MMP-063

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

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

INSTRUCTIONS

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

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

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

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

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

---

1. Petitioner Information

Name: [redacted]

Street Address: [redacted]

City, State, Zip Code: [redacted]

Telephone Number: [redacted]

Email Address: [redacted]

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

Opioid Use Disorder

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

☒ Yes, in Person

☐ Yes, by Telephone

☐ No

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
SEP 7 2016
OFFICE OF THE CHIEF OF STAFF

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

Note: Endnote reference numbers appear throughout the text of this petition in [brackets] and endnote references are attached to this petition as "Exhibit A".

Opioid Abuse Disorder is widely accepted in the medical community as a diagnosable condition for which the FDA has approved medical treatment. Both the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), published by the American Psychiatric Association, and the 2016 ICD-10, the diagnostic manual published by the World Health Organization, define and categorize criteria and medical coding for Opioid Dependence and abuse. While the wording used to describe this condition is referred to in various ways by health organizations, it is clearly generally accepted by the medical community and other experts as a valid, existing medical condition.

Previously, the DSM-IV identified both Opioid Dependency and Opioid Addiction as separate conditions, but the most current (2013) version, DSM-V, uses the broader definition of "Opioid Use Disorder."[1] The DSM-V lists "Opioid Intoxication," "Opioid Withdrawal," and "Unspecified Opioid-Related Disorder" as related conditions.[2]

The 2016 ICD-10 also recognizes "Opiate Related Disorders" including "Opioid Abuse," "Opioid Dependence," and "Opioid Use - Unspecified" with various subcategories for diagnosis including "Opioid Dependence with Withdrawal."[3]

According to the World Health Organization,
Opioids are psychoactive substances derived from the opium poppy, or their synthetic analogues. Examples are morphine and heroin. Worldwide, an estimated 69,000 people die from opioid overdose each year. In the United States of America alone in 2010, there were an estimated 16,651 deaths due to overdose on prescription opioids and 3,036 due to overdose on heroin. There are an estimated 15 million people who suffer from opioid dependence (i.e. an addiction to opioids). The majority of people dependent on opioids use illicitly cultivated and manufactured heroin, but an increasing proportion use prescription opioids. Due to their pharmacological effects, opioids in high doses can cause respiratory depression and death.[4]

Residents of New Jersey are painfully aware of the "Opiate Epidemic" that has affected our state for years, and continues to impact the lives of many New Jersey families. There are at least 128,000 heroin addicts currently living in New Jersey, and there have been over 5,000 opiate overdose deaths in New Jersey in the past decade.[5] This health crisis has been the focus of myriad state government efforts, and Governor Chris Christie has been vocal about addressing this issue.[6] The state has invested millions of dollars in attempts to decrease opioid addiction, yet real progress still remains to be seen.[7]

For many, prescription opioid use leads to abuse, and whether an individual abuses prescription medications or seeks street drugs to feed their addiction, the results can be the same: debilitating medical and psychological problems associated with drug use, and overdose death. Addiction to opioids transcends race, sex, and social strata. It affects youth, parents, students, professionals, blue collar workers, and families. No family is immune.

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.**

One or more treatments of Opioid Use Disorder can cause the patient's suffering, in addition to suffering caused by the condition itself.

According to the Office of National Drug Control Policy (ONDCP), there are 3 FDA-approved drugs used to treat Opioid Use Disorder: methadone, naltrexone, and buprenorphine (suboxone).[8] While these drugs can be effective for some patients, they can also cause suffering in the form of serious adverse side effects, drug interactions, and death, as described in question 7 below. All three FDA-approved treatments are generally accepted by the medical community and other experts as valid treatments for Opiate Use Disorder across the US and in New Jersey, evidenced as follows:

A simple google search reveals the prevalence of Opioid Addiction and Dependency medical treatment centers in the state of New Jersey. The Opiate Addiction & Treatment Resource (OATR) is a website based in North America which aims to provide accurate, up-to-date information about opioids, addiction and dependence, and available treatment options to the public.[9]

OATR's Suboxone Treatment Registry for New Jersey lists 512 medical practices, many of which employ numerous physicians, who prescribe Suboxone in our state.[10]

The OATR also lists 33 methadone clinics in New Jersey.

According to the ONDCP, medical treatment for Opioid Use Disorder is most effective when combined with support services: Because those who abuse opioids often abuse other substances as well, and because addiction is a chronic relapsing condition, a comprehensive approach to treatment should include assessment, diagnosis, treatment planning, psychosocial treatment,

medication monitoring to promote adherence, and a host of social services to support patients as they build new drug-free lives and enter long-term recovery. Services may need to continue indefinitely, as relapse can be a lifelong risk.[11]

Unfortunately, in New Jersey, despite the number of physicians prescribing medical treatments for Opioid Use Disorder, access to these support systems is often inaccessible as described below in Question 8.

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.**

Both Opioid Use Disorder itself as well as the conventional medical treatments can cause severe suffering, and can significantly impair the patient's ability to carry on activities of daily living.

SUFFERING RELATED TO THE CONDITION ITSELF
The DSM-V diagnostic criteria for Opioid Use Disorder describes the "Functional Consequences" of this condition as follows:[12]

- Lack of mucous membrane secretions, causing dry mouth and nose.
- Slowing of gastrointestinal activity and a decrease in gut motility can produce severe constipation.
- Visual acuity may be impaired as a result of pupillary constriction with acute administration.
- In individuals who inject opioids, sclerosed veins ("tracks") and puncture marks on the lower portions of the upper extremities are common. Veins sometimes become so severely sclerosed that peripheral edema develops, and individuals switch to injecting in veins in the legs, neck, or groin. When these veins become unusable, individuals often inject directly into their subcutaneous tissue ("skin-popping"), resulting in cellulitis, abscesses, and circular appearing scars from healed skin lesions.
- Tetanus and Clostridium botulinum infections are relatively rare but extremely serious consequences of injecting opioids, especially with contaminated needles.
- Infections may also occur in other organs and include bacterial endocarditis, hepatitis, and HIV infection. Hepatitis C infections, for example, may occur in up to 90% of persons who inject opioids.
- The prevalence of HIV infection can be high among individuals who inject drugs, a large proportion of whom are individuals with opioid use disorder. HIV infection rates have been reported to be as high as 60% among heroin users with opioid use disorder in some areas of the United States or the Russian Federation. However, the incidence may also be 10% or less in other areas, especially those where access to clean injection material and paraphernalia is facilitated
- Tuberculosis is a particularly serious problem among individuals who use drugs intravenously, especially those who are dependent on heroin; infection is usually asymptomatic and evident only by the presence of a positive tuberculin skin test. However, many cases of active tuberculosis have been found, especially among those who are infected with HIV. These individuals often have a newly acquired infection but also are likely to experience reactivation of a prior infection because of impaired immune function. Individuals who sniff heroin or other opioids into the nose ("snorting") often develop irritation of the nasal mucosa, sometimes accompanied by perforation of the nasal septum.
- Difficulties in sexual functioning are common. Males often experience erectile dysfunction during intoxication or chronic use. Females commonly have disturbances of reproductive function and irregular menses.

In relation to infections such as cellulitis, hepatitis, HIV infection, tuberculosis, and endocarditis, opioid use disorder is associated with a mortality rate as high as 1.5%–2% per year. Death most often results from overdose, accidents, injuries, AIDS, or other general medical complications. Accidents and injuries due to violence that is associated with buying or selling drugs are common. In some areas, violence accounts for more opioid-related deaths than overdose or HIV infection. Physiological dependence on opioids may occur in about half of the infants born to females with opioid use disorder; this can produce a severe withdrawal syndrome requiring medical treatment.[13]

According to the American Psychiatric Association, opioid intoxication and opioid withdrawal are classified as individual disorders in the DSM-V, because clinical intervention can be necessary to prevent overdose or dangerous medical side-effects.[14]

Withdrawal symptoms that are less serious but can cause significant suffering include the following:[15]

- Dysphoric mood
- Nausea or vomiting
- Muscle aches
- Lacrimation or rhinorrhea
- Pupillary dilation, piloerection, or sweating
- Diarrhea
- Yawning
- Fever
- Insomnia

The DSM-V notes that the signs or symptoms above "cause clinically significant distress or impairment in social, occupational, or other important areas of functioning."[16]

A new research study published August 2016 in the Addiction Journal is entitled "Yes, people can die from opiate withdrawal." The article (full text is attached to this petition as "Exhibit B") states that "It is generally thought that opiate withdrawal is unpleasant but not life-threatening, but death can, and does, occur. The complications of withdrawal are often underestimated and monitored inadequately. It is essential that clinical management programmes are put in place routinely in jails, prisons and other facilities where withdrawal is likely in order to avert these avoidable deaths."[17]

Most deaths and serious emergent medical complications in individuals with Opioid Use Disorder are due to accidental or intentional overdose.

The DSM-V states that:
Similar to the risk generally observed for all substance use disorders, opioid use disorder is associated with a heightened risk for suicide attempts and completed suicides. Particularly notable are both accidental and deliberate opioid overdoses. Some suicide risk factors overlap with risk factors for an opioid use disorder. In addition, repeated opioid intoxication or withdrawal may be associated with severe depressions that, although temporary, can be intense enough to lead to suicide attempts and completed suicides. Available data suggest that nonfatal accidental opioid overdose (which is common) and attempted suicide are distinct clinically significant problems that should not be mistaken for each other.[18]

The World Health Organization describes Opioid Overdose as follows:
Due to their effect on the part of the brain which regulates breathing, opioids in high doses can cause respiratory depression and death. An opioid overdose can be identified by a combination of three signs and symptoms referred to as the "opioid overdose triad". The symptoms of the triad are:

- pinpoint pupils
- unconsciousness
- respiratory depression.

Combining opioids with alcohol and sedative medication increases the risk of respiratory depression and death, and combinations of opioids, alcohol and sedatives are often present in fatal drug overdoses.
Because of their capacity to cause respiratory depression, opioids are responsible for a high proportion of fatal drug overdoses around the world. The number of opioid overdoses has increased in recent years, in part due to the increased use of opioids in the management of chronic non-cancer pain. In the United States of America alone in 2010, there were an estimated 16,651 deaths due to overdose on prescription opioids and 3,036 due to overdose on heroin.[19]

SUFFERING RELATED TO THE TREATMENTS OF OPIOID USE DISORDER
The 3 FDA-approved drugs used to treat Opioid Use Disorder - methadone, naltrexone, and buprenorphine (suboxone) - can cause suffering in the form of serious adverse side effects, drug interactions, and death. We provide here samples of FDA statements regarding the potential dangers of each of these drugs:

Methadone:
FDA ALERT [11/2006]: Death, Narcotic Overdose, and Serious Cardiac Arrhythmias
FDA has reviewed reports of death and life-threatening adverse events such as death, respiratory depression, and serious cardiac arrhythmias in patients receiving methadone. Fatalities have been reported in patients who were switched from chronic, high-dose treatment with other opioids to methadone and in patients initiating treatment with methadone. These adverse events may have resulted from unintentional methadone overdoses, drug interactions, and/or methadone's cardiac toxicities (QT prolongation and Torsades de Pointes). Some of the unintentional overdoses were due to prescribers not being aware of methadone's pharmacokinetics and potential adverse effects.[20]

Common side effects may include:[21]

- Constipation
- Nausea
- Sleepiness
- Vomiting
- Tiredness
- Headache
- Dizziness
- Abdominal pain

Naltrexone:
Side effects may include: [22]

- Vulnerability to Opioid Overdose
- Hepatotoxicity (significant liver dysfunction)
- Depression and Suicidality
- Serious allergic reactions
- Nausea
- Sleepiness
- Headache
- Dizziness

- Vomiting
- Decreased appetite
- Painful joints
- Muscle cramps
- Cold symptoms
- Trouble sleeping
- Toothache

Buprenorphine (Suboxone):
Serious side effects:[23]
- Respiratory problems
- Sleepiness, dizziness, and problems with coordination
- Dependency or abuse
- Liver problems
- Allergic reaction
- Opioid withdrawal
- Decrease in blood pressure

Common side effects:
- Nausea
- Vomiting
- Drug withdrawal syndrome
- Headache
- Sweating
- Numb mouth
- Constipation
- Swollen and/or painful tongue
- Intoxication
- Disturbance in attention
- Irregular heartbeat (palpitations)
- Decrease in sleep (insomnia)
- Blurred vision
- Back pain
- Fainting
- Dizziness
- Sleepiness

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.**

Despite the prevalence of treatment centers in New Jersey, many patients with Opioid Use Disorder are unable to access continuing treatment, especially the inpatient detoxification and rehabilitation centers that can be critical to their continued sobriety.

Sunrise House, an inpatient rehabilitation center in Sussex County, is part of the American Addiction Centers (AAC) family of addiction centers throughout the US. Their experts report the following in respect to the lack of access to services in New Jersey:

New Jersey has not been immune to the opioid epidemic that has devastated middleclass and suburban communities across the country. At least 33 percent of those struggling with addiction in the Garden State are denied access to treatment resources that could save their lives. In 2009, treatment facilities had to turn away at least 30,000 adults and 15,000 adolescents due to a shortage of resources, as well as high costs and insurance obstacles.

Those who do receive treatment rotate through emergency rooms and rehab programs, unable to receive a full course of treatment due to insurance limitations, not having enough money on hand, or being turned out because of relapse. NorthJersey.com writes that even the best insurance plans do not cover impatient stays for more than 14 days. Families are left with the choice of paying upwards of tens of thousands of dollars themselves (on treatment, but also travel expenses) or pulling their loved one out of treatment.

The National Council on Alcoholism and Drug Dependence attributed the treatment shortfall in New Jersey to insufficient funding and insufficient beds. This comes at a time when the abuse of heroin and prescription painkillers is at record highs. From 2008 to 2013, the number of behavioral health concerns (as a result of substance abuse) that have led to emergency room visits has doubled, and hundreds of people have died as a result of overdoses.[24]

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.]*

Although Opioid Use Disorder is not specifically recognized as a qualifying condition for medical cannabis in any US medical cannabis states, the medical community is becoming increasingly aware of the correlation between medical cannabis use and lower rates of opiate use and opiate overdose death rates in medical marijuana states, as referenced in studies #1 and #2 below. In effect, when physicians recommend medical cannabis for other qualifying medical conditions in which the prescription of opioids is part of the medically accepted treatment, they are witnessing their patients using lower dosages of opiate medications or discontinuing opiate use completely. Therefore, it is our belief that if Opiate Use Disorder itself is recognized as a qualifying condition for the New Jersey Medical Marijuana Program, the opiate epidemic in New Jersey could be effectively addressed through this process of harm reduction for users of both prescription and illicit opiates.

The very existence of New Jersey's Medical Marijuana Program supports the belief of physicians that medical cannabis is a viable alternative to prescription opiates, which in turn can significantly lower the rate of opiate prescriptions and the use of opiates in our communities.

There have been numerous articles published in peer-reviewed scientific journals that supports a finding that the use of marijuana can alleviate suffering caused by Opioid Use Disorder, and that the use of marijuana can help decrease or even eliminate patients' opiate use. Below is a list of articles from peer-reviewed scientific journals along with a brief excerpt from abstracts, conclusions, or results. Full text of the articles referenced is attached to this application as "Attachments 1-7". There are literally dozens more peer-reviewed journal articles that could be used to support this petition; we are happy to provide more literature upon request.

SUMMARY AND INDEX OF ATTACHED MEDICAL JOURNAL ARTICLES (Attachments 1-7):

1. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. Boehnke, Kevin F. et al. The Journal of Pain, Volume 17 , Issue 6 , 739 - 744
Highlights:

- Cannabis use was associated with 64% lower opioid use in patients with chronic pain.
- Cannabis use was associated with better quality of life in patients with chronic pain.
- Cannabis use was associated with fewer medication side effects and medications used.

Abstract: Opioids are commonly used to treat patients with chronic pain (CP), though there is little evidence that they are effective for long term CP treatment. Previous studies reported strong associations between passage of medical cannabis laws and decrease in opioid overdose statewide. Our aim was to examine whether using medical cannabis for CP changed individual patterns of opioid use. Using an online questionnaire, we conducted a cross-sectional retrospective survey of 244 medical cannabis patients with CP who patronized a medical cannabis dispensary in Michigan between November 2013 and February 2015. Data collected included demographic information, changes in opioid use, quality of life, medication classes used, and medication side effects before and after initiation of cannabis usage. Among study participants, medical cannabis use was associated with a 64% decrease in opioid use (n = 118), decreased number and side effects of medications, and an improved quality of life (45%). This study suggests that many CP patients are essentially substituting medical cannabis for opioids and other medications for CP treatment, and finding the benefit and side effect profile of cannabis to be greater than these other classes of medications. More research is needed to validate this finding.
Source:
Abstract – http://www.jpain.org/article/S1526-5900(16)00567-8/abstract
Full Text – http://www.jpain.org/article/S1526-5900(16)00567-8/fulltext
References – http://www.jpain.org/article/S1526-5900(16)00567-8/references

2. Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010 Bachhuber MA, Saloner B, Cunningham CO, Barry CL. JAMA Intern Med. 2014;174(10):1668-1673. doi:10.1001/jamainternmed.2014.4005.
Results: Three states (California, Oregon, and Washington) had medical cannabis laws effective prior to 1999. Ten states (Alaska, Colorado, Hawaii, Maine, Michigan, Montana, Nevada, New Mexico, Rhode Island, and Vermont) enacted medical cannabis laws between 1999 and 2010. States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate (95% CI, −37.5% to −9.5%; P = .003) compared with states without medical cannabis laws. Examination of the association between medical cannabis laws and opioid analgesic overdose mortality in each year after implementation of the law showed that such laws were associated with a lower rate of overdose mortality that generally strengthened over time: year 1 (−19.9%; 95% CI, −30.6% to −7.7%; P = .002), year 2 (−25.2%; 95% CI, −40.6% to −5.9%; P = .01), year 3 (−23.6%; 95% CI, −41.1% to −1.0%; P = .04), year 4 (−20.2%; 95% CI, −33.6% to −4.0%; P = .02), year 5 (−33.7%; 95% CI, −50.9% to −10.4%; P = .008), and year 6 (−33.3%; 95% CI, −44.7% to −19.6%; P < .001). In secondary analyses, the findings remained similar.
Source: http://archinte.jamanetwork.com/article.aspx?articleid=1898878#Abstract

3. Cannabis as an Adjunct to or Substitute for Opiates in the Treatment of Chronic Pain Lucas, Philippe. Journal of Psychoactive Drugs 08 Jun 2012; 44(2):125-133

Abstract: There is a growing body of evidence to support the use of medical cannabis as an adjunct to or substitute for prescription opiates in the treatment of chronic pain. When used in conjunction with opiates, cannabinoids lead to a greater cumulative relief of pain, resulting in a reduction in the use of opiates (and associated side-effects) by patients in a clinical setting. Additionally, cannabinoids can prevent the development of tolerance to and withdrawal from opiates, and can even rekindle opiate analgesia after a prior dosage has become ineffective. Novel research suggests that cannabis may be useful in the treatment of problematic substance use. These findings suggest that increasing safe access to medical cannabis may reduce the personal and social harms associated with addiction, particularly in relation to the growing problematic use of pharmaceutical opiates. Despite a lack of regulatory oversight by federal governments in North America, community-based medical cannabis dispensaries have proven successful at supplying patients with a safe source of cannabis within an environment conducive to healing, and may be reducing the problematic use of pharmaceutical opiates and other potentially harmful substances in their communities.
Source:
https://www.researchgate.net/publication/230652616_Cannabis_as_an_Adjunct_to_or_Substitute_for_Opiates_in_the_Treatment_of_Chronic_Pain

4. Is Cannabis use associated with less opioid use among people who inject drugs? Kral AH, Wenger L, Novak SP, Chu D, Corsi KF, Coffa D, Shapiro B, Blumenthal RN. Drug Alcohol Depend. 2015 Aug 1;153:236-41. doi: 10.1016/j.drugalcdep.2015.05.014. Epub 2015 May 22.

Conclusions: There is a statistical association between recent cannabis use and lower frequency of nonmedical opioid use among people who inject drugs (PWID). This may suggest that PWID use cannabis to reduce their pain and/or nonmedical use of opioids. However, more research, including prospective longitudinal studies, is needed to determine the validity of these findings.
Source: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4509857/

5. Cannabis as a substitute for alcohol and other drugs. Reiman A. Harm Reduction Journal. 2009;6:35. doi:10.1186/1477-7517-6-35.
Conclusion: The substitution of one psychoactive substance for another with the goal of reducing negative outcomes can be included within the framework of harm reduction. Medical cannabis patients have been engaging in substitution by using cannabis as an alternative to alcohol, prescription and illicit drugs.
Source: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2795734/

6. Cannabis in palliative medicine: Improving care and reducing opioid-related morbidity. Carter GT, Flanagan AM, Earleywine M, Abrams DI, Aggarwal SK, Grinspoon L. American Journal of Hospice and Palliative Medicine. 2011 Aug;28(5):297-303. doi: 10.1177/1049909111402318. Epub 2011 Mar 28.
Abstract: Unlike hospice, long-term drug safety is an important issue in palliative medicine. Opioids may produce significant morbidity. Cannabis is a safer alternative with broad applicability for palliative care. Yet the Drug Enforcement Agency (DEA) classifies cannabis as Schedule I (dangerous, without medical uses). Dronabinol, a Schedule III prescription drug, is 100% tetrahydrocannabinol (THC), the most psychoactive ingredient in cannabis. Cannabis contains 20% THC or less but has other therapeutic cannabinoids, all working together to produce therapeutic effects. As palliative medicine grows, so does the need to reclassify cannabis. This article provides an evidence-based overview and comparison of cannabis and opioids. Using this foundation, an argument is made for reclassifying cannabis in the context of improving palliative care and reducing opioid-related morbidity.
Source:
https://www.researchgate.net/publication/50891411_Cannabis_in_Palliative_Medicine_Improving_Care_and_Reducing_Opioid-Related_Morbidity

7. Medical Marijuana Laws Reduce Prescription Medication Use in Medicare Part D. Bradford AC, Bradford WD. Health Affairs 35, no.7 (2016):1230-1236 doi: 10.1377/hlthaff.2015.1661
Abstract: Legalization of medical marijuana has been one of the most controversial areas of state policy change over the past twenty years. However, little is known about whether medical marijuana is being used clinically to any significant degree. Using data on all prescriptions filled by Medicare Part D enrollees from 2010 to 2013, we found that the use of prescription drugs for which marijuana could serve as a clinical alternative fell significantly, once a medical marijuana law was implemented. National overall reductions in Medicare program and enrollee spending when states implemented medical marijuana laws were estimated to be $165.2 million per year in 2013. The availability of medical marijuana has a significant effect on prescribing patterns and spending in Medicare Part D.
Source: http://www.ouramazingworld.org/uploads/4/3/8/6/43860587/bradford2016.pdf

PATIENT TESTIMONY
In addition to attaching articles published in peer-reviewed scientific journals, we wish to submit the personal testimonies of card-holding Medical Marijuana patients living in New Jersey. These patients are already members NJ MMP due to their qualifying diagnoses, and wish to speak on their personal experiences with decreasing or eliminating the opiates prescribed to treat their conditions, through the use of medical cannabis.

"Marijuana helps many ailments, and diseases, but I can't think of a better use for marijuana than to be used for opiate addiction. Speaking from personal experience, I used to be an addict, and to be clear, there is only one thing that saved me from death. It

was not AA, it was not pharmaceuticals, all of which are used regularly to help addicts, but it was marijuana that pulled me up from the depths of an injected heroin habit, to COMPLETE and total sobriety. I have a life worth living now. And I credit it all to rigorous cannabis use. We need every tool available to fight this epidemic, and in my opinion, the most beneficial treatment is out of reach to so many. Please consider."
-Submitted by [redacted], NJ MMP patient

"Before cannabis I was taking 160 mg of oxycontin a day and up to 40 mgs of oxycodone immediate release for breakthrough pain, a day. I have been a chronic pain patient for most of my life. Narcotics have all but killed me. Cannabis has allowed me to substantially reduce the amount of narcotic pain medication I need. Cannabis is helpful for treating pain allowing the patient to reduce toxic meds, which eventually can result in no opiate use at all.
I know many chronic pain patients who have been able to come completely off opiates using cannabis, successfully staying off opiates and using cannabis as a non-toxic natural pain reliever and sleep aid.
Today I take 110 mg of oxycontin a day and up to 15 mg for breakthrough pain. I look forward to eventually eliminating narcotic meds and using cannabis to treat my pain, spasms and neurological issues."
-Submitted by [redacted], NJ MMP patient

"I am a medical cannabis patient. I use it for intractable musculoskeletal spasticity. I suffer from chronic pain and I have fibromyalgia. I've been using prescription pain killers (and I say killers literally) for 20 years. In 1996 I got cervical cancer had a hysterectomy and my story began. I started using lortab, then percocet, then OxyContin. I was definitely dependent. Don't think I was really even in pain any more. In 2008 I had to have back surgery. Because I was on 90 mg of Oxys they gave me fentanyl. This was crazy as I look back! I got up to 140 mg a day of Oxys before I said that's it. I was introduced to the MMP in December 2015 and today August 2016, I'm down to 20 mg of Oxys. My injured back is worse now according to MRI and I'm going off opioids! All I do is use cannabis instead. Thank god for this awesome very helpful plant."
-Submitted by [redacted], NJ MMP patient

"90 milligrams Roxi every 3 hours to ZERO by using cannabis."
-Submitted by [redacted], NJ MMP patient

"I am completely off of 12 years of oxy, valium and countless antidepressants that they "tried" on me. Cannabis is the only pain med I take, not even otc, ibuprofen etc."
-Submitted by [redacted], NJ MMP patient

"My qualifier is muscular spasticity. I was on (opiates) for 15 years, due to several spinal surgeries. 300 mgs of morphine a day plus a boatload of other drugs. My body was dependent, but not my mind. I went off them all cold turkey with the help of Cannabis, and am now proud to say 1 year later, I am off ALL opiates."
-Submitted by [redacted], NJ MMP patient

"I was using fentanyl patches, 75mcg every 2 days and was able to cut it out altogether using cannabis...I know that cannabis won't kill me like the patches could, damn opiates."
-Submitted by [redacted], NJ MMP Patient

"I've drastically reduced my intake of tramadol. It's not considered an opiate but it's still a pain medication."
-Submitted by [redacted], NJ MMP patient

Additional testimony from members of the community:

"I was treated for Stage III breast cancer in New Jersey in 2011, before the NJ Medical Marijuana Program was active. My physicians prescribed me a wide variety of drugs including opiates, which I used less of than was prescribed because of my fear of addiction. Despite my safe use under physician supervision, I suffered from multiple drug induced toxicity, which led to a 5-day inpatient stay at Princeton Hospital to detox after suffering from an episode that included a seizure, a potentially fatal heart arrhythmia, and loss of consciousness brought on by prescription drug use. Although I was using legally prescribed opiates at even lower doses than prescribed to me, I came close to dying from their effects, and after that episode, I illegally used cannabis to help cope with both my cancer-related pain and with the withdrawal symptoms of the pharmaceuticals I remained on after my hospitalization. Today I am healthy, have been in remission from cancer for more than 5 years, and do not use any opiates. I believe that cannabis played a critical role in my recovery."
-Submitted by [redacted], former resident of Princeton, NJ

"My sister [redacted] passed away on [redacted]. She was taken off life support at 1:15pm, I felt her last heartbeat at 1:50pm but the doctors didn't pronounce her until 1:57pm. I was left responsible to make all her medically related decisions because my mother wasn't in the best condition to make them as her power of attorney. All the medical testing showed that she was brain dead due to the lack of oxygen for a long period of time. I decided to take her off life support. A decision no one should ever have to make.
[redacted] started taking opiates at the age of 12 after she had surgery on both her feet. She had been born with a deformity that caused extreme pain and difficulty walking. Post op she suffered extreme pain to the point she couldn't sleep. She was in need of constant pain meds. This would be the beginning of her addiction to opiates.

At 14 years old [redacted] would suffer her first overdose of opiates. She had gotten access to lots of Percocets and took too many and would nearly die.
Fortunately, she was around friends that would think fast and get her the help she needed to save her life.
[redacted] would again overdose at the age of 31 from heroin. I asked her, "Why are you on heroin?"
She told me, "H was a lot easier to find, much cheaper and it helps relieve my pain just as good as prescription drugs did."
She also said that she wanted to get off of it but that the withdrawal was too hard and it could kill her if she did it cold turkey.
I had read several testimonies from former opiate addicts that said cannabis helped relieve their opiate withdrawal and made it easier to kick the addiction. I suggested that she should try it. She then gets access to high CBD oil and begins taking it while going through withdrawal.
She said, "I feel the physical side effects of the opiate withdrawal but it isn't as intense as it was when I didn't take cannabis."
My sister would be clean for a couple of weeks. It was the first time she was clean that long in 10 years.
She would die 6 months later."
-Submitted by [redacted]

This petition is dedicated to the memory of [redacted].

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.

Please find attached letters of support from physicians or other licensed health care professionals:
1. Dr. Andrew Medvedovsky, MD
2. Ken Wolski, RN
3. [redacted] Dispensary Director

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 [redacted]	Date 8/30/2016

QUESTION #9 ATTACHMENTS
ATTACHMENT #1

ARTICLES FROM PEER-REVIEWED SCIENTIFIC JOURNALS

Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. Boehnke, Kevin F. et al. The Journal of Pain, Volume 17 , Issue 6 , 739 - 744

American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY
ELSEVIER

The Journal of Pain, Vol ■, No ■ (■), 2016: pp 1-6
Available online at www.jpain.org and www.sciencedirect.com

Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain

Kevin F. Boehnke,* Evangelos Litinas,† and Daniel J. Clauw‡,§

**Department of Environmental Health Sciences, School of Public Health, University of Michigan, Ann Arbor, Michigan.*
†Om of Medicine, Ann Arbor, Michigan.
‡Departments of Anesthesiology, Medicine (Rheumatology), and Psychiatry, Medical School, University of Michigan, Ann Arbor, Michigan.
§Chronic Pain and Fatigue Research Center, Medical School, University of Michigan, Ann Arbor, Michigan.

Abstract: **Opioids are commonly used to treat patients with chronic pain (CP), though there is little evidence that they are effective for long term CP treatment. Previous studies reported strong associations between passage of medical cannabis laws and decrease in opioid overdose statewide. Our aim was to examine whether using medical cannabis for CP changed individual patterns of opioid use. Using an online questionnaire, we conducted a cross-sectional retrospective survey of 244 medical cannabis patients with CP who patronized a medical cannabis dispensary in Michigan between November 2013 and February 2015. Data collected included demographic information, changes in opioid use, quality of life, medication classes used, and medication side effects before and after initiation of cannabis usage. Among study participants, medical cannabis use was associated with a 64% decrease in opioid use (n = 118), decreased number and side effects of medications, and an improved quality of life (45%). This study suggests that many CP patients are essentially substituting medical cannabis for opioids and other medications for CP treatment, and finding the benefit and side effect profile of cannabis to be greater than these other classes of medications. More research is needed to validate this finding.**

Perspective: ***This article suggests that using medical cannabis for CP treatment may benefit some CP patients. The reported improvement in quality of life, better side effect profile, and decreased opioid use should be confirmed by rigorous, longitudinal studies that also assess how CP patients use medical cannabis for pain management.***

© 2016 by the American Pain Society

Key words: *Medical cannabis, opioids, chronic pain, side effects.*

Chronic pain (CP) is among the most common and expensive medical conditions, affecting >100 million Americans, and with total direct and indirect costs of up to $635 billion per year.[8] Despite their high prevalence, treatment of CP conditions is difficult. Treatments for CP conditions often require incremental lifestyle changes (exercise, sleep hygiene, stress reduction) and repeated doctor visits to monitor changes, which is increasingly challenging in the current economic and medical climate.[14] Furthermore, other potentially efficacious therapies (eg, cognitive behavioral therapy and complementary approaches) are not often covered by insurance. Finally, opioids—one of the most common medication used to treat CP—are ineffective for many types of CP, as well as being addictive and associated with significant morbidity and mortality.[1] Indeed, opioids are the most common prescription drug implicated in overdose deaths, involved in up to 75% of overdoses, and estimated to be responsible for at least 17,000 deaths annually.[10]

Received December 4, 2015; Revised February 23, 2016; Accepted March 7, 2016.

