803>)

[PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=253005981) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=253005981)

Langford RM, Mares J, Novotna A, Vachova M, Novakova I, Notcutt W, Ratcliffe S (2013) A double-blind, randomised, placebo-controlled, parallel-group study of THC? CBD oralmucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J Neurol* 260:984–997

[PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=23180178) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=23180178)

[CrossRef](http://dx.doi.org/10.1007/s00415-012-6739-4) (<http://dx.doi.org/10.1007/s00415-012-6739-4>)

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ionndis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analysis of studies that evaluate health care interventions: explanation and elaboration. *Ann Int Med* 15:W-65–W-94

Lynch ME (2008) The pharmacotherapy of chronic pain. *Rheum Dis Clin N Am* 34:369–385

[CrossRef](http://dx.doi.org/10.1016/j.rdc.2008.04.001) (<http://dx.doi.org/10.1016/j.rdc.2008.04.001>)

Lynch ME (2011) The need for a Canadian pain strategy. *Pain Res Manag* 16:77–80

[PubMedCentral](http://www.ncbi.nlm.nih.gov/pubmed/2054407) (<http://www.ncbi.nlm.nih.gov/pubmed/2054407>)

[PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=21199381) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=21199381)

[CrossRef](http://dx.doi.org/10.1111/j.1365-2125.2011.03970.x) (<http://dx.doi.org/10.1111/j.1365-2125.2011.03970.x>)

Lynch ME, Campbell F (2011) Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized controlled trials. *Br J Clin Pharmacol* 72:735–744

[PubMedCentral](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3243068) (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3243068>)

[PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=21126373) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=21126373)

[CrossRef](http://dx.doi.org/10.1111/j.1365-2125.2011.03970.x) (<http://dx.doi.org/10.1111/j.1365-2125.2011.03970.x>)

Lynch ME, Cesar-Rittenberg P, Hohmann AG (2014) A double-blind, placebo-controlled, crossover pilot trial with extension using oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. *J Pain Symptom Manag* 47:166–17323742737

[CrossRef](http://dx.doi.org/10.1016/j.jpain.2013.02.018) (<http://dx.doi.org/10.1016/j.jpain.2013.02.018>)

Moulin D, Clark AJ, Speechly M, Morley-Forster P (2002) Chronic pain in Canada, prevalence, treatment, impact and the role of opioid analgesia. *Pain Res Manag* 7:179–184

[PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=12518174) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=12518174)

[CrossRef](http://dx.doi.org/10.1098/rstb.2011.0381) (<http://dx.doi.org/10.1098/rstb.2011.0381>)

Pertwee RG (2012) Targeting the endocannabinoid system with cannabinoid receptor agonists: pharmacological strategies and therapeutic possibilities. *Philos Trans R Soc Lond B Biol Sci* 367:3353–3363

[PubMedCentral](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3481523) (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3481523>)

[PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=23108552) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=23108552)

[CrossRef](http://dx.doi.org/10.1098/rstb.2011.0381) (<http://dx.doi.org/10.1098/rstb.2011.0381>)

Pini LA, Guerzoni S, Cainazzo MM, Ferrari A, Sarchielli P, Tiraferri I, Ciccarese M, Zappaterra M (2012) Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. *J Headache Pain* 13:677–684

[PubMedCentral](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3481250) (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3481250>)

[PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=231070400) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=231070400)

[CrossRef](http://dx.doi.org/10.1007/s00415-012-6739-4) (<http://dx.doi.org/10.1007/s00415-012-6739-4>)

CrossRef (<http://dx.doi.org/10.1007/s10194-012-0490-1>)

Schuelert N, Johnson MP, Oskins JL, Jassal K, Chambers MG, McDougall JJ (2011) Local application of the endocannabinoid hydrolysis inhibitor URB597 reduces nociception in spontaneous and chemically induced models of osteoarthritis. *Pain* 152:975–981

PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=21173040)

CrossRef (<http://dx.doi.org/10.1016/j.pain.2010.11.025>)

Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, Ehler E (2014) A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *Eur J Pain* 18:999–1012

PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=24420902)

CrossRef (<http://dx.doi.org/10.1002/j.1532-2149.2013.00445.x>)

Skaper SD, DiMarzo V (2012) Endocannabinoids in nervous system health and disease: the big picture in a nutshell. *Phil Trans R Soc B* 367:3193–3200

PubMedCentral (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3481537/>)

PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=23108540)

CrossRef (<http://dx.doi.org/10.1098/rstb.2012.0313>)

Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, Garven A (2012) An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. *Pain* 153:2073–2082

PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=22921260)

CrossRef (<http://dx.doi.org/10.1016/j.pain.2012.06.024>)

Turcotte D, Doupe M, Torabi M, Gomori A, Ethans K, Esfahani F (2014) Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. *Pain Med*. doi:10.1111/pme.12569 (<http://dx.doi.org/10.1111/pme.12569>)

PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=25288189)

Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ (2003) Cannabis use for chronic non-cancer pain: results of a prospective survey. *Pain* 102(1–2):211–216

PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=12620613)

CrossRef ([http://dx.doi.org/10.1016/S0304-3979\(02\)10040-1](http://dx.doi.org/10.1016/S0304-3979(02)10040-1))

Ware MA, Fitzcharles M, Lawrence J, Shir Y (2010) The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. *Anesth Analg* 110:604–610

PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=20007734)

CrossRef (<http://dx.doi.org/10.1213/ANE.0b013e3181c76f70>)

Wilsey B, Marcotte TD, Deutsch R, Gouaux B, Sakai S (2013) Low-dose vaporised cannabis significantly improves neuropathic pain. *J Pain* 14:136–148

[PubMedCentral](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3506031/) (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3506031/>)

[PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=23237736) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=23237736)

[CrossRef](http://dx.doi.org/10.1016/j.jpain.2012.10.009) (<http://dx.doi.org/10.1016/j.jpain.2012.10.009>)

Zajicek JP, Hobart JC, Slade A, Barnes D, M. PG (2012) Multiple sclerosis and extract of cannabis: results of the MUSEC trial. *J Neurol Neurosurg Psychiatry* 83:1125–1132

[PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=22704600) (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=22704600)

[CrossRef](http://dx.doi.org/10.1136/jnnp.2012.302198) (<http://dx.doi.org/10.1136/jnnp.2012.302198>)

Copyright information

© Springer Science+Business Media New York 2015

About this article



CrossMark

Print ISSN

1557-1890

Online ISSN

1557-1904

Publisher Name

Springer US

[About this journal](#)

[Reprints and Permissions](#)

SPRINGER NATURE

© 2016 Springer International Publishing. Part of Springer Nature.

Not logged in · Not affiliated · 98.109.121.211

PubMed

Format: Abstract

Full text links



Clin Pharmacol Ther. 2011 Dec;90(6):844-51. doi: 10.1038/clpt.2011.188. Epub 2011 Nov 2.

Cannabinoid-opioid interaction in chronic pain.

Abrams DJ¹, Couey P, Shade SB, Kelly ME, Benowitz NL.

Author information

Abstract

Cannabinoids and opioids share several pharmacologic properties and may act synergistically. The potential pharmacokinetics and the safety of the combination in humans are unknown. We therefore undertook a study to answer these questions. Twenty-one individuals with **chronic pain**, on a regimen of twice-daily doses of sustained-release morphine or oxycodone were enrolled in the study and admitted for a 5-day inpatient stay. Participants were asked to inhale vaporized cannabis in the evening of day 1, three times a day on days 2-4, and in the morning of day 5. Blood sampling was performed at 12-h intervals on days 1 and 5. The extent of **chronic pain** was also assessed daily. Pharmacokinetic investigations revealed no significant change in the area under the plasma concentration-time curves for either morphine or oxycodone after exposure to cannabis. **Pain** was significantly decreased (average 27%, 95% confidence interval (CI) 9, 46) after the addition of vaporized cannabis. We therefore concluded that vaporized cannabis augments the analgesic effects of opioids without significantly altering plasma opioid levels. The combination may allow for opioid treatment at lower doses with fewer side effects.

