BEFORE THE IOWA MEDICAL CANNABIDIOL BOARD

Rebecca Lucas
Petition by *(Your Name)*

for the (**addition or removal**) of
Opioid dependency, tolerance, & use disorder
(medical condition, medical treatment or debilitating disease) to the list of debilitating medical conditions for which the medical use of cannabidiol would be medically beneficial.

PETITION FOR
ADDITION or REMOVAL
(Circle one)

Petitioner's Information			
Name (First, Middle, Last or Name of Organization): Rebecca Lucas			
Home Address (including Apartment or Suite #): 1953 E Market Street			
City: Des Moines	State: IA	Zip Code: 50137	
Telephone Number: 515-509-4556	Email Address: Rebecca.Lucas@medpharmiowa.com		
Is this the person/ organization to whom information about the petition should be directed?		**Yes** ✓	**No** ☐

Representative's Information (*If applicable*)			
Name (First, Middle, Last):			
Mailing Address (including Apartment or Suite #):			
City:	State:	Zip Code:	
Is this the person/ organization to whom information about the petition should be directed?		Yes ☐	No ☐

Telephone Number:	Email Address:

1. Please provide the name of the specific medical condition, medical treatment, or debilitating disease you are seeking to add to or remove from the list of debilitating medical conditions for which patients would be eligible to receive a medical cannabidiol registration card. *Please limit to **ONE** condition, treatment, or debilitating disease per petition.*

Recommended Action	Condition or Disease
☒ Add ☐ Remove	Opioid tolerance, dependency, and use disorder

2. Please provide a brief summary statement that supports the action urged in the petition. *Attach additional pages as needed.*

see petition attachment

3. Please provide a brief summary of any data or scientific evidence supporting the action urged in this petition. *Attach additional pages as needed*

See attached Petition

4. Please provide a list of any reference material that supports your petition.

See Attached Petition

5. Please provide a list of subject matter experts who are willing to testify in support of this petition (if any). The list of subject matter experts must contain names, background, email addresses, telephone numbers, and mailing addresses. *Attach additional pages if needed.*			
Name	(1)	(2)	(3)
Background			
Email address			
Telephone number			
Mailing address			

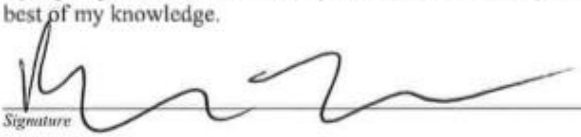
6. Please provide the names and addresses of other persons, or a description of any class of person, known by you to be affected by or interested in the proposed action which is the subject of this petition. *Attach additional pages if needed.*
See Attached Petition

7. Please indicate whether you have attached a brief in support of the action urged in the petition.	Yes	No
	✓	

8. Please indicate whether you are asking to make an oral presentation of the contents of the petition at a board meeting following submission of the petition.	Yes	No
	✓	

9. Acknowledgement and Signature

By signing this document I certify that the information provided in this petition is true and accurate to the best of my knowledge.



Signature

7-22-2019

Date (mm/dd/yyyy)

- Please fill out each section that is applicable to your petition. Failure to conform to what is required in this petition may result in a denial of consideration by the board.
  - You do not need to fill out sections asking for your representative's information if you do not have one.
  - For section **2**, please provide a short, essay-like summary of your argument.
  - For section **3**, please provide a short, essay-like summary of the articles and evidence that supports your position (if any).
  - For section **4**, please provide a list of articles that are in support of your position (if any).
  - For section **5**, please provide a list of experts that would be willing to testify in support of your position (if any). In the background section, please provide the reasons why they should be considered experts in the area: education, credentials, field of study, occupation, etc. This section is optional but will greatly aid in helping the board consider your petition.
  - For section **6**, please provide information about groups of people that will be affected if the petition were approved. This could include people suffering from a specific disease, advocacy groups, local government officials, etc.
  - Sections **7** and **8** are optional but may aid the board in considering this petition.
- Please be aware:
  - The board may request that you submit additional information concerning this petition. The board will notify you of the requested materials in the event that more information is needed.
  - The board may also solicit comments from any person on the substance of this petition. The board may also submit this petition for a public comment period where any interested person may comment.
  - The board has six months after you submit this form to either deny or grant the petition. If approved, you will be notified in writing that the board has recommended the addition or removal of the medical condition, treatment, or debilitating disease to the board of medicine. If denied, the board will notify you in writing the reasons for denial.

Opioid Use Disorder, Tolerance, and Dependency Petition

State of Iowa

8/2/2019

Table of Contents

Question may be directed to: Rebecca.Lucas@medpharmiowa.com

1. Summary

- Opioid use can lead to clinically significant negative impacts on lifestyle and well-being[1] in some patients.
    - Through Opioid tolerance, dependency, or use disorder
- Conventional treatments for use disorder include medications (Medication-assisted Treatment)
    - Medication based therapies often carry negative side effect profiles and low retention rates
- **Cannabinoids may reduce symptoms of opioid withdrawal – nausea, appetite loss, insomnia**
- **Cannabinoids may help taper opioids because of synergistic action**
- **Cannabinoids may help retention in treatment programs because of their analgesic properties**
    - **Especially during antagonist treatment**
- **Cannabinoids may decrease likelihood of relapse due to alternative pain management**

2. Opioid Basics

Opioids are a group of analgesic agents commonly used in clinical practice. Opioids are classified as such because they act on the opioid receptors in the brain the produce morphine-like effects. There are 3 classical opioid receptors, mu (MOP) kappa (KOP) and delta (DOP) receptors. These receptors are g-protein coupled and activated inhibitory G-proteins. Most clinically relevant opioid analgesics bind to MOP receptors in the central and peripheral nervous system in an agonist manner to elicit analgesia. Opioids may also be classified according to their mode of synthesis into alkaloids, semi-synthetic and synthetic compounds[24,25,26] Commonly known pharmaceutical opioids include: hydrocodone, oxycodone, oxymorphone, morphine, codeine, and fentanyl among others.