Dr. Clauw has performed consulting services for and/or served on scientific advisory boards of Pfizer, Lilly, Forest Laboratories, Johnson & Johnson, Purdue Pharma, Nuvo, Cerephex, Tonix, Iroko, Takaeda, Cerephex, IMC, Zynerba, and Samumed. He has received grant support from Pfizer, Forest, Merck, Nuvo, and Cerephex. Dr. Litinas is the Chief Medical Officer at Om of Medicine, a medical cannabis dispensary in Ann Arbor, Michigan.

Mr. Boehnke reports no conflicts of interest.

Address reprint requests to Daniel J. Clauw, MD, University of Michigan, 24 Frank Lloyd Wright Dr, PO Box 385, Ann Arbor, MI 48106. E-mail: dclauw@med.umich.edu

1526-5900/$36.00

© 2016 by the American Pain Society

http://dx.doi.org/10.1016/j.jpain.2016.03.002

Because of problems with the current treatment of pain, many patients and some providers have begun to re-examine the potential role for cannabis or cannabinoids for treating CP. Because there are no synthetic cannabinoids approved for treatment of CP in the United States, the most available form of cannabinoids for most patients is cannabis purchased from dispensaries or illegally. Cannabis has been legal in parts of the United States since 1996 for treatment of multiple conditions, including CP.[12] Randomized controlled trials have examined whether cannabis, cannabis extracts, or synthetic cannabinoids are efficacious in CP states, with a recent meta-analysis suggesting that there is moderate evidence that some types of CP states may be improved by use of cannabinoids.[15] In contrast, there have been relatively few studies of the effectiveness of cannabinoids in real-life settings. A study out of the Netherlands suggested that 53% of registered cannabis users consumed cannabis for enhanced pain control[7] although other studies have described uncertain efficacy for CP treatment.[6] Interestingly, legalization of medical cannabis was associated with a mean 24.8% decrease in opioid overdose deaths in multiple states across the United States.[2] Although suggestive that cannabis could act as a replacement or alternative for opioids, this finding was on an ecological level, so changes at an individual level could not be gauged.

In our current study, we surveyed medical cannabis cardholders in Michigan, who must receive a certification from a licensed physician that they have a condition deemed by the statute to justify cannabis use (eg, CP) to obtain their permit. We hypothesized that many cannabis users were using cannabis for CP reduction and as a substitute for opioids. We further hypothesized that we may find some evidence that cannabis was reported to be more effective for CP that is "centralized" in nature. By centralized in nature, we mean individuals in whom the central nervous system is playing a greater role in pain, which we have previously shown is associated with decreased responsiveness to opioids.[3,4,9] This is plausible because meta-analyses that have examined the efficacy of cannabinoids in neuropathic and centralized pain states have suggested that these compounds are generally efficacious,[13,15] whereas there is far less evidence for efficacy in nociceptive pain states.[16] Thus, we hypothesized that individuals with higher scores on the 2011 Survey Criteria for fibromyalgia—a continuous measure that can be used to diagnose fibromyalgia as well as to determine the degree of pain centralization in CP states[13]—would show better overall pain relief with cannabis compared with those using cannabis for CP with lower scores on this measure. If this were to be true, then this would provide very preliminary evidence that cannabis might be a more effective treatment of centralized or neuropathic pain states than opioids, a finding in line with recent meta-analyses of the effects of cannabis in randomized controlled trials in various pain conditions.[13,15]

Methods

Survey distribution was carried out in collaboration with owners of a local medical cannabis dispensary in Ann Arbor, Michigan, who helped recruit registered medical cannabis patients (18 years of age and older) to take the survey through the Qualtrics (Provo, UT) online survey platform. Study participants were enrolled between November 2013 and February 2015. Participant anonymity was maintained.

The survey contained 46 questions, detailing the medical condition(s) for which cannabis was used, method/frequency of cannabis use, changes in noncannabis medication use, changes in medication side effects, quality of life changes since starting cannabis use, and demographic information. As part of the survey, all participants completed the 2011 Fibromyalgia Survey Criteria (FM score), which gives a score from 0 to 31, with 31 indicating the most severe FM pain.[16] This value indicates a participant's FM score at the time of the survey, rather than their FM score before initiation of cannabis use. Survey questions of interest are shown in Table 1.

Statistics

The study population was examined using descriptive statistics. To ensure that no important information was missed by limiting analyses to fully completed questionnaires, sensitivity analyses were performed on the entire set of questionnaires, questionnaires that were ≥60% complete, ≥80% complete, and those that were fully completed (Table 2). There were very little differences between the outcomes, so analysis was limited to questionnaires that were fully completed. FM scores of participants were stratified into quartiles to examine whether degree of pain centralization was associated with outcomes of interest. Relationships between FM score quartile, opioid use change, quality of life change, when the study participant began using cannabis, and medication side effects were examined using Pearson correlation test. Student t-tests were used to examine whether cannabis use affected the number of medication classes (eg, opioids, nonsteroidal anti-inflammatory drugs, selective serotonin uptake inhibitor, disease modifying antirheumatic drugs, etc) taken, medication side effects, and paired t-tests were used to evaluate changes in these variables before and after initiation of cannabis use. Analysis of variance tests were used to examine whether changes in quality of life or opioid use were associated with FM score.

All analyses were carried out in R Studio version 0.98.1103 (R-Tools Technology Inc, Richmond Hill, Ontario, Canada).

Ethics Statement

This study was exempted from institutional review board oversight under protocol HUM00079724 at the University of Michigan. Participants freely consented to participate in the study, and were able to drop out at any time.

Table 1. Survey Questions Regarding Outcomes and Exposures of Interest

Survey Question	*Answer Options*
In a typical week, how often do you use cannabis?	• Less than once per week • One time • 2 to 3 times • 4 to 6 times • Daily
On a day that you do use cannabis, how often do you use it?	• Less than once • 1 to 2 times • 3 to 4 times • More than 5 times
When did you start using cannabis for medical purposes? Please give your answer in years.	Descriptive, ranges from 0 to 50 y
What classes of drugs were you using (check all that apply) before you started using cannabis? (Choose all that apply)	• Opioids (such as Vicodin*) • NSAIDs (such as aspirin) • Disease-modifying antirheumatic drugs • Antidepressants • Serotonin–norepinephrine reuptake inhibitors • Selective serotonin reuptake inhibitors • Other
On a scale of 1 to 10 (with 1 being not at all and 10 being significantly) how much did the side effects of the medications you took before using cannabis affect your ability to do the things you needed to accomplish each day?	1 through 10
On a scale of 1 to 10 (with 1 being not at all and 10 being significantly) how much do the side effects of the medications you take in combination with cannabis affect your ability to do the things you needed to accomplish each day?	1 through 10
How has your opioid prescription drug use changed since you started using cannabis? Increase or decrease (%). If your opioid use has increased by 30%, please write +30%. If your opioid use has decreased by 30%, please write in −30%.	−100% through +100%
Are you taking any of the following drugs or drug classes in combination with cannabis? (Choose all that apply)	• Opioids (such as Vicodin*) • NSAIDs (such as aspirin) • Disease-modifying antirheumatic drugs • Antidepressants • Serotonin–norepinephrine reuptake inhibitors • Selective serotonin reuptake inhibitors • Other

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.
*Vicodin manufactured by AbbVie Inc (North Chicago, IL).

Results

Of the 374 participants in the study, 244 of the participants used cannabis to treat CP. Sensitivity analyses showed that exclusion of incomplete questionnaires did not have a significant effect on outcomes (Table 2), so only the complete questionnaires of participants with CP were used (n = 185).

Table 2. Sensitivity Analysis of Outcomes of Interest

Outcome of Interest	*Entire Set of Questionnaires (N = 244)*	*Questionnaires That Were ≥60% Completed (N = 192)*	*Questionnaires That Were ≥80% Completed (N = 186)*	*Questionnaires That Were Fully Completed (N = 185)**
FM score	9.23 (5.52)	9.28 (5.54)	9.15 (5.40)	9.16 (5.42)
Opioid use change	−63% (46%)	−63% (47%)	−64% (44%)	−64% (45%)
Degree to which side effects of medication affect daily function (before using medical cannabis); scale from 1 to 10	6.44 (2.91)	6.42 (2.91)	6.46 (2.89)	6.51 (2.88)
Degree to which side effects of medication affect daily function (after using medical cannabis); scale from 1 to 10	2.77 (2.35)	2.78 (2.36)	2.78 (2.38)	2.79 (2.39)
Number of medication classes used (before cannabis use)	2.35 (1.43)	2.34 (1.44)	2.36 (1.44)	2.38 (1.44)
Number of medication classes used (after cannabis use)	1.82 (.94)	1.84 (.95)	1.83 (.95)	1.81 (.95)
Quality of life change	45% (28%)	45% (28%)	45% (29%)	45% (29%)

NOTE. All quantities reported as mean (SD).
*Only fully completed questionnaires were used for final analyses.

Table 3. Demographic Characteristics of the Study Population (n = 185)

Variable	Value
Sex	
Male	118 (64)
Female	65 (35)
Refuse to answer	2 (1)
Age	
18 to 25	32 (17)
26 to 35	40 (22)
36 to 45	32 (17)
46 to 55	25 (14)
56 to 65	46 (25)
66 to 75	9 (5)
Refuse to answer	1 (.5)
Weekly cannabis use	
<1 Time	1 (.5)
2 to 3 times	16 (9)
4 to 6 times	22 (12)
Daily	146 (79)
Daily cannabis use	
1 Time	22 (12)
2 Times	47 (25)
3 to 4 times	77 (42)
≥5 Times	38 (20)
Refuse to answer	1 (.5)
Opioid use before cannabis use	
Yes	119 (64)*
No	66 (36)
CP status	
Yes	185 (100)

NOTE. Data are presented as n (%).
*One participant chose not to respond to the question about change in opioid use.

Demographic information is summarized in Table 3. Of note, most participants (78.9%) smoked cannabis daily. Outcomes (opioid use change, quality of life change, number of medications, and medication side effects) in the total CP population and in FM score quartiles are summarized in Table 4.

Effects of Cannabis on Opioid Use

The mean change in self-reported opioid use among all respondents answering this question was −64%. Interestingly, in contrast to our hypothesis, the reduction of opioid use was the least drastic in the highest FM score quartile (−48%), which was significantly different from the lowest FM score quartile (−79%, $P = .03$) but not the second and third (−74% and −63%, $P = .14$ and .59, respectively).

Effects of Cannabis on Number of Medication Classes Used and Side Effects of Medications

The number of medication classes used after initiation of cannabis use was (1 + reported number) to account for cannabis use. Medications used before and after initiation of cannabis use are reported in Table 5. Although we focus in this article on opioid dosage reductions because this has become a major public health problem in the United States, there were comparable reductions in self-reported usage of many other classes of analgesic drugs. The mean number of medications classes used decreased significantly in all respondents before and after cannabis use (2.38 vs 1.81, respectively, $P < .001$).

Although we did not find our hypothesized findings that individuals with more centralized pain (eg, with a more fibromyalgia-like phenotype) reported increased effectiveness of cannabis, we did find that the degree of pain centralization predicted differential medication usage before and after cannabis usage. Participants in the fourth FM score quartile used a significantly greater number of medication classes than those in the first, second, and third quartiles before initiation of cannabis use ($P < .001$, $P < .001$, $P = .004$, respectively). After initiation of cannabis use, participants in the fourth FM score quartile continued to use a significantly greater number of medication classes compared with those in the other quartiles ($P < .001$, $P < .001$, $P = .068$ in the first, second, and third quartiles, respectively). Side effects of medication on everyday functioning decreased substantially after cannabis use (6.51 vs 2.79, $P < .001$). There were no differences in the change in medication side effects among FM score quartiles ($P = .86$).

Discussion

Our primary study hypothesis that patients would self-report that they derived more pain relief from cannabis if they had more centralized pain was not supported. In fact, patients with lower pain centralization levels noted the best improvements in quality of life, as well as the largest reductions in opioid usage. However, this study did yield several significant findings. Overall, since the initiation of medical cannabis use, CP patients reported significant decreases in medication side effects that affected their daily functioning (including opioids), decreases in total number of medications being taken, and improvements in quality of life. Reported reduction in opioid use and decreased medication side effects were significantly correlated ($r = .37$, $P = .0002$), indicating a potential health benefit of replacing opioids with cannabis. This "opioid-sparing" effect is consistent with the ecological study by Bachhuber et al,[2] and hints to potential synergistic effects between cannabis and opioids for reduction of severe CP. Indeed, a recent study in Australia reported that people with CP had better pain reduction when they combined opioids and cannabis.[5]

Limitations

Although suggestive, the cross-sectional study design limits inference from our data, because our outcomes of interest (changes in quality of life, opioid use, side effects of medication, and number of medications) were measured with potentially unreliable recall data. Indeed, some study participants had been

ARTICLE IN PRESS

Table 4. Outcomes of Interest in the Study Population

Outcome of Interest	CP (N = 185)	FM Score Quartile 1 (N = 56)	FM Score Quartile 2 (N = 42)	FM Score Quartile 3 (N = 43)	FM Score Quartile 4 (N = 44)
FM score	9.16 (5.42) n = 185	3.61 (1.27) n = 56	7.12 (0.74) n = 42	10.40 (1.22) n = 43	16.95 (3.70) n = 44
Opioid use change (−100% to +100%)	−64% (45%) n = 118	−79% (32%) n = 28	−74% (40%) n = 22	−63% (39%) n = 30	−48% (54%) n = 38
Degree to which side effects of medication affect daily function before using medical cannabis; scale from 1 (no effect) to 10 (significant effect)	6.51 (2.88) n = 136	5.89 (3.29) n = 38	5.7 (3.16) n = 27	7.06 (2.39) n = 35	7.22 (2.45) n = 36
Degree to which side effects of medication affect daily function after using medical cannabis; scale from 1 (no effect) to 10 (significant effect)	2.79 (2.39) n = 136	1.92 (1.96) n = 38	1.70 (1.29) n = 27	3.60 (2.76) n = 35	3.72 (2.46) n = 36
Change in medication side effects after initiation of cannabis	−3.72 (3.42) n = 136	−3.97 (3.72) n = 38	−4.00 (3.25) n = 27	−3.46 (3.31) n = 35	−3.50 (3.43) n = 36
Number of medication classes used (before cannabis use)	2.38 (1.44) n = 184	1.96 (1.36) n = 56	1.88 (1.10) n = 41	2.40 (1.35) n = 43	3.3 (1.46) n = 44
Number of medication classes used (after cannabis use)	1.81 (.95) n = 184	1.46 (.69) n = 56	1.54 (.67) n = 41	1.95 (1.11) n = 43	2.39 (.99) n = 44
Change in quality of life (−100% to +100%)	+45% (29%) n = 180	+54% (31%) n = 54	+43% (26%) n = 41	+44% (28%) n = 42	+38% (27%) n = 43

NOTE. FM score and quartiles for change in opioid use, quality of life, side effects of medications before and after cannabis use, and number of medication classes used before and after cannabis are presented. All quantities reported as mean (SD).

Table 5. Medication Classes Used Before and After Initiation of Cannabis Among the Study Population

Medication Type	Use Before Initiation of Cannabis, n/N (%)	Use After Initiation of Cannabis, n/N (%)
Opioids	119/184 (65)	33/184 (18)
Nonsteroidal anti-inflammatory drugs	115/184 (62)	38/184 (21)
Disease-modifying antirheumatic drugs	15/184 (8)	3/184 (2)
Antidepressants	72/184 (39)	25/184 (14)
Serotonin–norepinephrine reuptake inhibitors	13/184 (7)	3/184 (2)
Selective serotonin reuptake inhibitors	34/184 (18)	8/184 (4)
Other	69/184 (38)	40/184 (22)

NOTE. Study participants reported using fewer medication classes of all categories after initiation of cannabis use.

using cannabis for medical purposes for quite some time (median of 4 years). FM scores were measured at the time of the survey, so we were unable to know participant's baseline FM score before they started using cannabis, potentially biasing the data. Furthermore, our results may not be representative of the general population, because we only surveyed patrons of a medical cannabis dispensary. Finally, with the recent attention to opioid overuse and overdose, we considered the possibility that physicians would reduce the number of opioid prescriptions, which could have happened concurrently with our study. This could provide an explanation for the drastic decrease in the use of opioids that we report. However, the Michigan Department of Community Health and the Michigan Automated Prescription System showed consistent increases in the number opioid prescriptions written from 2007 to 2014 (7.7 million in 2007 to 9.7 million in 2014) and in the number of opioid units prescribed from 2011 to 2014 (over 620 million units total in 2011 to almost 677 million in 2014).[11,17] Although we do not know if the statewide trends apply to our study, our observed decreased opioid use is not consistent with these trends, suggesting that it may be due to other factors (including the use of cannabis).

Future Directions and Conclusions

Future studies can address these issues by using longitudinal study designs that recruit participants naive to cannabis and measure their pain levels before and after using cannabis. This would make the results more robust by taking into account temporality, and resolve issues of selection bias in our current study. We plan to continue recruiting participants for this study to validate the robustness of our results in a larger population. Because cannabis is a schedule I drug, much of the literature surrounding its efficacy as medication is anecdotal and/or not peer-reviewed.

Although we caution against using this study to change clinical practice toward cannabis, this study provides intriguing hints of the value of cannabis, as an effective pain medication and as an effective agent against opioid overuse and overdose.

References

1. Arnold LM, Clauw DJ, Dunegan LJ, Turk DC: A framework for fibromyalgia management for primary care providers. Mayo Clin Proc 87:488-496, 2012

2. Bachhuber MA, Salone B, Cunningham CO, Barry CL: Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999–2010. JAMA Intern Med 19104:1-6, 2014

3. Brummett C, Janda A, Schueller C, Tsodikov A, Morris M, Williams D, Clauw D: Survey criteria for fibromyalgia independently predict increased postoperative opioid consumption after lower-extremity joint arthroplasty. Anesthesiology 119:1434-1443, 2013

4. Clauw DJ: Fibromyalgia: A clinical review. JAMA 311: 1547-1555, 2014

5. Degenhardt L, Lintzeris N, Campbell G, Bruno R, Cohen M, Farrell M, Hall WD: Experience of adjunctive cannabis use for chronic non-cancer pain: Findings from the Pain and Opioids IN Treatment (POINT) study. Drug Alcohol Depend 147:144-150, 2015

6. Farrell M, Buchbinder R, Hall W: Should doctors prescribe cannabinoids? BMJ 348:g2737, 2014

7. Hazekamp A, Heerdink ER: The prevalence and incidence of medicinal cannabis on prescription in the Netherlands. Eur J Clin Pharmacol 69:1575-1580, 2013

8. Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education: Relieving pain in America: A blueprint for transforming prevention, care, education, and research. Washington, DC, National Academies Press (US), 2011

9. Janda AM, As-Sanie S, Rajala B, Tsodikov A, Moser SE, Clauw DJ, Brummett CM: Fibromyalgia survey criteria are associated with increased postoperative opioid consumption in women undergoing hysterectomy. Anesthesiology 122:1103-1111, 2015

10. Jones CM, Mack KA, Paulozzi LJ: Pharmaceutical overdose deaths, United States, 2010. JAMA 309:657-659, 2013

11. LARA. Department of Licensing and Regulatory Affairs: MAPS Statistics. Available at: http://www.michigan.gov/lara/0,4601,7-154-72600_72603_55478_55484—,00.html

12. Leung L: Cannabis and its derivatives: Review of medical use. J Am Board Fam Med 24:452-462, 2011

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

14. Phillips K, Clauw DJ: Central pain mechanisms in the rheumatic diseases: Future directions. Arthritis Rheum 65: 291-302, 2013

15. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidlkofer S, Westwood M, Kleijnen J: Cannabinoids for medical use. JAMA 313: 2456-2473, 2015

16. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB: Fibromyalgia criteria and severity scales for clinical and epidemiological studies: A modification of the ACR preliminary diagnostic criteria for fibromyalgia. J Rheumatol 38:1113-1122, 2011

17. Advisory Committee on Pain and Symptom Management: 2014: The "state" of pain in Michigan. Available at: https://www.michigan.gov/documents/lara/ACPSM_State_of_Pain_Report_to_Directors_Sept._2014_469555_7.pdf

Acknowledgments

We thank Mark Passerini and Keith Lambert at Om of Medicine for their help on this project, and the Om of Medicine staff for their help in administering the survey.

QUESTION #9 ATTACHMENTS
ATTACHMENT #2

ARTICLES FROM PEER-REVIEWED SCIENTIFIC JOURNALS

Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. JAMA Intern Med. 2014;174(10):1668-1673. doi:10.1001/jamainternmed.2014.4005.

ARTICLES FROM PEER-REVIEWED SCIENTIFIC JOURNALS

ARTICLE #2

Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. JAMA Intern Med. 2014;174(10):1668-1673. doi:10.1001/jamainternmed.2014.4005.

Original Investigation

Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010

Marcus A. Bachhuber, MD; Brendan Saloner, PhD; Chinazo O. Cunningham, MD, MS; Colleen L. Barry, PhD, MPP

Invited Commentary page 1673

IMPORTANCE Opioid analgesic overdose mortality continues to rise in the United States, driven by increases in prescribing for chronic pain. Because chronic pain is a major indication for medical cannabis, laws that establish access to medical cannabis may change overdose mortality related to opioid analgesics in states that have enacted them.

OBJECTIVE To determine the association between the presence of state medical cannabis laws and opioid analgesic overdose mortality.

DESIGN, SETTING, AND PARTICIPANTS A time-series analysis was conducted of medical cannabis laws and state-level death certificate data in the United States from 1999 to 2010; all 50 states were included.

EXPOSURES Presence of a law establishing a medical cannabis program in the state.

MAIN OUTCOMES AND MEASURES Age-adjusted opioid analgesic overdose death rate per 100 000 population in each state. Regression models were developed including state and year fixed effects, the presence of 3 different policies regarding opioid analgesics, and the state-specific unemployment rate.

RESULTS Three states (California, Oregon, and Washington) had medical cannabis laws effective prior to 1999. Ten states (Alaska, Colorado, Hawaii, Maine, Michigan, Montana, Nevada, New Mexico, Rhode Island, and Vermont) enacted medical cannabis laws between 1999 and 2010. States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate (95% CI, −37.5% to −9.5%; $P = .003$) compared with states without medical cannabis laws. Examination of the association between medical cannabis laws and opioid analgesic overdose mortality in each year after implementation of the law showed that such laws were associated with a lower rate of overdose mortality that generally strengthened over time: year 1 (−19.9%; 95% CI, −30.6% to −7.7%; $P = .002$), year 2 (−25.2%; 95% CI, −40.6% to −5.9%; $P = .01$), year 3 (−23.6%; 95% CI, −41.1% to −1.0%; $P = .04$), year 4 (−20.2%; 95% CI, −33.6% to −4.0%; $P = .02$), year 5 (−33.7%; 95% CI, −50.9% to −10.4%; $P = .008$), and year 6 (−33.3%; 95% CI, −44.7% to −19.6%; $P < .001$). In secondary analyses, the findings remained similar.

CONCLUSIONS AND RELEVANCE Medical cannabis laws are associated with significantly lower state-level opioid overdose mortality rates. Further investigation is required to determine how medical cannabis laws may interact with policies aimed at preventing opioid analgesic overdose.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Marcus A. Bachhuber, MD, Center for Health Equity Research and Promotion, Philadelphia Veterans Affairs Medical Center, 423 Guardian Dr, 1303-A Blockley Hall, Philadelphia, PA 19104 (marcus.bachhuber@gmail.com).

JAMA Intern Med. 2014;174(10):1668-1673. doi:10.1001/jamainternmed.2014.4005
Published online August 25, 2014.

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ by Vanessa Waltz on 08/31/2016

Chronic noncancer pain is common in the United States,[1] and the proportion of patients with noncancer pain who receive prescriptions for opioids has almost doubled over the past decade.[2] In parallel to this increase in prescriptions, rates of opioid use disorders and overdose deaths have risen dramatically.[3,4] Policies such as prescription drug monitoring programs, increased scrutiny of patients and providers, and enhanced access to substance abuse treatment have been advocated to reduce the risk of opioid analgesics[5]; however, relatively less attention has focused on how the availability of alternative nonopioid treatments may affect overdose rates.

As of July 2014, a total of 23 states have enacted laws establishing medical cannabis programs[6] and chronic or severe pain is the primary indication in most states.[7-10] Medical cannabis laws are associated with increased cannabis use among adults.[11] This increased access to medical cannabis may reduce opioid analgesic use by patients with chronic pain, and therefore reduce opioid analgesic overdoses. Alternatively, if cannabis adversely alters the pharmacokinetics of opioids or serves as a "gateway" or "stepping stone" leading to further substance use,[12-14] medical cannabis laws may increase opioid analgesic overdoses. Given these potential effects, we examined the relationship between implementation of state medical cannabis laws and opioid analgesic overdose deaths in the United States between 1999 and 2010.

Methods

The opioid analgesic overdose mortality rate in each state from 1999 to 2010 was abstracted using the Wide-ranging Online Data for Epidemiologic Research interface to multiple cause-of-death data from the Centers for Disease Control and Prevention.[15] We defined opioid analgesic overdose deaths as fatal drug overdoses of any intent (*International Statistical Classification of Diseases, 10th revision* [*ICD-10*], codes X40-X44, X60-X64, and Y10-Y14) where an opioid analgesic was also coded (T40.2-T40.4). This captures all overdose deaths where an opioid analgesic was involved including those involving polypharmacy or illicit drug use (eg, heroin). Analysis of publicly available secondary data is considered exempt by the University of Pennsylvania Institutional Review Board.

Three states (California, Oregon, and Washington) had medical cannabis laws effective prior to 1999.[6] Ten states (Alaska, Colorado, Hawaii, Maine, Michigan, Montana, Nevada, New Mexico, Rhode Island, and Vermont) implemented medical cannabis laws between 1999 and 2010. Nine states (Arizona, Connecticut, Delaware, Illinois, Maryland, Massachusetts, Minnesota, New Hampshire, and New York) had medical cannabis laws effective after 2010, which is beyond the study period. New Jersey's medical cannabis law went into effect in the last quarter of 2010 and was counted as effective after the study period. In each year, we first plotted the mean age-adjusted opioid analgesic overdose mortality rate in states that had a medical cannabis law vs states that did not.

Next, we determined the association between medical cannabis laws and opioid analgesic–related deaths using linear time-series regression models. For the dependent variable, we used the logarithm of the year- and state-specific age-adjusted opioid analgesic overdose mortality rate. Our main independent variable of interest was the presence of medical cannabis laws, which we modeled in 2 ways.

In our first regression model, we included an indicator for the presence of a medical cannabis law in the state and year. All years prior to a medical cannabis law were coded as 0 and all years after the year of passage were coded as 1. Because laws could be implemented at various points in the year, we coded the law as a fraction for years of implementation (eg, 0.5 for a law that was implemented on July 1). The coefficient on this variable therefore represents the mean difference, expressed as a percentage, in the annual opioid analgesic overdose mortality rate associated with the implementation of medical cannabis laws. To estimate the absolute difference in mortality associated with medical cannabis laws in 2010, we calculated the expected number of opioid analgesic overdose deaths in medical cannabis states had laws not been present and subtracted the actual number of overdose deaths recorded.

In our second model, we allowed the effect of medical cannabis laws to vary depending on the time elapsed since enactment, because states may have experienced delays in patient registration, distribution of identification cards, and establishment of dispensaries, if applicable. Accordingly, we coded years with no law present as 0, but included separate coefficients to measure each year since implementation of the medical cannabis law for states that adopted such laws. States that implemented medical cannabis laws before the study period were coded similarly (eg, in 1999, California was coded as 3 because the law was implemented in 1996). This model provides separate estimates for 1 year after implementation, 2 years after implementation, and so forth.

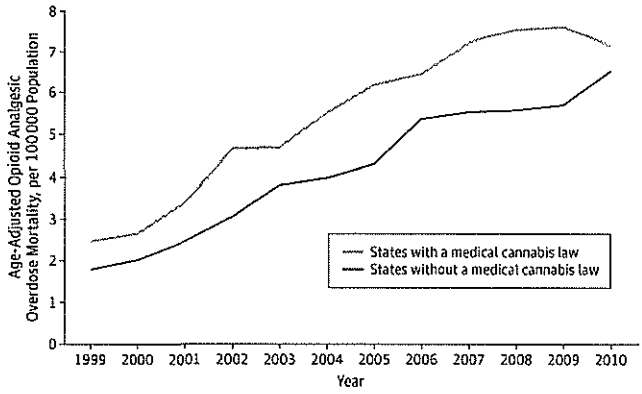
Each model adjusted for state and year (fixed effects). We also included 4 time-varying state-level factors: (1) the presence of a state-level prescription drug monitoring program (a state-level registry containing information on controlled substances prescribed in a state),[16] (2) the presence of a law requiring or allowing a pharmacist to request patient identification before dispensing medications,[17] (3) the presence of regulations establishing increased state oversight of pain management clinics,[18] and (4) state- and year-specific unemployment rates to adjust for the economic climate.[19] Colinearity among independent variables was assessed by examining variance inflation factors; no evidence of colinearity was found. For all models, robust standard errors were calculated using procedures to account for correlation within states over time.

To assess the robustness of our results, we performed several further analyses. First, we excluded intentional opioid analgesic overdose deaths from the age-adjusted overdose mortality rate to focus exclusively on nonsuicide deaths. Second, because heroin and prescription opioid use are interrelated for some individuals,[20-23] we included overdose deaths related to heroin, even if no opioid analgesic was coded. Third, we assessed the robustness of our findings to the inclusion of state-specific linear time trends that can be used to adjust for differential factors that changed linearly over the study period (eg, hard-to-measure attitudes or cultural changes). Fourth, we tested whether trends in opioid analgesic overdose mortality

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ by Vanessa Waltz on 08/31/2016

Figure 1. Mean Age-Adjusted Opioid Analgesic Overdose Death Rate



States with medical cannabis laws compared with states without such laws in the United States, 1999-2010.

Table. Association Between Medical Cannabis Laws and State-Level Opioid Analgesic Overdose Mortality Rates in the United States, 1999-2010

	Percentage Difference in Age-Adjusted Opioid Analgesic Overdose Mortality in States With vs Without a Law		
	Primary Analysis	Secondary Analyses	
Independent Variable[a]	Estimate (95% CI)[b]	Estimate (95% CI)[c]	Estimate (95% CI)[d]
Medical cannabis law	−24.8 (−37.5 to −9.5)[e]	−31.0 (−42.2 to −17.6)[f]	−23.1 (−37.1 to −5.9)[e]
Prescription drug monitoring program	3.7 (−12.7 to 23.3)	3.5 (−13.4 to 23.7)	7.7 (−11.0 to 30.3)
Law requiring or allowing pharmacists to request patient identification	5.0 (−10.4 to 23.1)	4.1 (−11.4 to 22.5)	2.3 (−15.4 to 23.7)
Increased state oversight of pain management clinics	−7.6 (−19.1 to 5.6)	−11.7 (−20.7 to −1.7)[e]	−3.9 (−21.7 to 18.0)
Annual state unemployment rate[g]	4.4 (−0.3 to 9.3)	5.2 (0.1 to 10.6)[e]	2.5 (−2.3 to 7.5)

[a] All models adjusted for state and year (fixed effects).

[b] $R^2 = 0.876$.

[c] All intentional (suicide) overdose deaths were excluded from the dependent variable; opioid analgesic overdose mortality is therefore deaths that are unintentional or of undetermined intent. All covariates were the same as in the primary analysis; $R^2 = 0.873$.

[d] Findings include all heroin overdose deaths, even if no opioid analgesic was involved. All covariates were the same as in the primary analysis. $R^2 = 0.842$.

[e] $P \leq .05$.

[f] $P \leq .001$.

[g] An association was calculated for a 1-percentage-point increase in the state unemployment rate.

predated the implementation of medical cannabis laws by including indicator variables in a separate regression model for the 2 years before the passage of the law.[24] Finally, to test the specificity of any association found between medical cannabis laws and opioid analgesic overdose mortality, we examined the association between state medical cannabis laws and age-adjusted death rates of other medical conditions without strong links to cannabis use: heart disease (*ICD-10* codes I00-I09, I11, I13, and I20-I51)[25] and septicemia (A40-A41). All analyses were performed using SAS, version 9.3 (SAS Institute Inc).