Comment in

The role of cannabinoids in **chronic pain** patients remains hazy. [*Clin Pharmacol Ther.* 2012]
Clearing the smoke around medical marijuana. [*Clin Pharmacol Ther.* 2011]

PMID: [22048225](#) DOI: [10.1038/clpt.2011.188](#)

[PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances, Grant Support

LinkOut - more resources

PubMed Commons

[PubMed Commons home](#)

0 comments

[How to join PubMed Commons](#)



HHS Public Access

Author manuscript

Peer reviewed and approved for publication

About author manuscripts

Submit a manuscript

[J Pain](#). Author manuscript; available in PMC 2014 Feb 1.

PMCID: PMC3566631

Published in final edited form as:

NIHMSID: NIHMS439212

[J Pain](#). 2013 Feb; 14(2): 136–148.

Published online 2012 Dec 11. doi: [10.1016/j.jpain.2012.10.009](https://doi.org/10.1016/j.jpain.2012.10.009)

Low Dose Vaporized Cannabis Significantly Improves Neuropathic Pain

[Barth Wilsey](#), MD, [Thomas D. Marcotte](#), PhD, Associate Professor, [Reena Deutsch](#), PhD, Statistician, [Ben Gouaux](#), Research Associate, [Staci Sakai](#), Research Associate, and [Haylee Donaghe](#), Research Associate

Barth Wilsey, VA Northern California Health Care System, Sacramento, CA, Department of Physical Medicine and Rehabilitation, University of California, Davis Medical Center;

[Contributor Information](#).

Corresponding Author: Barth L. Wilsey MD, VA Northern California Health Care System, UC Davis Medical Center, Email: blwilsey@ucdavis.edu

[Copyright notice](#) and [Disclaimer](#)

The publisher's final edited version of this article is available at [J Pain](#)

See commentary "[Response to Stacey and Moller's Letter to the Editor](#)" in *J Pain*, volume 10 on page 1252.

See other articles in PMC that [cite](#) the published article.

Abstract

Go to:

We conducted a double-blind, placebo-controlled, crossover study evaluating the analgesic efficacy of vaporized cannabis in subjects, the majority of whom were experiencing neuropathic pain despite traditional treatment. Thirty-nine patients with central and peripheral neuropathic pain underwent a standardized procedure for inhaling either medium dose (3.53%), low dose (1.29%), or placebo cannabis with the primary outcome being VAS pain intensity. Psychoactive side-effects, and neuropsychological performance were also evaluated. Mixed effects regression models demonstrated an analgesic response to vaporized cannabis. There was no significant difference between the two active dose groups' results ($p > 0.7$). The number needed to treat (NNT) to achieve 30% pain reduction was 3.2 for placebo vs. low dose, 2.9 for placebo vs. medium dose, and 25 for medium vs. low dose. As these NNT are comparable to those of traditional neuropathic pain medications, cannabis has analgesic efficacy with the low dose being, for all intents and purposes, as effective a pain reliever as the medium dose. Psychoactive effects were minimal and well-tolerated, and neuropsychological effects were of limited duration and readily reversible within 1–2 hours. Vaporized cannabis, even at low doses, may present an effective option for patients with treatment-resistant neuropathic pain.

Keywords: neuropathic pain, analgesia, cannabis, clinical trial, neuropsychological testing

INTRODUCTION

Go to:

Neuropathic pain, a disease of the peripheral or central nervous system, develops when peripheral nerves, spinal cord, or brain are injured or the sensory system simply fails to function in a customary manner. This may be caused by an underlying pathological process (e.g., neuropathy) or catastrophic injury (e.g., stroke or spinal cord injury). The pain should be considered maladaptive "in the sense that the pain neither protects nor supports healing and repair".¹⁵ Unfortunately, pharmacologic management of neuropathic pain can be quite challenging. In randomized clinical trials, no more than half of patients experience clinically meaningful pain relief from pharmacotherapy, where success is defined as partial relief.¹⁷ Given a lack of alternatives, validation of unconventional analgesics such as cannabis may address unmet needs.¹⁷ More than a decade ago, the National Institutes of Health (NIH)

Workshop on the Medical Utility of Marijuana concluded that neuropathic pain is a condition in which currently available analgesics are, at best, marginally effective, and suggested that cannabis might hold promise for many sufferers of this malady.⁵

In the last decade, there have been several studies that evaluated the short-term efficacy of smoked cannabis for neuropathic pain. Two trials enrolled patients with painful HIV peripheral neuropathy.^{1, 18} A significantly greater proportion of individuals reported at least 30% reduction in pain on cannabis (46%–52%) compared to placebo (18%–24%).^{1, 18} Contemporaneously, a human experimental model of neuropathic pain using intradermal injection of capsaicin was conducted in healthy volunteers,⁵³ and suggested that there may be a therapeutic window for smoked cannabis. Low dose cigarettes (2% delta-9-tetrahydrocannabinol (THC)) had no analgesic value, while high dose (8% THC) cigarettes were associated with reports of an increase in pain. But the medium dose of cannabis cigarettes used in this study (4% THC) provided significant analgesia. A fourth trial enrolled a heterogeneous neuropathic pain patient population (complex regional pain syndrome, peripheral neuropathy, focal nerve or spinal cord injury) and also pointed to a medium dose (3.53% THC) as being more advantageous than the high dose, but for a different reason.⁵⁸ Although medium- and high-dose cannabis were equi-analgesic, negative cognitive effects, particularly with memory, were evident to a much lower extent with the medium-dose (3.53% THC) compared to the high-dose (7% THC).⁵⁸

The purpose of the present study is to compare medium dose (3.53% THC) to low dose (1.29% THC) cannabis. If analgesia were maintained while cognitive and psychomimetic effects were moderated, a case could be made for using low-dose (1.29 % THC) preferentially. In addition to varying the concentration of THC studied, the present study examined vaporization as an alternative to smoking cannabis. The shortcomings of smoking marijuana, such as exposure to tar, have long been recognized as providing an obstacle to the approval of medicinal cannabis.⁴⁰ Cannabis vaporization is a technique that avoids the production of irritating respiratory toxins by heating cannabis to a temperature where active cannabinoid vapors form, but below the point of combustion where toxins are released.^{26, 41}

MATERIALS AND METHODS

Go to:

REGULATORY PROCESS

This study was approved by the Human Subjects Institutional Review Boards at the UC Davis Medical Center (UCDMC) and the Veterans Affairs of Northern California Health Care System (VANCHCS). The endorsement process also included mandated state review for a controlled substance involving the Research Advisory Panel of California. National review followed federal regulatory requirements for cannabis research with submissions to the Food and Drug Administration for an Investigational New Drug Application, the National Institute on Drug Abuse, and the Department of Health and Human Services.²⁰ The study was registered with ClinicalTrials.gov with identification [NCT01037088](https://clinicaltrials.gov/ct2/show/study/NCT01037088).

The cannabis was harvested at the University of Mississippi under the supervision of the National Institute on Drug Abuse (NIDA). NIDA routinely provides bulk cannabis ranging in strength from 1.29% to 7% THC, subject to the availability of current crop potency. Placebo cannabis is made from whole plant with extraction of cannabinoids. Following overnight delivery, the cannabis was stored in a freezer at the Sacramento VA Research Pharmacy, located in close proximity to the UC Davis Clinical Translational Science Center Clinical Research Center.

SUBJECTS

Participants were recruited from the UCDMC and VANCHCS Pain Clinics, newspaper advertisements, and newsletter postings. All candidates were initially screened via a telephone interview. Qualified candidates with a requisite neuropathic pain disorder (complex regional pain syndrome (CRPS Type I, formerly known as reflex sympathetic dystrophy),^{21, 32, 9} thalamic pain, spinal cord injury, peripheral neuropathy, radiculopathy or nerve injury) were interviewed and examined by the principal investigator.

All participants were required to refrain from smoking cannabis or taking oral synthetic delta-9-THC medications (i.e. Marinol®) for 30 days before study sessions to reduce residual effects; each participant underwent urine toxicology screening to, as much as feasible, confirm this provision. To further reduce unsystematic variation, subjects were instructed to take all other concurrent medications as per their normal routine during the 3 to 4 week study period.

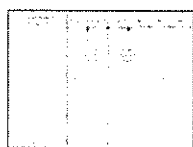
To reduce the risk of adverse psychoactive effects in naïve individuals,¹³ previous cannabis exposure was required of all subjects. To ensure that potential subjects did not have depression profound enough to compromise their ability to tolerate the psychoactive effects of cannabis, the PHQ-9 was administered as a screening tool.³⁹ Subjects with severe depression were excluded. Individuals whose PHQ-9 score indicated mild or moderate depression were offered referral for psychiatric treatment, if therapy was not already in progress. In addition, the Center for Epidemiological Studies-Depression Scale (CES-D) was administered using the three item subscale measuring suicidal ideation proposed by Garrison et al.^{23, 24} and others.¹³ If any of the items (“I felt life was not worth living”; “I felt like hurting myself”; “I felt like killing myself”) were answered affirmatively, the subject was not enrolled in the study.