While being effective for acute pain and cancer pain management, opioids have a lesser effect on management of chronic pain and/or neuropathic pain.[20,21]

2.1 Drawbacks

Opioids have some drawbacks in that they have adverse side effect profiles including death, high risk for addiction and dependence, but also because they tend to develop tolerance in many patients.[37] In fact the opioid signaling system is one of the most effective receptor systems in the body for tolerance development, though not all patients develop profound tolerance. In many cases doses do have to be increased over time to maintain analgesic benefit, even without conditions that are innately degenerative.[38]

The danger of opioids in addition to the risk of problematic use, is their potential for producing an overdose. Opioids are central nervous system depressants and when taken in a quantity that exceeds what the body can handle, they can depress breathing and precipitate heart failure.

Opioids are increasingly used as part of long-term therapy especially for chronic pain even without good data behind that decision. Many opioid use research papers only extend to 6 weeks of use, and not beyond. According to a 2015 review of the literature “evidence on long-term (greater than one year) therapy for chronic pain is very limited but suggests an increased risk of serious harms that appear to be

dose-dependent. More research is needed to understand long-term benefits, risk of abuse and related outcomes, and effectiveness of different opioid prescribing methods and risk mitigation strategies."[22] **In fact, as of the 2015 review, there were no placebo-controlled randomized trials looking at long-term opioid therapy, there were no studies with follow-up of at least a year looking at safety, pain, function, and quality of life.** In the opinion of University of Washington researchers, Cannabis is suggested to have more long-term effect evidence than opioids for pain management[67].

CDC guidelines also recommend that opioids are not first-line or routine therapy for chronic pain, and that if clinicians are using opioids, they should non-pharmacologic and nonopioid pharmacologic therapy as appropriate. Even so, physicians are comfortable prescribing opioids for long-term use. [23] As with all pharmaceuticals this should come down to a risk-benefit analysis.

Cannabis is also an analgesic that works on receptors that have endogenous mimetics. Although cannabis is like any other substance in that it can be used problematically, overconsumed, and in some cases can lead to symptoms of dependence in some scenarios, unlike opioids, high doses of cannabis are not lethal.[40]

3. Opioid Tolerance and Dependency

The FDA defines a patient as opioid tolerant if for at least 1 week he or she has been receiving oral morphine 60mg/day, transdermal fentanyl 25mcs/hour; oral oxycodone 30mg/day; oral hydromorphone 8mg/day; oral oxymorphone 25mg/day; or an equianalgesic amount of any other opioid. This would imply a lesser susceptibility to the effects of opioids both therapeutic and adverse, causing an need for dosage increase. Interestingly high doses of opioids can also induce hyperalgesia (increased pain). [39]

Opioid withdrawal symptoms can occur in opioid-dependent patients, both those receiving lower doses of opioids, those receiving lower doses of opioids to combat hyperalgesia, or those using an opioid antagonist in the treatment of OUD. Withdrawal does not only occur in those with use disorder, it can also occur in those attempting to taper dosage.

As is very understood at this point, opioids have a strong risk of dependency. In a representative sample of opioid naïve, cancer-free adults who received a prescription for opioid pain relievers, the likelihood of chronic opioid use increased with each additional day of medication supplied starting with the third day. Sharp increases were seen after the initial 10-day dose. This indicates a very quick onset to dependency. In fact, within a 10-day supply, about one-in-five patients become long-term users.[52]

4. Opioid Use Disorder

Opioid Use Disorder (OUD) is a medical condition characterized by opioid use leading to clinically significant negative impact on lifestyle and well-being[1]. Opioid use disorder is characterized in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM5) as having some of the following criteria[30]:

- Opioids are often taken in larger amounts or over a longer period of time than intended
- Persistent desire or unsuccessful efforts to cut down or control opioid use

- Time spend in activities necessary to obtain opioids, use opioids, or recover from its effects
- Craving or desire to use opioids
- Recurrent opioid use resulting in failure to fulfill major role obligations
- Continued opioid use despite having persistent or recurrent problems
- Recurrent opioid use in situations in which it is physically hazardous
- Continued use despite knowledge of having a persist or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids
- Tolerance to opioids (as defined DSM5 document)
- Withdrawal (as defined in DSM5 document)

Severity can then be classified based on ratings as either mild, moderate, or severe opioid use disorder.

While opioid use disorder is similar to other substance use disorders it has some unique features including: short time to physical dependence (4-8 weeks), severe withdrawal symptoms creating significant motivation to continue using opioids[33]

In non-cancer pain patients on long-term opioid therapy, prevalence of lifetime of moderate and severe OUD based on DSM5 criteria was 35%.[31] This is quite high compared to other pharmaceuticals.

Symptoms of OUD may include[32]

- Anxiety and Depression
- Nausea
- Increased Pain
- Potential for overdose

This is complicated by symptoms of withdrawal that persons with OUD experience when attempting to cease their opioid medication including:

- Rapid heartbeat
- Sweating
- Restlessness
- Pain
- Tremor
- Anxiety

In a report from the FDA's Patient-Focused Drug Development Initiative, patients affected by OUD emphasized the huge impact of their opioid addiction. This condition affects all aspects of individuals' lives – from their personal relationships to their ability to participate in their communities. Access to medication-assisted treatment (MAT) is often too expensive, or too restrictive to patients. There is also a perceived stigma against patients who pursue this type of therapy[8].