Results

The mean age-adjusted opioid analgesic overdose mortality rate increased in states with and without medical cannabis laws during the study period (Figure 1). Throughout the study period, states with medical cannabis laws had a higher opioid analgesic overdose mortality rate and the rates rose for both groups; however, between 2009 and 2010 the rate in states with medical cannabis laws appeared to plateau.

In the adjusted model, medical cannabis laws were associated with a mean 24.8% lower annual rate of opioid analgesic overdose deaths (95% CI, −37.5% to −9.5%; $P = .003$) (Table), compared with states without laws. In 2010, this translated to an estimated 1729 (95% CI, 549 to 3151) fewer deaths than expected. Medical cannabis laws were associated with lower rates of opioid analgesic overdose mortality, which generally strengthened in the years after passage (Figure 2): year 1 (−19.9%; 95% CI, −30.6% to −7.7%; $P = .002$), year 2 (−25.2%; 95% CI, −40.6% to −5.9%; $P = .01$), year 3 (−23.6%; 95% CI, −41.1% to −1.0%; $P = .04$), year 4 (−20.2%; 95% CI, −33.6% to −4.0%; $P = .02$), year 5 (−33.7%; 95% CI, −50.9% to −10.4%; $P = .008$), and year 6 (−33.3%; 95% CI, −44.7% to −19.6%; $P < .001$). The other opioid analgesic policies, as well as state unemployment rates, were not significantly associated with opioid analgesic mortality rates.

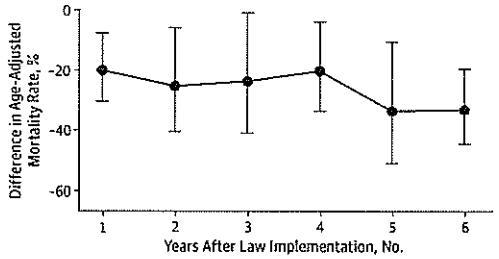
In additional analyses, the association between medical cannabis laws and opioid analgesic mortality rates was similar after excluding intentional deaths (ie, suicide) and when including all heroin overdose deaths, even if an opioid analgesic was not involved (Table). Including state-specific linear time trends

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ by Vanessa Waltz on 08/31/2016

in the model resulted in a borderline significant association between laws and opioid analgesic overdose mortality (−17.9%; 95% CI, −32.7% to 0.3%; $P = .054$). When examining the years prior to law implementation, we did not find an association between medical cannabis laws and opioid analgesic overdose mortality 2 years prior to law implementation (−13.1%; 95% CI, −45.5% to 38.6%; $P = .56$) or 1 year prior (1.2%; 95% CI, −41.2% to 74.0%; $P = .97$). Finally, we did not find significant associations between medical cannabis laws and mortality associated with heart disease (1.4%; 95% CI, −0.2% to 2.9%; $P = .09$) or septicemia (−1.8%; 95% CI, −7.6% to 4.3%; $P = .55$).

Figure 2. Association Between Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in Each Year After Implementation of Laws in the United States, 1999-2010



Point estimate of the mean difference in the opioid analgesic overdose mortality rate in states with medical cannabis laws compared with states without such laws; whiskers indicate 95% CIs.

Discussion

In an analysis of death certificate data from 1999 to 2010, we found that states with medical cannabis laws had lower mean opioid analgesic overdose mortality rates compared with states without such laws. This finding persisted when excluding intentional overdose deaths (ie, suicide), suggesting that medical cannabis laws are associated with lower opioid analgesic overdose mortality among individuals using opioid analgesics for medical indications. Similarly, the association between medical cannabis laws and lower opioid analgesic overdose mortality rates persisted when including all deaths related to heroin, even if no opioid analgesic was present, indicating that lower rates of opioid analgesic overdose mortality were not offset by higher rates of heroin overdose mortality. Although the exact mechanism is unclear, our results suggest a link between medical cannabis laws and lower opioid analgesic overdose mortality.

Approximately 60% of all opioid analgesic overdoses occur among patients who have legitimate prescriptions from a single provider.[26] This group may be sensitive to medical cannabis laws; patients with chronic noncancer pain who would have otherwise initiated opioid analgesics may choose medical cannabis instead. Although evidence for the analgesic properties of cannabis is limited, it may provide analgesia for some individuals.[27,28] In addition, patients already receiving opioid analgesics who start medical cannabis treatment may experience improved analgesia and decrease their opioid dose,[29,30] thus potentially decreasing their dose-dependent risk of overdose.[31,32] Finally, if medical cannabis laws lead to decreases in polypharmacy—particularly with benzodiazepines—in people taking opioid analgesics, overdose risk would be decreased. Further analyses examining the association between medical cannabis laws and patterns of opioid analgesic use and polypharmacy in the population as a whole and across different groups are needed.

A connection between medical cannabis laws and opioid analgesic overdose mortality among individuals who misuse or abuse opioids is less clear. Previous laboratory work has shown that cannabinoids act at least in part through an opioid receptor mechanism[33,34] and that they increase dopamine concentrations in the nucleus accumbens in a fashion similar to that of heroin and several other drugs with abuse potential.[33,35] Clinically, cannabis use is associated with modest reductions in opioid withdrawal symptoms for some people,[36,37] and therefore may reduce opioid use. In contrast, cannabis use has been linked with increased use of other drugs, including opioids[14,38-40]; however, a causal relationship has not been established.[14,41] Increased access to cannabis through medical cannabis laws could influence opioid misuse in either direction, and further study is required.

Although the mean annual opioid analgesic overdose mortality rate was lower in states with medical cannabis laws compared with states without such laws, the findings of our secondary analyses deserve further consideration. State-specific characteristics, such as trends in attitudes or health behaviors, may explain variation in medical cannabis laws and opioid analgesic overdose mortality, and we found some evidence that differences in these characteristics contributed to our findings. When including state-specific linear time trends in regression models, which are used to adjust for hard-to-measure confounders that change over time, the association between laws and opioid analgesic overdose mortality weakened. In contrast, we did not find evidence that states that passed medical cannabis laws had different overdose mortality rates in years prior to law passage, providing a temporal link between laws and changes in opioid analgesic overdose mortality. In addition, we did not find evidence that laws were associated with differences in mortality rates for unrelated conditions (heart disease and septicemia), suggesting that differences in opioid analgesic overdose mortality cannot be explained by broader changes in health. In summary, although we found a lower mean annual rate of opioid analgesic mortality in states with medical cannabis laws, a direct causal link cannot be established.

This study has several limitations. First, this analysis is ecologic and cannot adjust for characteristics of individuals within the states, such as socioeconomic status, race/ethnicity, or medical and psychiatric diagnoses. Although we found that the association between medical cannabis laws and lower opioid overdose mortality strengthened in the years after implementation, this could represent heterogeneity between states that passed laws earlier in the study period vs those that passed the laws later. Second, death certificate data may not correctly classify cases of opioid analgesic overdose deaths, and reporting of opioid analgesics on death certificates may differ among states; misclassification could bias our results in either direction. Third, although fixed-effects models can adjust for time-invariant characteristics of each state and state-invariant time

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ by Vanessa Waltz on 08/31/2016

effects, there may be important time- and state-varying confounders not included in our models. Finally, our findings apply to states that passed medical cannabis laws during the study period and the association between future laws and opioid analgesic overdose mortality may differ.

Conclusions

Although the present study provides evidence that medical cannabis laws are associated with reductions in opioid analgesic overdose mortality on a population level, proposed mechanisms for this association are speculative and rely on indirect evidence. Further rigorous evaluation of medical cannabis policies, including provisions that vary among states,[14,42] is required before their wide adoption can be recommended. If the relationship between medical cannabis laws and opioid analgesic overdose mortality is substantiated in further work, enactment of laws to allow for use of medical cannabis may be advocated as part of a comprehensive package of policies to reduce the population risk of opioid analgesics.

ARTICLE INFORMATION

Accepted for Publication: May 2, 2014.

Published Online: August 25, 2014. doi:10.1001/jamainternmed.2014.4005.

Author Affiliations: Center for Health Equity Research and Promotion, Philadelphia Veterans Affairs Medical Center, Philadelphia, Pennsylvania (Bachhuber); Robert Wood Johnson Foundation Clinical Scholars Program, University of Pennsylvania, Philadelphia (Bachhuber); Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia (Bachhuber, Saloner, Barry); Robert Wood Johnson Health and Society Scholars Program, University of Pennsylvania, Philadelphia (Saloner); Division of General Internal Medicine, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, New York (Cunningham); Department of Health Policy and Management, the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Barry).

Author Contributions: Dr Bachhuber had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Bachhuber, Saloner, Barry.
Acquisition, analysis, or interpretation of data: Bachhuber, Cunningham, Barry.
Drafting of the manuscript: Bachhuber, Saloner.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Bachhuber, Saloner, Barry.
Study supervision: Cunningham, Barry.

Conflict of Interest Disclosures: Dr Cunningham's husband was recently employed by Pfizer Pharmaceuticals and is currently employed by Quest Diagnostics. No other disclosures are reported.

Funding/Support: This work was funded by National Institutes of Health (NIH) grants R01DA032110 and R25DA023021 and the Center for AIDS Research at the Albert Einstein College of Medicine and Montefiore Medical Center grant NIH AI-51519. Dr Saloner received funding support from the Robert Wood Johnson Foundation Health and Society Scholars Program. Dr Bachhuber received funding support from the Philadelphia Veterans Affairs Medical Center and the Robert Wood Johnson Foundation Clinical Scholars Program.

Role of the Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The findings and conclusions of this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the US government.

Correction: This article was corrected on August 27, 2014, to fix a typographical error in Figure 1 and on September 10, 2014, to fix an incorrect term in the Discussion.

REFERENCES

1. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain*. 2012;13(8):715-724.

2. Daubresse M, Chang HY, Yu Y, et al. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000-2010. *Med Care*. 2013;51(10):870-878.

3. Centers for Disease Control and Prevention. Vital signs: overdoses of prescription opioid pain relievers—United States, 1999-2008. *MMWR Morb Mortal Wkly Rep*. 2011;60(43):1487-1492.

4. Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. *JAMA*. 2013;309(7):657-659.

5. National Center for Injury Prevention and Control Division of Unintentional Injury Prevention. Policy impact: prescription painkiller overdoses. http://www.cdc.gov/homeandrecreationalsafety/pdf/policyimpact-prescriptionpainkillerod.pdf. Published November 2011. Accessed January 27, 2014.

6. National Conference of State Legislatures. State medical marijuana laws. http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx. Published July 7, 2014. Accessed July 14, 2014.

7. Nevada Division of Public and Behavioral Health. Medical Marijuana Program Monthly Report. http://health.nv.gov/MedicalMarijuana_Reports.htm. January 2, 2014. Accessed January 27, 2014.

8. Licensing and Regulatory Affairs Bureau of Health Care Services. Michigan Medical Marihuana Act Statistical Report for Fiscal Year 2013. http://www.michigan.gov/documents/lara/BHCS_MMMP_MCL_333.26426i12345_Report_FINAL_12-4-13_441658_7.pdf. Published December 4, 2013. Accessed January 31, 2014.

9. Oregon Public Health Authority. Oregon Medical Marijuana Program statistics. https://public.health.oregon.gov/diseasesconditions/chronicdisease/medicalmarijuanaprogram/pages/data.aspx. Published January 1, 2014. Accessed January 31, 2014.

10. Montana Department of Public Health and Human Services. Montana Marijuana Program Registry information. http://www.dphhs.mt.gov/marijuanaprogram/mmpregistryinformation.pdf. Published January 1, 2014. Accessed January 31, 2014.

11. Cerdá M, Wall M, Keyes KM, Galea S, Hasin D. Medical marijuana laws in 50 states: investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence. *Drug Alcohol Depend*. 2012;120(1-3):22-27.

12. Fiellin LE, Tetrault JM, Becker WC, Fiellin DA, Hoff RA. Previous use of alcohol, cigarettes, and marijuana and subsequent abuse of prescription opioids in young adults. *J Adolesc Health*. 2013;52(2):158-163.

13. *Marijuana and Medicine: Assessing the Science Base*. Washington, DC: National Academies Press; 1999.

14. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med*. 2014;370(23):2219-2227.

15. Centers for Disease Control and Prevention. CDC WONDER. National Vital Statistics System: 2010: Multiple Cause of Death Data. http://wonder.cdc.gov/mcd.html. Accessed May 30, 2014.

16. National Alliance for Model State Drug Laws. Prescription Drug Monitoring Program dates of operation. March 2014. http://www.namsdl.org/library/1E4C142E-1372-636C-DD7711E627D4B892/. Accessed April 2, 2014.

17. Office for State Tribal Local and Territorial Support Centers for Disease Control and Prevention. Menu of state prescription drug identification laws. http://www.cdc.gov/phlp/docs/menu-pdil.pdf. Published June 30, 2013. Accessed January 27, 2014.

18. Office for State Tribal Local and Territorial Support Centers for Disease Control and Prevention. Menu of pain management clinic regulation. http://www.cdc.gov/phlp/docs/menu-pmcr.pdf. Published September 28, 2012. Accessed January 27, 2014.

19. US Bureau of Labor Statistics. Annual state unemployment. http://www.bls.gov/lau/home.htm. Accessed February 5, 2014.

20. Unick GJ, Rosenblum D, Mars S, Ciccarone D. Intertwined epidemics: national demographic trends in hospitalizations for heroin- and opioid-related overdoses, 1993-2009. *PLoS One*. 2013;8(2):e54496. doi:10.1371/journal.pone.0054496.

21. Khosla N, Juon HS, Kirk GD, Astemborski J, Mehta SH. Correlates of non-medical prescription drug use among a cohort of injection drug users in Baltimore City. *Addict Behav*. 2011;36(12):1282-1287.

22. Cicero TJ, Ellis MS, Surratt HL. Effect of abuse-deterrent formulation of OxyContin. *N Engl J Med*. 2012;367(2):187-189.

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ by Vanessa Waltz on 08/31/2016

23. Peavy KM, Banta-Green CJ, Kingston S, Hanrahan M, Merrill JO, Coffin PO. "Hooked on" prescription-type opiates prior to using heroin: results from a survey of syringe exchange clients. *J Psychoactive Drugs*. 2012;44(3):259-265.

24. Angrist J, Pischke J. *Mostly Harmless Econometrics: An Empiricist's Companion*. Princeton, NJ: Princeton University Press; 2009.

25. Sidney S, Beck JE, Tekawa IS, Quesenberry CP, Friedman GD. Marijuana use and mortality. *Am J Public Health*. 1997;87(4):585-590.

26. Centers for Disease Control and Prevention. CDC grand rounds: prescription drug overdoses—a US epidemic. *MMWR Morb Mortal Wkly Rep*. 2012; 61(1):10-13.

27. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. *Br J Clin Pharmacol*. 2011;72(5):735-744.

28. Kumar RN, Chambers WA, Pertwee RG. Pharmacological actions and therapeutic uses of cannabis and cannabinoids. *Anaesthesia*. 2001;56 (11):1059-1068.

29. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. *Clin Pharmacol Ther*. 2011;90(6):844-851.

30. Lynch ME, Clark AJ. Cannabis reduces opioid dose in the treatment of chronic non-cancer pain. *J Pain Symptom Manage*. 2003;25(6):496-498.

31. Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med*. 2010;152(2):85-92.

32. Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*. 2011; 305(13):1315-1321.

33. Tanda G, Pontieri FE, Di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common μ_1 opioid receptor mechanism. *Science*. 1997;276(5321):2048-2050.

34. Scavone JL, Sterling RC, Van Bockstaele EJ. Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. *Neuroscience*. 2013;248:637-654.

35. Ashton CH. Pharmacology and effects of cannabis: a brief review. *Br J Psychiatry*. 2001;178: 101-106.

36. Hermann D, Klages E, Welzel H, Mann K, Croissant B. Low efficacy of non-opioid drugs in opioid withdrawal symptoms. *Addict Biol*. 2005;10 (2):165-169.

37. Scavone JL, Sterling RC, Weinstein SP, Van Bockstaele EJ. Impact of cannabis use during stabilization on methadone maintenance treatment. *Am J Addict*. 2013;22(4):344-351.

38. Lynskey MT, Heath AC, Bucholz KK, et al. Escalation of drug use in early-onset cannabis users vs co-twin controls. *JAMA*. 2003;289(4):427-433.

39. Yamaguchi K, Kandel DB. Patterns of drug use from adolescence to young adulthood, III: predictors of progression. *Am J Public Health*. 1984; 74(7):673-681.

40. Fergusson DM, Horwood LJ. Early onset cannabis use and psychosocial adjustment in young adults. *Addiction*. 1997;92(3):279-296.

41. Kandel DB. Does marijuana use cause the use of other drugs? *JAMA*. 2003;289(4):482-483.

42. Pacula RL, Sevigny EL. Marijuana liberalization policies: why we can't learn much from policy still in motion. *J Policy Anal Manage*. 2014;33(1):212-221.

Invited Commentary

Legalization of Medical Marijuana and Incidence of Opioid Mortality

Marie J. Hayes, PhD; Mark S. Brown, MD

The rapid acceleration of prescription opioid-related overdose deaths in the United States is correlated with the availability of stronger opioid medications, as well as a change in medical practice from withholding opioid medication because of dependence risk[1] to treating patients with chronic pain with opioids. Subsequently, the pendulum of concern has swung again, driven by the public health crisis of rising opioid analgesic addiction, overdose, and death. Opioid medications are problematic as a treatment for chronic pain. Opioid pharmaceuticals cause other adverse effects when used for long periods, such as tolerance, hyperalgesia, and gastrointestinal complications, making this class of drugs a poor choice for long-term use. As is well known, prescription opioids also have great abuse potential due to their influence on stress and reward circuits in the brain, promoting nonmedical use and abuse and diversion of prescription medications.

Related article page 1668

In this issue, Bachhuber et al[2] examine the link between medical marijuana laws and unintentional overdose mortality in which an opioid analgesic was identified. Using Centers for Disease Control and Prevention data, states with and without medical marijuana laws were contrasted for age-adjusted, opioid-related mortality. Overall, the incidence of opioid analgesic-associated mortality rose dramatically across the study period (1999-2010). States with medical marijuana laws had higher overdose rates than did those without such laws when population-adjusted mortality was analyzed across years, although the rise in deaths over the study period was similar for both groups. In contrast, a convincing protective effect of medical marijuana laws was found in a covariate-adjusted, time-series model in which opioid analgesic mortality declined steadily based on years since medical marijuana laws were enacted, termed *implementation*. The model included an analysis of the impact of critical policies for prescription opioid regulatory efforts: prescription monitoring programs, pharmacist collection of patient information, state and oversight of pain management clinics, as well as state unemployment rates. In states with medical marijuana laws, age-adjusted overdose deaths in which opioids were present declined in yearly estimates since medical marijuana law implementation. Indeed, across the 13 states that approved medical marijuana laws in the study period, the decline in opioid overdose mortality strengthened over time, achieving a mean decline of 24.8%. Worthy of note, a weak contribution was found for state oversight policies such as prescription monitoring and pain management clinics; this finding has been reported previously.[3] The striking implication is that medical marijuana laws, when implemented, may represent a promising approach for stemming runaway rates of nonintentional opioid analgesic-related deaths. If true, this finding upsets the applecart of conventional wisdom regarding the public health implications of marijuana legalization and medicinal usefulness.

The difficulty in endorsing the medical marijuana protective hypothesis is that medical marijuana laws are heterogeneous across states, engender controversy in state legisla-

Copyright 2014 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ by Vanessa Waltz on 08/31/2016

QUESTION #9 ATTACHMENTS
ATTACHMENT #3

ARTICLES FROM PEER-REVIEWED SCIENTIFIC JOURNALS

Cannabis as an Adjunct to or Substitute for Opiates in the Treatment of Chronic Pain. Lucas, Philippe. Journal of Psychoactive Drugs 08 Jun 2012; 44(2):125-133

Journal of Psychoactive Drugs, 44 (2), 125–133, 2012
Copyright © Taylor & Francis Group, LLC
ISSN: 0279-1072 print / 2159-9777 online
DOI: 10.1080/02791072.2012.684624

Routledge
Taylor & Francis Group

Cannabis as an Adjunct to or Substitute for Opiates in the Treatment of Chronic Pain

Philippe Lucas, M.A.[a]

Downloaded by [University of Montana] at 10:35 08 June 2012

Abstract — There is a growing body of evidence to support the use of medical cannabis as an adjunct to or substitute for prescription opiates in the treatment of chronic pain. When used in conjunction with opiates, cannabinoids lead to a greater cumulative relief of pain, resulting in a reduction in the use of opiates (and associated side-effects) by patients in a clinical setting. Additionally, cannabinoids can prevent the development of tolerance to and withdrawal from opiates, and can even rekindle opiate analgesia after a prior dosage has become ineffective. Novel research suggests that cannabis may be useful in the treatment of problematic substance use. These findings suggest that increasing safe access to medical cannabis may reduce the personal and social harms associated with addiction, particularly in relation to the growing problematic use of pharmaceutical opiates. Despite a lack of regulatory oversight by federal governments in North America, community-based medical cannabis dispensaries have proven successful at supplying patients with a safe source of cannabis within an environment conducive to healing, and may be reducing the problematic use of pharmaceutical opiates and other potentially harmful substances in their communities.

Keywords — addiction, cannabis, harm reduction, opiates, substitution effect

The medical use of cannabis can be traced back at least 5,000 years. The oldest reports originate in China and Egypt. It appears in a medical context in the Vedas, India's oldest religious text, and there are reports of its use as a medicine from fragments of Assyrian texts dating back to 700 B.C. The famous Chinese doctor Hua T'uo (approx. 100 A.D.) reportedly made use of a wine and cannabis mixture as an anaesthetic for surgical operations (Russo 2007; Fankhauser 2002).

There are numerous reports of the medicinal properties of cannabis from early in the nineteenth century, the most noted of which is an 1839 report titled "On the Preparations of the Indian Hemp, or Gunjah" by the Irish doctor William B. O'Shaughnessy (1843) where he describes diverse applications for cannabis, including rheumatism, rabies, cholera, tetanus, cramps and delirium tremens. A few years later Ernst Freiherr von Bibra published the renowned *Narcotics and the Human Being*, devoting thirty pages to the therapeutic use of cannabis preparations and hashish (Von Bibra 1855).

By the late nineteenth century, cannabis-based preparations were manufactured and marketed by Burroughs-Wellcome & Co. In England; and Bristol-Meyers Squib, Parke-Davis, and Eli Lilly in North America. The development of vaccines to prevent the spread of common infectious diseases, the increased use of opiates (with the introduction of the hypodermic syringe), and the discovery of aspirin at the end of the nineteenth and early twentieth century resulted in cannabis-based medicines losing their prevalence in the market place and Western pharmacopoeia (Grinspoon & Bakalar 1993). The U.S. Pharmacopoeia

[a]Research Affiliate, Centre for Addictions Research of BC, Victoria, BC, Canada.
Please address correspondence to Philippe Lucas, 1104 Topaz Ave., Victoria, BC, V8T2M7 Canada; email: plucasyyj@gmail.com

Downloaded by [University of Montana] at 10:35 08 June 2012

listed cannabis until 1941, stating that it can be used for treating fatigue, coughing, rheumatism, asthma, delirium tremens, migraine headaches, and the cramps and depressions associated with menstruation (Mikuria 1973).

Although modern research into therapeutic applications for cannabis has been seriously stymied by its prohibition in most of the Western world, extensive anecdotal reports and a growing body of laboratory and clinical research suggest that it may have many medicinal uses, including hunger stimulation for wasting syndrome; anti-emetic and anti-nausea properties in AIDS or cancer chemotherapy; antispasmodic properties for multiple sclerosis, epilepsy and other neurological dysfunctions; reducing intra-ocular eye pressure in glaucoma; and analgesic properties in a large number of chronic pain conditions (Hazekamp & Grotenhermen 2010; Ben Amar 2006; Grotenhermen & Russo 2002).

CANNABIS AND CHRONIC PAIN

The Canadian Psychological Association (CPA) defines chronic pain as being pain that doesn't go away, lasts over six months, or extends beyond the expected recovery time after an accident or medical intervention. Additionally, they suggest that chronic pain is a highly variable condition with many different causes:

> There are different types of chronic pain, many of which are not clearly understood. Chronic pain may be associated with an illness or disability, such as cancer, arthritis or phantom limb pain. Some types of chronic pain start after an accident. Others may start as acute episodes but then the pain becomes constant over time, such as low back pain. With some types of chronic pain, like migraine headaches, the pain is recurrent, rather than constant. There are many other kinds of chronic pain, such as chronic postsurgical pain, fibromyalgia, temporomandibular disorders, etc. While in some cases the cause of pain is known, in many other cases it is not clear why pain persists (CPA 2007).

Although statistics regarding chronic pain are difficult to come by, the CPA website states that:

> About one in ten Canadians has chronic pain. Chronic pain affects both sexes and while it is most common in middle age, it can occur at any age—from infancy to the elderly. Chronic pain can make simple movements hurt, disrupt sleep, and reduce energy. It can impair work, social, recreational, and household activities. People who have been injured in accidents may develop anxiety symptoms as well as pain. Chronic pain can have a negative impact on financial security, and can provoke alcohol or drug abuse. It can disrupt marital and family relationships . . . Given the impact pain can have on quality of life, it is no surprise that more than a quarter of all people who develop chronic pain also experience significant depression or anxiety (CPA 2007).

While numerous products are available for the relief of many different types of pain, there remains a significant group of patients for whom traditional pharmacological pain control is incomplete or ineffective. Existing pharmacological treatments with known side effects are widely used for analgesia, but may show a lack of efficacy in certain conditions (Russo 2008a). These agents include:

- Non-opioid analgesics
- Opioid analgesics
- Anticonvulsants
- Antimigraine drugs
- Tricyclic antidepressants
- Anti-inflammatories
- Steroids

Despite modern progress on the understanding and treatment of pain over the last century as well as a recent North American emphasis on treating pain stemming from other medical conditions, many problems still remain in providing safe and effective analgesia for all those with a legitimate need for pain relief (Russo 2008a).

Chronic pain is highly subjective in nature, and sufferers of the same chronic pain condition may experience very different symptomology. Fibromyalgia, a chronic pain syndrome of unknown origins associated with depression and chronic fatigue is a good example of this effect. It is interesting to note that Russo (2008a, b) has theorized that intractable and difficult to treat pain conditions like fibromyalgia may be related to a condition he terms *clinical endocannabinoid deficiency* (CECD), which is an imbalance in the body's own internal cannabinoid system. Furthermore there are numerous different origins for chronic pain—visceral, somatic, neurogenic, etc.—which may explain why so many sufferers report poor control with standard pharmaceuticals. Therefore chronic pain sufferers are in no way homogeneous, indicating the need for variable and individual treatment regimens and dosages (Mersky & Bogduk 1994).

In Europe, chronic musculoskeletal pain of a disabling nature affects over 25% of elderly people (Frondini et al. 2007). Responses to a 2005 poll indicate that 19% of adults (38 million) in the U.S. have chronic pain, and 6% (or 12 million) have utilized cannabis in attempts to treat it (ABC News 2005). Ware and colleagues (2005) report that 25% of chronic pain sufferers in the U.K. use cannabis, and that medical cannabis was largely associated with "younger age, male gender and previous recreational use." A further assessment of cannabis use and chronic pain by Ware and Beaulieu and Ware (2007) found that "there is increasing evidence that cannabinoids are safe and effective for refractory chronic pain conditions including neuropathic pain associated with multiple sclerosis, rheumatoid arthritis, and peripheral neuropathy associated with HIV/AIDS", concluding that more research is needed.

CANNABINOID RECEPTORS AND ANALGESIA

Over the last 15 years, CB1 and CB2 receptors have been identified (Pertwee 2002). CB1 receptors are of particularly high concentration in the central nervous

Downloaded by [University of Montana] at 10:35 08 June 2012

system, including several areas of the central nervous system that mediate the perception of pain (Walker et al. 1999). CB2 receptors are found mostly in immune tissue, such as leukocytes, the spleen and tonsils. These receptors are absent from the brain stem, thus explaining the lack of classic opioid side effects such as respiratory depression. This may prove to be an advantage of cannabinoid-based drugs over opiates. Another similarity with the opioid system is the existence of endogenous cannabinoid receptor agonists, the most studied of which is anandamide (Pertwee 2002). Evidence shows that this endocannabinoid can serve as a neuromodulator or neurotransmitter (DiMarzo et al. 1998), and it has been found that cannabinoid receptors outside of the brain and spine are affected when skin or flesh is cut or injured; anandamide is released and helps modulates the pain associated with injury. Rats treated with a chemical blocker for anandamide showed an extended and more severe response to pain (Calignano et al. 1998). There is recent evidence that anandamide and methandamide can activate vanilloid receptors on sensory neurons. The extent to which exogenous or endogenous cannabinoids can modulate pain through vanilloid receptors that are known to be present on nociceptive sensory neurons has yet to be fully established (Pertwee 2002).

HUMAN STUDIES ON CANNABINOIDS AS ANALGESICS

Although human studies on the therapeutic effects of cannabis have been significantly limited by a restrictive legal regime and the unavailability of cannabis products to conduct such studies, available research suggests that cannabis has strong potential as an analgesic. An early study of synthetic delta-9-tetrahydrocannabinol (hereafter referred to as "THC" for the rest of this paper) administered orally in 10 to 25 mg doses was shown to relieve pain in cancer patients without significant effects on mood (Davies et al. 1974). A study by Blake and colleagues (2006) examining the effects of Sativex, an oromucosal whole plant cannabis extract with a THC/CBD ratio of 50:50, on rheumatoid arthritis reported significant analgesic effect compared to placebo. Although some mild or moderate adverse effects like dizziness were reported by the active treatment group, Sativex was generally well-tolerated.

In a study to determine the effect of smoked cannabis on pain related to HIV-associated sensory neuropathy and an experimental pain model, researchers found that smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain (Abrams et al. 2007). A study by Wilsey and colleagues (2008) on smoked cannabis and neuropathic pain compared the effect of high THC (7%) cannabis with low THC (3.5%) cannabis and placebo. The results showed that both active preparations were effective at reducing pain, with no apparent correlation between dose levels and pain relief. Although some moderate adverse effects were identified, the treatment was well-tolerated.

Ware and colleagues (2010) recently published results from a randomized clinical trial on smoked cannabis and chronic pain, finding that 9.4% THC cannabis used three times daily for five days reduced the intensity of pain and improved sleep in patients compared to placebo, and was well tolerated by the 21 patients who concluded the study. Although study participants reported mild or moderate adverse effects, these were comparable to the adverse effects of non-smoked pharmaceutical cannabinoid medicines.

CANNABINOIDS AND OPIOIDS IN THE TREATMENT OF CHRONIC PAIN

Opiates are among the most widely prescribed treatments for chronic pain in the world (Dhalla, Mamdani & Sivilotti 2009; Compton & Volkow 2006). Evidence of the medical use of opiates dates back at least to the Ebers Papyrus from 1500 B.C. (Brownstein 1993), and there is little doubt that despite the potential for serious side effects, including death, and the ongoing development of alternative approaches to pain relief, pharmaceutical opiates will continue to be one of the most effective tools available for the treatment of chronic pain. However, a major personal and public health concern associated with the use of pharmaceutical opiates is dependence. In fact, according to the US Substance Abuse and Mental Health Services Administration, the dependence on and abuse of pharmaceutical medications is currently the fastest growing form of problematic substance use in North America (SAMHSA 2007). As a result of this increase in the use and abuse of prescription pharmaceuticals, Moore and colleagues (2007) report that serious adverse events and deaths resulting from prescription drug use in the U.S. nearly tripled between 1998 and 2005. Addiction to and abuse of pharmaceutical opiates has been identified as one of the main personal and public health concerns associated with this trend (Dhalla, Mamdani & Sivilotti 2009; Fischer et al. 2008; Compton & Volkow 2006).

The following research suggests that when used in conjunction with opiates, cannabinoids can lead to a greater cumulative relief of pain, which may in turn result in a reduction in the use of opiates (and associated side effects) by patients in a clinical setting (Cichewicz et al. 1999). This may not only have positive impact on patient pain levels and overall quality of life, but also on the overall morbidity and mortality associated with pharmaceutical opiates, and on the high levels of opiate addiction in both patients and the general population.