Candidates with a history or diagnosis of these serious mental illnesses were also excluded. Medical illnesses were also evaluated, and potential subjects were excluded if they had uncontrolled hypertension, cardiovascular disease, chronic pulmonary disease (e.g. asthma, COPD), and/or active substance abuse. Routine laboratory analysis included a hematology screen, blood chemistry panel, and urinalysis. Urine drug toxicologies for opioids, benzoylcegonine (cocaine metabolite), benzodiazepines, cannabinoids, and amphetamines were also performed using urine immunoassay quick tests.

DESIGN

The study used a randomized, double-blind, placebo-controlled, crossover design employing medium dose (3.53% delta-9-THC), low-dose (1.29% delta-9-THC), and placebo cannabis. Two doses of medication and a cumulative dosing scheme^{14, 27} were employed to determine dosing relationships for analgesia, psychoactive and cognitive effects.

Our previous cannabis study produced a robust placebo response for the primary outcome, pain intensity.⁵⁸ Although overcome by the efficacy of cannabis, we sought a methodology to reduce this effect inasmuch as we were using a lower dose in the present study. Clinical trials involving at least five different medications for neuropathic pain have been associated with unanticipated negative results whereby no significant difference between active study medication and placebo was evident, in the context of at least one positive trial.¹⁶ Experience from the psychiatric literature suggests that trials with flexible dose designs are almost twice as likely to demonstrate significant differences between antidepressant medications and placebo than fixed dose trials.³⁶ Higher placebo response rates in the fixed dose trials might be explained by an increase in expectations of receiving a beneficial treatment. In order to reduce this potential confound, we incorporated the use of flexible dosing into the present study and allowed subjects to inhale four to eight puffs of cannabis (or placebo) during the second administration period at 180 minutes ([Figure 1](#)). This methodology has been previously accomplished for treatment of neuropathic pain with a cannabinoid (Sativex®)⁴ and a GABAergic analogue (Lyrica®)⁵² where patients self-titrated their overall dose and pattern of dosing according to their response to and tolerance of the medicine.



[Figure 1](#)

Experimental procedures and timing of cannabis vaporization sessions

PROCEDURES

After informed consent was obtained, participants were scheduled for three, 6-hour experimental sessions at the UC Davis Clinical Translational Science Center Clinical Research Center. The sessions were separated by at least 3 days to permit the metabolic breakdown of THC metabolites.²⁸ The intervals between sessions ranged from 3 to 14 days with a mean (SD) of 7.0 (1.8) days. Participants received either low dose, medium dose, or placebo cannabis at each visit in a crossover design, with each patient receiving each treatment once, in random order (using a web-based random number-generating program, “Research Randomizer” (<http://www.randomizer.org>)). The allocation schedule was kept in the pharmacy and concealed from other study personnel. Patients were assigned to treatment after they signed a consent form. Patients and assessors were blinded to group assignments. At the end of each study session, an assessment of the unmasking of the blinding was performed by asking subjects to “guess” whether they had received active cannabis or placebo during that session.

The cannabis was stored in a freezer at -20°C until the day before use. At least 12 hours before each session, 0.8 g of cannabis was thawed and humidified by placing the medication above a saturated NaCl solution in a closed humidifier at room temperature. The cannabis was vaporized using the Volcano[®] vaporizer (Storz & Bickel America, Inc., Oakland, CA). The vapor was collected in a vaporizer bag with a specially designed mouthpiece that allowed one to willfully interrupt inhalation repeatedly without loss of vaporized cannabis to the atmosphere. As a matter of precaution to prevent contamination of the breathing space of observers, this procedure was conducted under a standard laboratory fume hood with constant ventilation in a room with an ambient temperature of 22°C and a humidity of 40% to 60%.

A cued-puff procedure known as the “Foljin Puff Procedure” standardized the administration of the cannabis.¹⁴ Participants were verbally signaled to “hold the vaporizer bag with one hand and put the vaporizer mouthpiece in their mouth” (30 seconds), “get ready” (5 seconds), “inhale” (5 seconds), “hold vapor in lungs” (10 seconds), “exhale and wait” before repeating puff cycle (40 seconds). Subjects inhaled four puffs at 60 minutes. At 180 minutes, the balloon was refilled and deploying the flexible dose design described previously, subjects inhaled four to eight puffs. Thus, the minimum and maximum cumulative doses for each visit were eight and twelve puffs, respectively. Participants were observed constantly and could signal that they wanted to stop inhalation for whatever reason by raising their hand.

An assessment was performed before the administration of vaporized cannabis or placebo and hourly thereafter ([Figure 1](#)) for six hours. Vital signs (blood pressure, respiratory rate, and heart rate) were recorded at baseline and at every hour to ensure well-being of subjects.

Participants were allowed to engage in normal activities, such as reading, watching television, or listening to music, between puff cycles and assessment periods. After each session, participants were accompanied home by a responsible adult. Upon completion of study sessions, participants were compensated with a modest stipend for their participation (prorated at \$25 per hour).

OUTCOME MEASUREMENTS

Spontaneous pain relief, the primary outcome variable, was assessed by asking participants to indicate the intensity of their current pain on a 100-mm visual analog scale (VAS) between 0 (no pain) and 100 (worst possible pain). As a secondary measure of pain relief, we used the Patient Global Impression of Change.¹⁹

The Neuropathic Pain Scale,²² an 11-point box ordinal scale with several pain descriptors, was another secondary outcome. When present, allodynia (the sensation of unpleasantness, discomfort, or pain when the skin in a painful area of the subject’s body was lightly stroked with a foam paint brush), was measured using a 100-mm VAS. Heat-pain threshold was determined by applying mild-to-moderately painful heat to the most painful area of the subjects’ body using the commercially available Medoc TSA 2001 Peltier thermode.³¹ This device applied a constant 1-degree Centigrade per second increasing thermal stimulus until the patient pressed the response button, indicating that the temperature change was considered painful; the heat pain threshold (mean of three attempts) was recorded in degrees Centigrade. Separate subjective intensities for “any drug effect,” “good drug effect,” and “bad drug

effect,” were measured using a 100-mm VAS anchored by “not at all” at 0 and “extremely” at 100. In addition, psychoactive effects, including “high,” “drunk,” “impaired,” “stoned,” “like the drug effect,” “sedated,” “confused,” “nauseated,” “desire more of the drug,” “anxious,” “down,” and “hungry” were measured similarly. Mood was measured using 6, 100-mm VAS ratings for feeling: sad vs. happy; anxious vs. relaxed; jittery vs. calm; bad vs. good; paranoid vs. self-assured; and fearful vs. unafraid. Subjects were prompted to provide their current rating for the foregoing items at each measurement of these subjective states.

Neurocognitive assessments focused on several domains: attention and concentration, learning and memory, and fine motor speed. Subjects completed the Wechsler Adult Intelligence Scale (WAIS-III) Digit Symbol Test,⁵⁷ a test of concentration, psychomotor speed, and graphomotor abilities. This pen and paper test involved having subjects substitute a series of symbols with numbers as quickly and accurately as possible during a 120-second period. The results were expressed as the number of correct substitutions. The Hopkins Verbal Learning Test Revised (HVLT) provided information on the ability to learn and immediately recall verbal information, as well as the ability to retain, reproduce, and recognize this information after a delay.⁷ Alternate forms (A through F) were used to minimize practice effects.^{8,6} A list of 12 words (four words from each of three semantic categories) were presented, and the subject was asked to recall as many words as possible in any order. After a 20-minute delay, the subject was asked to recall the words once again (i.e., delayed recall). The Grooved Pegboard Test,³⁸ a test of fine motor coordination and speed, was also administered. In this test, subjects were required to place 25 small metal pegs into holes on a 3" × 3" metal board as quickly as possible. All pegs were alike, and have a ridge on one side, which corresponds to a randomly oriented notch in each hole on the metal board. First the dominant hand was tested, the task was subsequently repeated with the non-dominant hand, and the total time for each test was recorded. A five-minute limit was employed for those unable to complete the task.