5. Impact of Opioid Use

- In 2016, a reported 2.1 million individuals ages 12 and older had symptoms consistent with OUD in the United States[12].
- Drug overdose is the leading cause of accidental death in the US, with 52,404 lethal drug overdoses in 2015[11].
- In 2012, 259 million prescriptions were written for opioids, which is more than enough to give every American adult their own bottle of pills[5].
- In 2015, 276,000 adolescents were current nonmedical users of pain relievers, with 122,000 having an addiction to prescription pain relievers[4].

In Iowa between 2013-2016, there were over 4000 opioid related hospitalizations in Polk and surrounding counties. This figure includes all opioid-related healthcare facility or hospital admissions. With an average cost of daily hospital stay in Iowa around $1500, this has a huge financial impact on the patients and taxpayers of Iowa – around $2 million annually[7]. In 2017, there were 103 opioid related deaths in the state of Iowa. This is an increase from 86 deaths in 2016[9].

6. Conventional Treatments for Opioid Use Disorders

Currently there are a variety of medical treatment options for opioid use disorder. These include pharmaceutical and behavioral interventions. Pharmacotherapy options also known as medication-assisted treatment (MAT) include the following medications with Methadone being the preferred method of treatment recommended by the CDC[18,19]. Sativex, a 1:1 ratio of CBD to THC is also included as a comparison in blue.

Name	Mode	Notes
Methadone (synthetic opioid)	Opioid agonist	• **Deaths have been noted during initiation of treatment (drug interaction, too rapid of titration, cardiac effects)** • Respiratory depressant effects lasting longer than analgesic effects • **Potential to overdose** • "Methadone poses risks of opioid addiction, abuse and misuse, which can lead to overdose and death" • Some patients that have become tolerant to opioids may not respond to methadone • Patients may experience severe withdrawal symptoms • Contraindicated for those with use disorders
Buprenorphine	Partial opioid agonist	• **Drug misuse and abuse most frequently reported post-marketing adverse effect** • **Potential for significant respiratory depression and death** • Chronic administration produces opioid-type physical dependence • Abrupt discontinuation may result in opioid withdrawal syndrome • Side effects include withdrawal syndromes (22% of patients)
Naltrexone (Synthetic cogener of oxymorphone)	Opioid antagonist	• **Potential for fatal overdose (opioid toxicity)**

		• Generally used more for opioid detoxification after withdrawal from opioids • Contraindicated for those: on opioids, with opioid use disorder, or in acute opioid withdrawal • **Must be off opioids for 7-10 days before starting treatment** • Side effects of: depression, suicide, attempted suicide, and suicidal ideation • Patient adherence problems
Sativex GW Pharmaceuticals 1:1 ratio of CBD:THC	Cannabinoid	• No initiation deaths noted to date • No potential of fatal overdose • Those tolerant to opioids generally still responsive to cannabinoids due to different imitation receptors • Patients may experience non-severe withdrawal symptoms (irritability) • Low risk of dependency (<9%)

Sources for table: 14, 15, 17, 27, 28, 29

In theory these conventional medications work to block the euphoric or sedating effects of opioids and mitigate withdrawal symptoms.

All MAT prescription treatments carry side effects and risks such as anxiety, insomnia, hallucinations, headache, and drowsiness as well as risk of fatal overdose[8].

One of the prime examples is Methadone. Despite its favorable efficacy, methadone's relatively short duration of analgesic effect, coupled with long elimination half-life, and drug-drug interaction profile increases its toxicity and risk of adverse effects. In 2010, methadone-related visits to the ER occurred at a rate 23x greater than prescribed opioids. As a secondary concern, literature has found increased mortality associated with therapeutic use of methadone for treatment of use disorders.[16]

Individuals with OUD are already at a higher risk of addiction and substance abuse because of their condition. This needs to be a consideration when looking into prescription treatments for OUD. While these treatments often have better safety profiles than opioids, long-term dependence on medications should not be the desired outcome. The struggle with MAT-type programs are their low adherence profiles of those that actually continue treatment. Some studies indicate that 6-month retention rates in these types of programs could be as low as 20%.[41]

Interestingly, increasing numbers of those patients going through opioid addiction and receiving MAT antagonists (blocking the effect of opioids) frequently encounter situations where they have pain conditions that need effective pain control strategies. Part of the problem in adherence in those OUD patients taking Naltrexone (antagonist) is the occurrence of these types of events. It is possible that cannabis therapy could increase the adherence of Naltrexone by contributing to pain relief during the time of treatment. This reduces the risk of relapse due to having to re-put these types of patients back on opioids. This provides a tool to harm reduction specialists that may increase success of MAT type programs.

Another aspect of OUD treatment is behavioral modification through therapy, counseling, and other activities (yoga, meditation, etc.) These treatment options are low risk, but also lack wide-spread success in universal applications. Accountability groups, rehabilitation, and group counseling focus on modifying an individuals' motivations towards their opioid dependence. As with other medical treatment options, accessibility and stigma play a part in patient non-compliance[8]. Psychological therapies alone are shown to be less effective than pharmaceutical therapies and pharmaceutical in addition to psychological therapies[18]

Chronic relapse in OUD is a serious risk factor for cardiovascular function, overdose, and mortality[6]. Unfortunately, over 90% of those that have had a nonfatal opioid overdose are prescribed opioids within a year of overdose.[51] Not surprising, this increases the risk for repeated overdose. Development of consistently effective treatment options is integral to patient health and well-being.