A randomized double-blind crossover placebo-controlled study of oral medication for pain in ten terminal cancer patients comparing 5, 10, 15, and 20 mg of THC in

Downloaded by [University of Montana] at 10:35 08 June 2012

single doses with placebo found a significant dose-related analgesic effect at the two higher doses (Noyes et al. 1975a). A larger follow-up study of 36 terminally ill patients with cancer pain was designed to compare 10 and 20 mg THC with 60 and 120 mg codeine and placebo. The results suggest that 10 mg THC was slightly less effective than 60 mg codeine, and that 20 mg THC was slightly more effective than 120 mg of codeine (Noyes et al. 1975b).

A later single-patient study examining the analgesic effects of oral doses of 5mg of THC, 50 mg of codeine, and placebo showed that both active preparations were significantly more effective than placebo at relieving MS-related pain. The only major reported difference between the active drugs was that THC relieved spasticity better than codeine (Maurer et al. 1990).

A study by Pinsger (2006) on the effects of nabilone (a synthetic cannabinoid) as an adjunct to existing chronic pain therapy resulted in reduced pain and improved quality of life. Although some mild to moderate side effects were noted, the majority of patients reported overall benefits when compared to their usual chronic pain treatment.

A clinical study by Nurmikko (2007) examining the effects of Sativex as an adjunct to existing stable analgesia in patients suffering from peripheral neuropathic pain showed that 26% of participants reported more than 30% reductions in pain intensity, compared with 15% in those using placebo. Adverse events were few and largely mild or moderate.

A randomized clinical study by Skrabek and colleagues (2008) on nabilone as an adjunct treatment for 15 patients affected by fibromyalgia reported significant benefits in pain and overall function. Mild side-effects were reported, including weight gain, but participants indicated overall increases in quality of life.

Narang and colleagues (2008) conducted a phase 1 and phase 2 study examining the efficacy of dronabinol as an adjunct to opioid therapy for the treatment of chronic pain. Both studies showed that dronabinol decreased pain intensity and increased quality of life compared to baseline opiate therapy. The findings also reported mild to moderate side effects including drowsiness, but patients also reported an improvement in the quality of sleep and overall satisfaction with the treatment compared to placebo.

Additionally, studies also show that cannabinoids can prevent the development of tolerance to and withdrawal from opiates (Cichewicz & Welch 2003), and can even rekindle opiate analgesia after a prior dosage has become ineffective (Russo 2008a; Cichewicz & McCarthy 2003). Furthermore, research by Blume and colleagues (2011) and Ramesh and colleagues (2011) suggests that cannabinoid receptors might interrupt signaling in the opioid receptor systems, affecting both cravings for opiates and withdrawal severity.

GATEWAY OR SAFER SUBSTITUTE?

Despite its low potential for individual harm or abuse and minimal impact on public health and associated social costs, the medical use of cannabis remains controversial with police, physicians, and policymakers. One of the main concerns cited by opponents is that it could lead to either dependence on cannabis, or potentially be a "gateway" to the use of and addiction to hard drugs. The premise of the *gateway* or *stepping stone* hypothesis is that the use of one substance may subsequently lead to the use of another. In regards to illicit substance use, this theory suggests that the use of cannabis may facilitate the use of potentially more harmful/addictive substances such as opiates, cocaine, or amphetamines. The evidential foundation for this theoretical construct is based on research indicating that most people who use so-called "hard" drugs such as heroin or cocaine report a prior use of cannabis. Lessem and colleagues (2006: 499) state that:

> The "gateway theory" is comprised of two interrelated observations. The first is that marijuana use is associated with later, non-marijuana, illicit drug use, and the second is that there is a temporal ordering of substance experimentation in which lower order substances, which are more commonly used, precede the use of higher order substances. Thus, typically one licit substance such as alcohol or cigarettes is used first in a sequence. Marijuana is usually the first illicit substance used before progressing on to using other illicit substances.

While most studies have focused on the social or economic determinants that could lead cannabis users to experiment with other substances (Wagner & Anthony 2002; Pacula et al. 2002), some research suggests that this progression may be due to biological changes in individuals exposed to cannabis (Lessem et al. 2006).

However, both social and clinical research has convincingly debunked the gateway or stepping stone hypothesis. The Senate Special Committee on Illegal Drugs final report on cannabis (Nolin et al. 2002) reviewed all of the available evidence on the topic and drew the following conclusions:

> We feel that the available data show that it is not cannabis itself that leads to other drug use but the combination of the following factors:
>
> - Factors related to personal and family history that predispose to early entry on a trajectory of use of psychoactive substances starting with alcohol;
> - Early introduction to cannabis, earlier than the average for experimenters, and more rapid progress towards a trajectory of regular use;
> - Frequenting of a marginal or deviant environment;
> - Availability of various substances from the same dealers.

Thus, while it may be true that many people who use "hard" drugs have also used cannabis, the reasons range

Downloaded by [University of Montana] at 10:35 08 June 2012

from social factors such as poverty to the illegal status of the substance, which results in black market control over its distribution. As the Canadian Senate discovered, drug use trends in Canada simply do not support the *gateway* or *stepping stone* hypothesis, concluding that "if we come back to trends in drug use in the population, while more than 30% have used cannabis, less than 4% have used cocaine and less than 1% heroin" (Nolin et al. 2002: 126).

The counterpoint to gateway theory is *substitution effect*, an economic theory that suggests that variations in the availability of one product (through changes in cost or social policy), may affect the use of another:

> Within a behavioral economic framework, reinforcer interactions are classified into multiple categories; two commodities may be "substitutes" for one another (e.g., two forms of opioid drugs); they may be "complementary," whereby the value of one is enhanced by consumption of the other; or they may be "independent," such that the reinforcing functions of one are not altered by the presence or absence of the other (Hursh et al. 2005: 24).

Changes in the use of cannabis, opiates, or other drugs—whether for medical or recreational use—can be the result of: (a) economic shifts affecting end-user costs; (b) changes in policy which effect availability; (c) legal risk and associated repercussions; or (d) psychoactive/pharmacological substitution. In regards to psychoactive substitution, Hursh and colleagues (2005: 25) suggest that "pharmacological therapies for the treatment of drug abuse can also be conceptualized as alternative commodities that either substitute for illicit drug use (e.g., agonist therapy) or reduce the potency of illicit drugs directly (e.g., narcotic antagonist therapy)." Perhaps the best example of the viability of psychoactive substitution is the now-common prescription use of methadone as a substitute to injection heroin use. This substitution reduces some of the risks associate with injection drug use, including overdose and disease transmission, since drug levels are constant and predictable, and methadone is taken orally rather than injected. Additionally, since methadone is less expensive than heroin (and is subsidized by provincial health registries in Canada), this substitution has the added potential benefit of reducing drug-related theft and crime. However, many methadone patients have reported health concerns associated with its use as well, and recent research suggests that prescription heroin or opiates may be a safer and more effective alternative for users than either black-market heroin or methadone (NAOMI Study Team 2008).

As suggested earlier, not all psychoactive substitution is the result of a deliberate decision made on an individual basis. At the population level it is often the unintended result of public policy shifts or other social changes, such as cost, criminalization or availability. In an examination of hospital drug episodes in 13 U.S. states that decriminalized the personal recreational use of cannabis in the 1970s, Model (1993) found that users shifted from using harder drugs to marijuana after its legal risks were decreased. Findings from Australia's 2001 *National Drug Strategy Household Survey* (AIHW 2002) specifically identify substitution effect, indicating 56.6% of heroin users substituted cannabis when their substance of choice was unavailable. The survey also found that 31.8% of people who use pharmaceutical analgesics for nonmedical purposes reported using cannabis when painkillers weren't available. This evidence strongly suggests that the increased availability of cannabis (through a reduction of penalties or actual regulated, legal access) might lead to a population level reduction in the licit and illicit use of opiates and pharmaceutical analgesics and the associated personal, social and public health harms and costs.

The illegal status of cannabis across most of the world has made clinical trials on cannabis as a treatment for problematic substance use nearly impossible, but a number of studies on both humans and animals suggest that the cannabinoid system plays a role in dependence and addiction to both licit and illicit substances. Current research shows that behavioral effects and motivational responses induced by nicotine can be modulated by the endocannabinoid system (Balerio, Aso & Maldonado 2006).

Additionally, a study by the New York State Psychiatric Institute on people with cocaine dependence and comorbid attention deficit hyperactivity disorder has shown that cannabis users were more successful than other patients in abstaining from cocaine use (Aharonovich et al. 2006). An earlier study by Labigalini Jr. and colleagues (1999) also noted this effect on people with a dependence on crack cocaine, reporting that 68% of the 25 subjects who self-medicated with cannabis in order to reduce cravings were able to give up crack altogether. Researchers theorized that this phenomenon is biological and psychological. Addiction to stimulants result in a decline in the cerebral activity involving serotonin transmitters, which is believed to result in increased impulsiveness and craving. Cannabinoids act as seratoninenergic agonists, and as serotonin levels increase, impulsiveness and craving decline. Reports from study subjects also suggested that the ritual of preparing cannabis to smoke helped reduce the habituated psychological dependence associated with the preparation of crack cocaine.

More recently, a study by Reiman (2009) of 350 cannabis patients who purchased their medicine from a community-based dispensary in Berkeley suggests that many patients report using it as a substitute for other potentially more dangerous substances, particularly pharmaceuticals. Results show that 40% report using cannabis as a substitute for alcohol, 26% as a substitute for illicit drugs, and 66% as a substitute for prescription drugs. Patients cited a number of reasons for using cannabis instead of pharmaceutical drugs: 65% reported less adverse

side effects, 57% cited better symptom management, and 34% found that cannabis had less withdrawal potential than their other medications. A similar survey study of 400 patients is currently underway in four medical cannabis dispensaries located in British Columbia, Canada.

Finally, exploratory research suggests that cannabis use does not interfere with formal substance abuse treatment. Data from the California Outcomes Measurement System (CalOMS) were compared for medical (authorized) marijuana users (N = 18) and non-marijuana users who were admitted to a public substance abuse treatment program in California. Behavioral and social treatment outcomes recorded by clinical staff at discharge and reported to the California Department of Alcohol and Drug Programs were assessed for both groups, and although the sample was small, cannabis use did not seem to compromise substance abuse treatment among the medical marijuana using group, who (based on these preliminary data) fared equal to or better than nonmedical marijuana users in several important outcome categories (e.g., treatment completion, criminal justice involvement, medical concerns) (Schwartz 2010).

MAXIMIZING THE POTENTIAL BENEFITS OF MEDICAL CANNABIS USE

While much of the research cited above suggests that cannabinoids can be safe and effective adjuncts or alternatives to pharmaceutical opiates, the illegality of cannabis and the associated stigma in patients who might benefit from its use has significantly hampered research into therapeutic potential of both whole-plant preparations and pharmaceutical cannabinoid treatments (Lucas 2009). As a result, the international prohibition on cannabis has not only led to significant social costs with little impact on overall usage rates in the general population, it may also be inadvertently leading to increased suffering and addiction in patients suffering from chronic pain.

In light of recent evidence that cannabis not only helps relieve the symptoms of a number of serious conditions, but might also increase the success rate of both HIV/AIDS and hepatitis C treatment (Abrams et al. 2007; Sylvestre, Clements & Malibu 2006), it can be argued that the governments throughout the world have a moral, ethical obligation to ensure that this medicine is legally available to patients who might benefit from its use. The same argument could be made if cannabis is shown to be effective in reducing the non-prescription use of other potentially more dangerous licit and illicit substances, including pharmaceutical opiates.

In an essay on the globalization of ayahuasca, which is an entheogenic plant-based medicine from the Amazon basin that, like cannabis, has a long history of traditional use, Tupper (2007:5) suggests that:

> . . . a shift to a generative metaphor of drugs as "tools" offers a much more nuanced way to conceiving of the risks and benefits posed by ayahuasca practices. Rather than essentializing psychoactive substances as inherently dangerous, to regard them as tools—ancient technologies for altering consciousness . . . allows for a realistic assessment of their potential benefits and harms according to who uses them, in what contexts and for what purposes.

Although this may appear reflective of a harm reduction approach to drugs, Tupper insists that conceptualizing drugs as "tools" necessitates a move beyond policies simply based on reducing potential harms, suggesting that benefits also need to be explored and where possible, maximized by government policies and practices. He continues:

> The philosophy of harm reduction is also further illuminated by a shift to the generative metaphor of drugs as tools. To the extent that policy-makers or practitioners emphasize a behaviour's potential risks, the harm reduction policy approach is justified. However, the tool metaphor for psychoactive substances warrants a corollary notion of "benefit maximization," the other side of the harm reduction coin. Instead of approaching drug policy from a deficit perspective . . . the tool metaphor opens discursive avenues for realistic policy considerations of benefits as well as harms.

As with ayahuasca, the concept of harm reduction may not be wholly appropriate to maximize the potential health benefits of medical cannabis. A great deal of research indicates that cannabis is far less dangerous than licit substances like alcohol and tobacco, and safer than many over-the-counter or prescription pharmaceuticals (Grotenhermen & Russo 2002; Grinspoon 1999; Grinspoon & Bakalar 1998), and many have suggested that the greatest potential harms of cannabis use are based on a its illegal status, including arrest or the vagaries of the black-market (Nolin et al. 2002). In this light, harm reduction policies associated with the use of other substances that are designed to prevent the spread of infectious disease, reduce the likelihood of overdose and stem addiction and related crime—such as needle-exchange, safe consumption sites, heroin maintenance or opiate substitution—don't readily apply to the use and distribution of medical cannabis.

Research suggests that community-based medical cannabis dispensaries appear to both reduce the potential harms and maximize the benefits of medical cannabis use by removing some of the social stigma associated with the therapeutic use of cannabis and by separating medical cannabis access from the potential dangers of the black market (i.e. lack of safety and quality assurances, pressure to try other illicit substances, prohibition–associated harms such as arrest and prosecution) (Lucas 2010, 2009, 2008; Reiman 2009, 2006; Belle-Isle & Hathaway 2007; Belle-Isle 2006). Additionally, they increase access to a safe consistent supply of medical cannabis within an environment conducive to health and healing, which may be directly

Downloaded by [University of Montana] at 10:35 08 June 2012

and indirectly leading to a reduction in the use of pharmaceuticals, alcohol and illicit substances in their community. Moreover, nonprofit dispensaries like the Vancouver Island Compassion Society (VICS) contribute to the overall social capital of their client-members through membership, joint knowledge creation, and inclusion and participation in a social movement informed by public health, harm reduction and human rights (Lucas 2009; Belle-Isle & Hathaway 2007; Belle-Isle 2006: Reiman 2006). As such this community-based, patient-centered model is growing in both legitimacy and popularity, and is now the predominant means for patients access in Canada and in many U.S. state-run medical cannabis programs (Lucas 2010, 2009; Reiman 2006).

DISCUSSION

Evidence is growing that cannabis can be an effective treatment for chronic pain, presenting a safe and viable alternative or adjunct to pharmaceutical opiates. Addiction to pharmaceutical opiates has been noted by the medical community as one of the common side-effects of extended use by patients (such as those suffering from chronic pain), and a growing body of research suggests that some of the biological actions of cannabis and cannabinoids may be useful in reducing this dependence. Therefore cannabis has the potential to both relieve suffering for those suffering from chronic pain, and to reduce morbidity and mortality often associated the use and abuse of pharmaceutical opiates.

Since both the potential harms of pharmaceutical opiates and the relative safety of cannabis are well established, research on substitution effect suggests that cannabis may be effective in reducing the use and dependence of other substances of abuse such as illicit opiates, stimulants and alcohol. As such, there is reason to believe that a strategy aiming to maximize the therapeutic potential benefits of both cannabis and pharmaceutical cannabinoids by expanding their availability and use could potentially lead to a reduction in the prescription use of opiates, as well as other potentially dangerous pharmaceutical analgesics, licit and illicit substances, and thus a reduction in associated harms. The resulting public health benefits would include lower rates of alcohol-related automobile accidents, less domestic violence, reductions in drug-related crimes such as break-ins and petty theft, and reduced drug and alcohol-related morbidity and mortality.

International experience appears to support this premise. A recent report by the European Monitoring Center for Drugs and Drug Addiction shows that the Netherlands long-time policy of de facto cannabis decriminalization has resulted in some of the lowest drug-induced death rates in Europe, while countries with more severe cannabis laws and drug policies, such as Norway and Sweden, rank among the highest (EMCDDA 2009). Despite such compelling evidence, much of the world's current and long-standing prohibitionist approach to cannabis continues to act as a barrier to these potential personal and public health benefits, and to criminalize otherwise law-abiding citizens as well as many critically and chronically ill patients.

Community-based dispensaries have emerged as a disjointed but effective social movement focused on the principles of harm reduction and human rights. Although they remain largely unregulated or even illegal in much of Canada and U.S., these dispensaries have been successful in establishing a safe and consistent supply of medical cannabis, advocating for patient rights, and adding to society's knowledge and understanding of the therapeutic potential of cannabis through scientific research. Additionally, evidence suggests that they are reducing the problematic use of opiates, alcohol and other substances in their communities. If we are to ever benefit from drug policies based on science, reason and compassion, national governments will need to abandon the misinformation that underscores drug prohibition, and to start promoting and supporting research into cannabis and cannabinoids as both a relatively safe and effective medicine in the treatment of chronic pain and other serious medical conditions, and as a potential "exit drug" for problematic substance use.

REFERENCES

ABC News. 2005. *ABC News/USA Today/Stanford Medical Center Poll: Pain.* Available at http://abcnews.go.com/images/Politics/979a1TheFightAgainstPain.pdf

Abrams, D.; Jay, C.A.; Shade, S.B.; Vizoso, H.; Reda, H. 2007. Cannabis in painful HIV-associated sensory neuropathy—A randomized placebo-controlled trial. *Neurology* 68: 515–21.

Aharonovich, E.; Garawi, F.; Bisaga, A.; Brooks, D.; Raby, W.N.; Rubin, E.; Nunes, E.V & Levin, F.R. 2006. Concurrent cannabis use during treatment for comorbid ADHD and cocaine dependence: Effects on outcome. *American Journal of Drug and Alcohol Abuse* 32 (4): 629–35.

Australian Institute of Health and Welfare (AIHW). 2002. 2001 *National Drug Strategy Household Survey: First results.* AIHW cat. no. PHE 35. Drug Statistics Series No. 9. Canberra: AIHW. Available at http://www.aihw.gov.au/publication-detail/?id=6442467340

Balerio, G.; Aso, N. E. & Maldonado, R. 2006. Role of the cannabinoid system in the effects induced by nicotine on anxiety-like behaviour in mice. *Psychopharmacology* Jan 14: 1–10.

Beaulieu, P. & Ware, M.A. 2007. Reassessment of the role of cannabinoids in the management of pain. *Current Opinions in Anaesthesiology* Oct 20 (5): 473–77.

Belle-Isle. L. 2006. *Cannabis as Therapy for People Living With HIV/AIDS: Our Right. Our Choice.* Canadian AIDS Society. Available at http://www.cdnaids.ca/files.nsf/pages/cannabis_as_therapy_eng/file/Cannabis_as_Therapy_eng.pdf

Downloaded by [University of Montana] at 10:35 08 June 2012

Downloaded by [University of Montana] at 10:35 08 June 2012

Belle-Isle, L. & Hathaway, A. 2007. Barriers to access to medical cannabis for Canadians living with HIV/AIDS. *AIDS Care* 19 (4): 500–06.

Ben Amar, M. 2006. Cannabinoids in medicine: A review of their therapeutic potential. *Journal of Ethnopharmacology* 105 (1–2): 1–25.

Blake, D.R.; Robson, P.; Ho, M.; Jubb, R.W. & McCabe, C.S. 2006. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology* 45 (1): 50–52.

Blume, L.; Bass, C.; Childers, S.; Dalton, G.; Richardson, J.; Selley D.; Xiao, R. & Howlett A. 2011. Cannabinoid receptor interacting protein 1A (CRIP1A) modulates striatal neuropharmacology and signal transduction in cannabinoid, dopamine and opioid receptor systems. Presented at the 21st Annual Symposium on the Cannabinoids. International Cannabinoid Research Society, Research Triangle Park, NC. USA.

Brownstein, M.J. 1993. A brief history of opiates, opioid peptides, and opioid receptors. *Proceedings of the National Academy of Science* 90 (12): 5391–93.

Calignano, A.; La Rana, G.; Giuffrida, A. & Piomelli, D. 1998. Control of pain initiation by endogenous cannabinoids. Nature 394: 277–81.

Canadian Psychological Association (CPA). 2007. *Chronic Pain.* Available at www.cpa.ca/psychologyfactsheets/chronicpain/

Cichewicz, D.L. & McCarthy, E.A. 2003. Antinociceptive synergy between delta(9)-tetrahydrocannabinol and opioids after oral administration. *Journal of Pharmacology and Experimental Therapeutics* 304 (3): 1010–15.

Cichewicz, D.L. & Welch, S.P. 2003. Modulation of oral morphine antinociceptive tolerance and naloxone-precipitated withdrawal signs by oral Delta 9-tetrahydrocannabinol. *Journal of Pharmacology and Experimental Therapeutics* 305 (3): 812–17.

Cichewicz, D.L.; Martin, Z.L.; Smith, F.L. & Welch, S.P. 1999. Enhancement of mu opioid antinociception by oral delta9- tetrahydrocannabinol: Dose-response analysis and receptor identification. *Journal of Pharmacology and Experimental Therapeutics* 289 (2): 859–67.

Compton, W. & Volkow, N. 2006. Major increases in opioid analgesic abuse in the United States: Concerns and strategies. *Drug & Alcohol Dependence* 81: 103–07.

Davies, B.H.; Weatherstone, R.M.; Graham, J.D.P. & Griffiths, R.D. 1974. A pilot study of orally administered delta-1-(trans)-tetrahydrocannabinol in the management of patients undergoing radiotherapy for carcinoma of the bronchus. *British Medical Journal of Pharmacology* 1: 301–06.

Dhalla, I.; Mamdani, M. & Sivilotti, M. 2009. Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *Canadian Medical Association Journal* 181 (12): 891–96.

DiMarzo, V.; Melck, D.; Bisogno, T. & DePetrocellis, L. 1998. Endocannabinoids: Endogenous cannabinoid receptor ligands with neuromodulatory action. *Trends in Neuroscience* 21 (12): 521–28.

European Monitoring Center for Drugs and Drug Addiction (EMCDDA). 2009. *2009 Annual Report on The State of the Drugs Problem in Europe.* Available at http://www.emcdda.europa.eu/publications/annual-report/2009

Fankhauser, M. 2002. History of cannabis in Western medicine. In: F. Grotenhermen & E. Russo (Ed.) *Cannabis and Cannabinoids*. New York: Hayward Integrative Press.

Fischer, B.; Rehm, J.; Goldman, B. & Popova, S. 2008. Non-medical use of prescription opioids and public health in Canada: An urgent call for research and intervention development. *Canadian Journal of Public Health* 99: 182–84.

Frondini, C.; Lanfranchi, G.; Minardi, M. & Cucinotta, D. 2007. Affective, behavior and cognitive disorders in the elderly with chronic musculoskelatal pain: The impact on an aging population. *Archives of Gerontology and Geriatrics* 44 (Supplement 1): 167–71.

Grinspoon, L. 1999. Medical marijuana in a time of prohibition. *International Journal of Drug Policy* 10: 145–56.

Grinspoon, L. & Bakalar, J. B. 1998. Missed opportunities—Beneficial uses of illicit drugs. In: R. Coomber (Ed.) *The Control of Drugs and Drug Users*. Amsterdam: Harwood Academic Press.

Grinspoon, L. & Bakalar, J.B. 1993. *Marijuana the Forbidden Medicine.* New Haven, CT: Yale University Press.

Grotenhermen, F. & Russo, E. 2002. *Cannabis and Cannabinoids.* New York: Haworth Press.

Hazekamp, A. & Grotenhermen, F. 2010. Review on clinical studies with cannabis and cannabinoids 2005–2009. *Cannabinoids 2010* 5 (Special issue): 1–21.

Hursh, S. R.; Galuska, C.M.; Winger, G. & Woods, J.H. 2005. The economics of drug abuse: A quantitative assessment of drug demand. *Molecular Interventions* 5: 20–28.

Labigalini Jr., E.; Rodrigues, L.R. & Da Silveira, D.X. 1999. Therapeutic use of cannabis by crack addicts in Brazil. *Journal of Psychoactive Drugs* 31 (4): 451–55.

Lessem, J.M.; Hopfer, C.J.; Haberstick, B.C.; Timberlake, D.; Ehringer, M.A.; Smolen, A. & Hewitt, J.K. 2006. Relationship between adolescent marijuana use and young adult illicit drug use. *Behavior Genetics* 36 (4): 498–506.

Lucas, P. 2010. Patient-centered strategies to counter stigma, oppression and forced incarceration in the C/S/X and medical cannabis movements. *Interface* 2 (2): 149–67.

Lucas, P. 2009. Moral regulation and the presumption of guilt in Health Canada's medical cannabis policy and practice. *International Journal of Drug Policy* 20: 296–303.

Lucas, P. 2008. Regulating compassion; An overview of Health Canada's medical cannabis policy and practice. *Harm Reduction Journal* 5: 5.

Maurer, M.; Henn, V.; Dittrich, A. & Hoffman, A. 1990. Delta-9-THC shows antispastic and analgesic effects in a single case double blind trial. *European Archives of Psychiatry and Clinical Neuroscience* 240 (1): 1–4.

Mersky, H. & Bogduk, N. 1994. *Classification of Chronic Pain. Descriptions of Chronic Pain Syndromes and Definition of Pain Terms.* International Association for the Study of Pain. Seattle, WA: IASP Press.

Mikuriya, T. 1973. *Marijuana: Medical Papers 1839–1972.* Oakland, CA: Medi-Comp Press.

Model, K. 1993. The effect of marijuana decriminalization on hospital emergency drug episodes: 1975-1978. *Journal of the American Statistical Association* 88: 423.

Moore, T.J.; Cohen, M.R. & Furberg, C.D. 2007. Serious adverse drug events reported to the Food and Drug Administration, 1998–2005. *Archives of Internal Medicine* 167 (16): 1752–59.

NAOMI Study Team. 2008. *Reaching the Hardest to Reach—Treating the Hardest-to-Treat: Summary of the Primary Outcomes of the North American Opiate Medication Initiative (NAOMI).* Available at http://vancouver.ca/fourpillars/documents/NAOMIResultsSummary-Oct172008.pdf

Narang, S.; Gibson, D.; Wasan, A.D.; Ross, E.L.; Michna, E.; Nedeljkovic, S.S. & Jamison, R.N. 2008. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *Journal of Pain* 9 (3): 254–64.

Nolin, P.C.; Kenny, C.; Banks, T.; Malieu, S. & Rossiter, E. 2002. *Report of the Senate Special Committee on Illegal Drugs.* Ottawa: Senate of Canada.

Noyes, R.; Brunk, S.F.; Baram, D.A. & Canter, A. 1975a. Analgesic effects of delta-9-THC. *Journal of Clinical Pharmacology* 15 (2–3): 139–43.

Noyes, R.; Brunk, S.F.; Avery, D.H. & Canter, A. 1975b. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clinical Pharmacology and Therapeutics* 18 (1): 84–89.

Nurmikko, T.J.; Serpell, M.G.; Hoggart, B.; Toomey, P.J.; Morlion, B.J. & Haines, D. 2007. Sativex successfully treats neuropathic pain

characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial. *Pain* 133 (1–3): 210–20.

O'Shaughnessy, W.B.O. 1843. On the preparations of the Indian hemp, or gunjah. *Provincial Medical Journal* 363–69.

Pacula, R.L.; Grossman, M.; Chaloupka, F.J.; O'Malley, P.M.; Johnston, L.D. & Farrelly, M.C. 2002. Marijuana and youth. In: J. Gruber (Ed.) *Risky Behavior among Youths: An Economic Analysis*. Chicago: University of Chicago Press.

Pertwee, R.G. 2002. Sites and mechanisms of action. In: F. Grotehhermen & E. Russo (Eds.) *Cannabis and Cannabinoids*. New York: Hayworth Press.

Pinsger, M.; Schimetta, W.; Volc, D.; Hiermann, E.; Riederer, F & Pölz, W. 2006. Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain: A randomized controlled trial. [in German] *Wien Klin* 118 (11–12): 327–35.

Ramesh, D.; Owens, R.; Kinsey, S.; Cravatt, B.; Sim-Selley, L. & Lichtman, A. 2011. Effects of chronic manipulation of the endocannabinoid system on precipitated opioid withdrawal. Presented at the 21st Annual Symposium on the Cannabinoids. International Cannabinoid Research Society, Research Triangle Park, NC, USA.

Reiman, A. 2009. Cannabis as a substitute for alcohol and other drugs. *Harm Reduction Journal* 6: 35.

Reiman, A. 2006. Cannabis Care: Medical cannabis facilities as health service providers. Dissertation. School of Social Welfare/Alcohol Research Group, University of California, Berkeley.

Russo, E.B. 2008a. Cannabinoids in the management of difficult to treat pain. *Therapeutics and Clinical Risk Management* 4 (1): 245–59.

Russo, E.B. 2008b. Clinical endocannabinoid deficiency (CECD): Can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? *Neuroendocrinology Letters* (2): 192–200.

Russo, E.B. 2007. History of cannabis and its preparations in saga, science, and sobriquet. *Chemistry and Biodiversity* 4: 1614–48.

Reiman, A. 2006. Cannabis care: Medical cannabis facilities as health service providers. Dissertation, School of Social Welfare/Alcohol Research Group, University of California, Berkeley.

Schwartz, R. 2010. Medical marijuana users in substance abuse treatment. *Harm Reduction Journal* 7 (3): 1–9.

Skrabek, R.Q.; Galimova, L.; Ethans, K.; Perry, D. 2008. Nabilone for the treatment of pain in fibromyalgia. *Journal of Pain* 9 (2): 164–73.

Substance Abuse and Mental Health Services Administration (SAMHSA). 2007. *Results from the 2006 National Survey on Drug Use and Health: National Findings*. NSDUH Series H-32, DHHS Publication No. SMA 07-4293. Rockville, MD: Office of Applied Studies.

Sylvestre, D.L.; Clements, B. & Malibu, Y. 2006. Cannabis use improves retention and virological outcomes in patients treated for hepatitis C. *European Journal of Gastroenterology and Hepatology* 18 (10): 1057–63.

Tupper, K.W. 2007. The globalization of ayahuasca: Harm reduction or benefit maximization? *International Journal of Drug Policy* 19 (4): 297–303.

Von Bibra, E. 1855. *Die Narkotischen Genussmittel und der Mensch*. Nuremberg: Verlag von Wilhelm Schmidt.

Wagner, F.A. & Anthony, J.C. 2002. Into the world of illegal drug use: Exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine. *American Journal of Epidemiology* 155 (10): 918–25.

Walker, J.M.; Hohmann, A.G.; Martin, W.J.; Strangman, N.M.; Huang, S.M. & Tsou, K. 1999. The neurobiology of cannabinoid analgesia. *Life Sciences* 65 (6–7): 665–73.

Ware, M.A.; Adams, H. & Guy, G.W. 2005. The medicinal use of cannabis in the UK: Results of a nationwide survey. *International Journal of Clinical Practice* 59 (3): 291–95.

Ware, M.A.; Wang, T.; Shapiro, S.; Robinson, A.; Ducruet, T.; Huynh, T.; Gamsa, A.; Bennett, G.J. & Collet, J-P. 2010. Smoked cannabis for chronic neuropathic pain: A randomized controlled trial. *Canadian Medical Association Journal* 182 (14): 1–8.

Wilsey, B.; Marcotte, T.; Tsodikov, A.; Millman, J.; Bentley, H.; Gouaux, B. & Fishman, S. 2008. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *Journal of Pain* 9 (6): 506–21.

Downloaded by [University of Montana] at 10:35 08 June 2012

QUESTION #9 ATTACHMENTS
ATTACHMENT #4

ARTICLES FROM PEER-REVIEWED SCIENTIFIC JOURNALS

Is Cannabis use associated with less opioid use among people who inject drugs?
Kral AH, Wenger L, Novak SP, Chu D, Corsi KF, Coffa D, Shapiro B, Blumenthal RN. Drug Alcohol Depend. 2015 Aug 1;153:236-41. doi: 10.1016/j.drugalcdep.2015.05.014. Epub 2015 May 22.

HHS Public Access
Author manuscript
Peer-reviewed and accepted for publication
About author manuscripts | Submit a manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2016 Aug 1.
Published in final edited form as:
Drug Alcohol Depend. 2015 Aug 1; 153: 236–241.
Published online 2015 May 22. doi: 10.1016/j.drugalcdep.2015.05.014

PMCID: PMC4509857
NIHMSID: NIHMS700422

Is Cannabis use associated with less opioid use among people who inject drugs?