Performance on neuropsychological tests often improves as a result of practice effects.³⁴ This can be somewhat ameliorated by the use of alternate forms.⁸ For this study, we used 6 separate versions of the Hopkins Verbal Learning Test and incorporated a practice testing session at the time of the screening interview in order to lessen early practice effects. Despite our attempts to limit practice effects (using alternate forms, conducting a pre-baseline practice session), these effects cannot be completely eliminated when subjects are tested repeatedly over a brief period. However, this is likely to result in increased variance, thus attenuating the treatment effect. In addition, practice effects were also mitigated by the use of a placebo arm.

STATISTICAL METHODOLOGY

Linear mixed models with subjects treated as a random effect were used to model the primary and secondary pain and neuropsychological response measures. This methodology takes into account the repeated measures aspect of the within-subjects cross-over study design, incorporating information from observations for each subject at different treatment doses and multiple timepoints within each dose. For initial modeling, terms were included for dose (placebo cannabis vs. low-dose (1.29% delta-9-THC) vs. medium dose (3.53% delta-9-THC) treated as a categorical variable), time (0 vs 60 vs 120 vs 180 vs 240 vs 300 minutes treated as a continuous variable), and dose x time interaction. Additional terms were also included for the sequence in which the treatments were administered (e.g., low-placebo-medium vs. low-medium-placebo, etc.) and for second-order time (time²). The quadratic term is intended to model a U-shaped response curve if responses initially increase (decrease), reach a maximum (minimum), then decrease (increase) back to baseline levels or thereabouts. For each outcome measure, each of these last two terms were omitted from subsequent models and not reported if non-significant.

Dose effects at each timepoint were tested with mixed modeling after re-coding time as a categorical factor and including dose and dose x time terms (plus a term for sequence if significant in the initial model). The direction of disparity among the doses was accomplished using Tukey Honestly Significant Difference (HSD) comparison tests for differences of effects over all timepoints and contrasts within each timepoint. No other adjustments for multiple statistical comparisons were made. Models were fitted using residual maximum likelihood methods. Effect sizes for the neuropsychological testing results were calculated as Z-scores relative to the mean and standard deviation for

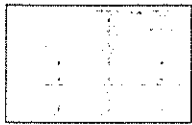
placebo. All response observations, including information from subjects who did not complete all experimental sessions, were included in the analyses. Similar mixed model analyses were performed on the primary pain outcome after adjustment for psychomimetic side effects to allow testing for marginal effects of the study drug on pain that were independent of subjective responses. The proportions of subjects with a 30% pain reduction rate were estimated with 95% score confidence intervals (CI) and compared between each of the active doses and placebo with Chi-square tests. A 5% significance level was used for all testing.

RESULTS

Go to:

RECRUITMENT AND WITHDRAWALS

Between December 2009 and March 2011, 59 patients were consented to enroll in the study. Twenty subjects did not receive study medication: 9 withdrew for various reasons and 11 were disqualified following a medical evaluation with subsequent disclosure of exclusionary criteria on a physical exam or laboratory finding. Thirty-nine subjects participated in 111 six-hour study sessions ([Figure 2](#) Consort Flow Chart). No participant dropped out due to an experimental intervention. Furthermore, there were no study related serious adverse events.



[Figure 2](#)
Consort Flow Chart

The demographic make-up of the 39 subjects is presented in [Table 1](#). The mean (standard deviation) age was 50 (11) years. The majority were males (28 of 39 subjects). Most patients had peripheral neuropathic pain; 6 met the IASP diagnostic criteria for complex regional pain syndrome (CRPS) type 1, [21, 32, 9](#) 2 had causalgia, 6 had diabetic neuropathy; 3 had idiopathic peripheral neuropathy, 3 had post-herpetic neuralgia, 3 had brachial plexopathy, and 3 had lumbosacral radiculopathy. Thirteen subjects had central neuropathic pain; 9 had pain related to spinal cord injury, 3 had involvement of the central neuroaxis by multiple sclerosis and 1 had thalamic pain.



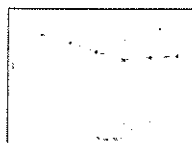
[Table 1](#)
Demographics and characteristics of patients (N = 39)

Median (range) time from the diagnosis of neuropathic pain to study enrollment was 9 years (6 months to 43 years). All patients had used cannabis before, as required by inclusion criteria. The median (range) time from most recent exposure to cannabis prior to the screening visit was 9.6 years (1 day to 45 years). Of the 39 patients who completed at least one study visit, 16 were current marijuana users and 23 were ex-users. The use of cannabis varied considerably between current marijuana users and ex-users. Current users and ex-users were similar in terms of the number of patients who smoked daily (6 current users versus 5 ex-users [when they had used]) and had used approximately once every two weeks (8 users versus 6 ex-users). On the other hand, there were only 2 users versus 12 ex-users who used cannabis rarely (once every four weeks or less).

PRIMARY EFFICACY MEASUREMENT: PAIN INTENSITY

The primary analysis compared patients' mean VAS pain intensities before and after consuming vaporized marijuana. The mean (SD) pain intensity at baseline was 58 (23) prior to administration of placebo, and 53 (23) and 57 (24) for the lower (1.29%) and medium (3.53%) doses of cannabis, respectively, on a 0–100 mm VAS, which were not significantly different ([Table 2](#)). A treatment effect was noted with cumulative dosing, with the magnitude of differences between the doses changing over time (treatment by time interaction: $p=0.0133$, [Table 2](#)). Although separation of the active agents from placebo is visible by time 60 min ([Figure 3](#)), significant separation occurred for the first time at 120 min ($p=0.0002$). Increasing analgesia was apparent after the second inhalation of vaporized

cannabis at time 180 min ($p < 0.0001$). A significant separation was still evident at times 240 min ($p = 0.0004$) and 300 min ($p = 0.0018$); the analgesic benefits remained stable at these timepoints ([Figure 3](#)). Tukey's HSD test revealed that both active doses of cannabis produced equianalgesic responses that were significantly better than placebo. Ten of the 38 (26%) subjects who were exposed to placebo had a 30% reduction in pain intensity (95% CI: 15–42%) as compared to 21 of the 37 (57%) exposed to the low dose (95% CI: 41–71%) and 22 of the 36 (61%) receiving the medium dose of cannabis (95% CI: 45–75%). These differences are statistically significant (placebo vs. low: $p = 0.0069$; placebo vs. medium: $p = 0.0023$). There was no significant difference between the two active dose groups' results ($p > 0.7$). The number needed to treat (NNT) to achieve 30% pain reduction was 3.2 for placebo vs. low dose, 2.9 for placebo vs. medium dose and 25 for medium vs. low dose.



[Figure 3](#)

VAS Pain Intensity

[Table 2](#)

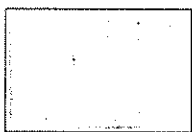
Significance levels for estimators of **Primary Outcome Pain Intensity and Related Measures** and dose effects at specified timepoints

We adjusted the pain intensity regression analysis for the type of pain (central pain (N=13) vs. peripheral pain (N=26)). Previous effects were maintained but the pain-type covariate was not significant ($p > 0.8$). Order of treatment administration (placebo, 1.29%, 3.53%) in this cross-over study was not a significant factor effecting the primary outcome variable ($p > 0.9$). Generous spacing of patient visits was designed to alleviate this potential concern.

When subjects “guessed” whether they had received placebo or active study medication, participants were correct 63% of the time for placebo, 61% of the time for 1.3% THC, and 89% of the time for 3.5% THC. The actual dose and the subject's opinion about the dose were significantly associated ($P < 0.0001$, Chi-square test). The mechanisms of the analgesic treatment effects were further evaluated by adding psychomimetic effects (e.g., feeling stoned, high, drunk, etc.) as a covariate to the mixed model regressions to determine if there is a reduction or elimination of the analgesic effects of cannabis at cannabinoid receptors in the experience of pain. The effect of the cannabis treatment maintained significance (all $p < 0.0001$) above and beyond any influence of the 15 different side effects.