7. Opioid and Cannabinoid Synergy

Cannabinoids and opioids both produce analgesia through g-protein-coupled mechanisms, the cannabinoid receptors and the opioid receptors respectively. These mechanisms help block the release of pain-propagating neurotransmitters in the brain and spinal cord. In addition, cannabinoid and opioid receptors are often co-located in many of the same areas in the brain. The extent of overlapping expression provide basis for the clear interactions between the opioid and cannabinoid systems.

Many studies have indicated that cannabinoids can enhance the pain-relieving properties of opioids. This term, where cannabis is used in conjunction with opioids and where a similar effect can be achieved with less opioids is termed "opioid sparing".

For example, the effects of morphine have been found to be enhanced by crude cannabis extract as well as orally administered THC. Evidence in recent years have looked at synergy between the two signaling pathways, showing promise for both combination care as well as novel treatments for opioid addiction and abuse by reducing quantities of opioids consumed as well as lowering rates of physical dependence.[36] The synergistic effects in pain control is likely why we see many patients taper their opioids while on cannabis, while also retaining pain control.

For a more in-depth look at endogenous opioids, opioid receptors and the colocalization of CB receptors with opioid receptors please see Appendix 2 for Cichewicz (2004).

For an excellent review of the behavioral, anatomical, and molecular data characterizing these interactions please see Bushlin et al "Cannabinoid-opioid interactions during neuropathic pain and analgesia" (2010)[70]

8. Cannabinoid Therapy for Opioid Dependence and Disorder – Literature

The below discusses briefly the areas in which cannabis may play a role. As in many areas of cannabis, research is still growing. While there are some weaknesses in many studies including selection bias, cross-sectional design, and self-reports, studies do suggest that cannabis may reduce opioid use and harms. While not comprehensive, the following are a selection of literature related to Opioid use, tolerance, and dependency either directly or non-directly (symptomatically) and its association with

cannabis. Cannabinoid-based therapy has been shown to potentially reduce the physiological impact of opioid withdrawal, and to improve the success of patients undergoing MAT and other behavior modification therapies with a positive safety profile[3].

8.1 Opioid Tapering

As seen above in the above section "Opioid and Cannabinoid Synergy and Mode of Action", opioids and cannabinoids show synergism in analgesic effect that can lead to tapering of opioid doses. Animal model papers that exhibit this synergistic effect directly include

- Chen et al "Opioid-sparing Effects of Cannabinoids on Morphine Analgesia: Participation of CB1 and CB2 Receptors"[42]

Human papers include the following which are focused on either direct decrease in opioids, or the potential for decrease in opioids due to the synergistic or additive effect of cannabis and opioids.

Cooper et al. "Impact of co-administration of oxycodone and smoked cannabis on analgesia and abuse liability[68]

Double-blind, placebo-controlled, within-subject study to determine if cannabis enhances the analgesic effects of low dose oxycodone using an experimental model of pain and its effects on abuse liability.

- Cannabis at subtherapeutic levels as well as oxycodone at subtherapeutic levels (2.5mg) failed to elicit analgesia
    - Combined they did increase pain threshold and tolerance
- Oxycodone did not increase subjective ratings associated with cannabis abuse
- Oxycodone did not increase cannabis self-administration
- **Cannabis enhances the analgesic effects of sub-threshold oxycodone without increases in cannabis abuse liability.**

Narang et al. "Efficacy of Dronabinol as an Adjuvant Treatment for Chronic Pain Patients on Opioid Therapy"[44]

Assessment of patients taking opioids for chronic pain to determine THC's potential analgesic effects as an adjuvant treatment on those on stable doses of opioids. Phase 1 of this study was randomized, single-dose, double-blinded, placebo-controlled, and crossover.

- The addition of THC resulted in additional analgesia among patients taking opioids for chronic non-cancer pain.
- **The additional analgesic effect achieved on the same level of opioid could assist patients in tapering opioid dose or helping break opioid tolerance**

Schleider et al "Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer"[48]

This observational study of over 2500 cancer patients in Israel explored dosage, symptom improvement and pharmaceutical use after initiation of medical cannabis use.

- Patients taking up to 1000mg THC/day = 90g/90 days
- **Over 90% reported improvement in their condition symptoms (sleep, pain, nausea)**
    - **Sleep, pain, and nausea are also symptoms of opioid withdrawal**
- Significant improvements in pain with treatment
- **45% of those taking cannabis decreased or stopped taking opioids**

Haroutonian et al. "The Effect of Medicinal Cannabis on Pain and Quality-Of-Life Outcomes in Chronic Pain"[60]

Prospective, open-label study to determine the long-term effect of medical cannabis treatment on pain in participants with treatment-resistant chronic pain

- **Self-tapering on opioid consumption was observed**
    - **Opioid consumption decreased at 6-month follow-up by 44% (p<0.001)**
- **Secondary significance: Pain severity and symptom scores improved in patients receiving medical cannabis**

MN Dept of Health "Intractable Pain Patients in the Minnesota Medical Cannabis Program: Experience of Enrollees During the First Five Months"[61]

Report drawing from enrollment, purchasing, system and side effect ratings at time of each purchase, and survey results to describe the experience of patients newly enrolled in the program for intractable pain during the first five months of this as a qualifying condition (n=2290)