Alex H. Kral,[☒1] Lynn Wenger,[1] Scott P. Novak,[1] Daniel Chu,[3] Karen F. Corsi,[2] Diana Coffa,[4] Brad Shapiro,[4,5] and Ricky N. Bluthenthal[3]

[1]RTI International, 351 California Street Suite 500, San Francisco, CA 94104, USA. O: +14154070752
[2]Department of Psychiatry, University of Colorado Denver School of Medicine, 1557 Ogden St., Denver, CO 80218, USA. O: +17209421804
[3]Department of Preventive Medicine, Institute for Prevention Research, Keck School of Medicine, University of Southern California, Soto Street Building, SSB, 2001 N. Soto Street, 3rd Floor, Rm 302R, MC 9239, Los Angeles, California 90032-3628, USA. O: +13234428236
[4]Department of Family and Community Medicine, University of California San Francisco, San Francisco, CA
[5]Department of Psychiatry, University of California San Francisco, San Francisco, CA
[☒]Corresponding author.
Alex H. Kral: akral@rti.org; Karen F. Corsi: Karen.Corsi@ucdenver.edu; Ricky N. Bluthenthal: rbluthen@usc.edu

Copyright notice and Disclaimer

Publisher's Disclaimer

The publisher's final edited version of this article is available at Drug Alcohol Depend
See other articles in PMC that cite the published article.

Abstract

Go to:

Background

Clinical, experimental, and ethnographic research suggests that cannabis may be used to help manage pain. Ethnographic research has revealed that some people are using cannabis to temper their illicit opioid use. We seek to learn if there is an association between cannabis use and the frequency of nonmedical opioid use among people who inject drugs (PWID).

Methods

PWID were recruited using targeted sampling methods in Los Angeles and San Francisco, California, 2011–2013. We limited analysis to people who used opioids in past 30 days (N=653). Outcome variable: number of times used any opioids non-medically in past 30 days. Explanatory variable: any cannabis use past 30 days. Statistics: multivariable linear regression with a log-transformed outcome variable.

Results

About half reported cannabis use in the past 30 days. The mean and median number of times using opioids in past 30 days were significantly lower for people who used cannabis than those who did not use cannabis (mean: 58.3 vs. 76.4 times; median: 30 vs 60 times, respectively; $p<0.003$). In multivariable analysis, people who used

cannabis used opioids less often than those who did not use cannabis (Beta: −0.346; 95% confidence interval: −0.575, −0.116; p<0.003).

Conclusions

There is a statistical association between recent cannabis use and lower frequency of nonmedical opioid use among PWID. This may suggest that PWID use cannabis to reduce their pain and/or nonmedical use of opioids. However, more research, including prospective longitudinal studies, is needed to determine the validity of these findings.

Keywords: cannabis, opioids, injection drug use, PWID, epidemiology

1. INTRODUCTION

Go to:

The therapeutic applications of cannabis were first documented in the oldest known pharmacopeia, written by the Emperor of China, Shen Nung in 2737 BC, where it was recommended for over a wide variety of ailments, from gout to parasitic infections (Li, 1974). Since that time, there has been a stream of medical claims that cannabis eases limb-muscle spasms, is an effective analgesic and has antianxiety and antiemetic properties (Baker et al, 2003), Cannabis was part of the American pharmacopeia for much of the 19th and early 20th centuries, until the US federal government began restricting its use in the late 1930s (Bostwick, 2012), In 1970, the US Congress categorized cannabis as a Schedule I drug under the Controlled Substances Act, declaring it to have high abuse potential and no medical value, thereby rendering its use illegal (Cohen, 2010),

The past two decades has seen an increase in debate about the use of cannabis for medicinal purposes, with California becoming the first U.S. state to authorize medicinal cannabis in 1996 (O'Connell and Bou-Matar, 2007). To date, twenty-three states and the District of Columbia have passed laws that allow adult use of medical cannabis (Portal Labs, 2014). Additionally, as of February, 2014, four states-- Alaska, Colorado, Oregon, Washington-- and the District of Columbia, have legalized possession, manufacture and sale of cannabis for people 21 years of age and older to use recreationally (Merica, 2014).

There is a growing body of literature documenting the therapeutic benefits of cannabis (Bostwick, 2014; Grotenhermen and Muller-Vahl, 2012; Kalant, 2014; Lucas, 2012; Walsh et al, 2013). Reports of improved appetite and reduction in muscle pain, nausea, anxiety, depression and paresthesia have been associated with cannabis use among people with HIV (Woolridge et al, 2005). Cannabis use for pain relief is also common among people living with chronic noncancer pain (Degenhardt et al, 2014). In addition to pain relief, individuals who use cannabis for therapeutic reasons report effective symptom relief for anxiety and sleep disturbances (Walsh et al, 2013). Cannabis may also act to relieve inflammation and has been found to have a useful place in the treatment of rheumatic diseases (Kalant, 2014). Multiple review articles have systematically documented the therapeutic potential of cannabis as treatment for nausea, loss of appetite in HIV and cancer patients, spasticity in multiple sclerosis and spinal cord injuries, neuropathic pain, non-neuropathic pain, Tourette syndrome, and glaucoma (Abrams et al, 2011; Ben Amar, 2006; Grotenhermen and Muller-Vahl, 2012; Kumar et al, 2001; Raby et al, 2009; Robson, 2001).

Due to potential side effects (including overdose) associated with opioid use (Centers for Disease and Prevention, 2011) and the decrease in analgesic efficacy over time (Lee et al, 2011), there is a need to explore alternative medications to opioids in the management of severe pain. While controversial, cannabis is being explored as a possible complement (Abrams et al, 2011) or alternative to opioids for reducing pain (Carter et al, 2015; Elikkottil et al, 2009; Lucas, 2012). Clinical and pre-clinical studies have documented the synergistic relationship between opioids and cannabis. In a review article, Elikottil and colleagues (2009) assessed the synergistic

relationship between opioids and cannabis in both experimental studies with mice and rats and clinical studies with healthy subjects. They conclude that combining smaller doses of cannabis and opioids resulted in positive analgesic effects with fewer side effects than a larger dose of either drug alone. Abrams and colleagues (2011) also found that among chronic pain patients who were treated with opioids, vaporized cannabis augments the analgesic effects of opioids, which may allow for opioid treatment at lower doses with fewer side effects. Similar to clinical and experimental research, data from a community-based study of people who have been prescribed opioids for chronic non-cancer pain found that cannabis use for pain relief purposes was common and that study participants reported greater pain relief in combination with opioids than when opioids were used alone (Degenhardt et al, 2014).

Qualitative studies have recently found that people who use heroin report that they are able to temper or reduce their heroin use by using cannabis. In a sample of street-recruited PWID, study participants reported smoking cannabis to reduce anxiety and cravings experienced while transitioning away from daily heroin use (Wenger et al, 2014). In another qualitative study, Peters found that medical cannabis patients consistently reported using cannabis to substitute or wean off prescription opioids (Peters, 2013). All patients who were taking opioids reported reducing their overall drug use, specifically opioids, by using cannabis. Patients also reported that cannabis was preferred over opioids, eased withdrawal from opioids, and in some cases was more effective in relieving pain.

In this paper, we test whether there is a statistical association between cannabis use and the frequency of nonmedical opioid use in a large cross-sectional sample of street-recruited PWID.

2. METHODS

Go to:

2.1 Study Procedures

We used targeted sampling methods to recruit PWID in Los Angeles and San Francisco, California, USA (Bluthenthal and Watters, 1995; Kral et al, 2010; Watters and Biernacki, 1989). Eligibility criteria included injection drug use in the past 30 days and being 18 years of age or older. Study staff verified that potential participants had injected drugs by inspecting them for signs of recent venipuncture ("tracks"; Cagle et al, 2002). Each participant went through an informed consent process before enrolling in the study. The study involved a quantitative survey interview which served the dual purposes of collecting quantitative data on a large sample of PWID and providing study staff with information about eligibility into a sub-study that involved a qualitative interview. We only report on results of the quantitative survey in this manuscript. The survey involved a one-on-one, computer-assisted personal interview (CAPI) conducted by a trained interviewer which lasted between 30 and 45 minutes (Questionnaire Development System, NOVA Research, Bethesda, MD). After completion of the survey, participants were remunerated $20. All study procedures were approved by the Institutional Review Boards at the two institutions where the research was carried out: University of Southern California and RTI International.

2.2 Study Sample

The study was conducted between April, 2011 and April, 2013 in Los Angeles and San Francisco, during which time 777 PWID completed the quantitative survey. Because this analysis involves assessing whether the frequency of opioid use among PWID is different from those who use cannabis and those who do not use cannabis, we restricted the sample to the 653 PWID who reported any (a) use of heroin alone or in combination with other drugs (including cocaine or methamphetamine) or (b) nonmedical use of opioid pills or methadone.

2.3 Study Measures

Our outcome variable was the number of times a participant used opioids in the past 30 days (people could use opioids many times per day). This variable was the sum of the answers to questions about the number of times in the past 30 days that the participant reported using heroin (injected and non-injected), "speedball" (mix of heroin and cocaine, injected and non-injected), "goofball" (mix of heroin and methamphetamine, injected and non-injected), non-prescribed methadone (used), and nonmedical use of opiate pills (injected and non-injected). Our explanatory variable was whether the participant responded yes to the question "Have you used marijuana in the last 30 days?" Note that we used the word "marijuana" in the survey instrument, as opposed to cannabis, because this study took place in California, USA, where marijuana is the most common term for cannabis. The following factors were candidate confounding variables: socio-demographic and socioeconomic characteristics, including., age, gender, housing status, income, and sexual orientation, study site (Los Angeles or San Francisco), drug use history (years of injection), recent (last 30 days) crack cocaine, powder cocaine, methamphetamine, alcohol use, and health-related items such as mental health diagnoses, HIV status, health insurance, and drug treatment experience.

2.4 Statistical Analysis

We used descriptive statistics (e.g., frequencies, means, standard deviations, medians, interquartile ranges) to examine all variables. Given that the outcome variable (number of times used opioids nonmedically) is continuous and not normally distributed, we conducted a standard log transformation for the bivariate and multivariable analyses. Then we conducted bivariate analyses to assess whether the explanatory variable (cannabis use) was associated with our log transformed outcome variable by using t-tests and ANOVA. We also assessed whether the potential confounding variables were associated with the explanatory variable and outcome variable. Statistical significance threshold was predetermined to be at $p<0.05$. We also evaluated multicollinearity using a diverse range of approaches (e.g., Martingale residuals, model-based correlations) for key variables that are typically found to be highly interrelated in other studies by assessing correlations among potential confounding variables in the same domain (e.g., drug use, demographics, health). In the multivariable analysis, we used linear regression. The final multivariate model included the explanatory variable, as well as whether they had health insurance, were in substance abuse treatment in the past 30 days, and any potential confounding variables significant at the $p<0.05$ levels. All statistics were computed using SPSS/PASW Statistics 18.0 (released July 30, 2009).

3. RESULTS

Go to:

The sample was nearly three-quarters men, one-third African American, one-third Latino, and one-third Caucasian, with the majority being over 50 years old (Table 1). Nearly one half reported having used cannabis in the past 30 days. Nearly all reported having used heroin in the past 30 days (95%), followed by nonmedical use of opioids (38%), methadone (26%), speedball use (20%), and goofball use (15%). The mean (and standard deviation) number of times participants used opioids nonmedically in the past 30 days was 67.5 (78.22) and the median (and interquartile range) was 43 (12.5, 93). Heroin accounted for the vast majority (76% of the number of times opioids were used nonmedically in the past 30 days (mean=51.1 times; see Figure 1).

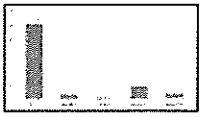


Figure 1

Mean opioid episodes by type of opioid used in past 30 days

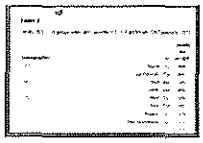


Table 1

Demographics of people who inject opioids in Los Angeles and San Francisco, 2011-2013 (N=653)

The mean and median number of times opioids were used in past 30 days were significantly lower for people who used cannabis than those who did not use cannabis in the past 30 days (mean= 58.3 times [standard deviation=79.4] vs. mean=76.4 times [standard deviation=76.1]; median: 30 vs 60 times, respectively; $p<0.003$). We created a variable that consisted of quintiles of the number of times opioids were used in the past 30 days. The quintile cut-offs were 1 to 6 times, 7 to 29 times, 30 to 57 times, 58 to 103 times, and 104 or more times. Cannabis use was more prevalent among the lower quintiles of opioid use than the higher quintiles (Figure 2; chisquare value=27.923; degrees of freedom=4; $p<0.001$). In multivariable analysis, cannabis use in the past 30 days was highly significantly negatively associated (Beta= −0.346; 95% confidence interval=−0.575, −0.116; degrees of freedom=7; $p<0.003$) with the log transformed variable for number of times used opioids in past 30 days, while controlling for age, age at first injection, being Latino, recruited in Los Angeles, having no health insurance, and no methadone treatment in past month (Table 2).

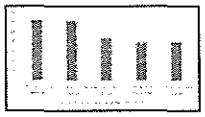


Figure 2

Percent Who Used Cannabis past 30 days by Quintiles of Number of Opioid Episodes in past 30 days

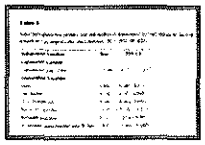


Table 2

Association between cannabis use and number of times used opioids in past 30 days, among people who inject opioids in Los Angeles and San Francisco, 2011–2013 (N=652)

4. DISCUSSION

Go to:

We found that in this sample of street-recruited PWID who use opioids in Los Angeles and San Francisco, people who use cannabis used opioids less frequently. A number of possible explanations exist for this phenomenon. It is possible that PWIDs who use cannabis have a qualitatively different set of motivations than those who do not, or that PWIDs who use cannabis have a less severe form of opioid use disorder than those who do not. Alternatively, it may be that cannabis is deliberately or unconsciously used by PWIDs to decrease or manage opioid use. Given previous research on the potential for both substances to be used to reduce pain (Abrams et al. 2011; Ben Amar, 2006; Bostwick, 2014; Degenhardt et al. 2014; Grotenhermen and Muller-Vahl, 2012; Kalant, 2014; Kumar et al. 2001; Lucas, 2012; Robson, 2001; Walsh et al. 2013; Woolridge et al. 2005), it is also feasible that cannabis is being used by street-recruited PWID to self-treat pain. Reductions in opioid use might be deliberately achieved by substituting cannabis to treat pain, psychic distress, cravings, or withdrawal. Conversely, cannabis might incidentally reduce opioid use by satisfying some of the same needs that are satisfied by opioids, leading PWID to unintentionally reduce their frequency of opioid use. In addition, it is interesting that none of the other substance use variables (cocaine, methamphetamine, alcohol, etc.) were significantly associated with frequency of opioid use, suggesting there may be something unique about the relationship between cannabis and opioid use. While this study cannot prove a causal connection or elucidate a mechanism, increased access to and decreased stigma associated with cannabis in many U.S. states provides new opportunities to conduct

observational studies on the various therapeutic uses of cannabis, including its use to reduce pain or opioid use. Such studies should include various opioid using populations, including pain patients, people who use heroin or other illicit opioids, and patients on buprenorphine or methadone for maintenance therapy of opioid use disorders, and should employ a range of methods from epidemiological cohorts to qualitative and ethnographic studies.

It is noteworthy that about one-half of PWID who use opioids reported having used cannabis in the past month in these two California cities. Medicinal cannabis has been legal in California since state proposition 215 passed in 1996. In this study, we did not assess whether the participants had obtained cannabis legally, and if so, for what therapeutic purpose. For the purposes of this study, it does not necessarily matter how the study participants obtained their cannabis or whether or not it was used according to medical prescription.

While there is a statistical association in our study between cannabis use and the number of times opioids were used nonmedically, we do not want to imply that there is necessarily causation. Though socio-demographic and socio-economic factors were accounted for and corrected for in our statistical analysis, it remains possible that the differences between groups are due to other, unexamined differences between the cannabis using and non-using cohorts. The average age of our cross-section was higher than many studies of PWID, which may have contributed to a higher burden of pain and therefore magnification of the impact of cannabis on opioid use. Age and age of initiation were included in our multivariable analysis of the main effect to help control for age-related influences. Other socio-demographic and socio-economic factors significantly impacted opioid use, including Latino ethnicity, residence in Los Angeles rather than San Francisco, young age, and age at first use. The impact of cannabis remained significant even after controlling for these variables, but in order to better assess whether there is causation, we would suggest prospective longitudinal observational studies and experimental studies that assess whether changes in cannabis use are associated with changes in opioid use. We also want to point out that our outcome variable- number of times used opioids – is only a proxy for amount of opioids that were used. Heroin accounted for the majority of the number of times opioids were used and it is not possible to determine how much heroin was used each time, nor the potency of the heroin used. In the clinical literature, there is a conversion methodology to aid clinicians in dosing patients. (Svendsen et al. 2011) The "morphine equivalent" standard helps calibrate to a common metric for comparison based on potency. Obviously, the active pharmaceutical ingredients involving cannabis and opioids are different, so there is no direct and objective way to compare potency and therefore, symptom relief. It is also not feasible to derive a morphine equivalent from self-reported use of heroin (or drugs used with heroin) because the potency of heroin varies greatly.

The study is also limited in that it did not collect much data with respect to the explanatory variable (cannabis use). For example, we do not have any dose-related information, including standard units of cannabis consumed per episode. We also did not collect data on types of cannabis, different routes of administration (smoking, eating, and topical application), amount of cannabis used, or cannabidiol and tetrahydrocannabinol levels. A prospective study needs to better assess cannabis use, enabling us to assess whether the amount, frequency, and type of cannabis use is associated with number of times opioids are used. Finally, we did not assess directly whether people were consciously using cannabis to either manage pain or to moderate their opioid use. Future studies of the association among cannabis use and opioid use should specifically ask about motivations for use and whether people use cannabis in these ways. They should also assess whether cannabis is used to try to reduce use of other illicit drugs, or whether this is an unintended but possibly helpful consequence of cannabis use.

Despite these limitations, the present study should stimulate more research about the relationship between cannabis and opioid use among PWID. It is among the first epidemiological observational studies, of which we are aware, to examine the association between cannabis and opioid use among nonmedical opioid users recruited in street settings. Nonetheless, we need to learn more about whether this is a meaningful association. This may be

achieved through more rigorous prospective studies that are designed to study this association using longitudinal epidemiological and qualitative research methods.

Highlights

- People who inject drugs (PWID) were recruited using targeted sampling in Los Angeles and San Francisco, CA
- About one-half of PWID reported cannabis use in the past 30 days
- PWID who use cannabis used opioids less often than those who did not use cannabis

Footnotes

Go to:

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

REFERENCES

Go to:

1. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. Clin. Pharmacol. Ther. 2011;90:844–851. [PubMed]
2. Baker D, Pryce G, Giovannoni G, Thompson AJ. The therapeutic potential of cannabis. Lancet Neurol. 2003;2:291–298. [PubMed]
3. Ben Amar M. Cannabinoids in medicine: a review of their therapeutic potential. J. Ethnopharmacol. 2006;105:1–25. [PubMed]
4. Bluthenthal RN, Watters JK. Multimethod research from targeted sampling to HIV risk environments. NIDA Res. Monogr. 1995;157:212–230. [PubMed]
5. Bostwick JM. Blurred boundaries: the therapeutics and politics of medical marijuana. Mayo Clin. Proc. 2012;87:172–186. [PMC free article] [PubMed]
6. Bostwick JM. The use of cannabis for management of chronic pain. Gen. Hosp. Psychiatry. 2014;36:2–3. [PubMed]
7. Cagle HH, Fisher DG, Senter TP, Thurmond RD, Kaster AJ. In: Classifying Skin Lesions Of Injection Drug Users: A Method For Corroborating Disease Risk. Substance Abuse and Mental Health Services Administratin, Treatment CfSA, editor. Rockville, MD: 2002.
8. Carter GT, Javaher SP, Nguyen MH, Garret S, Carlini BH. Re-branding cannabis: the next generation of chronic pain medicine? Pain Manage. 2015;5:13–21. [PubMed]
9. Centers for Disease Control and Prevention. Vital signs: overdoses of prescription opioid pain relievers--United States, 1999–2008. MMWR. 2011;60:1487–1492. [PubMed]
10. Cohen PJ. Medical marijuana 2010: it's time to fix the regulatory vacuum. J. Law Med. Ethics. 2010;38:654–666. [PubMed]
11. Degenhardt L, Lintzeris N, Campbell G, Bruno R, Cohen M, Farrell M, Hall WD. Experience of adjunctive cannabis use for chronic non-cancer pain: findings from the Pain and Opioids IN Treatment (POINT) study. Drug Alcohol Depend. 2014;147:144–150. [PubMed]
12. Elikkottil J, Gupta P, Gupta K. The analgesic potential of cannabinoids. J. Opioid Manage. 2009;5:341–357. [PMC free article] [PubMed]

13. Grotenhermen F, Muller-Vahl K. The therapeutic potential of cannabis and cannabinoids. Dtsch Arztebl Int. 2012;109:495–501. [PMC free article] [PubMed]
14. Kalant H. Cannabis in the treatment of rheumatic diseases: suggestions for a reasoned approach. J. Rheumatol. 2014;42:146–148. [PubMed]
15. Kral AH, Malekinejad M, Vaudrey J, Martinez AN, Lorvick J, McFarland W, Raymond HF. Comparing respondent-driven sampling and targeted sampling methods of recruiting injection drug users in San Francisco. J. Urban Health. 2010;87:839–850. [PMC free article] [PubMed]
16. Kumar RN, Chambers WA, Pertwee RG. Pharmacological actions and therapeutic uses of cannabis and cannabinoids. Anaesthesia. 2001;56:1059–1068. [PubMed]
17. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011;14:145–161. [PubMed]
18. Li HL. An archaelogical and historical account of cannabis in China. Econ. Bot. 1974;28:437–448.
19. Lucas P. Cannabis as an adjunct to or substitute for opiates in the treatment of chronic pain. J. Psychoactive Drugs. 2012;44:125–133. [PubMed]
20. Merica D. Oregon, Alaska and Washington, D.C. legalize marijuana. CNN. 2014
21. O'Connell TJ, Bou-Matar CB. Long term marijuana users seeking medical cannabis in California (2001–2007): demographics, social characteristics, patterns of cannabis and other drug use of 4117 applicants. Harm Reduct. J. 2007;4:16. [PMC free article] [PubMed]
22. Peters DC. Patients and caregivers report using medical marijuana to decrease prescription narcotics use. Humboldt J. Soc. Relat. 2013;35:24–40.
23. Portal Labs. Medical Marijuana Laws for Patients. Public Health Law Research. 2014;2015
24. Raby WN, Carpenter KM, Rothenberg J, Brooks AC, Jiang H, Sullivan M, Bisaga A, Comer S, Nunes EV. Intermittent marijuana use is associated with improved retention in naltrexone treatment for opiate-dependence. Am. J. Addict. 2009;18:301–308. [PMC free article] [PubMed]
25. Robson P. Therapeutic aspects of cannabis and cannabinoids. Br. J. Psychiatry. 2001;178:107–115. [PubMed]
26. Svendsen K, Borchgrevink P, Fredheim O, Hamunen K, Mellbye A, Dale O. Choosing the unit of measurement counts: the use of oral morphine equivalents in studies of opioid consumption is a useful addition to defined daily doses. Palliat. Med. 2011;25:725–732. [PubMed]
27. Walsh Z, Callaway R, Belle-Isle L, Capler R, Kay R, Lucas P, Holtzman S. Cannabis for therapeutic purposes: patient characteristics, access, and reasons for use. Int. J. Drug Policy. 2013;24:511–516. [PubMed]
28. Watters JK, Biernacki P. Targeted sampling: options for the study of hidden populations. Soc. Probl. 1989;36:416–430.
29. Wenger LD, Lopez AM, Comfort M, Kral AH. The phenomenon of low-frequency heroin injection among street-based urban poor: drug user strategies and contexts of use. Int. J. Drug Policy. 2014;25:471–479. [PMC free article] [PubMed]
30. Woolridge E, Barton S, Samuel J, Osorio J, Dougherty A, Holdcroft A. Cannabis use in HIV for pain and other medical symptoms. J. Pain Symptom Manage. 2005;29:358–367. [PubMed]

QUESTION #9 ATTACHMENTS
ATTACHMENT #5

ARTICLES FROM PEER-REVIEWED SCIENTIFIC JOURNALS

Cannabis as a substitute for alcohol and other drugs. Reiman A. Harm Reduction Journal. 2009;6:35. doi:10.1186/1477-7517-6-35.

BioMed Central The Open Access Publisher

HARM REDUCTION JOURNAL

this article | search | submit a manuscript | register

Harm Reduct J. 2009; 6: 35.
Published online 2009 Dec 3. doi: 10.1186/1477-7517-6-35

PMCID: PMC2795734

Cannabis as a substitute for alcohol and other drugs

Amanda Reiman[1]

[1]School of Social Welfare, University of California, Berkeley, 120 Haviland Hall, Berkeley, CA 94720, USA
Corresponding author.
Amanda Reiman: areiman@berkeley.edu

Received 2009 Sep 28; Accepted 2009 Dec 3.

Copyright ©2009 Reiman; licensee BioMed Central Ltd.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

This article has been cited by other articles in PMC.

Abstract

Go to:

Background

Substitution can be operationalized as the conscious choice to use one drug (legal or illicit) instead of, or in conjunction with, another due to issues such as: perceived safety; level of addiction potential; effectiveness in relieving symptoms; access and level of acceptance. This practice of substitution has been observed among individuals using cannabis for medical purposes. This study examined drug and alcohol use, and the occurrence of substitution among medical cannabis patients.

Methods

Anonymous survey data were collected at the Berkeley Patient's Group (BPG), a medical cannabis dispensary in Berkeley, CA. (N = 350) The sample was 68% male, 54% single, 66% White, mean age was 39; 74% have health insurance (including MediCal), 41% work full time, 81% have completed at least some college, 55% make less than $40,000 a year. Seventy one percent report having a chronic medical condition, 52% use cannabis for a pain related condition, 75% use cannabis for a mental health issue.

Results

Fifty three percent of the sample currently drinks alcohol, 2.6 was the average number of drinking days per week, 2.9 was the average number of drinks on a drinking occasion. One quarter currently uses tobacco, 9.5 is the average number of cigarettes smoked daily. Eleven percent have used a non-prescribed, non OTC drug in the past 30 days with cocaine, MDMA and Vicodin reported most frequently. Twenty five percent reported growing up in an abusive or addictive household. Sixteen percent reported previous alcohol and/or drug treatment, and 2% are currently in a 12-step or other recovery program. Forty percent have used cannabis as a substitute for alcohol, 26% as a substitute for illicit drugs and 66% as a substitute for prescription drugs. The most common reasons given for substituting were: less adverse side effects (65%), better symptom management (57%), and less

withdrawal potential (34%) with cannabis.

Conclusion

The substitution of one psychoactive substance for another with the goal of reducing negative outcomes can be included within the framework of harm reduction. Medical cannabis patients have been engaging in substitution by using cannabis as an alternative to alcohol, prescription and illicit drugs.

Background

Go to:

It has been observed that those who use large amounts of cannabis frequently use other drugs as well, especially alcohol. This can create a potential synergistic effect, resulting in increased harms [1-4]. Economic research has looked at the substitution and complimentarity of particular substances by modelling the effects of price fluctuation on use, although the limits of such research have been noted [5]. When considering youth, Pacula has found cannabis and alcohol to be compliments. As beer prices rose, cannabis use declined [6]. This could potentially be because the introduction of alcohol into an adolescent environment increases the likelihood of other substance being brought into that environment; once the presence of alcohol decreases, the presence of other substances might decrease as well. Among adults, amphetamine has been found to be a substitute for those who's drug of choice is alcohol, and alcohol as a substitute for those who cannot obtain MDMA and cocaine [7,8]. This research suggests that through various patterns, individuals are making personal decisions about alcohol and drug substitution.

For the purposes of this study, substitution was operationalized as the conscious choice to use one drug (legal or illicit) instead of, or in conjunction with, another due to issues such as: perceived safety; level of addiction potential; effectiveness in relieving symptoms; access and level of acceptance. The substitution of cannabis for alcohol and other drugs has been observed among individuals using cannabis for medical purposes. Medical cannabis patients are regular cannabis users with a stable supply, and their access to cannabis not granted under a standardized prescription system, yet still legitimized by a doctor's recommendation (self-medication). This, in addition to the legal protection given to patients in California, increases the freedom of choice regarding the use of cannabis as a substitute among this population. A survey of 11 medical cannabis doctors in California found that all doctors had seen patients who were using cannabis as a substitute for alcohol. Furthermore, one said that over half of her patients reported preferring cannabis to alcohol, and another reported that 90% of his patients reduced their alcohol use after beginning the use of medical cannabis [4]. The dual use of alcohol and cannabis has been observed in several research studies on medical cannabis patients. First, previous alcohol abuse was reported in 59 of 100 medical cannabis users in a University of California, San Francisco study. Furthermore, 16 of 100 subjects reported previous alcohol dependence [9].

Beyond the population of medical cannabis patients, substituting cannabis or other drugs for alcohol has been described as a radical alcohol treatment protocol. If alcohol negatively affects a person's level of functioning, cannabis or another drug might be an alternative for the user. Charlton has suggested that the radical approach of substitution with substances such as benzodiazepine might be used to address heavy alcohol use in the British Isles by incorporating the idea of self-medication into his discussion by his assertion that "the drug-substitution strategy is based on the assumption that most people use lifestyle (recreational) drugs rationally for self-medication purposes" (p. 457). It is posited that people might substitute a safer drug with less negative side-effects if it were socially acceptable and available [10].

The first cannabis substitution study was a single subject study conducted by Tod Mikuriya in 1970, in which a female (age 49) who was an alcoholic was instructed to substitute cannabis for alcohol. The subject was also administered Antabuse to assist in her abstention from alcohol. The subject reported increased ego strength,

useful behaviour, ability to control cannabis intake, euphoria and tranquilization. In addition, there were improvements in concentration, disposition, physical health, ability to revisit social situations and ability to appropriately express anger [11]. The issue was revisited in 2001 with a study of 104 medical cannabis patients in California who used cannabis in an effort to stop the use of other drugs, in particular alcohol. For example, participants may have been previous alcoholics who have replaced their alcohol use with a daily regimen of cannabis. Demographic data were collected as well as information on family alcohol history and alcohol and cannabis usage patterns. The authors included both descriptive statistics and excerpts from interviews. With respect to family alcohol history, 55% of participants reported having one or two alcoholic parents. Most of the participants (90%) listed alcohol as their primary drug of choice, although a few participants had also had addiction issues with heroin, cocaine, amphetamine and other drugs. One interesting finding in this study is that 45% of patients reported using cannabis to relieve pain that they suffered as a result of an alcohol related injury [12].

Cannabis substitution has also been discussed as part of a harm reduction framework. A record review of 92 medical cannabis patients who used marijuana as a substitute for alcohol was conducted with the goal of describing these patients and determining the reported efficacy of treatment. Fifty-three percent of participants reported being raised by at least one alcoholic/addict parent. Concerning reported health problems, 64% of the sample identified alcoholism or cirrhosis of the liver as their presenting problem. Thirty six percent identified themselves as alcohol abusers but listed another health problem as their primary concern. As in Mikuriya's 2001 study, 21% of the sample reported having been injured in an alcohol related incident. When addressing the efficacy of cannabis as a substitute for alcohol, all participants reported cannabis substitution as very effective (50%) or effective (50%). Ten percent of the patients reported being abstinent from alcohol for more than a year and attributed their success to cannabis. Twenty one percent of patients had a return of alcoholic symptoms when they stopped using cannabis. Reasons for stopping the cannabis use ranged from entering the armed forces to being arrested for using cannabis [13].

Previous alcohol use, treatment, and substitution were also documented in a sample of 130 medical cannabis patients in the San Francisco Bay Area. Twenty four had reported previous alcohol treatment. Half of the sample reported using cannabis as a substitute for alcohol, 47% for illicit drugs and 74% using it as a substitute for prescription drugs. The most common reason reported for using cannabis as a substitute was fewer side effects from cannabis and better symptom management from cannabis [14].