SECONDARY OUTCOMES

Global Impression of Change In addition to VAS ratings for pain intensity, the degree of relief was monitored by a seven-point scale of patient global impression of change. As with the VAS ratings, cannabis provided a greater degree of relief than placebo at every time point ([Table 2](#)). Once again, the low and medium dose groups showed virtually identical results which were significantly beyond the placebo effect ([Figure 4](#)). Pain relief appears to be maximal after the second dosing at 180 minutes post-baseline, but the peak effect drops off 1–2 hours later (time²: $p = 0.0050$).



[Figure 4](#)

Global Impression of Change

Neuropathic Pain Scale Measurements from the Neuropathic Pain Scale (NPS) indicate that smoking cannabis positively affected several of the multidimensional pain descriptors associated with neuropathic pain ([Table 3](#)). Modeling of intensity, unpleasantness, and deep pain resulted in significant dose effects (all $p < 0.0001$), and these effects changed over time (all dose x time interactions $p < 0.03$), with significance reached starting one hour after the first set of dosing and continuing for the duration of observation (all $p < 0.045$). Taking all timepoints into

consideration, the Tukey HSD tests showed that for each of these pain outcomes, the two active drug doses had the same overall effects, which were significantly better than the placebo's effect. Sharpness, burning, and aching pain levels were significantly different among the doses (all $p < 0.001$). Both active doses had equal effects on sharpness which were both significantly stronger than the placebo's effect; both the medium dose and placebo were less effective for burning pain than the low dose but equal to each other; and the low dose significantly reduced aching more than the medium dose which, in turn, significantly reduced aching more than placebo. Levels relating to cold, sensitivity, and superficial pain show complex interactions and effects not easily interpretable in a general way. Itching presents no significant dose or dose x time interactions. With the exception of the baseline dose effect on sensitivity, for all four of these outcomes there were no significant dose effects when considering each timepoint separately, and Tukey HSD tests did not identify any significantly different overall dose effect (Table 3).

Table 3

Significance levels for estimators of Neuropathic Pain Scale measures and dose effects at specified timepoints.

Allodynia Levels of baseline allodynia were unexplainably significantly lower for the placebo treatment arm. Once the placebo treatment was administered, levels increased slightly or remained constant, while after being treated with cannabis, levels generally decreased over time. This differential response is reflected in the significant dose x time interaction term ($p = 0.0093$), but overall dose responses did not differ at any post-baseline times (See Table 2).

Heat Pain Threshold Mild to moderately painful heat stimuli delivered to the most painful area of the participant's body produced no significant change in response to treatment over time ($p > 0.05$) as well as no indication of treatment differences ($p > 0.05$) at any time point (data not shown).

Subjective and Psychoactive Effects Using several variables to explore side effects, the categorical main effect of treatment (low dose vs. medium dose vs. placebo) as well as treatment by time interaction effects were considered in the modeling (Table 4).

Table 4

Subjective and Psychoactive Effects

Subjective Effects In the medium dose group, the VAS for "any drug effect" and "good drug effect" reached pinnacles at 180 minutes at means of 46 and 48 out of 100 mm, respectively, after the second cumulative dose. There was a significant main effect of treatment ($p < 0.0001$ at all time points) with the low dose being below that of the medium dose and the placebo values being lower than both. An interaction with time was not apparent ($p > 0.05$) as the effects for all doses were similarly influenced by cumulative dosing after the initial administration and consistently receded slowly during the recovery phase when testing occurred at 240 and 300 minutes. Significant quadratic effects reflect the recovery after the second dosing (both $p < 0.02$).

Although there was an overall significant dose effect on a "bad drug effect" ($p = 0.0031$), this difference was not evident for the active groups when compared to placebo except at 240 minutes. ($p = 0.0025$). However, this effect was very minimal at a mean of 14 out of 100 mm and thus, unlikely to be clinically important.

Psychoactive Effects There was a significant effect of treatment ($p < 0.003$ at all time points) for the VAS "feeling high" with the low dose again being below that of the medium dose and the placebo values being lower than both. "Feeling stoned" was also scored greater for the medium dose group ($p < 0.004$ at all time points); again, the VAS "feeling stoned" revealed that the low dose was below that of the medium dose and the placebo values were equal or lower than the former. Considering the entire time course, both treatment groups differed from placebo but not from each other on "feeling drunk" ($p < 0.0001$), but significance occurred only at 180 minutes with administration of the second dose ($p = 0.0174$). However, this was of questionable clinical relevance as the mean VAS measures

varied between 6 and 13 out of 100 mm for the three groups at this time point (data not shown). The treatment groups differed from placebo on “feeling impaired” at 180 minutes ($p \leq 0.0001$) and 240 minutes ($p = 0.0027$). As with the other side-effects mentioned above, this was not meaningful clinically given the low values encountered.

Somewhat more suggestive of an agreeable effect was the sensation of “like the drug effect”, with means by timepoint that varied between 27 and 43 out of 100 mm for the two active dose groups (data not shown). There was a significant main effect of treatment ($p < 0.0001$), with significance reached at all time points, (all $p < 0.002$), once again with the low dose being below that of the medium dose and the placebo values being lower than both. While the main effect of treatment for “desire more of the drug” was significant ($p = 0.0312$), over the entire time course, the low dose scores were higher than those for placebo, but the medium dose results were no different from either of the other two. Significance was not seen at any single timepoint (data not shown).

“Feeling sedated” was endorsed during every dose session with a significant main effect of treatment ($p < 0.0001$) and at all time points ($p < 0.05$), but there was no interaction with time ($p > 0.05$). As with other side effects, the effect was highest with the medium dose, moderate with the low dose and lowest with the placebo (data not shown). But the clinical significance was fairly small as the highest mean sedation was 21 out of 100 mm (anchored by “not at all” at 0 and “extremely” at 100) one hour after the second vaporization session at 240 minutes with the medium dose (3.53% THC) and the highest mean sedation for the low dose (1.29%) and placebo were 17 at time 180 and 10 at time 60, respectively. Likewise, “feel confused” had an overall significant main effect of treatment ($p < 0.0001$) and time point-specific significance ($p < 0.05$) at times 120, 180 and 240 minutes. Again, the ordering of effect strength was as expected: $3.53 > 1.29 > 0$; however, this was not a clinically meaningful issue with a maximum level of 16 out of 100 mm among all doses at all timepoints (data not shown). Effects on “feeling nauseated” were also not likely to be clinically relevant as these values never exceeded 8 out of 100 mm. The main dose effect ($p = 0.0255$) revealed more nausea for the medium dose than for placebo, but in fact, active study medication only separated from placebo at one time point, 240 minutes (data not shown). “Feeling hunger” differed between doses ($p = 0.0008$) but showed a recovery effect by the end of the observation period (dose² $p < 0.0001$). Although Tukey’s HSD test shows the higher dose resulted in significantly more hungry feelings than for the medium dose and placebo which were equal to each other, no one time point showed a significant dose difference (data not shown). “Feeling anxiety” and “feeling down” were not prominently affected by cannabis in this study. All the VAS values at the six different time points did not differ significantly between groups ($p > 0.05$) and there were no significant main effects (data not shown).

For all of the above subjective and psychoactive side effects, no interaction with time occurred ($p > 0.05$) implying that whatever differences existed between and among the active and placebo cannabis doses, fluctuations of responses were in similar directions for all doses over the six time points.

Mood Mood was measured using VAS for feeling: sad vs. happy; anxious vs. relaxed; jittery vs. calm; bad vs. good; paranoid vs. self-assured; and fearful vs. unafraid. Any mood measure with significant dose effects over the entire time period either had no treatment effect at any specific timepoint or if there was one, the effect sizes (mean differences between timepoint-significant doses) were all less than 10 out of 100 mm for these locally developed mood scales and, thus, probably not important considerations (data not shown).

Neuropsychological Testing Results of the five neuropsychological tests are presented in [Table 5](#). The main effects of dose and time model the cognitive effects over time associated with the given dose of cannabis. The pre-treatment scores (time 0) had non-significant differences at time 0 ($p > 0.05$). This was predictable as participants did not have residual effects from previous treatments and had been instructed not to use marijuana for 30 days prior to study entry or during the intervals between study sessions.