- High level of benefit for pain seen with 60% of patients, and 43% of health care providers
    - 6 or 7 rating on a 7-point scale
- Benefit second most mentioned was improved sleep
- **58% of pain patients were on other pain medications when initiating the program**
    - **Of those known to be taking opioids at baseline 62% were able to reduce or eliminate opioid usage after six months (Data from their healthcare providers)**
    - Of those receiving at least 30% reduction in pain scores, 8% of patients were taking 214mg THC/day = 19.2g/90 days' supply
        - "disorientation as a side effect reported by <3% of patients

Abrams et al "Cannabinoid-opioid interaction in Chronic Pain"[66]

Study where 21 patients with chronic pain that were also on morphine or oxycodone were co-medicated with vaporized cannabis

- Pain with co-administration was significantly decreased
- No increase was seen in plasma opioid levels
- Cannabis augments the anageis effects of opioids without significantly altering plasma opioid levels
- **Combination may allow for opioid treatment at lower doses with fewer side effects**

8.2 Reduction of opioid tolerance/opioid reward:

Mori et al "Effects of dronabinol on morphine-induced dopamine-related behavioral effects in animals"[46]

The study examined the effects of dronabinol (synthetic THC) on morphine-induced dopamine-related behaviors in rats and ferrets.

- Dronabinol suppressed rewarding effects of morphine
- Morphine-induced increases in dopamine were significantly reduced by Dronabinol
- **THC could be usement as an adjuvant in preventing the adverse effects of opioids when being used to control pain**

Ahmad et al "Cannabinoid Transmission in the Prelimbic Cortex Bidirectionally Controls Opiate Reward and Aversion Signaling through Dissociable Kappa Versus u-Opiate Receptor Dependent Mechanisms"[69]

A study using an unbiased conditioned place preference paradigm with rats to examine the role of CB1 transmission during opiate reward learning

- Activation of inhibition of Cannabinoid Receptor 1 (CB1) transmission within the prelimbic cortical division of the medial prefrontal cortex bidirectionally regulates the motivational valence of opiates
- **CB1 activation switched morphine reward signaling into an aversive stimulus**
- THC works to activate CB1 receptors, and thus may be able to mediate reward stimulus of opioids

Hurd et al "Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals with Heroin Use Disorder: A Double-Blind Randomized Placebo-Controlled Trial" (2019)[47]

This exploratory double-blind randomized placebo-controlled trial assessed the acute, short-term and protracted effects of CBD administration on drug cue-induced craving and anxiety in drug-abstinent individuals with Heroin use disorder.

- Heroin is an opioid made from morphine
- Acute Cannabidiol administration, in contrast to placebo, significantly reduced both craving and anxiety induced by the presentation of salient drug cues
- Cannabidiol also showed significant protracted effects
- Cannabidiol reduced the drug cue-induced physiological measures of heart rate and salivary cortisol levels
- **While not specifically with a pharmaceutical opioid "CBD's potential to reduce cue-induced craving and anxiety provides a strong basis for further investigation of this phytocannabinoid as a treatment option for opioid use disorder"**

Wiese et al "Emerging Evidence for Cannabis' Role in Opioid Use Disorder" (2018)[13]

General review on Cannabis potential in Opioid tapering or use disorder

- 26-36 million people abuse opioids worldwide

- Alternative OUD treatment is needed to supplement treatment with methadone and buprenorphine
- Highlights evidence that CB1 receptor plays a role in opioid reward behaviors
- Cannabis has the potential to ease withdrawal symptoms, reduce opioid consumption, and reduce opioid overdose deaths
- **Relative safety prole of cannabis makes it a good candidate for addition to medical treatment for OUD**

8.3 Amelioration of withdrawal symptoms

THC and CBD can be used to attenuate symptoms of withdrawal. This can be seen in both animal models and human models both when looking directly at symptoms concurrent with withdrawal and directly at OUD-related withdrawal. In animal models, this manifests in the decrease of withdrawal signs observed in opioid dependent mice or rats when cannabinoids are given[43.] Interestingly, the effects of cannabinoids on withdrawal are somewhat paradoxical. Endogenous cannabinoids seem to have no role in somatic withdrawal[53,54,55,56], whereas in animal models of withdrawal symptoms, exogenous CB1 agonists readily alleviate somatic symptoms of withdrawal[57,58,59].

8.3.1 General Withdrawal

Yamaguchi et al. "Endogenous cannabinoid, 2-arachidonoylglycerol, attenuates naloxone-precipitated withdrawal signs in morphine-dependent mice"[57]

Study examining the effects of THC on withdrawal symptoms in mice with morphine dependency precipitated by MAT therapy chemical Naloxone.

- **Treatment with THC significantly attenuated symptoms of withdrawal**
- **Secondary significance: potential use in Naloxone treatment for decrease of withdrawal symptoms and increase in retention in treatment program**

Bisaga et al: "The Effects of Dronabinol During Detoxification and the Initiation of Treatment with Extended Release Naltrexone"[45]

In this double-blind, placebo-controlled study, researchers examined whether Dronabinol, a synthetic THC, could have an effect on opioid withdrawal symptoms and treatment retention. This study also looked at factors like smoking of cannabis in relation to treatment retention

- Administration of synthetic THC reduced the severity of opiate withdrawal during acute detoxification
- Participants who elected to smoke cannabis during the trial were more likely to complete treatment
    - More likely to have lower insomnia and anxiety
- Cannabis was used safely in conjunction with Naltrexone.
- **Findings suggest cannabis may help alleviate withdrawal symptoms**

- **Secondary Significance: potential use in Naltrexone (Naloxone) treatment and points to the role of the endocannabinoid system in preventing opioid dependence relapse**

8.3.2 Pain

Ware et al. "Cannabis for the Management of Pain: Assessment of Safety Study" (COMPASS) (2015)

In this prospective cohort study, a standardized herbal cannabis product was evaluated vs control to assess safety (serious/non-serious adverse events) as well as secondary outcomes of pain, mood, quality of life.