The personal health practice of substitution among medical cannabis patients can provide information concerning non-traditional and alternative means used by individuals to personally address their health issues without official involvement in the health care system. Furthermore, examining substitution among this population might translate into the development of more effective, client-centred treatment practices within the field of addiction.

Methods

Go to:

The survey sample for this study consisted of 350 medical cannabis patients between the ages of 18 and 81 from the San Francisco Bay Area, California. Participants are members of Berkeley Patients Group (BPG), a medical cannabis dispensing collective in Berkeley, CA. The sample was 68.4% male (N = 238), 66.2% White (N = 231) and 14.6% Multi-racial (N = 51). The mean age was 39.43.

A survey was created by the researcher, with portions adapted from a patient survey administered by Dr. Frank Lucido at his medical practice in Berkeley, CA. The survey had five sections: demographic information, medical information, cannabis use pattern, alcohol and drug use and service utilization. Participants were asked the quantity and frequency of alcohol, tobacco and drug (prescription and illicit) use as well as current and past

alcohol and/or drug treatment. Participants were also asked about whether they use cannabis as a substitute for alcohol, illicit drugs or prescription drugs and why to investigate medical cannabis as a treatment for alcohol and/or drug dependence.

The survey data were collected by the researcher at BPG. The researcher approached patients as they came into BPG and asked if they would like to participate in an anonymous survey being conducted by BPG. If patients were not able to fill out the survey, it was administered by the researcher. The survey included an explanation of the study and the right to refuse to participate or to stop the survey at any time. Data collection occurred for the most part during the hours of 1-5 pm and took place during the week and on weekends. Data were analyzed in SPSS, and frequencies were calculated.

There are several limitations of this study. First, due to the close proximity to the campus of the University of California, Berkeley, there might be an over-representation of college students in this sample. This might affect data on employment status, age, marital status, income and to a lesser extent, gender and race. Secondly, although data were collected in the middle of the day regularly for several months, it is possible that some patients might come to BPG at times when data collection was not occurring. Furthermore, patients who are extremely ill might not be able to stay and fill out a survey. The sample itself prevents the generalization of these results to the greater population of cannabis users, as medical cannabis patients might differ in substantial ways from the general population, especially concerning areas of substance using behaviour, and patients from Berkeley Patient's Group may not represent the greater population of medical cannabis patients. Furthermore, there are not formal measures of alcohol drug related problems on the survey, making it impossible to explore the behavioural implications of cannabis substitution. Finally, although the survey was anonymous, the legal status of medical cannabis might prevent some patients from filling out surveys and some participants from being completely forthcoming with information. Furthermore, although the practice of substitution was described to participants in the survey, the data do rely on self report and the participant's own reality concerning their substitution behaviour.

Results

Go to:

Alcohol, Tobacco and Other Drug Use

Fifty three percent of the sample reported that they currently drink alcohol. The average number of drinking days per week was 2.63 (N = 180). The average number of drinks on drinking days was 2.88 (N = 163). One quarter of the sample currently smoke tobacco. The average number of cigarettes smoked per day is 9.54 (N = 80). Eleven percent of the sample reported using a drug other than cannabis, a prescription or over the counter drug in the past 30 days. Cocaine, MDMA and Vicodin were reported most frequently (N = 5), followed by LSD (N = 4), mushrooms and Xanax (N = 3).

Treatment

One quarter of the sample reported growing up in an alcoholic or abusive household, 16.4% reported previous alcohol or substance abuse treatment, and 2.4% are currently in a 12-step or some other type of substance abuse or alcohol dependence program.

Substitution

As shown in Table 1, forty percent of the sample reported using cannabis as a substitute for alcohol, 26% reported using it as a substitute for illicit drugs, and 65.8% use it as a substitute for prescription drugs. Referring to Table 2, sixty five percent reported using cannabis as a substitute because it has less adverse side effects than

alcohol, illicit or prescription drugs, 34% use it as a substitute because it has less withdrawal potential, 17.8% use it as a substitute because its easier to obtain cannabis than alcohol, illicit or prescription drugs, 11.9% use it as a substitute because cannabis has greater social acceptance, 57.4% use it as a substitute because cannabis provides better symptom management, and 12.2% use it as a substitute for some other reason.

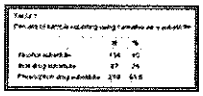


Table 1

Percent of sample reporting using cannabis as a substitute

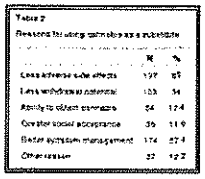


Table 2

Reasons for using cannabis as a substitute

Discussion

Go to:

Research has suggested that medical cannabis patients might use more alcohol than non patients, and might have a higher instance of alcohol abuse than the general population [3,9]. Drinking patterns among the BPG sample were average, with 53.4% of the sample being current drinkers, the mean number of drinking days per week being 2.63 and the mean number of drinks on occasion being 2.88. When looking at the national rate of alcohol use, 55% of the U.S. population 18+ is a current drinker, compared to 53% of the BPG sample. The national data report 7.8% of the 18+ national sample have used an illicit drug in the past month, compared to 11% of the BPG sample [15]. The study of 100 patients from San Francisco found a much higher rate of tobacco smoking (78% vs. 24.9% of the BPG sample) [9].

When considering previous alcohol and/or substance abuse treatment, 16.4% of the BPG sample reported previous treatment for alcohol or substance abuse; this was the same percentage found in Reiman's sample of 130 medical cannabis patients [14]. Mikuriya found in 2001 and 2004 that 55% and 53% of patients respectively reported having one or two alcoholic parents [12,13]. One quarter of this sample reported growing up in an alcoholic or abusive household.

As previously discussed, research on medical cannabis patients has alluded to the use of cannabis as a substitute for alcohol, illicit or prescription drugs [9-13]. This phenomenon was also reflected in the data on substitution from the BPG sample, as 40% of participants reported using cannabis as a substitute for alcohol, 26% as a substitute for illicit drugs and 65.8% as a substitute for prescription drugs. These substitution rates were very similar to those found by Reiman [14]. Additionally, three patients noted during the survey that they used cannabis to quit smoking tobacco.

Eighty five percent of the BPG sample reported that cannabis has much less adverse side effects than their prescription medications. Additionally, the top two reasons listed by participants as reasons for substituting cannabis for one of the substances previously mentioned were less adverse side effects from cannabis (65%) and better symptom management from cannabis (57.4%).

Conclusion

Go to:

The substitution of one psychoactive substance for another with the goal of reducing negative outcomes can be included within the framework of harm reduction. Medical cannabis patients have been engaging in substitution by using cannabis as an alternative to alcohol, prescription and illicit drugs. This brings up two important points. First, self determination, the right of an individual to decide which treatment or substance is most effective and least harmful for them. If an individual finds less harm in cannabis than in the drug prescribed by their doctor, do

they have a right to choose? Secondly, the recognition that substitution might be a viable alternative to abstinence for those who are not able, or do not wish to stop using psychoactive substances completely. Due to a potential conflict between the use of medical cannabis and philosophies of recovery programs such as Alcoholics Anonymous, some dispensaries offer harm reduction based recovery groups aimed at those in recovery who use medical cannabis. Mikuriya has suggested the development of 12 Step groups tailored towards those who want to take advantage of the cost free, fellowship driven nature of 12 Step programs, but wish to use cannabis actively during recovery [13]. The lack of drug and alcohol related problem measures utilized in this study calls for a further investigation into the relationship of such problems and the use of cannabis as a substitute. To that end, more research needs to be done on the possibilities for substitution that lie in the field of addiction, and on the individuals who have already successfully incorporated substitution into their health care regime.

Competing interests

Go to:

The author declares that she has no competing interests.

Author information

Go to:

Amanda Reiman MSW, PhD, is currently the Coordinator of Academic Programs and a Lecturer in the School of Social Welfare at the University of California, Berkeley. She is also the current Chairwoman of the Berkeley Medical Cannabis Commission.

Authors' contributions

Go to:

AR conceived the study design, created and administered the survey, entered the data into the computer, analyzed the data and wrote the final report.

Acknowledgements

Go to:

The author would like to thank the patients at BPG for taking the time to share their experiences, and to honor the memory of Tod H. Mikuriya, a pioneer in this field. This research was presented at the 2009 International Cannabinoid Research Symposium in Lake Charles, IL.

References

Go to:

1. Looby A, Earleywine M. Negative consequences associated with dependence in daily cannabis users. Substance Abuse Treatment, Prevention and Policy. 2007;2:3–10. doi: 10.1186/1747-597X-2-3. [PMC free article] [PubMed] [Cross Ref]
2. Midanik L, Tam T, Weisner C. Concurrent and simultaneous drug and alcohol use: Results of the 2000 National Alcohol Survey. Drug and Alcohol Dependence. 2007;90:72–80. doi: 10.1016/j.drugalcdep.2007.02.024. [PMC free article] [PubMed] [Cross Ref]
3. Ogborne A, Smart R, Adlaf E. Self-reported medical use of marijuana: A survey of the general population. Canadian Medical Association Journal. 2000;162:1685–1686. [PMC free article] [PubMed]
4. Mikuriya T. Medical Marijuana in California, 1996-2006. O'Shaughnessy's: Journal of the California Cannabis Research Medical Group. 2007;Spring:2. 8-10.
5. Williams J, Pacula R, Chaloupka F, Wechsler H. Limits of current economic analyses of the demand for illicit drugs. Substance Use and Misuse. 2006;41:607–609. doi: 10.1080/10826080500521771. [PubMed] [Cross Ref]
6. Pacula R. Does increasing the beer tax reduce marijuana consumption? Journal of Health Economics. 1998;17:557–585. doi: 10.1016/S0167-6296(97)00039-8. [PubMed] [Cross Ref]

7. Sumnall H, Tyler E, Wagstaff G, Cole J. A behavioural economic analysis of alcohol, amphetamine, cocaine, and ecstasy purchases by polysubstance misusers. Drug and Alcohol Dependence. 2004;76:93–99. doi: 10.1016/j.drugalcdep.2004.04.006. [PubMed] [Cross Ref]
8. Petry N. A behavioral economic analysis of polydrug abuse in alcoholics: asymmetrical substitution of alcohol and cocaine. Drug and Alcohol Dependence. 2001;62:31–39. doi: 10.1016/S0376-8716(00)00157-5. [PubMed] [Cross Ref]
9. Harris D. Self-reported marijuana effects and characteristics of 100 San Francisco medical marijuana club members. Journal of Addictive Diseases. 2000;19:89–103. doi: 10.1300/J069v19n03_07. [PubMed] [Cross Ref]
10. Charlton BG. Diazepam with your dinner. Sir? The lifestyle drug-substitution strategy: A radical alcohol policy. Qualitative Journal of Medicine. 2005;98:457–459. [PubMed]
11. Mikuriya T. Cannabis as a treatment for alcoholism. Psychedelic Review. 1970;11:71–73.
12. Mikuriya T, Mandel J. Cannabis substitution: Harm reduction treatment for alcoholism and drug dependence. 2001. http://www.mikuriya.com/cw_cansub.html Retrieved October 13, 2005.
13. Mikuriya T. Cannabis as a substitute for alcohol: A harm-reduction approach. Journal of Cannabis Therapeutics. 2004;4:79–93. doi: 10.1300/J175v04n01_04. [Cross Ref]
14. Reiman A. Patient Profiles: Medical cannabis patients and health care utilization patterns. Complementary Health Practice Review. 2000;12:31–50. doi: 10.1177/1533210107301834. [Cross Ref]
15. Substance Abuse and Mental Health Services Administration. Results from the 2006 National Survey on Drug Use and Health: National Findings. Office of Applied Studies, NSDUH Series H-32, DHHS Publication No. SMA 07-4293. Rockville, MD. 2007.

Articles from Harm Reduction Journal are provided here courtesy of **BioMed Central**

QUESTION #9 ATTACHMENTS
ATTACHMENT #6

ARTICLES FROM PEER-REVIEWED SCIENTIFIC JOURNALS

Cannabis in palliative medicine: Improving care and reducing opioid-related morbidity. Carter GT, Flanagan AM, Earleywine M, Abrams DI, Aggarwal SK, Grinspoon L. American Journal of Hospice and Palliative Medicine. 2011 Aug;28(5):297-303. doi: 10.1177/1049909111402318. Epub 2011 Mar 28.

American Journal of Hospice and Palliative Medicine
http://ajh.sagepub.com/

Cannabis in Palliative Medicine: Improving Care and Reducing Opioid-Related Morbidity

Gregory T. Carter, Aaron M. Flanagan, Mitchell Earleywine, Donald I. Abrams, Sunil K. Aggarwal and Lester Grinspoon

AM J HOSP PALLIAT CARE published online 28 March 2011
DOI: 10.1177/1049909111402318

The online version of this article can be found at:
http://ajh.sagepub.com/content/early/2011/04/07/1049909111402318

Published by:
SAGE
http://www.sagepublications.com

Additional services and information for *American Journal of Hospice and Palliative Medicine* can be found at:

Email Alerts: http://ajh.sagepub.com/cgi/alerts

Subscriptions: http://ajh.sagepub.com/subscriptions

Reprints: http://www.sagepub.com/journalsReprints.nav

Permissions: http://www.sagepub.com/journalsPermissions.nav

Downloaded from ajh.sagepub.com at UNIV WASHINGTON LIBRARIES on April 22, 2011

American Journal of Hospice
& Palliative Medicine®
000(00) 1-7
© The Author(s) 2011
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1049909111402318
http://ajhpm.sagepub.com
SAGE

Cannabis in Palliative Medicine: Improving Care and Reducing Opioid-Related Morbidity

Gregory T. Carter, MD, MS[1], Aaron M. Flanagan, MD[2], Mitchell Earleywine, PhD[3], Donald I. Abrams, MD[4], Sunil K. Aggarwal, MD, PhD[5], and Lester Grinspoon, MD[6,7]

Abstract

Unlike hospice, long-term drug safety is an important issue in palliative medicine. Opioids may produce significant morbidity. Cannabis is a safer alternative with broad applicability for palliative care. Yet the Drug Enforcement Agency (DEA) classifies cannabis as Schedule I (dangerous, without medical uses). Dronabinol, a Schedule III prescription drug, is 100% tetrahydrocannabinol (THC), the most psychoactive ingredient in cannabis. Cannabis contains 20% THC or less but has other therapeutic cannabinoids, all working together to produce therapeutic effects. As palliative medicine grows, so does the need to reclassify cannabis. This article provides an evidence-based overview and comparison of cannabis and opioids. Using this foundation, an argument is made for reclassifying cannabis in the context of improving palliative care and reducing opioid-related morbidity.

Keywords

cannabis, medical marijuana, opioids, hospice, chronic pain, palliative medicine

Introduction

Palliative care medicine is a relatively new subspecialty, arising out of a need for better ways to treat patients with advanced, potentially "life-limiting" conditions. As palliative medicine emergences as a sovereign entity, distinctly different from hospice care, more practitioners are broadening the scopes of their practice to include these services. However, this will require a distinct paradigm shift, away from the "hospice mindset" with respect to the way drugs are prescribed, with drug safety becoming an increasingly important issue. When treating pain in a terminal cancer patient, using opioid drugs will typically provide good relief.[1] However, in hospice, mortality is a forthcoming and expected outcome. This may not be the case in palliative medicine where the patients seek aggressive treatment for pain yet death may not occur for some time. Here, the successful use of opioids will warrant more frequent patient reassessments and significant pharmacovigilance.

This growth in palliative medicine comes at a time when there have been near epidemic increases in deaths related to prescription of opioid analgesics.[2-13] A number of studies have now clearly linked risk of fatal and nonfatal opioid overdose to prescription use, with the risk increasing with the prescribed dosages.[12-14] According to the Centers for Disease Control and Prevention (CDC), from the years 1999 to 2006, the number of prescription opioid poisoning deaths in the United States (US) nearly doubled, from approximately 20 000 to 37 000.[15] This increase coincided with a nearly 4-fold increase in the use of prescription opioids nationally.

In 2006, Washington State had a rate of poisoning involving opioid painkillers significantly higher than the national rate.[15] A subsequent analysis of overdose deaths involving prescription opioids from 2004 to 2007 revealed that 1668 persons died from prescription of opioid-related overdoses during that time period.[15] Nearly 60% of decedents were male, with most deaths occurring in the 45 to 54 years of age range.[15] A 7-fold higher death rate was noted among persons enrolled in Medicaid programs, compared to those not enrolled. The opioids most commonly involved in the deaths were methadone (64%),

[1] Hospice Services, Providence Medical Group, Olympia, WA, USA
[2] Providence Medical Group, Olympia, WA, USA
[3] Department of Psychology, University at Albany State University of New York, Albany, NY, USA
[4] University of California, San Francisco, CA, USA
[5] Physical Medicine and Rehabilitation, The Rusk Institute of Rehabilitation Medicine, New York University, USA
[6] Department of Psychiatry, Harvard Medical School, USA
[7] Massachusetts Mental Health Center, Boston, MA, USA

Corresponding Author:
Gregory T. Carter, 410 Providence Lane, Building 2, Olympia, WA 98531, USA
Email: gtcarter@uw.edu

Downloaded from ajh.sagepub.com at UNIV WASHINGTON LIBRARIES on April 22, 2011

oxycodone (23%), and hydrocodone (14%), which highlights the particular toxicity of methadone.[15]

Contrast these morbid trends with this well-documented fact: no one has ever died from an overdose of cannabis.[16-20] Cannabis has no known lethal dose.[16-20] If cannabis-based medicines were more widely used to treat pain, potentially thousands of deaths from opioid toxicity may have been prevented. In the past decade, many states have relegalized cannabis for medicinal purposes.[21] This is based on a continually growing body of evidence demonstrating the efficacy of cannabis in treating neuropathic pain, muscle spasms, fibromyalgia, cacechexia, among others conditions.[21-36] Yet, the laws differ considerably from state to state, with considerable ambiguity what constitutes acceptable medical use.[23] Despite state laws, the Federal United States Drug Enforcement Agency (DEA) laws, as determined by the Controlled Substances Act (CSA), still classify cannabis as a Schedule I drug, the most tightly restricted category, reserved for drugs that have no currently accepted medical use. Thus, there is uniform set of quality control standards in place to assure the quality, consistency, and availability of medicinal cannabis for patients receiving palliative care.

How Did We Get Here?

Against the advice of the American Medical Association, the use of cannabis for any purpose, including medicinal, was criminalized in the United States by 1942.[37-40] Prior to then, there were many cannabis-based medications commercially manufactured by companies including Eli-Lilly, Parke Davis, and Sharp Dohme (now Merck Sharp Dohme).[1] Cannabis was criminalized largely due to the actions of Harry Anslinger, head of the Federal Bureau of Narcotics in the 1930s, who was a notoriously strong opponent of cannabis.[38] Multiple government-sponsored panels, including the National Commission on Marijuana and Drug Abuse (the Shafer Commission), appointed by the then President Richard Nixon have recommended that possession of cannabis for personal use no longer be an offense and that casual distribution of small amounts of cannabis for no remuneration or insignificant remuneration no longer be an offense.[40] The commission further concluded that neither the cannabis user nor the drug itself can be said to constitute a danger to public safety.[40] Despite the commission's recommendations, an infuriated Nixon and Congress ignored the report. Since then, almost 15 million Americans have been arrested on cannabis charges, with little evidence of any impact on cannabis use in either adults or youths.[41-53]

Thus, over the past 75 years, there have been further developments in opioid-based medicine, while research in cannabinoid-based medicines has grounded nearly to a halt. Today, opioids are available in a multitude of strengths, in pills, patches, injectables, implantables, etc, while the only form of a cannabinoid-based medicine available in the United States is dronabinol (Marinol). Dronabinol is 100% Delta-9 tetrahydrocannabinol (THC), the most psychoactive ingredient in cannabis.[54] Natural cannabis contains, at most, 20% THC.[55-57]

Opioids versus Cannabinoids: A Brief Overview

Opioids and cannabinoids have many things in common. They are both among the world's oldest-known class of drugs, with documentation of usage dating back many thousands of years. They both produce their pharmacological effect via actions at specific receptors, found throughout the body.[1,21] Both of these classes of compounds are also made endogenously in the human body and are part of the normal regulatory, homeostatic processes necessary for life.[58-61] Without endorphins (opioids) and endocannabinoids (cannabinoids), our bodies would not function properly.

Opioids

Any chemical that works by binding to opioid receptors is considered an opioid.[62,63] Opioid receptors are found principally in the central and peripheral nervous system and the gastrointestinal tract.[63] The receptors in these organ systems mediate both the beneficial and untoward side effects of opioids.[63,64]

In hospice and palliative care, opioids are the "gold standard" for analgesic medications, being cost- and clinically effective, and generally well-tolerated for treating moderate–to-severe pain. However, in a recent study of 50 641 persons receiving hospice services, approximately 20% had moderate or severe constipation due to morphine use.[65] However, long-term toxicity is not an issue in hospice but becomes a major problem in the management of chronic pain.

Cannabinoids

There are 2 known cannabinoid receptor subtypes. Subtype 1 (CB1) is expressed primarily in the brain, whereas subtype 2 (CB2) is expressed primarily in the periphery.[61,66-70] Dense CB1 receptor concentrations have been found in the cerebellum, basal ganglia, and hippocampus, accounting for the effects of cannabis on motor tone, coordination, and mood state.[71-81] Low concentrations are found in the respiratory centers of the brainstem, accounting for the remarkably low toxicity of cannabis.[81] Lethal doses for cannabis in humans have not been described.[1]

A detailed biochemical discussion of the remarkably complex cannabis genus is beyond the scope of this article. There are at least 3 species: cannabis sativa, cannabis indica, and cannabis ruderalis, with each containing over 400 distinct chemical moieties.[82-85] There are at least 85 known cannabinoids that have been isolated from the cannabis plant.[82-85] The cannabinoids are lipophilic, 21 carbon terpenes, and include delta-9 THC and delta-8 THC, which produce the majority of psychoactive effects.[54] Other major cannabinoids include cannabidiol (CBD) and cannabinol (CBN), both of which significantly modify the effects THC and have distinct effects of their own. CBD appears to modulate and reduce any untoward effects of THC.[83-90] Much less is known about CBN, although it appears to have distinct pharmacological properties that are quite different from CBD.[83] Cannabadiol has significant

Downloaded from ajh.sagepub.com at UNIV WASHINGTON LIBRARIES on April 22, 2011

anticonvulsant, sedative, and other pharmacological activities likely to interact with the effects of THC.[83] Cannabadiol may induce sleep and may provide some protection against seizures for epileptics.[83] Of relevance for pain management, in addition to analgesia, the following dose-dependent pharmacologic actions have been observed in studies: muscle relaxation, anti-inflammatory effects, neuroprotection in ischemia and hypoxia, enhanced well-being, and anxiolysis.[1-4] The ratios of the various cannabinoids differ according to the plant strain, and, to some extent, how the plant is grown.[82]

Potential analgesic sites of action for cannabinoids have been identified at brain, spinal cord, and peripheral levels.[87-90] There are strong data indicating that neurons in the rostroventral medulla and periaqueductal grey are involved in the brain-mediated analgesic effects of cannabinoids.[91] There are also spinal mechanisms of analgesia, including cannabinergic inhibition of gamma amino butyric acid (GABA), glycine, and glutamate release.[66,71,72] There is also a growing body of evidence showing a peripheral analgesic action of cannabinoids, particularly if inflammation is present.[76] Animal studies have demonstrated analgesic effects of locally delivered cannabinoids at doses that would not be systemically effective.[60] The mechanisms of these peripheral analgesic actions are not completely understood, but appear to be related to the anti-inflammatory effects of cannabinoids.[59,61] Cannabinoids have profound effects on cytokine production, although the direction of such effects is variable and not always mediated by cannabinoid receptors.[81] Another proposed mechanism for the anti-inflammatory actions is cannabinoid-induced increased production of eicosanoids that promote the resolution of inflammation. This differentiates cannabinoids from cyclooxygenase-2 inhibitors that suppress the synthesis of eicosanoids that promote the induction of the inflammatory process.[92,93]

The Argument Against Dronabinol

Dronabinol is 100% delta-9 THC, the most psychoactive ingredient in cannabis.[54] Natural cannabis contain, at best, 20% THC.[55,56] There are varying physiological effects when the other cannabinoid forms are present, as is the case with natural cannabis plant material.[94] The Food and Drug Administration first licensed and approved dronabinol in 1986 for the treatment of nausea and vomiting associated with chemotherapy and expanded this in 1992 for the treatment of anorexia associated with weight loss in patients with acquired immunodeficiency syndrome (AIDS) wasting.[94] Most patients find dronabinol too sedating and associated with too many psychoactive effects.[2,14] Dronabinol is not an appropriate substitute for natural cannabis.

Re-scheduling Cannabis

As previously noted, drugs are categorized (scheduled) by the DEA, as determined by the CSA. Schedule I is a category of drugs not considered legitimate for medical use because of limited utility and a high potential for dependence. Sharing this schedule with cannabis are heroin, lysergic acid, and methamphetamine. Schedule II is a category of drugs considered to have a strong potential for abuse or addiction, but that also have legitimate medical use. Included here are opium, morphine, cocaine, and oxycodone. Schedule III drugs are felt to have even less abuse or addiction potential than Schedule I or II drugs and have a beneficial medical use. Included here are dronabinol, hydrocodone, amphetamine-based stimulants, and short-acting barbiturates. Schedule IV and V drugs are felt to have even less risks. Schedule IV drugs include benzodiazepines, while Schedule V drugs include antidiarrheals and antitussives that contain opioid derivatives.

For further perspective, while the DEA considers cannabis a Schedule I drug, it does not schedule carisoprodol (Soma) at all, implying that this agency does not consider it a dangerous drug. Carisoprodol is a widely used muscle relaxant whose active metabolite is the barbiturate meprobamate. Carisoprodol also shows serotonergic activity at higher levels and has produced overdose in humans.[95,96] Abrupt cessation in patients taking large doses of carisoprodol will produce withdrawal, characterized by vomiting, insomnia, tremors, psychosis, and ataxia.[95,96]

Given that dronabinol, being 100% THC and highly psychoactive, is Schedule III, and the potentially addictive drug carisoprodol is unscheduled, it is perplexing how cannabis remains a Schedule I drug. In our opinion, ideally cannabis should be unscheduled. At the very least, it should be reclassified to Schedule III or higher.

Debunking the Smoking Argument

Cannabis does not need to be smoked to be effectively used as medicine. While cannabis smoke does not cause lung cancer, it can potentially irritate bronchial mucosal membranes. However, cannabinoids are volatile and will vaporize at temperatures in the range of 250°F, much lower than actual combustion.[97-99] Heated air is drawn through cannabis and the active compounds vaporize, which are then inhaled. This rapid deliver of the cannabinoids allows for easy titration to desired effect, much as with smoking yet without health risks.[97-99] Additionally, cannabis can be ingested orally or applied topically in a liniment.[1]

Side Effects of Cannabis

As with any drug, cannabis is not without side effects. Medical use of cannabis is also distinctly different from recreational use. A patient does not need to be intoxicated to get a beneficial medical effect.[100,101] Cannabis may induce euphoria and, as such, may be psychologically addictive. There is no severe physical withdrawal syndrome associated with cannabis. Cannabis addiction is amenable to treatment.[46] Cannabis may induce paranoia and disorientation in novice users. Many of the undesired psychoactive effects of cannabis are due to THC, which is among the reasons that dronabinol is not a suitable alternative.

Downloaded from ajh.sagepub.com at UNIV WASHINGTON LIBRARIES on April 22, 2011

However, newer medicinal strains of cannabis are lower in THC and higher in the nonpsychoactive, more therapeutic cannabinoids, such as CBD and CBN. These compounds further improved the efficacy of cannabis.[102-104] With simple trial and error, most patients are able to get the right combination of cannabinoids that meet their needs. Dosing paradigms for medicinal cannabis have been previously described.[17,18]

Conclusion

Despite being hampered by legal restrictions, the available medical research on cannabis indicates that cannabis is effective in treating a number of problems commonly encountered in palliative medicine. Many patients in a palliative care setting who are currently on long-term opioids for chronic pain could potentially be treated with either cannabis alone or in combination with a lower dose of opioids. From a pharmacological perspective, cannabinoids are considerably safer than opioids and have broad applicability in palliative care. Had cannabis not been removed from our pharmacopeia 7 decades ago and remained available to treat chronic pain, potentially thousands of lives that have been lost to opioid toxicity could have been prevented. As our population ages and palliative medicine continues to grow as a specialty, the argument for cannabis to be reclassified by the DEA as a scheduled III or higher becomes increasingly important.

As palliative medicine practitioners, our specialty should embrace the scientific process, which continues to document the therapeutic effects of cannabis. As is often the case in hospice, we must be willing to advocate for our patients who want to legitimately access a medicine that could potentially be very beneficial for them and is safer than other options such as opioids. The medicinal cannabis user should not be considered a criminal in any state and the DEA and our legal system should be using science and logic as the basis of policy making rather than political or societal bias.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interests with respect to the authorship and/or publication of this article

Funding

The author(s) received no financial support for the research and/or authorship of this article.

References

1. Vigano A, Bruera E, Suarez-Almazor ME. Age, pain intensity and opioid dose in patients with advanced cancer. *Cancer*. 1998; 83(6):1244-1250.
2. Franklin GM, Mai J, Wickizer T, Turner JA, Fulton-Kehoe D, Grant L. Opioid dosing trends and mortality in Washington State workers' compensation, 1996-2002. *Am J Ind Med*. 2005;48(2): 91-99.
3. Jumbelic MI. Deaths with transdermal fentanyl patches. *Am J Forensic Med Pathol*. 2010;31(1):18-21.
4. Campbell CI, Weisner C, Leresche L, et al. Age and gender trends in long-term opioid analgesic use for noncancer pain. *Am J Public Health*. 2010;100(12):2541-2547.
5. Solomon DH, Rassen JA, Glynn RJ, et al. The comparative safety of opioids for nonmalignant pain in older adults. *Arch Intern Med*. 2010;170(22):1979-1986.
6. Franklin GM, Rahman EA, Turner JA, Daniell WE, Fulton-Kehoe D. Opioid use for chronic low back pain: a prospective, population-based study among injured workers in Washington state, 2002-2005. *Clin J Pain*. 2009;25(9):743-751.
7. Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. *Arch Intern Med*. 2010;170(22):1968-1978.
8. Pergolizzi J, Böger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract*. 2008;8(4):287-313.
9. Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. *BMJ*. 2010;26(341):c5475.
10. Wunsch MJ, Nakamoto K, Nuzzo PA, Behonick G, Massello W, Walsh SL. Prescription drug fatalities among women in rural Virginia: a study of medical examiner cases. *J Opioid Manag*. 2009; 5(4):228-236.
11. Paulozzi LJ, Xi Y. Recent changes in drug poisoning mortality in the United States by urban-rural status and by drug type. *Pharmacoepidemiol Drug Saf*. 2008;17(10):997-1005.
12. Shah NG, Lathrop SL, Reichard RR, Landen MG. Unintentional drug overdose death trends in New Mexico, USA, 1990-2005: combinations of heroin, cocaine, prescription opioids and alcohol. *Addiction*. 2008;103(1):126-136.
13. Coffin PO, Galea S, Ahern J, Leon AC, Vlahov D, Tardiff K. Opiates, cocaine and alcohol combinations in accidental drug overdose deaths in New York City, 1990-98. *Addiction*. 2003; 98(6):739-747.
14. Piercefield E, Archer P, Kemp P, Mallonee S. Increase in unintentional medication overdose deaths: Oklahoma, 1994-2006. *Am J Prev Med*. 2010;39(4):357-363.
15. Centers for Disease Control and Prevention (CDC). Overdose deaths involving prescription opioids among Medicaid enrollees - Washington, 2004-2007. *MMWR Morb Mortal Wkly Rep*. 2009;58(42):1171-1175.
16. Walden N, Earleywine M. How high: quantity as a predictor of cannabis-related problems. *Harm Reduct J*. 2008;5:20.
17. Aggarwal SK, Kyashna-Tocha M, Carter GT. Dosing medical marijuana: rational guidelines on trial in Washington State. *Med Gen Med*. 2007;9(3):52.
18. Carter GT, Weydt P, Kyashna-Tocha M, Abrams DI. Medical marijuana: rational guidelines for dosing. *IDrugs*. 2004;7(5): 464-470.
19. Klein TW, Lane B, Newton CA, Friedman H. The cannabinoid system and cytokine network. *Proc Soc Exp Biol Med*. 2000; 225(1):1-8.