Table 5

Significance levels for Neuropsychological measures and dose effects at specified timepoints

The Dominant Hand Grooved Pegboard Test demonstrated significant dose effect differences at 60 minutes ($p=0.0007$) and 240 minutes ($p=0.0023$ with participants taking a maximum of 10 seconds longer at these timepoints to complete this psychomotor task with the low dose cannabis than with the medium or placebo doses. Although the results do not appear to reflect a typical dose-response relationship, statistically significant differences occur only between placebo and each of the two active study doses according to the Tukey test. Significant dose effect differences were also seen on the Non-Dominant Hand Grooved Pegboard Test at two time points; 120 minutes ($p=0.0035$) and 180 minutes ($p=0.0325$), although in this case both low and medium doses of cannabis increased the completion time. Similar to that seen with the dominant hand, participants on cannabis took a maximum of 10 seconds longer than under placebo conditions.

The Digit Symbol Test also demonstrated significant dose effect differences at 60 minutes ($p=0.0415$) and 180 minutes ($p=0.0006$), corresponding to study drug administration). Participants were completed fewer items on both active study drug doses, compared to placebo. Interestingly, some recovery was seen one hour after each administration of medication at times 120 minutes and 240 minutes, in that there were no significant differences in performance.

The Hopkins Verbal Learning Test (HVLT) demonstrated significant dose effect differences at 60 minutes ($p=0.0256$), 180 minutes ($p<0.0001$) and 240 minutes ($p=0.0002$). The effects tracked with study drug administration and both active study drugs resulted in worse performance than placebo. Based on the Tukey HSD test, the medium dose performance was worse than the low dose, and the low dose was worse than placebo. The differences in the number of words recalled between sessions with active study medication and the placebo session was less than 2 out of a maximum number of 36 words (3 trials of 12 words each).

The HVLT - delayed recall demonstrated significant dose effect differences at 120 minutes ($p=0.0273$), 180 minutes ($p=0.0013$) and 240 minutes ($p=0.0060$). The medium dose resulted in fewer words retained than the other doses. Although the absolute differences were small (1–2 words out of a maximum of 12), Tukey's HSD test confirmed that the low dose did not differ from the placebo condition whereas the medium dose did separate from placebo not only at three time points, but after considering all times together as well.

As expected, cannabis produced a general cognitive decline, as indicated by the difference of scores between treatment groups on all tests over time. Most effect sizes were small, with the greatest dose effects seen on learning and memory, where effect sizes were in the small to medium range ([Table 6](#)).

Table 6

Effect Sizes of Neuropsychological Tests

DISCUSSION

Go to:

In the present study, we substituted low dose (1.29% THC) for the high dose (7% THC) previously utilized in our first study,⁵⁸ and compared this measured quantity to medium dose (3.53% THC) cannabis. In addition, we discarded smoking as a delivery technique in favor of vaporizing cannabis to reduce exposure to harmful pyrolytic compounds.^{25, 2} Both the low and medium doses proved to be salutary analgesics for the heterogeneous collection of neuropathic pain conditions studied. Both active study medications provided statistically significant 30% reductions in pain intensity when compared to placebo. The low dose vs. placebo NNT was 3.2; that for the medium dose vs. placebo was 2.9. Both values are similar in magnitude to previous HIV-associated painful sensory neuropathies studies evaluating smoked cannabis,^{1, 18} and are in the range of two commonly deployed anticonvulsants used to treat neuropathic pain (pregabalin, NNT = 3.9; gabapentin, NNT = 3.8).^{44, 3} Furthermore, as pointed out by Ellis et. al.,¹⁸ cannabis is superior to the results obtained for amitriptyline^{37, 51} and mexiletine.³⁷

Both the 1.29% and 3.53% vaporized THC study medications produced equal antinociception at every time point. Of note, the side-effect profiles of the low and medium doses were negligible with minimal psychomimetic effects,

as measured by locally-developed mood scales. Likewise, neuropsychological differences were nominally different between the two active doses and placebo. Participants on 3.53% cannabis had worse performance than those on 1.29% for learning and memory, while delayed memory was not different between 1.29% cannabis and placebo. Both doses had equivalent effects on the attention measure, with participants doing worse when on cannabis. Participants on 1.29% cannabis had a slightly worse performance than when on 3.53% cannabis during testing of psychomotor skills with the dominant hand. Both doses had equivalent effects on non-dominant hand performance, which in turn was better than testing under placebo conditions.

In general, the effect sizes on cognitive testing were consistent with the minimal doses of THC employed, with the greatest dose effects seen on learning and memory, where effect sizes were in the small to medium range and unlikely to have significant impact on daily functioning. In support of this viewpoint, evidence has accumulated that frequent recreational users become tolerant to many cannabis-related performance-impairing effects.^{35, 34, 30, 29, 33, 46} In recent comparisons of cannabis-related effects on cognitive performance of frequent and infrequent users, cannabis significantly reduced performance on tasks assessing perceptual motor control, motor inhibition, and divided attention among occasional cannabis users.^{48, 49} In contrast, among frequent users, cognitive performance was largely unaffected.

Separate appraisals using the Patient Global Impression of Change and the multidimensional NPS revealed that both active agents alleviated pain compared with placebo. Interestingly, evoked pain brought about by lightly touching skin using a foam paintbrush or through testing heat pain threshold with the commercially available Medoc TSA 2001 Peltier thermode (Medoc, Ramat Yishai, Israel) did not confirm an analgesic effect of cannabis. These results are similar to those in our first study⁵⁸ and that of another study involving the use of smoked cannabis in patients with human immunodeficiency virus (HIV)-associated sensory neuropathy.¹ The lack of an effect on the experimental heat pain threshold suggests that the analgesic effect of cannabis in treating acute pain would be less than optimal; this is consistent with the recommendation that cannabinoids are not suitable for post-operative pain.¹⁰

Undesirable consequences of smoking cannabis (i.e., psychological and/or cognitive effects) were identifiable but, consistent with a survey showing that these side-effects are acceptable to patients with chronic pain,⁵⁵ no participant withdrew because of tolerability issues. Subjects receiving active agent endorsed a “good drug effect” more than a “bad drug effect” and the latter was at issue only for the higher dose of cannabis. Similarly, feeling “high,” “stoned,” or “impaired” were less problematic for the lower strength cannabis. In general, side effects and changes in mood were relatively inconsequential, and again similar to a survey of cannabis users, many who reported daily treatment with cannabis for chronic pain to be a satisfactory experience.⁵⁰ A reasonable explanation would be that patients self titrate cannabis, balancing analgesia against negative side effects.

One limitation of this study was the inclusion of patients with complex regional pain syndrome type I. In the past, this disorder was classified among the more classical neuropathic pain conditions.⁴⁵ This situation changed when a proposal to redefine neuropathic pain was published, which resulted in an exclusion of CRPS Type I from being classified as a neuropathic pain.⁴⁵ As this protocol was devised at a time when it was standard practice to consider the diagnosis of CRPS Type I among neuropathic pain conditions, we included subjects with this diagnosis. When evaluated without the inclusion of the six subjects with this condition, the primary analysis involving VAS pain intensity did not substantially change (data not shown).

Another potential limitation in the present study is unmasking of blinding secondary to the psychoactive effects of cannabis. Few studies assess masking, but two cross-over trials tested maintenance of the blind by asking participants to “guess” assignment at different points of the study. Results suggest that participants, whether they are naïve or experienced cannabis users, are in the first week of a crossover trial no more likely than by chance to guess assignment.^{18, 56} In the current study, we asked subjects to “guess” which session was placebo and which involved active study medication. Participants were correct 63% of the time for placebo, 61% of the time for 1.3% THC, and 89% of the time for 3.5% THC. All subjects “guessed” correctly (active medication, not placebo) for the

3.5% THC if it was not given as the first dose, fewer guessed accurately if it was the first dose. Thus, unmasking of blinding is certainly of concern particularly with cross-over designs whereby the subject gains familiarity with different study medications. However, we do not believe that unblinding by psychoactive and subjective effects, which are very difficult to keep masked in any study, should obviate the conclusion that active study medication resulted in superior analgesia compared to placebo. The effect of the cannabis treatment on analgesia maintained significance above and beyond any influence of the 15 different side effects and therefore, an independent effect of study medication was evident.