- Control vs. Test (125mg/gram cannabis) x 1 year
- Studied primary outcome (serious/non-serious adverse events), safety outcomes, pain, mood, and quality of life
- 215 test subjects (141 current users and 58 ex-users) and 216 control subjects.
- Median dose = 2.5g/day = 300mg THC/day = 27g/90 days
- No difference in risk of serious adverse events between groups
- **Significant reduction in average pain intensity in cannabis user's vs control**

National Academies of Science "The Therapeutic effects of Cannabis and cannabinoids"[65]

Comprehensive review done by the National Academies of Science on Cannabinoids in regard to their treatment of symptomology.

- **"There is conclusive or substantial evidence that cannabis or cannabinoids are effective for the treatment of chronic pain in adults"**

8.3.3 Nausea

While most literature for this area is in the realm of cancer and chemotherapy-induced nausea, we do see effects of cannabinoids for decrease of nausea. In Bedowski's review of the literature[62] "oral cannabinoids have been shown to have similar or improved efficacy compared with conventional antiemetics for resolution of nausea and/or vomiting". In other papers looking at secondary measures of effectiveness such as Shlieder et al and the Minnesota data we can also see improvements in nausea scores. In addition, the National Academies of Science cites that "there is conclusive or substantial evidence that cannabis or cannabinoids are effective as anti-emetics in the treatment of chemotherapy-induced nausea and vomiting"; this would indicate that cannabinoids do have some potential for nausea.

8.3.4 Anxiety

Cannabinoids have shown promise in the management of generalized anxiety via reduction of anxiety-like behavor.[49,50] While it is well-known that anxiety or paranoia can also be increased at higher levels, this is likely due to a biphasic effect of cannabis at appropriate vs. inappropriate dosages. More current work has looked at varying ratios of CBD:THC as a way to address some of these side effects, however on the whole we see an anti-anxiety effect that could be helpful with those with withdrawal symptoms.

Patients within Iowa's program are titrated through low-dosing to a dose where side effect profiles are known to the patient before going to standardized dosing. In this way the lowest appropriate dose can be found, and a lower potential side-effect profile could be attained.

8.3.5 Insomnia

Findings with sleep in different condition and cannabinoids effects are mixed but show various effects of cannabinoid administration on several aspects of sleep. Recent findings indicated that CBD may hold promise for REM sleep behavior disorder and excessive daytime sleepiness, while THC may reduce nightmares and may improve sleep among patients with chronic pain.[63,64]

Additionally here is a selected paper:

Russo et al "Cannabis, Pain, and Sleep: Lessons from Therapeutic Clinical Trials of Sativex, a Cannabis-based Medicine"[71]

Review examining modern studies on the effects of THC and CBD on sleep especially in the context of medical treatment of neuropathic pain using a product that is plant derived with a 1:1 ratio of CBD:THC.

- Data from over 2000 subjects in numerous Phase I-III studies
- **3mg-300mg Sativex per day (1.5-150mg THC/day)**
    - **Up to 27g/90 day supply**
- **Marked improvement in subjective sleep parameters in patients with wide variety of pain conditions**
- Acceptable adverse event profile
- No tolerance to the benefit of Sativex on pain or sleep
- No need for dosage increases have been noted in safety extension studies up to 4 years.

8.4 Potential to increase retention in treatment programs

Socias et al. "High-intensity cannabis use is associated with retention in opioid agonist treatment: a longitudinal analysis" (2018)[41]

Given the criticality of retention in MAT-type programs in reducing opioid-related morbidity and mortality, researchers in Canada followed 820 patients in opioid agonist treatment centers. Participants were followed for a median of 81 months to determine whether daily cannabis use had any bearing on retention in treatment programs.

- Retention in centers is linked to decreased all-cause and overdose mortality risk
- Daily cannabis use was associated with 21% greater odds of retention in treatment centers at 6 months
- Cannabis use may help with retention of those in OUD treatment centers

I would like to note at this junction that there are other studies similar to this one that find no association or for a few a negative effect. This may be due to differences in program requirements for MAT in these studies related to cannabis use such as elimination of privileges if cannabis use is documented. This may lead those using cannabis to more frequently drop out of these types of studies as there is risk for consequence because of cannabis use.

8.5 Nationwide Data

Bradford et al. Association Between US State Medical Cannabis Laws and Opioid Prescribing in the Medicare Part D Population (2018).[2]

This article studies the relationship between implementation of medical cannabis laws and relative rate of opioid prescription among Medicare Part D patients. The goal of this article was to determine if medical cannabis policy could be used to reduce opioid prescriptions and the occurrence of opioid-related overdose

- States with active dispensaries saw 3.742 million fewer daily doses of opioids filled
- States with personal cultivation laws saw 1.792 million fewer daily doses filled
- Hydrocodone use was decreased by 2.320 million daily doses (17.4%)
- Prescriptions for all opioids decreased by more than 3.5M daily doses/year when states opened medical cannabis dispensaries
- **Medical cannabis may be used as a harm-reduction tool in the US opioid epidemic**

Bradford and Bradford. "Medical Marijuana Laws Reduce Prescription Medication Use in Medicare Part D" (2016)[35]