Downloaded from ajh.sagepub.com at UNIV WASHINGTON LIBRARIES on April 22, 2011

20. Pertwee RG. Cannabinoid receptor ligands: clinical and neuropharmacological considerations, relevant to future drug discovery and development. *Expert Opin Investig Drugs*. 2000;9(7):1553-1571.
21. Aggarwal SK, Carter GT, Sullivan MD, Morrill R, ZumBrunnen C, Mayer JD. Medicinal use of cannabis in the United States: historical perspectives, current trends, and future directions. *J Opioid Manag*. 2009;5(3):153-168.
22. Aggarwal SK, Carter GT, Sullivan MD, Morrill R, ZumBrunnen C, Mayer JD. Characteristics of patients with chronic pain accessing treatment with medicinal cannabis in Washington State. *J Opioid Manag*. 2009;5(5):257-286.
23. Carter GT, Mirken B. Medical marijuana: politics trumps science at the FDA. *Medscape Gen Med*. 2006;8(2):46.
24. Carter GT, Rosen BS. Marijuana in the management of amyotrophic lateral sclerosis. *Am J Hosp Palliat Care*. 2001;18(4):264-270. PMID:11467101.
25. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *CMAJ*. 2010;182(14):E694-E701.
26. El-Alfy AT, Ivey K, Robinson K, et al. Antidepressant-like effect of delta9-tetrahydrocannabinol and other cannabinoids isolated from *Cannabis sativa L. Pharmacol Biochem Behav*. 2010;95(4):434-442.
27. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology*. 2008;(2):1-9.
28. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain*. 2008;9:506-521.
29. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology*. 2007;68(7):515-521.
30. Abrams DI, Vizoso HP, Shade SB, et al. Vaporization as a smokeless cannabis delivery system: a pilot study. *Clin Pharmacol Ther*. 2007;82(5):572-578.
31. Rocha FCM, Oliveira LMQR, Da Silveira DX. Therapeutic use of *Cannabis sativa* on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *Eur J Cancer Care*. 2008;17(4):431-443.
32. Hampson AJ, Grimaldi M, Lolic M, Wink D, Rosenthal R, Axelrod J. Neuroprotective antioxidants from marijuana. *Ann N Y Acad Sci*. 2000;899:274 82.
33. Nagayama T, Sinor AD, Simon RP, et al. Cannabinoids and neuroprotection in global and focal cerebral ischemia and in neuronal cultures. *J Neurosci*. 1999;19(8):2987 95.
34. Amtmann D, Weydt P, Johnson KL, Jensen MP, Carter GT. Survey of cannabis use in patients with amyotrophic lateral sclerosis. *Am J Hosp Palliat Care*. 2004;21(2):95-104.
35. Grinspoon L, Bakalar JB. The use of cannabis as a mood stabilizer in bipolar disorder: anecdotal evidence and the need for clinical research. *J Psychoactive Drugs*. 1998;30(2):171-177.
36. Denson TF, Earleywine M. Decreased depression in marijuana users. *Addict Behav*. 2006;31(4):738-42.
37. Carter GT, Abood ME, Aggarwal SK, Weiss MD. Cannabis and amyotrophic lateral sclerosis: practical and hypothetical applications, and a call for clinical trials. *Am J Hosp Palliat Med*. 2010;27(5):347-356.
38. McWilliams JC. Unsung partner against crime: Harry J. Anslinger and the Federal Bureau of Narcotics, 1930-1962. *Pa Mag Hist Biogr*. 1989;113(2):207-236.
39. Hollister LE. Criminal laws and the control of drugs of abuse. An historical view of the law (or, it's the lawyer's fault). *J Clin Pharmacol J New Drugs*. 1969;9(6):345-348.
40. Nahas GG, Greenwood A. The first report of the National Commission on marihuana (1972): signal of misunderstanding or exercise in ambiguity. *Bull N Y Acad Med*. 1974;50(1):55-75.
41. Paschall MJ, Flewellng RL, Grube JW. Using statewide youth surveys to evaluate local drug use policies and interventions. *Contemp Drug Probl*. 2009;36(3-4):427-446.
42. Eaton DK, Kann L, Kinchen S, et al. Centers for Disease Control and Prevention (CDC): Youth risk behavior surveillance – United States, 2009. *MMWR Surveill Summ*. 2010;59(5):1-142.
43. Grinspoon L, Bakalar JB, Zimmer L, Morgan JP. Marijuana addiction. *Science*. 1997;277(5327):749.
44. Barnwell SS, Earleywine M. Simultaneous alcohol and cannabis expectancies predict simultaneous use. *Subst Abuse Treat Prev Policy*. 2006;1(11):29.
45. Earleywine M. Schizotypy, marijuana, and differential item functioning. *Hum Psychopharmacol*. 2006;21(7):455-461.
46. Denson TF, Earleywine M. Pothead or pot smoker? A taxometric investigation of cannabis dependence. *Subst Abuse Treat Prev Policy*. 2006;10(1):22.
47. Barnwell SS, Earleywine M, Wilcox R. Cannabis, motivation, and life satisfaction in an internet sample. *Subst Abuse Treat Prev Policy*. 2006;12(1):2.
48. Smucker Barnwell S, Earleywine M, Gordis EB. Alcohol consumption moderates the link between cannabis use and cannabis dependence in an internet survey. *Psychol Addict Behav*. 2005;19(2):212-216.
49. Earleywine M. Marijuana arrests and increase in marijuana use disorders. *JAMA*. 2004;292(7):802.
50. Grinspoon L, Bakalar JB. The war on drugs–a peace proposal. *N Engl J Med*. 1994;330(5):357-60.
51. Looby A, Earleywine M. Negative consequences associated with dependence in daily cannabis users. *Subst Abuse Treat Prev Policy*. 2007;10(2):3.
52. Lavender JM, Looby A, Earleywine M. A brief cannabis-associated problems questionnaire with less potential for bias. *Hum Psychopharmacol*. 2008;23(6):487-493.
53. Van Dam NT, Earleywine M, DiGiacomo G. Polydrug use, cannabis, and psychosis-like symptoms. *Hum Psychopharmacol*. 2008;23(6):475-485.
54. Taylor EC, Lenard K, Loev B. Tetrahydrocannabinol analogs. Synthesis of 2-(3-methyl-2-octyl)-3-hydroxy-6,6,9-trimethyl-7,8,9,10-tetrahydrodibenzo(b,d)pyran. *Tetrahedron*. 1967;23(1):77-85.
55. Etienne PM, de Meijer M, Bagatta A, et al. The inheritance of chemical phenotype of *Cannabis sativa L. Genetics*. 2003;163(1):335-346.
56. Hillig KW, Mahlberg PG. A chemotaxonomic analysis of cannabinoid variation in Cannabis (Cannabaceae). *Am J Bot*. 2004;91(6):966-975.

Downloaded from ajh.sagepub.com at UNIV WASHINGTON LIBRARIES on April 22, 2011

57. Cristiana Moliterni VM, Cattivelli L, Ranalli P, Mandolino G. The sexual differentiation of *Cannabis sativa L*: a morphological and molecular study. *Euphytica*. 2005;140(1-2):95-106.
58. DeSanty KP, Dar MS. Involvement of the cerebellar adenosine A(1) receptor in cannabinoid induced motor incoordination in the acute and tolerant state in mice. *Brain Res*. 2001;29,905(1-2): 178-187.
59. Di Marzo V, Fontana A, Cadas H, et al. Formation and inactivation of endogenous cannabinoid anandamide in central neurons. *Nature*. 1994;372(6507):686-691.
60. Egertova M, Elphick MR. Localisation of cannabinoid receptors in the rat brain using antibodies to the intracellular C-terminal of CB1. *J Comp Neurol*. 2000;422:159-171.
61. Tsou K, Brown S, Mackie K, Sanudo-Pena MC, Walker JM. Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. *Neuroscience*. 1998;83(2): 393-411.
62. Okie S. A flood of opioids, a rising tide of deaths. *N Engl J Med*. 2010;18;363(21):1981-1985.
63. Chapman CR, Lipschitz DL, Angst MS, et al. Opioid pharmacotherapy for chronic non-cancer pain in the United States: a research guideline for developing an evidence-base. *J Pain*. 2010;11(9):807-829.
64. Bishop MF, Stephens L, Goodrich M, Byock I. Medication kits for managing symptomatic emergencies in the home: a survey of common hospice practice. *J Palliat Med*. 2009;12(1):37-44.
65. Strassels SA, Maxwell TL, Iyer S. Constipation in persons receiving hospice care. *J Pain. Symptom Manage*. 2010;40(6):810-820.
66. Meng ID, Manning BH, Martin WJ, Fields HL. An analgesic circuit activated by cannabinoids. *Nature*. 1998;395(6700):381-383.
67. Martin WJ, Hohmann AG, Walker JM. Suppression of noxious stimulus-evoked activity in the ventral posterolateral nucleus of the thalamus by a cannabinoid agonist: Correlation between electrophysiological and antinociceptive effects. *J Neurosci*. 1996; 16(20):6601-6611.
68. Lichtman AH, Cook SA, Martin BR. Investigation of brain sites mediating cannabinoid-induced antinociception in rats: evidence supporting periaqueductal gray involvement. *J Pharmacol Exp Ther*. 1996;276(2):585-593.
69. Tsou K, Brown S, Mackie K, Sanudo-Pena MC, Walker JM. Immunohistochemical distribution of cannabinoid CB1 receptors in the rat central nervous system. *Neuroscience*. 1998;83(2): 393-411.
70. Ong WY, Mackie K. A light and electron microscopic study of the CB1 cannabinoid receptor in the primate spinal cord. *J Neurocytol*. 1999;28(1):39-45.
71. Farquhar-Smith WP, Egertova M, Bradbury EJ, McMahon SB, Rice ASC, Elphick MR. Cannabinoid CB1 receptor expression in rat spinal cord. *Mol Cell Neurosci*. 2000;15:510-521.
72. Hohmann AG, Briley EM, Herkenham M. Pre- and postsynaptic distribution of cannabinoid and mu opioid receptors in rat spinal cord. *Brain Res*. 1999;822(1-2):17-25.
73. Sanudo-Pena MC, Strangman NM, Mackie K, Walker JM, Tsou K. CB1 receptor localization in rat spinal cord and roots, dorsal root ganglion and peripheral nerve. *Acta Pharmacol Sin*. 1999;20(12):1115-1120.
74. Hohmann AG, Herkenham M. Regulation of cannabinoid and mu opioid receptors in rat lumbar spinal cord following neonatal capsaicin treatment. *Neurosci Lett*. 1998;252(1):13-16.
75. Chapman V. The cannabinoid CB1 receptor antagonist, SR141716A, selectively facilitates nociceptive responses of dorsal horn neurones in the rat. *Br J Pharmacol*. 1999;127(8): 1765-1767.
76. Smith PB, Martin BR. Spinal mechanisms of delta 9-tetrahydrocannabinol-induced analgesia. *Brain Res*. 1992; 578(1-2):8-12.
77. Morisset V, Urban L. Cannabinoid-induced inhibition of excitatory transmission in substantia gelatinosa neurones of the rat spinal cord. *Soc Neurosci Abstr*. 2000;26:812-814.
78. Fox A, Kesingland A, Gentry C, et al. The role of central and peripheral CB1 receptors in the antihyperalgesic activity of cannabinoids in a model of neuropathic pain. *Pain*. 2001;92(1-2):91-100.
79. Agarwal N, Pacher P, Tegeder I, et al. Cannabinoids mediate analgesia largely via peripheral type 1 cannabinoid receptors in nociceptors. *Nat Neurosci*. 2007;10(7):870-879.
80. Farquhar-Smith WP, Egertova M, Bradbury EJ, McMahon SB, Rice ASC, Elphick MR. Cannabinoid CB1 receptor expression in rat spinal cord. *Mol Cell Neurosci*. 2000;15:510-521.
81. Nguyen PT, Selley DE, Sim-Selley LJ. Statistical Parametric Mapping reveals ligand and region-specific activation of G-proteins by CB1 receptors and non-CB1 sites in the 3D reconstructed mouse brain. *Neuroimage*. 2010;52(4):1243-1251.
82. Fischedick JT, Glas R, Hazekamp A, Verpoorte R. A qualitative and quantitative HPTLC densitometry method for the analysis of cannabinoids in *Cannabis sativa L. Phytochem Anal*. 2009;20(5): 421-426.
83. Borrelli F, Aviello G, Romano B, Orlando P, Capasso R, Maiello F, Guadagno F, Petrosino S, Capasso F, Di Marzo V, Izzo AA. Cannabidiol. a safe and non-psychotropic ingredient of the marijuana plant *Cannabis sativa*, is protective in a murine model of colitis. *J Mol Med*. 2009;87(11):1111-1121.
84. Zanelati TV, Biojone C, Moreira FA, Guimarães FS, Joca SR. Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors. *Br J Pharmacol*. 2010;159(1): 122-128.
85. Jones NA, Hill AJ, Smith I, et al. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. *J Pharmacol Exp Ther*. 2010;332(2):569-577.
86. Morgan CJ, Freeman TP, Schafer GL, Curran HV. Cannabidiol attenuates the appetitive effects of delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis. *Neuropsychopharmacology*. 2010;35(9):1879-1885.
87. Russo EB. Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? *Neuro Endocrinol Lett*. 2008;29(2):192-200.
88. Lakhan SE, Rowland M. Whole plant cannabis extracts in the treatment of spasticity in multiple sclerosis: a systematic review. *BMC Neurol*. 2010;9:59-61.
89. McAllister SD, Hurst DP, Barnett-Norris J, Lynch D, Reggio PH, Abood ME. Structural mimicry in class A G protein-coupled receptor rotamer toggle switches: the importance of the

Downloaded from ajh.sagepub.com at UNIV WASHINGTON LIBRARIES on April 22, 2011

F3.36(201)/W6.48(357) interaction in cannabinoid CB1 receptor activation. *J Biol Chem.* 2004;279(46):48024-48037.

90. Burstein SH, Zurier RB. Cannabinoids, endocannabinoids, and related analogs in inflammation. *AAPS J.* 2009;11(1):109-119.
91. Lichtman AH, Cook SA, Martin BR. Investigation of brain sites mediating cannabinoid-induced antinociception in rats: evidence supporting periaqueductal gray involvement. *J Pharmacol Exp Ther.* 1996;276(2):585-593.
92. González-Muniesa P, Bing C, Trayhurn P. Upregulation of the expression of inflammatory and angiogenic markers in human adipocytes by a synthetic cannabinoid, JTE-907. *Horm Metab Res.* 2010;42(10):710-717.
93. Cencioni MT, Chiurchiù V, Catanzaro G, et al. Anandamide suppresses proliferation and cytokine release from primary human T-lymphocytes mainly via CB2 receptors. *PLoS One.* 2010;5(1): e8688.
94. Schedules of controlled substances: rescheduling of the Food and Drug Administration approved product containing synthetic dronabinol [(-) - [DELTA] less than 9 greater than - (trans)-tetrahydrocannabinol] in sesame oil and encapsulated in soft gelatin capsules from schedule II to schedule III. Department of Justice (DOJ), Drug Enforcement Administration (DEA). Final rule. *Fed Regist.* 1999;64(127):35928-30.
95. Reeves RR, Burke RS. Carisoprodol: abuse potential and withdrawal syndrome. *Curr Drug Abuse Rev.* 2010;3(1):33-38.
96. Fass JA. Carisoprodol legal status and patterns of abuse. *Ann Pharmacother.* 2010;44(12):1962-7.
97. Van Dam NT, Earleywine M. Pulmonary function in cannabis users: support for a clinical trial of the vaporizer. *Int J Drug Policy.* 2010;21(6):511-513.
98. Earleywine M, Barnwell SS. Decreased respiratory symptoms in cannabis users who vaporize. *Harm Reduct J.* 2007;4:11.
99. Melamede R. Cannabis and tobacco smoke are not equally carcinogenic. *Harm Reduct J.* 2005;18(2):21.
100. Grinspoon L, Bakalar JB. Marihuana as medicine. A plea for reconsideration. *JAMA.* 1995;273(23):1875-1876.
101. Grinspoon L, Bakalar JB, Doblin R. Marijuana, the AIDS wasting syndrome, and the U.S. government. *N Engl J Med.* 1995; 333(10):670-671.
102. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain.* 2004;112(3):299-306.
103. Frank B, Serpell MG, Hughes J, Matthews JN, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ.* 2008;336(7637):199-201.
104. Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. *Anesth Analg.* 2010;110(2):604-610.

Downloaded from ajh.sagepub.com at UNIV WASHINGTON LIBRARIES on April 22, 2011

QUESTION #9 ATTACHMENTS
ATTACHMENT #7

ARTICLES FROM PEER-REVIEWED SCIENTIFIC JOURNALS

Medical Marijuana Laws Reduce Prescription Medication Use in Medicare Part D.
Bradford AC, Bradford WD. Health Affairs 35, no.7 (2016):1230-1236 doi: 10.1377/hlthaff.2015.1661

HealthAffairs

At the Intersection of Health, Health Care and Policy

Cite this article as:
Ashley C. Bradford and W. David Bradford
Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D
Health Affairs 35, no.7 (2016):1230-1236
doi: 10.1377/hlthaff.2015.1661

The online version of this article, along with updated information and services, is available at:
http://content.healthaffairs.org/content/35/7/1230

For Reprints, Links & Permissions : http://content.healthaffairs.org/1340_reprints.php

Email Alertings : http://content.healthaffairs.org/subscriptions/etoc.dtl

To Subscribe : https://fulfillment.healthaffairs.org

Health Affairs is published monthly by Project HOPE at 7500 Old Georgetown Road, Suite 600, Bethesda, MD 20814-6133. Copyright ©
by Project HOPE - The People-to-People Health Foundation. As provided by United States copyright law (Title 17, U.S. Code), no part of
may be reproduced, displayed, or transmitted in any form or by any means, electronic or mechanical, including photocopying or by information storage or retrieval systems, without prior written permission from the Publisher. All rights reserved.

Not for commercial use or unauthorized distribution

Downloaded from http://content.healthaffairs.org/ by *Health Affairs* on July 9, 2016 by HW Team

By Ashley C. Bradford and W. David Bradford

DOI: 10.1377/hlthaff.2015.1661
HEALTH AFFAIRS 35,
NO. 7 (2016): 1230–1236
©2016 Project HOPE—
The People-to-People Health
Foundation, Inc.

Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D

Ashley C. Bradford is a master of public administration student in the Department of Public Administration and Policy at the University of Georgia, in Athens.

W. David Bradford (bradfowd@uga.edu) is the Busbee Chair in Public Policy in the Department of Public Administration and Policy at the University of Georgia.

ABSTRACT **Legalization of medical marijuana has been one of the most controversial areas of state policy change over the past twenty years. However, little is known about whether medical marijuana is being used clinically to any significant degree. Using data on all prescriptions filled by Medicare Part D enrollees from 2010 to 2013, we found that the use of prescription drugs for which marijuana could serve as a clinical alternative fell significantly, once a medical marijuana law was implemented. National overall reductions in Medicare program and enrollee spending when states implemented medical marijuana laws were estimated to be $165.2 million per year in 2013. The availability of medical marijuana has a significant effect on prescribing patterns and spending in Medicare Part D.**

In the past twenty years, the drive in many states to legalize medical marijuana has gained widespread public attention, though there has been no corresponding change to federal marijuana laws. In the late 1980s evidence began to emerge that the use of marijuana has a positive effect on the lives of many people suffering from a variety of ailments. Nevertheless, marijuana is still federally classified as a Schedule I drug (the most restrictive category, according to the Controlled Substances Act of 1970), which means that it is deemed to have "no currently acceptable medical use in treatment in the United States," a high potential for abuse, and "a lack of accepted safety for use...under medical supervision."[1(p40)] This classification imposes significant barriers not only to obtaining marijuana products for clinical use but also to conducting primary research on the pharmacological and behavioral impacts of marijuana use.

Despite such barriers, twenty-four states and the District of Columbia have adopted laws legalizing the use of marijuana for medical purposes. Surprisingly, although there is a rapidly growing literature about many indirect effects of medical marijuana laws, almost nothing is known about how these state health policies affect clinical care or spending in the health care sector. In this article we investigate how implementing state-level medical marijuana laws changes prescribing patterns and program and patient expenditures in Medicare Part D for prescription drugs approved by the Food and Drug Administration (FDA).

There is significant variation across state medical marijuana policies.[2] Every state that currently allows the use of medical marijuana requires a licensed physician to recommend that use and requires that the recommendation be made only if a patient presents with one or more illnesses from a state-approved list.[3] Home cultivation of marijuana is sometimes permitted, though every state that passed a medical marijuana law since 2009 has included some form of regulated dispensary program.[1] Some states allow caregivers to distribute marijuana.[1,4] In addition, the legal possession limit differs greatly across states.[5]

The findings from research on the effects of the medical use of marijuana have been extremely mixed. Historically, opponents of medical marijuana legalization have cited addiction, criminal

Downloaded from http://content.healthaffairs.org/ by *Health Affairs* on July 9, 2016 by HW Team

activity, marijuana's status as a so-called gateway drug, and marijuana's lack of demonstrated medical value as reasons for keeping the drug illegal.[5] However, the causal link between the use of marijuana and the use of harder drugs has never been proven definitively, nor has the link between medical marijuana and criminal activity.

In a 2013 study Mark Anderson and coauthors reported that traffic fatalities dropped 8–11 percent following the passage of state medical marijuana legislation.[6] Sarah Lynne-Landsman and coauthors analyzed data from the Youth Risk Behavior Survey using a difference-in-differences design to estimate the effects of medical marijuana laws on adolescent marijuana use.[7] That study found no effect on self-reported prevalence or frequency of use. In contrast, Melanie Wall and colleagues reported that states that passed a medical marijuana law had significantly higher rates of marijuana use and abuse among adolescents, compared to states with no such law, though the estimated effects were largely associations.[8] In a later study that attempted to replicate the results of Wall and colleagues, Sam Harper and coauthors found that when researchers used statistical methods that identified causal effects, the effect of medical marijuana laws on drug use largely disappeared.[9]

These findings are representative of an unsettled literature. Earlier studies did not generally use statistical methods such as those of Harper and coauthors, but later studies did—and the later studies tended to find only insignificant effects or a mix of significant and insignificant ones.

One issue that has received surprisingly little attention is the question of whether medical marijuana is being used clinically to any significant degree. To the extent that physicians recommend the use of marijuana to their patients to manage conditions that it can treat, according to clinical evidence, one would expect marijuana to be primarily a substitute for existing prescription medications (for patients who did not respond to previous therapy or who respond better to marijuana than to previous treatment). Nonetheless, there are no published studies that investigate whether states' approval of medical marijuana changes the prescribing patterns for pharmaceuticals approved by the FDA.

In this study we asked two straightforward questions. First, does implementing a medical marijuana law change prescribing patterns in Medicare Part D for traditional (FDA-approved) drugs that treat conditions marijuana itself might treat? Second, if it does, what is the effect on overall spending—both by Medicare and by enrollees out of pocket—of such changes?

Conceptual Framework

Two competing forces can drive prescription behavior when a medical marijuana law is implemented. The primary effect one expects is that prescribing for FDA-approved drugs will fall when a medical marijuana law is put in place, because marijuana is often a substitute for existing therapies. For most FDA-approved prescription drugs for which medical marijuana can serve as a replacement, we hypothesized that prescribing would decline.

However, this substitution effect model does not account for the secondary effect from demand expansion that might result from the introduction of a new product. When new products are made available, information sets change because of influences such as discussion of the treatment option in the media. Media coverage may draw new patients into physicians' offices, much as direct-to-consumer advertising does.[10–12] If not all new patients are diverted to marijuana, then prescription drug use might rise, even if those drugs and marijuana are clinical substitutes for each other.

Glaucoma is a notable condition for which demand expansion might swamp substitution. Clinical evidence is very strong that while marijuana sharply reduces intraocular pressure, the effect lasts only about an hour.[13] As a result, new patients who seek glaucoma treatment after learning about the potential benefits of marijuana are likely to receive a prescription for an FDA-approved drug. The prognosis for untreated glaucoma is very ominous. Thus, we expected that prescribing for glaucoma drugs would remain unchanged or even rise with the implementation of a medical marijuana law.

Study Data And Methods

DATA Our data came from the Medicare Part D Prescription Drug Event Standard Analytic File for the period 2010–13. These data contain information on all prescription drugs paid for under Medicare Part D. Each record in the data represents a specific drug prescribed by a physician in a given year and contains information on the total number of daily doses filled and the total expenditures (the amount paid by Medicare, patients' out-of-pocket expenditures, and any low-income subsidies for deductibles and copayments under the Affordable Care Act). We linked these data to basic information on the prescribing physicians, including sex, specialty, and location of home and business addresses.[14] The baseline data contained more than eighty-seven million physician-drug-year observations.

We restricted the analysis to drugs that treat conditions for which marijuana might be an al-

Downloaded from http://content.healthaffairs.org/ by *Health Affairs* on July 9, 2016 by HW Team

ternative treatment. We obtained guidance on which conditions were in that category from the states' medical marijuana legislation, which explicitly mentions certain conditions;[15] from summaries of the clinical evidence in a 1999 Institute of Medicine review;[13] and from a recent comprehensive meta-analysis.[16] We selected nine broad clinical condition categories to study, based on the intersection of this reviewed clinical evidence and the list of conditions mentioned in state medical marijuana laws. A list of these condition categories and information about the clinical evidence for the use of marijuana in treating them appear in Exhibit 1.

Once the relevant condition categories were selected, we had to determine which drugs to study. In clinical practice, patients may be prescribed drugs that have been formally approved by the FDA to treat their diagnosed conditions (an on-label prescription) or drugs that do not have such formal approval (an off-label prescription).[17] If we chose only drugs that were on label, we might have overlooked a large number of drugs that were used to treat the condition categories listed in Exhibit 1.

For our analysis, we extracted data on all drugs that were in a drug class that had at least one on-label option to treat one or more of the condition

EXHIBIT 1

Nine medical condition categories with at least one drug approved by the Food and Drug Administration for on-label use, and level of evidence for marijuana as a treatment for conditions in the category

	Condition category								
	Anxiety	**Depression**	**Glaucoma**	**Nausea**	**Pain**	**Psychosis**	**Seizures**	**Sleep disorders**	**Spasticity**
CLINICAL EVIDENCE OF MEDICAL MARIJUANA EFFECT ON CONDITIONS IN EACH CATEGORY									
Institute of Medicine (1999)[a]	Present	—[b]	Insufficient	Present	Present	—[b]	Insufficient	—[b]	Insufficient
Whiting et al. (2015)[c]	Very low	Very low	—[b]	Low	Moderate	Low	—[b]	Low or very low	Low to moderate
DRUG CLASSES WITH AT LEAST ONE ON-LABEL OPTION FOR TREATING CONDITIONS IN EACH CATEGORY									
Adrenal cortical steroids					•				
Analgesics					•				
Antiarrhythmic agents							•		
Anticonvulsants	•	•			•	•	•	•	
Antidepressants	•	•			•	•			
Antidiarrheal agents				•					
Antiemetic or antivertigo agents				•	•				
Antimalarial agents					•				
Antipsychotics		•				•			
Antirheumatics					•				
Anxiolytics, sedatives, and hypnotics	•					•		•	
Central nervous system stimulants								•	
Functional bowel disorder agents					•				
Immunostimulants									•
Muscle relaxants					•				•
Ophthalmic preparations			•						
Proton pump inhibitors				•					
Respiratory inhalant products					•				
Sedatives and hypnotics	•					•		•	
Smoking cessation agents	•	•							

SOURCE Authors' analysis of principal findings in Institute of Medicine, Marijuana and medicine (Note 13 in text); and Whiting PF, et al. Cannabinoids for medical use (Note 16 in text). **NOTES** The nine condition categories were selected based on their inclusion in at least four states' medical marijuana laws and the two comprehensive clinical studies cited in the exhibit. [a]Classifying evidence of effect as either present (without rating the strength of the evidence) or insufficient. [b]No review of the effects of marijuna were provided for conditions in these categories. [c]Classifying evidence of effect on a scale from moderate to very low.

Downloaded from http://content.healthaffairs.org/ by *Health Affairs* on July 9, 2016 by HW Team

Our research suggests that more widespread state approval of medical marijuana could provide modest budgetary relief.

categories listed in Exhibit 1. This resulted in a set of both on- and off-label drugs used to treat each of our study condition categories, while excluding off-label drugs that were pharmacologically far removed from the on-label options.

We saved these prescription data in separate analytic data sets, one for each condition category listed in Exhibit 1. We aggregated the data to the physician-year level, so that each line in the data represented the number of daily doses (and associated Medicare program and enrollee out-of-pocket costs) that were filled for all prescriptions written by each physician in the particular condition category each year. The final physician-level analytic data sets, which were aggregations of all Medicare Part D prescriptions for our selected drugs, ranged in size from 588,808 observations for the spasticity diagnosis sample to 2,496,608 observations for the pain diagnosis sample.

More details on the data and data construction methods can be found in the online Appendix.[18]

BASIC MODELS The key variable of interest was an indicator of when prescriptions were filled in a state and year with an effective medical marijuana law in place—that is, where it was legal for state residents either to use home-grown marijuana or to purchase marijuana in a dispensary and where such a dispensary was open. Covariates included physician and state characteristics. We also included county-level demographic variables from the Area Health Resources Files that were expected to influence the aggregate demand for drugs dispensed under Medicare Part D.[19]

We used a simple difference-in-differences regression framework estimated separately for each of the nine condition categories listed in Exhibit 1. All models were estimated with least squares regressions. Each of the estimated models were corrected for clustering at the physician level. Details of the model variables are included in the Appendix.[18]

In addition to estimating changes in prescribing patterns with the implementation of a medical marijuana law, we estimated changes in Medicare Part D payments (including government low-income subsidies for copayments and deductibles) and patients' out-of-pocket spending. Details of how we conducted this analysis can be found in the Appendix.[18]

LIMITATIONS Our study had several limitations. First, previous studies have suggested that Medicare patients may make up a relatively small percentage of people who use medical marijuana and that only 13–27 percent of people who used medical marijuana were ages fifty and older.[20,21] Thus, while our study illuminated the behaviors of a generally older population in response to implementation of medical marijuana laws, future research is needed to understand the prescription drug use responses of younger people.

Second, our study of prescribing behavior at the physician level could not explore important remaining questions about the mechanism of the response. It is certainly plausible that forgoing medications with known safety, efficacy, and dosing profiles in favor of using marijuana (despite its reasonably favorable safety profile) could be harmful under some circumstances. In addition, patients who switch from a prescription drug that requires regular physician monitoring to marijuana, which requires no monitoring, may interact with the health care community less often overall than they did before switching to marijuana, and adherence to other important treatment regimens could be compromised. Again, we leave exploration of these important issues to future research.

Study Results

Our simple bivariate comparisons demonstrated that, with the exception of glaucoma, fewer prescriptions were written for any of our study condition categories when a medical marijuana law was in effect (Exhibit 2). When we controlled for other factors that might have been driving differences in prescribing across states that did and did not have medical marijuana law in effect, we found similar results.

The results for our difference-in-differences models of daily doses filled were extremely consistent across condition categories (Exhibit 3). For seven of the categories—all but glaucoma and spasticity—we found that implementing an effective medical marijuana law led to a reduction of between 265 daily doses (for depression) and 1,826 daily doses (for pain) filled per physician per year. The effects of a medical marijuana law on those seven categories were all significant ($p < 0.01$), with magnitudes that were econom-

Downloaded from http://content.healthaffairs.org/ by *Health Affairs* on July 9, 2016 by HW Team

EXHIBIT 2

Daily doses filled per physician per year in states with and without a medical marijuana law

Condition category	Annual number of daily doses prescribed per physician in states: Without a medical marijuana law	With a medical marijuana law	Difference
Anxiety	11,220.29	10,113.77	1,106.51***
Depression	9,576.73	8,296.25	1,280.47***
Glaucoma	2,551.40	2,616.04	−64.64***
Nausea	10,067.92	9,040.22	1,027.70***
Pain	31,810.07	28,165.54	3,644.53***
Psychosis	11,421.46	10,298.60	1,122.86***
Seizures	9,398.60	8,028.74	1,369.85***
Sleep disorders	7,557.97	6,942.94	615.03***
Spasticity	2,067.82	1,645.43	422.38***

SOURCE Authors' analysis of data for 2010–13 from the disease-specific extracts in the Medicare Part D Prescription Drug Event Standard Analytic File. ***$p < 0.01$

ically important. We found no statistically or economically significant effect on glaucoma or spasticity.