Marijuana cigarettes are prepared from the leaves and flowering tops of the plant, and a typical marijuana cigarette contains 0.5–1 g of plant material.⁴³ The usual THC concentration varies between 10 and 40 mg, but concentrations >100 mg per cigarette have been detected. Several years ago, it was opined that there are too many variables in the published clinical trials with cannabis to use those studies as a basis for deriving doses.¹² In the present study, subjects consumed unknown amounts of cannabis as the residual vaporized cannabis was emptied into the atmosphere after they consumed 4–8 puffs. Thus, we are not able to comment upon the amount of cannabis consumed. A recent survey of the amount of medicinal cannabis used per week varied from three grams or less (40.1%) to seven or more grams (23.3%).⁵⁰ There being no information as to the concentration of cannabis consumed by those surveyed, it is not feasible to provide any insight whether or not those medicinal cannabis patients were or were not receiving low or high concentrations of THC.

Not being well standardized, medicinal cannabis has no mandatory labeling for concentration or purity.¹¹ Eventually, the production of cannabis may undergo quality control measures and standardization through regulation and licensure of producers. Otherwise, purity, concentration and product labeling will not be dependable and quantitative prescribing will not be feasible. Labeling standards may eventually include warning labels and restrictions,¹¹ similar to those on tobacco and alcohol products as well as dosages and timing directions. In this manner, the use of low doses could potentially be prescribed by physicians interested in helping patients use cannabis effectively while minimizing cognitive and psychological side-effects. Viewed with this in mind, the present study adds to a growing body of literature supporting the use of cannabis for the treatment of neuropathic pain. It provides additional evidence of the efficacy of vaporized cannabis as well as establishes low dose cannabis (1.29%) as having a favorable risk-benefit ratio.

PERSPECTIVE

The analgesia obtained from a low dose of THC (1.29%) is a meaningful outcome was clinically significant. In general, the effect sizes on cognitive testing were consistent with this minimal dose. As a result, one might not anticipate a significant impact on daily functioning.

Footnotes

Go to:

Disclosures

We acknowledge the University of California's Center for Medicinal Cannabis who provided critical support and guidance. They derived direct financial support from the California legislature as well as logistic and scientific support from several national stakeholders (i.e., Food and Drug Administration, Department of Health and Human Services, National Institute on Drug Abuse, and the Drug Enforcement Agency), whose assistance was invaluable. This material is the result of work that was supported by resources from the VA Northern California Health Care System, Sacramento, California. Although the UC Davis CTSC is located in the VA Northern California Health Care System facility, the contents found in this study do not represent the views of the Department of Veterans Affairs or the United States Government. This publication was made possible by Grant Number UL1 RR024146 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. Information on NCRR is available at <http://www.ncrr.nih.gov/>. Information on Re-

engineering the Clinical Research Enterprise can be obtained from <http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp>

The authors have no conflicts of interest to report.

Contributor Information

Go to:

Barth Wilsey, VA Northern California Health Care System, Sacramento, CA, Department of Physical Medicine and Rehabilitation, University of California, Davis Medical Center.

Thomas D. Marcotte, Department of Psychiatry, University of California, San Diego.

Reena Deutsch, Department of Psychiatry, University of California, San Diego.

Ben Gouaux, Department of Psychiatry, University of California, San Diego.

Staci Sakai, UC Davis CTSC Clinical Research Center.

Haylee Donaghe, UC Davis CTSC Clinical Research Center.

References

Go to:

1. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, Kelly ME, Rowbotham MC, Petersen KL. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology*. 2007;68:515–21. [[PubMed](#)]
2. Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL. Vaporization as a smokeless cannabis delivery system: a pilot study. *Clinical Pharmacology and Therapeutics*. 2007;82:572–8. [[PubMed](#)]
3. Backonja MM. Use of anticonvulsants for treatment of neuropathic pain. *Neurology*. 2002;59:S14–7. [[PubMed](#)]
4. Barnes MP. Sativex: clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain. *Expert Opinion on Pharmacotherapy*. 2006;7:607–15. [[PubMed](#)]
5. Beaver WT, Buring J, Goldstein A, Johnson K, Jones R. Ad Hoc Group of Experts, Report to the Director. National Institutes of Health; 1997. Workshop on the Medical Utility of Marijuana. p. 19 of 36.
6. Beglinger LJ, Gaydos B, Tangphao-Daniels O, Duff K, Kareken DA, Crawford J, Fastenau PS, Siemers ER. Practice effects and the use of alternate forms in serial neuropsychological testing. *Arch Clin Neuropsychol*. 2005;20:517–29. [[PubMed](#)]
7. Benedict R, Schretlen D, Groninger L, Brandt J. Hopkins Verbal Learning Test-Revised: Normative data and analysis of inter-form and test-retest reliability. *The Clinical Neuropsychologist*. 1998;12:43–55.
8. Benedict RH, Zgaljardic DJ. Practice effects during repeated administrations of memory tests with and without alternate forms. *Journal of Clinical and Experimental Neuropsychology*. 1998;20:339–52. [[PubMed](#)]
9. Bruehl S, Harden RN, Galer BS, Saltz S, Bertram M, Backonja M, Gayles R, Rudin N, Bhugra MK, Stanton-Hicks M. External validation of IASP diagnostic criteria for Complex Regional Pain Syndrome and proposed research diagnostic criteria. *International Association for the Study of Pain. Pain*. 1999;81:147–54. [[PubMed](#)]
10. Campbell FA, Tramer MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *BMJ (Clinical research ed)*. 2001;323:13–6. [[PMC free article](#)] [[PubMed](#)]
11. Cannabis and the Regulatory Void: Background Paper and Recommendations. California Medical Association, Marijuana Technical Advisory Committee; 2011.
12. Carter GT, Weydt P, Kyashna-Tocha M, Abrams DI. Medicinal cannabis: rational guidelines for dosing. *IDrugs*. 2004;7:464–70. [[PubMed](#)]

13. Chabrol H, Choquet M. Relationship between depressive symptoms, hopelessness and suicidal ideation among 1547 high school students. *L'Encephale*. 2008;35:443–7. [[PubMed](#)]
14. Chait LD, Corwin RL, Johanson CE. A cumulative dosing procedure for administering marijuana smoke to humans. *Pharmacology, Biochemistry, and Behavior*. 1988;29:553–7. [[PubMed](#)]
15. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. *Annual Review of Neuroscience*. 2009;32:1–32. [[PMC free article](#)] [[PubMed](#)]
16. Dworkin RH, Katz J, Gitlin MJ. Placebo response in clinical trials of depression and its implications for research on chronic neuropathic pain. *Neurology*. 2005;65:S7–19. [[PubMed](#)]
17. Dworkin RH, Turk DC, Walco GA, Wells CD, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpää ML, Baron R, Haanpää ML, Kent JL, Krane EJ, Lebel AA, Levy RM, Mackey SC, Mayer J, Miaskowski C, Raja SN, Rice AS, Schmader KE, Stacey B, Stanos S, Treede RD. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clinic Proceedings*. 2010;85:S3–14. [[PMC free article](#)] [[PubMed](#)]
18. Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, Bentley H, Atkinson JH. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology*. 2009;34:672–80. [[PMC free article](#)] [[PubMed](#)]
19. Farrar JT, Young JP, Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2010;94:149–58. [[PubMed](#)]
20. Federal Guidelines Announcement of the Department of Health And Human Services' Guidance On Procedures for The Provision of Marijuana for Medical Research Release. National Institutes of Health; May 21, 1999.
21. Galer BS, Bruehl S, Harden RN. IASP diagnostic criteria for complex regional pain syndrome: a preliminary empirical validation study. *International Association for the Study of Pain. The Clinical Journal of Pain*. 2000;14:48–54. [[PubMed](#)]
22. Galer BS, Jensen MP. Development and preliminary validation of a pain measure specific to neuropathic pain: the Neuropathic Pain Scale. *Neurology*. 2007;48:332–8. [[PubMed](#)]
23. Garrison CZ, Addy CL, Jackson KL, McKeown RE, Waller JL. A longitudinal study of suicidal ideation in young adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1991;30:597–603. [[PubMed](#)]
24. Garrison CZ, Jackson KL, Addy CL, McKeown RE, Waller JL. Suicidal behaviors in young adolescents. *American Journal of Epidemiology*. 1990;133:1005–14. [[PubMed](#)]
25. Gieringer D, St Laurent J, Goodrich S. Cannabis Vaporizer Combines Efficient Delivery of THC with Effective Suppression of Pyrolytic Compounds. *Journal of Cannabis Therapeutics*. 2004;4
26. Gieringer D. Marijuana research: Waterpipe study. *Multidisciplinary Association for Psychedelic Studies Bulletin*. 1996;6:59–66.
27. Greenwald MK, Stitzer ML. Antinociceptive, subjective and behavioral effects of smoked marijuana in humans. *Drug and Alcohol Dependence*. 2000;59:261–75. [[PubMed](#)]
28. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clinical Pharmacokinetics*. 2003;42:327–60. [[PubMed](#)]
29. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology*. 1999;141:385–94. [[PubMed](#)]

30. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology*. 1999;141:395–404. [[PubMed](#)]
31. Hansson P, Lindblom U. *Hyperalgesia and Allodynia*. New York, NY: Raven Press; 1992. Hyperalgesia assessed with quantitative sensory testing in patients with neurogenic pain: pp. 335–43.
32. Harden RN, Bruehl S, Galer BS, Saltz S, Bertram M, Backonja M, Gayles R, Rudin N, Bhugra MK, Stanton-Hicks M. Complex regional pain syndrome: are the IASP diagnostic criteria valid and sufficiently comprehensive? *Pain*. 1999;83:211–9. [[PubMed](#)]
33. Hart CL, van Gorp W, Haney M, Foltin RW, Fischman MW. Effects of acute smoked marijuana on complex cognitive performance. *Neuropsychopharmacology*. 2001;25:757–65. [[PubMed](#)]
34. Heaton R, Marcotte T. *Clinical Neuropsychological Tests and Assessment Techniques*. In: Boller F, Grafman J, editors. *Handbook of Neuropsychology*. Amsterdam: Elsevier Science; 2000.
35. Heishman SJ, Arasteh K, Stitzer ML. Comparative effects of alcohol and marijuana on mood, memory, and performance. *Pharmacology, Biochemistry, and Behavior*. 1997;58:93–101. [[PubMed](#)]
36. Khan A, Khan SR, Walens G, Kolts R, Giller EL. Frequency of positive studies among fixed and flexible dose antidepressant clinical trials: an analysis of the food and drug administration summary basis of approval reports. *Neuropsychopharmacology*. 2003;28:552–7. [[PubMed](#)]
37. Kiebertz K, Simpson D, Yiannoutsos C, Max MB, Hall CD, Ellis RJ, Marra CM, McKendall R, Singer E, Dal Pan GJ, Clifford DB, Tucker T, Cohen B. A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection. AIDS Clinical Trial Group 242 Protocol Team. *Neurology*. 2008;51:1682–8. [[PubMed](#)]
38. Klove H. *Clinical neuropsychology*. In: Forster FE, editor. *Medical Clinics of North America*. New York, NY: Saunders; 1963.
39. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *Journal of General Internal Medicine*. 2001;16:606–13. [[PMC free article](#)] [[PubMed](#)]
40. *Marijuana and Medicine. Assessing the Science Base*. Washington, D.C: National Academy Press; 1999.
41. McPartland JM, Pruitt PL. Medical marijuana and its use by the immunocompromised. *Altern Ther Health Med*. 1997;3:39–45. [[PubMed](#)]
42. Medical marijuana and the mind. More is known about the psychiatric risks than the benefits. *Harvard Mental Health Letter*. 2010;26(10):1–3. [[PubMed](#)]
43. Mello N, Mendelson J. Cocaine and Other Commonly Abused Drugs: Introduction, Cocaine, Marijuana and Cannabis Compounds, Methamphetamine, Lysergic Acid Diethylamide (LSD), Phencyclidine (PCP), Other Drugs of Abuse, Polydrug Abuse. In: Fauci A, Braunwald E, Kasper D, Hauser S, Longo D, Jameson J, Loscalzo J, editors. *Harrison's Principles of Internal Medicine*. 18. New York City, NY: The McGraw-Hill Companies, Inc; 2012.
44. Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. *Cochrane database of systematic reviews (Online)* 2010:CD007076. [[PMC free article](#)] [[PubMed](#)]
45. Naleschinski D, Baron R. Complex regional pain syndrome type I: neuropathic or not? *Current Pain and Headache Reports*. 2010;14:196–202. [[PubMed](#)]
46. Nordstrom BR, Hart CL. Assessing cognitive functioning in cannabis users: cannabis use history an important consideration. *Neuropsychopharmacology*. 2006;31:2798–9. author reply 800–1. [[PubMed](#)]

47. Rahn EJ, Hohmann AG. Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside. *Neurotherapeutics*. 2009;6:713–37. [[PMC free article](#)] [[PubMed](#)]
48. Ramaekers JG, Kauert G, Theunissen EL, Toennes SW, Moeller MR. Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. *Journal of Psychopharmacology (Oxford, England)* 2011;23:266–77. [[PubMed](#)]
49. Ramaekers JG, Theunissen EL, de Brouwer M, Toennes SW, Moeller MR, Kauert G. Tolerance and cross-tolerance to neurocognitive effects of THC and alcohol in heavy cannabis users. *Psychopharmacology*. 2011;214:391–401. [[PMC free article](#)] [[PubMed](#)]
50. Reinerman C, Nunberg H, Lanthier F, Heddleston T. Who are medical marijuana patients? Population characteristics from nine California assessment clinics. *Journal of Psychoactive Drugs*. 2011;43:128–35. [[PubMed](#)]
51. Shlay JC, Chaloner K, Max MB, Flaws B, Reichelderfer P, Wentworth D, Hillman S, Brizz B, Cohn DL. Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: a randomized controlled trial. Terry Bein Community Programs for Clinical Research on AIDS. *Jama*. 1998;280:1590–5. [[PubMed](#)]
52. Vranken JH, Dijkgraaf MG, Kruis MR, van der Vegt MH, Hollmann MW, Heesen M. Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain*. 2010;136:150–7. [[PubMed](#)]
53. Wallace M, Schulteis G, Atkinson JH, Wolfson T, Lazzaretto D, Bentley H, Gouaux B, Abramson I. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. *Anesthesiology*. 2007;107:785–96. [[PubMed](#)]
54. Ward AS, Comer SD, Haney M, Foltin RW, Fischman MW. The effects of a monetary alternative on marijuana self-administration. *Behavioural Pharmacology*. 1997;8:275–86. [[PubMed](#)]
55. Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ. Cannabis use for chronic non-cancer pain: results of a prospective survey. *Pain*. 2003;102:211–6. [[PubMed](#)]
56. Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, Gamsa A, Bennett GJ, Collet JP. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *CMAJ*. 2010;182:E694–701. [[PMC free article](#)] [[PubMed](#)]
57. Wechsler D. Administration and Scoring Manual. 3. San Antonio, TX: The Psychological Corporation, Harcourt Brace & Co; 1997. Wechsler Adult Intelligence Scale.
58. Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, Fishman S. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain*. 2008;9:506–21. [[PMC free article](#)] [[PubMed](#)]



Journal

International Review of Psychiatry >

Volume 21, 2009 - Issue 2

249

Views

0

CrossRef citations

9

Altmetric

Research article

Interaction of the cannabinoid and opioid systems in the modulation of nociception


Sandra P. Welch , PhD

Page 143-151 | Published online: 11 Jul 2009

 Download citation  <http://dx.doi.org/10.1080/09540260902782794>

Select Language ▼

Translator disclaimer

 Full Article Figures & data References Metrics Reprints & Permissions PDF

Abstract

Cannabinoids and opioids produce antinociceptive synergy. Cannabinoids such as Δ -9-tetrahydrocannabinol (THC) release endogenous opioids and endocannabinoids such as anandamide (AEA) also alter endogenous opioid tone. Opioids and cannabinoids bind distinct receptors that co-localize in areas of the brain involved with the processing of pain signals. Therefore, it is logical to look at interactions of these two systems in the modulation of both acute and chronic pain. These drugs are often co-abused. In addition, the lack of continued effectiveness of opioids due to tolerance development limits the use of such drugs. The cost to society and patients in terms of dollars, loss of productivity, as well as quality of life, is staggering. This review summarizes the data indicating that with cannabinoid/opioid therapy one may be able to produce long-term antinociceptive effects at doses devoid of substantial side effects, while preventing the neuronal biochemical changes that accompany tolerance. The clinical utility of modulators of the endocannabinoid system as a potential mimic for THC-like drugs in analgesia and tolerance-sparing effects of opioids is a critical future direction also addressed in the review.



People also read

Review article

Cannabinoids in pain management: CB1, CB2 and non-classic receptor ligands

Mellar P Davis

Expert Opinion on Investigational Drugs

11 Jul 2014