The purpose of this study was to determine if in medical states medical cannabis may be used as an alternative by patients to clinical alternatives such as opioids. Researchers used data on all prescriptions filled by Medicare Part D enrollees from 2010, focusing on prescriptions in condition areas where there would be overlap with benefits from Cannabis

- Overall reductions in Medicare program and enrollee spending when states implemented medical cannabis programs
    - Estimated savings of $165.2M/year (2013)
- Research suggests that more widespread state approval of medical marijuana could provide modest budgetary relief
- Reductions seen in all condition areas besides glaucoma
    - 265 daily doses less for depression filled per physician/year
    - 1,826 daily doses less for pain filled per physician/year
    - Statistically significant ($p<0.01$)
- No reductions seen in condition areas that have no overlap with medical cannabis
    - Blood thinners, antivirals, antibiotics
- **In states that implemented medical cannabis programs reductions were seen in prescriptions filled for conditions, especially pain medication**

Boehnke et al. "Medical Cannabis Use is Associated with Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients with Chronic Pain" (2016).

Significance:

- Identified lack of evidence that opioids are effective for treatment of long-term chronic pain among adult patients
- Analyzed linked between medical cannabis for chronic pain and opioid use

- **Treatment with medical cannabis resulted in improved quality of life, better side effect profile, and decreased opioid use**

Iowa Reports:

In the state of Iowa, 68% of patients are certified for conditions directly related to pain (untreatable pain, cancer with severe or chronic pain, and terminal illness with severe pain)[10]. Many of these patients were using opioid-based therapy to manage their symptoms prior to seeking treatment with medical cannabis. In the dispensary, we have seen patients be able to decrease their use of other pain-management medications in conjunction with use of medical cannabis without increasing their risk of serious adverse effects. Many patients have worked with their physicians to reduce the number of opioids that they are being prescribed resulting in improved quality of life and decreased risk occurrence of opioid related hospitalization or death. While this is anecdotal in nature, this petition to add a new condition should be based, at least in part, off the available data for patients within the affected state

MN Reports:

The medical cannabis program in Minnesota surveyed patients with intractable pain. Their survey showed that out of 568 reports, 340 (58%) indicated a reduction in medications used to reduce pain – with 221 (37.7%) patients reporting reduction in use of opioids in pain management.

9. Other Notes of Interest

New Mexico's Medical Cannabis board recently (2019) approved Opiate Disorder as a qualifying condition for Medical Cannabis in New Medico. In her State of the State address, New Mexico Governor Michelle Grisham directed the Department of health to include opioid addiction stating. "We will be tough, smart, and we will proceed with empathy for the families caught in the opioid crisis. We will not stand in the way of our neighbors." New Jersey also recently approved Opioid Use Disorder. The reasoning behind the approval from their commissioner and MD Dr. Elnahal can be found as Appendix A[34].

Other countries have also discussed the use of exploring cannabis as a tool for opioid withdrawal and dependence. The Canadian Mental Health Association put out a report in 2018 detailing the opioid crisis in Canada and encouraged exploration of "promising new research on cannabis as an alternative form of treatment to substitute opioids for pain management, to manage withdrawal symptoms and/or treat substance abuse"[34 This] effort is spearheaded by harm reduction workers. In 2017, the High Hopes Foundation created a small booth that is staffed by the Overdose Prevention Society and distributes cannabis capsules, oils, and edibles to help curb opioid use. The British Columbia Emergency Health Services and the Vancouver Police have publicly stated their support, recognizing that cannabis presents "fewer harms when compared to opioids and that it can be an effective **harm reduction too**l during the opioid crisis."

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Appendix A: Approval Reasoning for OUD in New Jersey from Dr. Elnahal.

Opioid Use Disorder

From my independent review of the petitions, I am granting the petition that seeks to add opioid use disorder to the MMP. In coming to this conclusion, I reviewed this condition against the six regulatory criteria cited above and find that it meets the requirements for inclusion in the MMP, with the condition that physicians prescribing medical marijuana for this disorder do so in conjunction with their patient's medication-assisted treatment, instead of as a singular treatment for the disorder.

Regarding the first factor, which is whether the condition is generally accepted in the medical community as a valid medical condition, I find that opioid use disorder is a valid condition. According to the U.S. Department of Health and Human Services, Centers for Disease Control

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[57] Anxiety Sensitivity and Distress Intolerance as Predictors of Cannabis Dependence Symptoms, Problems, and Craving: The Mediating Role of Coping Motives. Farris SG, Metrik J, Bonn-Miller MO, Kahler CW, Zvolensky MJ. J Stud Alcohol Drugs. 2016 Nov;77(6):889-897.

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and Prevention, opioid use disorder is "[a] problematic pattern of opioid use that causes significant impairment or distress."[59] Additionally, there are multiple ICD-10-CM codes for opioid use disorder.[60] Because opioid use disorder has a common medical definition and maintains several ICD-10-CM codes, I find that opioid use disorder is a valid condition recognized by the medical community.

Under the second factor, I must consider whether the treatments for the condition, if the treatments are causing the patient suffering, are generally accepted by the medical community and other experts as valid treatments for the condition. As noted in the petition, the generally accepted treatment for opioid use disorder is medication-assisted treatment (MAT), which includes methadone, naltrexone, and buprenorphine (suboxone). I agree. As stated by the U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration (SAMHSA), MAT is the "gold standard" for treatment of opioid use disorder.[61] According to SAMHSA, MAT consists of FDA-approved medications, namely methadone, buprenorphine or naltrexone, in combination with behavioral therapies, "to provide a whole-patient approach to the treatment of substance use disorders."[62] Side effects from MAT medications include insomnia, headaches, abdominal pain, body aches and vomiting, to name a few.[63] Thus, I find that the treatment for opioid use disorder, specifically MAT medications, is recognized and accepted by the medical community. And, while I agree that MAT medications are an effective treatment for opioid use disorder, there are serious side effects that come with this treatment. Accordingly, I also find that MAT medications can cause a patient's suffering.