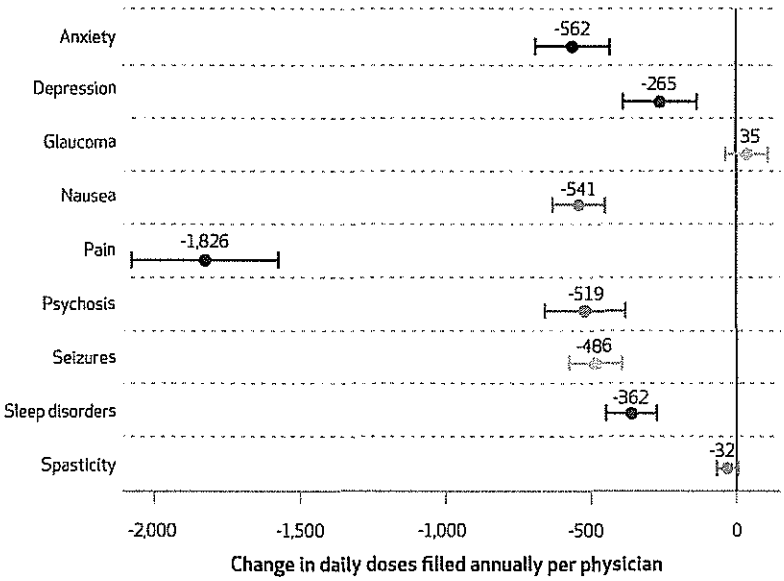
To confirm that these effects were causally related to implementing a medical marijuana law, and not due to some unobserved characteristic of the states that affected general prescribing and adoption of a medical marijuana law, we selected drugs from four classes—blood-thinning agents, phosphorous-stimulating agents, antivirals used to treat influenza, and antibiotics—in which there is no evidence of any beneficial (or harmful) effect from the use of medical marijuana.

We found no changes after implementation of a medical marijuana law in the number of daily doses filled in condition categories with no medical marijuana indication. This provides strong evidence that the observed shifts in prescribing patterns were in fact due to the passage of the medical marijuana laws. Results from these models are presented in the Appendix.[18]

Our analysis suggested that prescription drug spending in Medicare Part D—that is, both program and enrollee spending—fell by $104.5 million in 2010 and that cost savings had risen to $165.2 million by 2013 (Exhibit 4). The savings accrued from only seventeen states and the District of Columbia—jurisdictions that had implemented a medical marijuana law by 2013. Assuming the remaining states are of similar size, we forecast that if all states were to have adopted a medical marijuana laws by 2013, total spending by Medicare Part D would have been $468.1 million less in that year than it would have been had no state adopted such a law. That amount would have represented just under 0.5 percent of all Medicare Part D spending in 2013.

EXHIBIT 3

Average numbers of daily doses filled for prescription drugs annually per physician in states with a medical marijuana law, by condition categories studied, compared to the average numbers in states without a law



SOURCE Authors' analysis. **NOTES** To interpret this exhibit, negative numbers indicate that fewer daily doses of the indicated prescription drugs were filled in states with medical marijuana laws than in states without them. Dots represent the estimated effect (regression coefficient) of the implementation of a law, and lines represent the upper and lower bounds of 95% confidence intervals. Data were aggregated to all prescriptions in a disease category by physician.

Discussion

As of June 2016 twenty-four states and the District of Columbia had passed a medical marijuana law (though not all states had fully implemented their laws by that time), and there is a growing academic literature on the effects of these laws. Researchers have investigated negative externalities associated with medical marijuana, such as spillovers from medical marijuana to recreational use of the drug among adults and youth, and changes in the number of traffic fatalities following the implementation of a medical marijuana law, among other topics.

Remarkably, there is no literature that investigates the extent to which marijuana is used medically as a result of implementing medical marijuana laws at the state level. In this article we provide the first, albeit somewhat indirect, evidence on the clinical impact of medical marijuana availability by examining the impact of medical marijuana laws on the use of all FDA-approved prescription drugs paid for by the Medicare Part D program.

Generally, we found that when a medical marijuana law went into effect, prescribing for FDA-

Downloaded from http://content.healthaffairs.org/ by *Health Affairs* on July 9, 2016 by HW Team

approved prescription drugs under Medicare Part D fell substantially. The only exceptions were for spasticity- and glaucoma-related drugs. Ultimately, we estimated that nationally the Medicare program and its enrollees spent around $165.2 million less in 2013 as a result of changed prescribing behaviors induced by seventeen states and the District of Columbia—the jurisdictions that had legalized medical marijuana by then.

Policies surrounding the appropriate use of medical marijuana are the subject of intense and ongoing debate, and the research we have presented here has direct implications for multiple aspects of the evolution of those policies. State reforms to medical marijuana policies are constrained by the current status of marijuana as a Schedule I drug under the Controlled Substances Act. That status prohibits any sale of marijuana under federal law because the drug is defined to have a high potential for abuse and no medical benefit; thus, many state laws now contradict federal law. Our findings and existing clinical literature imply that patients respond to medical marijuana legislation as if there are clinical benefits to the drug, which adds to the growing body of evidence suggesting that the Schedule I status of marijuana is outdated.

Additionally, at a time when Medicare is under increased fiscal pressure, our research suggests that more widespread state approval of medical marijuana could provide modest budgetary relief. Although some of the savings are likely to be a transfer of costs from the Medicare program to beneficiaries who would have purchased marijuana out of pocket, saving $468.1 million annually is not trivial. As noted above, that would represent about 0.5 percent of total Part D spending for 2013.

Finally, while we did not directly test the impact on governmental programs other than Medicare—most importantly, Medicaid—finding significant cost savings for Medicare suggests that other programs might also enjoy budgetary reductions when medical marijuana laws are implemented. Lowering the costs of Medicare and other programs is not a sufficient justification for approving marijuana for medical use, a decision that is complex and multidimensional. Nonetheless, these savings should be considered when changes in marijuana policy are discussed. ■

EXHIBIT 4

Estimated annual change in national Medicare spending after implementation of state medical marijuana laws, by year

Year	Estimated change ($)
2010	−104,513,189
2011	−114,995,271
2012	−130,491,985
2013	−165,193,681
2010–13	−515,194,125

SOURCE Authors' analysis of data for each year from the disease-specific extracts in the Medicare Part D Prescription Drug Event Standard Analytic File. **NOTES** "Medicare spending" consists of spending by the program and beneficiaries' out-of-pocket spending. More information on the cost calculations is available in the online Appendix (see Note 18 in text).

The authors thank seminar participants at the University of North Carolina at Chapel Hill and Texas A&M University for comments on an earlier presentation of this research.

Downloaded from http://content.healthaffairs.org/ by *Health Affairs* on July 9, 2016 by HW Team

NOTES

1 O'Keefe K. State medical marijuana implementation and federal policy. J Health Care Law Policy. 2013;16(1): 39–58.

2 Cerdá M, Wall M, Keyes KM, Galea S, Hasin D. Medical marijuana laws in 50 states: investigating the relationship between state legalization of medical marijuana and marijuana use, abuse, and dependence. Drug Alcohol Depend. 2012;120(1–3): 22–7.

3 Frequently accepted illnesses include chronic pain, nausea, cachexia (weakening or wasting of the body), wasting syndrome resulting from HIV, glaucoma, AIDS, and cancer. For more details on specific state policies, see ProCon.org. 24 legal medical marijuana states and DC: laws, fees, and possession limits [Internet]. Santa Monica (CA): ProCon.org; c 2016 [cited 2016 May 25]. Available from: http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881

4 Pacula RL, Hunt P, Boustead A. Words can be deceiving: a review of variation among legally effective medical marijuana laws in the United States. J Drug Policy Anal. 2014; 7(1):1–19.

5 Chu Y-WL. The effects of medical marijuana laws on illegal marijuana use. J Health Econ. 2014;38(1):43–61.

6 Anderson DM, Hansen B, Rees DI. Medical marijuana laws, traffic fatalities, and alcohol consumption. J Law Econ. 2013;56(2):333–69.

7 Lynne-Landsman SD, Livingston MD, Wagenaar AC. Effects of state medical marijuana laws on adolescent marijuana use. Am J Public Health. 2013;103(8):1500–6.

8 Wall MM, Poh E, Cerdá M, Keyes KM, Galea S, Hasin DS. Adolescent marijuana use from 2002 to 2008: higher in states with medical marijuana laws, cause still unclear. Ann Epidemiol. 2011;21(9):714–6.

9 Harper S, Strumpf EC, Kaufman JS. Do medical marijuana laws increase marijuana use? Replication study and extension. Ann Epidemiol. 2012;22(3):207–12.

10 Bradford WD, Kleit AN, Neitert PJ, Steyer T, McIlwain T, Ornstein S. How direct-to-consumer television advertising for steoarthritis drugs affects physicians' prescribing behavior. Health Aff (Millwood). 2006;25(5):1371–7.

11 Keith A. Regulating information about aspirin and the prevention of heart attack. Am Econ Rev. 1995; 85(2):96–9.

12 Rubin P. Economics of prescription drug advertising. Journal of Research in Pharmaceutical Economics. 1991;3(4):29–39.

13 Institute of Medicine. Marijuana and medicine: assessing the science base. Washington (DC): National Academies Press; 1999.

14 For the years 2010–12, when the data originated from a request by ProPublica under the Freedom of Information Act of 1966, only physician National Provider Identifier (NPI) numbers appeared in the public use Medicare Part D Prescription Drug Event Standard Analytic File data. We merged information on physician characteristics and practice location and the analysis file according to the NPI number and the National Plan and Provider Enumeration System of the Centers for Medicare and Medicaid Services.

15 For more details on state laws with links to legislative language, see Note 3.

16 Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 2015;313(24):2456–73.

17 For example, beta-blockers such as metaprolol and propranolol have been used for decades to treat hypertension, cardiac dysrhythmias, and other related diagnoses. Researchers have noted that beta-blockers also control physical sensations associated with anxiety (such as rapid heartbeat, tightness in the chest, and trembling) and that when patients do not feel these sensations, their psychological experience of anxiety is significantly reduced. As a result, these drugs are widely prescribed for situational and other forms of anxiety, even though they are not officially approved for that indication by the FDA. An estimated 52 percent of prescriptions for beta-blockers in the period 1999–2002 were for off-label use. See Lin HW, Phan K, Lin SJ. Trends in off-label beta-blocker use: a secondary data analysis. Clin Ther. 2006;28(10): 1736–46; discussion 1710–1.

18 To access the Appendix, click on the Appendix link in the box to the right of the article online.

19 Health Resources and Services Administration. Area Health Resources Files (AHRF) [Internet]. Rockville (MD): HRSA; [cited 2016 May 25]. Available from: http://ahrf.hrsa.gov/download.htm

20 Nunberg H, Kilmer B, Pacula RL, Burgdorf JR. An analysis of applicants presenting to a medical marijuana specialty practice in California. J Drug Policy Anal. 2011;4(1):1.

21 Reinarman C, Nunberg H, Lanthier F, Heddleston T. Who are medical marijuana patients? Population characteristics from nine California assessment clinics. J Psychoactive Drugs. 2011;43(2):128–35.

Downloaded from http://content.healthaffairs.org/ by *Health Affairs* on July 9, 2016 by HW Team

Attachment for Question #10

LETTERS FROM PHYSICIANS AND HEATHCARE PROFESSIONALS

RA PAIN SERVICES
ANDREW MEDVEDOVSKY, M.D.

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

RE: Chronic Pain, PTSD, and Opioid-Dependence

To Whom It May Concern:

My name is Andrew Medvedovsky, MD and I am a Board Certified Neurologist and Pain Medicine Specialist, full time physician with RA Pain services and director of New Jersey Alternative Medicine practicing in Blackwood, NJ. I am writing this letter to support adding Chronic Pain, PTSD, and Opioid Dependence as qualifying conditions for New Jersey Medical Marijuana Program.

RA Pain Services is a comprehensive Pain Management Practice with multiple locations in south NJ with 15 Physicians. I treat patients with extensive neurological and orthopedic conditions causing chronic pain including traumatic brain injury, headaches, neuropathy, spinal stenosis, and failed back surgery syndrome. We provide patients with various treatments including therapy, injections, appropriate medications, and counseling. Unfortunately, despite extensive treatments with conventional therapies so many of my patients continue to suffer with intractable chronic pain that is managed with long term opioid therapy that leads to dependence, addiction, and multitude of side effects. I offer patients counseling and addiction treatment, but that often fails are replaces one opioid with a different opioid (Suboxone).

According to the CDC from 1999 to 2014, more than 165,000 people have died in the U.S. from overdoses related to prescription opioids. Overdose rates were highest among people aged 25 to 54 years. In 2014, almost 2 million Americans abused or were dependent on prescription opioids. These statistics are alarming and these numbers are still on the rise. Observational studies are my personal

experience with treating thousands of patients with chronic pain, medical marijuana has offered patients dramatic benefits with pain control and the ability to significantly reduce the usage of chronic opioids.

Many of my patients are veterans who suffered extensive physical injuries while on duty and are prescribed opioids to manage their pain. Unfortunately, so many of veterans suffering chronic pain also suffer with PTSD which leads to prescription of multiple pain killers and medications to managed anxiety, depression and sleep. Veterans who suffer with PTSD are at increased risk to become opioid dependence and overdose on prescriptions medications.

In July of 2015 I registered with NJ department of health MMP Program. I currently have close to 600 patients enrolled in New Jersey Medical Program suffering with one of the qualifying conditions. The patients who are enrolled have dramatically reduced the usage of opioid pain killers, sedatives for sleep, anxiety and depression. Their quality of life and functionality has been significantly better. Most patients who are enrolled in the program have severe musculoskeletal spasticity secondary to spinal conditions, but also suffer with Chronic pain, PTSD from the injuries they suffered, and opioid dependence from long term usage. I have witnessed first-hand the drastic pain relief that medical cannabis provides patients, allowing them to reduce usage of opioids and live a productive and functional life.

During my Neurology and Pain Medicine Training at Virginia Commonwealth University in Richmond I spent four years working with Veterans at the Hunter-Holmes McGuire Veterans hospital. I evaluated and treated patients with head trauma, headaches, epilepsy, and chronic pain. Majority of the patients I treated also suffered with PTSD that did not respond to the multiple psychotropic medications they were prescribed. Many veterans shared their personal first-hand experience with how much cannabis helped with anxiety, nightmares, flashbacks, and improved their quality of life.

RA PAIN SERVICES
ANDREW MEDVEDOVSKY, M.D.

As a Board Certified Neurologist and Pain Medicine Specialist I strongly believe that adding chronic Pain a qualifying diagnosis to NJ Medical Marijuana Program will benefit thousands of patients who are suffering with relentless chronic pain. It will allow patients to reduce the need for opioids and other dangerous medications.

I have experienced first-hand how medical marijuana has helped patients suffering with PTSD, who have failed to respond to multitude of prescription medications. Medical marijuana offers a safer treatment for thousands of veterans and other patients who suffer with PTSD that impairs their ability to function and live productive lives. I strongly support that adding PTSD as qualifying diagnosis will help thousands of patients.

The national opioid epidemic is a crisis that will continue to kill thousands of people unless a safer and alternative solution is available. I have seen first-hand the positive benefits of medical cannabis in helping patients wean off opioids, managing withdrawal symptoms of nausea, vomiting, diarrhea, anxiety, and pain. Using medical marijuana in a controlled environment under supervision of trained physicians will offer patients a much safer and alternative avenue.

In conclusion, please accept my recommendation and support in adding Chronic Pain, PTSD, and opioid-dependence on the list of NJ Medical Marijuana Program qualifying conditions.

Sincerely,

Andrew Medvedovsky, M.D.
Board Certified Neurologist
Board Certified Pain Medicine Specialist
Director New Jersey Alternative Medicine

[redacted]
Trenton, NJ [redacted]

August 30, 2016

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

Re: Adding Opiate Use Disorder as a qualifying condition for marijuana therapy

To Whom It May Concern:

I have practiced as a registered nurse (RN) since 1976, and I am currently licensed in New Jersey (#[redacted]) and Pennsylvania (#[redacted]). I am writing to recommend that Opiate Use Disorder be added as a qualifying medical condition in the New Jersey Medicinal Marijuana Program (MMP). I am the executive director of the Coalition for Medical Marijuana – New Jersey (CMMNJ). The mission of CMMNJ, an all-volunteer 501 (c)(3) nonprofit educational organization and public charity is, "To bring about safe and legal access to medical marijuana for New Jersey patients who are under the care of licensed physicians and nurse practitioners."

In both my work as a nurse, and in my 13 years with CMMNJ, I have interacted with hundreds of patients who suffer from Opiate Use Disorder, including addiction and dependency. Many of the cardholding MMP patients I have worked with have reported to me that they have either significantly decreased, or have entirely eliminated, their use of opiate medications through the use of marijuana/cannabis. I have also been contacted by numerous patients who do not qualify for the state's MMP, who are concerned about their opiate use and would very much like to be able to legally access cannabis in an effort to reduce or eliminate their opiate use.

Numerous studies, published in peer-reviewed scientific journals, support the efficacy of cannabis in decreasing or eliminating opiate use in patients who have addiction or dependency issues. I fully support and agree with the studies' findings, which reflect my own firsthand observations as a medical professional. The opiate epidemic in New Jersey is a major public health crisis that affects our family members, our friends, our colleagues, our neighbors, and our community. Previous efforts to remedy this situation have failed to create significant change. For many who suffer from Opiate Use Disorder, I believe that marijuana/cannabis could greatly alleviate suffering, and help them to lead healthy and productive lives. I strongly urge you to include Opiate Use Disorder as a qualifying condition for the state's MMP.

Sincerely,

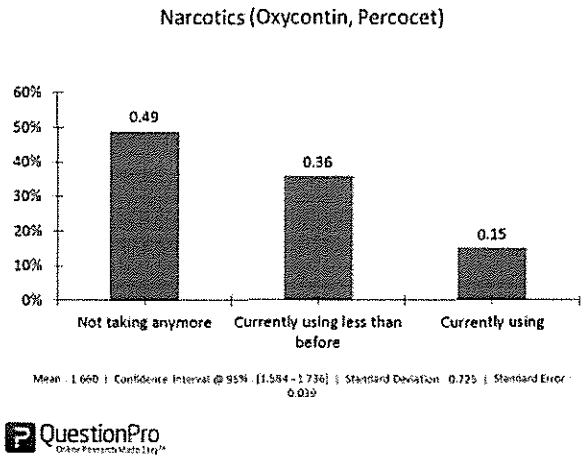
RN

Kenneth R. Wolski, RN, MPA
Executive Director, Coalition for Medical Marijuana--New Jersey, Inc. www.cmmnj.org
[redacted]

[redacted]
Letter of Support
August 30, 2016

Being in the Medical Cannabis industry for the past six years and managing two dispensary operations in two states, I have witnessed and heard from thousands of patients first hand in how Cannabis has helped stop, lower, or aid in the reduction of their opiate usage. Although, Opioid Use Disorder has not yet been approved in any states as a qualifying medical condition for the use of Medical Marijuana, patients and physicians are beginning to recognize and talk about its benefits all over the world. We are hearing a new story every day in the media as well.

I recently rolled out a patient survey to all of our (NJ Alternative Treatment Center) patients. We had 500 patients that participated in a 25 question survey. One of the question was related to narcotics usage. Out of the 500 patients who took the survey 49% of the medical marijuana patients are no longer taking narcotics since beginning cannabinoid treatment, and another 36% are currently using less than before. Those results are amazing!



In addition, from a personal level, I have witnessed my son who struggled with opiate addiction for several years and the use of Cannabis I believe truly helped him remain clean from opiates. It not only helped relieve severe withdrawal symptoms when coming off the drug, but eases the urge to use that so strongly remain with opiate addiction disorder patients forever. I am proud to say that my son has just hit the two-year mark of remaining free of opiates. It has saved his life in my opinion.

I wholeheartedly support adding Opiate Addiction Disorder to the list of qualifying conditions for medical marijuana. I believe now is the time to consider using medical marijuana to combat the opiate epidemic that has participated in the enormous amount of overdose deaths from heroin and other prescription drugs. I hear from patients every day that are looking for an alternative to narcotics and I believe that replacing harmful opiates with cannabis is a positive solution to the very serious problem our country is facing and will continue to face unless something changes.

Thank you for your consideration,

[redacted]
Dispensary Operations Director

EXHIBIT A - ENDNOTES

[1] Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013).American Psychiatric Association.
Retrieved from: http://pcssmat.org/wp-content/uploads/2014/02/5B-DSM-5-Opioid-Use-Disorder-Diagnostic-Criteria.pdf

[2] American Psychiatric Association. DSM-5 Diagnostic Codes Related to Substance Use Disorders.
Retrieved from: http://www.buppractice.com/node/2633

[3] World Health Organization. ICD-10-CM-Diagnosis Codes.
Retrieved from: http://www.icd10data.com/ICD10CM/Codes/F01-F99/F10-F19/F11-

[4] World Health Organization. Information Sheet on Opioid Overdose.
Retrieved from: http://www.who.int/substance_abuse/information-sheet/en/

[5] Stephen Stirling, Herointown, N.J. 2016.
Retrieved from: http://www.njspotlight.com/stories/16/02/04/finding-ways-to-tame-epidemic-of-opioid-addiction-plaguing-new-jersey/

[6] Lilo H. Stainton, Finding Ways to Tame Opioid Addiction Plaguing New Jersey
Retrieved from: http://www.njspotlight.com/stories/16/02/04/finding-ways-to-tame-epidemic-of-opioid-addiction-plaguing-new-jersey/

[7] Lilo H. Stainton, Finding Ways to Tame Opioid Addiction Plaguing New Jersey
Retrieved from: http://www.njspotlight.com/stories/16/02/04/finding-ways-to-tame-epidemic-of-opioid-addiction-plaguing-new-jersey/

[8] Office of National Drug Control Policy, Medication-Assisted Treatment for Opioid Addiction
Retrieved from: https://www.whitehouse.gov/sites/default/files/ondcp/recovery/medication_assisted_treatment_9-21-20121.pdf

[9] Opiate Addiction & Treatment Resource (OATR).
Retrieved from: http://www.opiateaddictionresource.com/home

[10] Opiate Addiction & Treatment Resource (OATR), Suboxone Treatment Directory for New Jersey
Retrieved from: http://www.opiateaddictionresource.com/treatment/suboxone_treatment_directory/nj_suboxone

[11] Office of National Drug Control Policy, Medication-Assisted Treatment for Opioid Addiction Retrieved from: https://www.whitehouse.gov/sites/default/files/ondcp/recovery/medication_assisted_treatment_9-21-20121.pdf

[12] American Psychiatric Association. DSM 5 Opioid Use Disorder Diagnostic Criteria.
Retrieved from: http://pcssmat.org/wp-content/uploads/2014/02/5B-DSM-5-Opioid-Use-Disorder-Diagnostic-Criteria.pdf

[13] American Psychiatric Association. DSM 5 Opioid Use Disorder Diagnostic Criteria. Retrieved from: http://pcssmat.org/wp-content/uploads/2014/02/5B-DSM-5-Opioid-Use-Disorder-Diagnostic-Criteria.pdf

[14] American Psychiatric Association. DSM 5 Opioid Use Disorder Diagnostic Criteria. Retrieved from: http://pcssmat.org/wp-content/uploads/2014/02/5B-DSM-5-Opioid-Use-Disorder-Diagnostic-Criteria.pdf

[15] American Psychiatric Association. DSM-5 Criteria for Opioid Withdrawal. Retrieved from: http://www.buppractice.com/node/2645

[16] American Psychiatric Association. DSM-5 Criteria for Opioid Withdrawal. Retrieved from: http://www.buppractice.com/node/2645

[17] Darke, S., Larney, S., and Farrell, M. (2016) Yes, people can die from opiate withdrawal. Addiction, doi: 10.1111/add.13512.
Retrieved from: http://onlinelibrary.wiley.com/doi/10.1111/add.13512/full

[18] American Psychiatric Association. DSM 5 Opioid Use Disorder Diagnostic Criteria. Retrieved from: http://pcssmat.org/wp-content/uploads/2014/02/5B-DSM-5-Opioid-Use-Disorder-Diagnostic-Criteria.pdf

[19] World Health Organization. Information Sheet on Opioid Overdose.
Retrieved from: http://www.who.int/substance_abuse/information-sheet/en/

[20] FDA Postmarket Drug Safety Information for Patients and Providers.
Retrieved from: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM142839.pdf

[21] FDA Drug Safety Guide.
Retrieved from: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM311370.pdf

[22] FDA Medwatch Safety Information.
Retrieved from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm374896.htm

[23] FDA Drug Safety.
Retrieved from: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM225677.pdf

[24] The Current State of New Jersey's Substance Abuse & Mental Health Treatment Industry.
Retrieved from: http://sunrisehouse.com/research/new-jersey-treatment-industry/

EXHIBIT B

Yes, people can die from opiate withdrawal. Darke, S., Larney, S., and Farrell, M. (2016) Addiction Journal, doi: 10.1111/add.13512.

ADDICTION
SSA SOCIETY FOR THE STUDY OF ADDICTION
EDITORIAL
doi:10.1111/add.13512

Yes, people can die from opiate withdrawal

It is generally thought that opiate withdrawal is unpleasant but not life-threatening, but death can, and does, occur. The complications of withdrawal are often underestimated and monitored inadequately. It is essential that clinical management programmes are put in place routinely in jails, prisons and other facilities where withdrawal is likely in order to avert these avoidable deaths.

Death is an uncommon, but catastrophic, outcome of opioid withdrawal. The complications of the clinical management of withdrawal are often underestimated and monitored inadequately. In this commentary we highlight the under-reported risk of death, discuss deaths that occurred during opioid withdrawal in United States and British custodial settings and explore implications for clinical management.

The opioid withdrawal syndrome is well-delineated [1]. Signs and symptoms include dysphoria, insomnia, pupillary dilation, piloerection, yawning, muscle aches, lacrimation, rhinorrhea, nausea, fever, sweating, vomiting and diarrhoea. For short-acting opioids, such as heroin, symptom severity peaks typically at around 2–3 days. The syndrome is generally characterized as a flu-like illness, subjectively severe but objectively mild, that stands in stark contrast to the life-threatening benzodiazepine and alcohol withdrawal syndromes. Indeed, it is often said and, was stated publicly by one prominent medical practitioner, that '...no one dies of opiate withdrawal' [2].

How could someone die during opiate withdrawal? The answer lies in the final two clinical signs presented above, vomiting and diarrhoea. Persistent vomiting and diarrhoea may result, if untreated, in dehydration, hypernatraemia (elevated blood sodium level) and resultant heart failure. There are documented cases of such deaths occurring during the withdrawal process, all in jail settings, that date back to the late 1990s. In 1998, Judith McGlinchey was incarcerated in the United Kingdom and went into heroin withdrawal [3]. She exhibited persistent vomiting, sudden weight loss and dehydration. The cause of death was attributed to hypoxic brain damage caused by a cardiac arrest. A case of failure of duty of care was argued successfully before the European Court of Human Rights. Recent years have seen a number of similar cases reported in the public press between 2013 and 2016 that occurred in United States jails. We are aware of 10 such reported cases, six females and four males, ranging in age from 18 to 49 years [Supporting information, Appendix S1].

All such deaths are preventable, given appropriate medical management. In each case the process of death appeared prolonged, with ample time to treat the person successfully. Why, then, did they occur? These were cases of neglect, or a lack of medical resources to support the individual. Intravenous re-hydration, for instance, is not regarded as appropriate in non-health-care settings. There is a failure to identify the seriousness of the level of dehydration, and to assume that a quiet prisoner is a good prisoner. Jails process more drug withdrawals than any other single institution, but often do not have medical resources to manage severe withdrawal. Indeed, one study of US jails found that only a quarter had alcohol or drug detoxification services [4].

There is an urgent need to raise awareness of the risk of a fatal outcome in the presence of poor clinical governance. People can, and do, die from opiate withdrawal. The recent substantial increases in heroin use in the United States [5] make the management of heroin withdrawal a major clinical issue for the correctional system, as opiate users comprise more than a substantial proportion prison populations [6]. Moreover, as jails are the entry point to the correctional system, they are the most likely to have to deal with acute withdrawal among opioid-dependent inmates.

Can anything be done? Withdrawal protocols for jails exist in the United States [7]. Despite this, the medical management of withdrawal is often described as suboptimal by heroin-dependent inmates [8]. In the cases of the reported deaths in jails this was clearly so. Opiate withdrawal needs to be recognized within the correctional system, and elsewhere, as potentially life-threatening and managed accordingly. This is of particular importance for jails, which are short-stay, local facilities where a heroin user may be incarcerated within an hour of being arrested on the street.

An alternative to withdrawal is to provide opiate substitution therapy to opiate-dependent inmates entering the correctional system. The provision of treatment in such settings has been implemented successfully in many jurisdictions, and is associated with lower mortality rates and better clinical outcomes post-release than those who are opioid-dependent at entry and have an enforced withdrawal [9,10]. One recent study reported that continued maintenance treatment was associated with a 93% reduction of risk of death in custody during a 10-year period [10]. Similar action providing effective drug treatment is required across custodial settings. This is particularly so for the United States, given the recent epidemic of heroin and opioid dependence, as the number of heroin users entering jails and prison will, in all probability, increase substantially in coming years.

© 2016 Society for the Study of Addiction

Heroin withdrawal is not a trivial matter. The rising number of deaths from withdrawal in United States jails has received scant attention to date. Given appropriate clinical management, such deaths need not occur.

Declaration of interests

None.

Acknowledgements

The National Drug and Alcohol Research Centre at the University of NSW is supported by funding from the Australian Government.

Keywords Dehydration, management, mortality, opiates, prisons, withdrawal.

SHANE DARKE, SARAH LARNEY & MICHAEL FARRELL
National Drug and Alcohol Research Centre, University of New South Wales, Sydney, New South Wales 2052, Australia
E-mail: s.darke@unsw.edu.au

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders I*. Washington, DC: American Psychiatric Association; 2013.
2. Dalrymple T. Withdrawal from heroin is a trivial matter. *Spectator* 7 January 2009. Available at: http://www.spectator.co.uk/2009/01/withdrawal-from-heroin-is-a-trivial-matter/) (accessed 15 May 2016).
3. Mowbray A. R. *Cases, Materials, and Commentary on the European Convention on Human Rights*. Oxford: Oxford University Press; 2012.
4. Fiscella K., Pless N., Meldrum S., Fiscella P. Alcohol and opiate withdrawal in US jails. *Am J Public Health* 2004; 94: 1522–4.
5. Hedegaard H., Chen L. H., Warner M. *Drug-poisoning deaths involving heroin: United States, 2000–2013*. In: NCHS data brief, no 190. Hyattsville, MD: National Center for Health Statistics, p. 2015.
6. Nunn A., Zaller N., Dickman S., Trimbur C., Nijhawan A., Rich J. D. Methadone and buprenorphine prescribing and referral practices in U.S. prison systems: results from a nationwide survey. *Drug Alcohol Depend* 2009; 105: 83–8.
7. Federal Bureau of Prisons Detoxification of Chemically Dependent Inmates. In: *Clinical Practice Guidelines*. Washington DC: Federal Bureau of Prisons; 2014.
8. Mitchell S. G., Kelly S. M., Brown B. S., Reisinger H. S., Peterson J. A., Ruhf A. *et al.* Incarceration and opioid withdrawal: the experiences of methadone patients and out-of-treatment heroin users. *J Psychoact Drugs* 2009; 41: 145–52.
9. Larney S., Gisev N., Farrell M., Dobbins T., Burns L., Gibson A. *et al.* Opioid substitution therapy as a strategy to reduce deaths in prison: retrospective cohort study. *BMJ Open* 2014; 4: e004666.
10. Rich J. D., McKenzie M., Larney S., Wong J. B., Tran L., Clarke J. *et al.* Methadone continuation versus forced withdrawal on incarceration in a combined US prison and jail: a randomised, open-label trial. *Lancet* 2015; 386: 350–9.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1 Reported custodial deaths during opioid withdrawal.

© 2016 Society for the Study of Addiction