As for the third factor, which is whether 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, I find that opioid use disorder itself as well as the treatment for this condition cause severe suffering for patients inflicted with this condition. It is without question that opioid use disorder causes severe suffering for an individual stricken with this condition. According to the U.S. Department of Health and Human Services, Office of the Surgeon General, "[o]pioid addiction typically involves a pattern of: (1) intense intoxication, (2) the development of tolerance, (3) escalation in use, and (4) withdrawal signs that include profound negative emotions and physical symptoms, such as bodily discomfort, pain, sweating, and intestinal distress."[64] With increased use, the individual not only must take the opioid to avoid the severe withdrawal side effects, but the individual will also experience intense cravings for the opioid and preoccupation with using the opioid.[65] As such, an individual living with opioid use disorder can experience suffering that ranges from severe psychosocial impairment to overdosing and even death.[66] With these side effects, a patient is unable to engage

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[59] See https://www.cdc.gov/drugoverdose/opioids/terms.html (last visited January 17, 2019).
[60] See ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/ICD10CM/2018/ (last visited January 17, 2019).
[61] See https://addiction.surgeongeneral.gov/sites/default/files/Spotlight-on-Opioids_09192018.pdf (last visited January 17, 2019).
[62] See Ibid.
[63] See https://medlineplus.gov/druginformation.html (last visited January 17, 2019).
[64] See https://addiction.surgeongeneral.gov/sites/default/files/Spotlight-on-Opioids_09192018.pdf (last visited January 17, 2019).
[65] Ibid.
[66] Ibid.

in activities of daily living, thereby diminishing his or her quality of life. Thus, the condition itself causes the patients with this disorder to suffer immensely.

While opioid use disorder, in and of itself, causes extensive suffering, the treatment for the disorder can also cause significant suffering. Specifically, MAT medications can cause headaches, vomiting, body aches and insomnia.[67] All of these side effects can prevent a patient from engaging in activities of daily living, thereby diminishing one's quality of life. Accordingly, I find that opioid use disorder as well as the medications used to treat this condition cause severe suffering.

Under the fourth factor, I must evaluate the availability of conventional medical therapies, other than those that cause suffering, to alleviate the patient's suffering caused by the condition and/or the treatment thereof. Unfortunately, the treatment for opioid use disorder that causes the patient suffering, specifically MAT medications, is the most effective and viable conventional medical therapy offered for this condition. As such, I find that there is an absence of effective alternative medical therapies to the conventional therapies currently prescribed for opioid use disorder that cause patients to suffer.

Regarding the fifth factor, which is whether there is generally accepted evidence in the medical community that the use of marijuana alleviates suffering relating to the condition, I find that there is sufficient evidence that the use of medical marijuana may relieve the suffering related to opioid use disorder when it is used in conjunction with MAT. There is a recent publication by the Cannabis and Cannabinoid Research Journal that sets forth emerging evidence that the use of medical cannabis in conjunction with MAT has the potential to "ease opioid withdrawal symptoms, reduce opioid consumption, ameliorate opioid cravings, prevent opioid relapse, improve [opioid use disorder] treatment retention, and reduce overdose deaths."[68] However, the publication notes that these findings are preliminary and that additional research, which is hampered by the federal government's designation of marijuana as a Schedule I drug, should be conducted on this promising form of treatment for opioid use disorder.[69] While I acknowledge that there is little research on the effectiveness of medical marijuana, either alone or in conjunction with MAT, as a treatment for opioid use disorder, given the current opioid epidemic consuming our great State, the citizens of New Jersey suffering from this horrible disorder simply cannot wait for the removal of the political barriers that are preventing research on this promising treatment in order to receive a medication that may ultimately safe their lives.

Moreover, as declared under Executive Order No. 219 (2017), "[t]he abuse of and addiction to opioid drugs is a public health crisis in New Jersey, necessitating the marshalling of all appropriate resources to combat its harmful effects on the citizens of our State." This crisis is further evidenced by the staggering number of deaths resulting from opioid overdoses that occur each year in New Jersey. In fact, overdose deaths have more than doubled since 2013. In 2013, there were 1,336 drug-related deaths; in 2016, that number increased to 2,221.[70] For 2018, the

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[67] See Footnote 6.

[68] See Wiese B, Wilson-Poe AR (2018) Emerging evidence for cannabis' role in opioid use disorder, Cannabis and Cannabinoid Research 3:1, 179–189, DOI: 10.1089/can.2018.0022.

[69] Ibid.

[70] See https://www.njcares.gov/

number of deaths is projected to jump to a staggering 3,163.[71] With opioid overdose deaths climbing at such an alarming rate, I am compelled to find that the research to date on the beneficial use of medical cannabis as an adjunct to MAT for the treatment of opioid use disorder is sufficient evidence that this form of treatment may alleviate the suffering relating to the disorder and prevent overdose deaths. Indeed, I cannot ignore these disturbing numbers and allow more of our citizens to succumb to this disorder when there is at least some research suggesting that the use of medical marijuana in conjunction with MAT may be an effective treatment for opioid use disorder and ultimately prevent a patient's demise. As such, in giving effect to Executive Order 219's call to garner all possible resources to combat the opioid crisis, I find that the available research I have reviewed establishes sufficient evidence that the use of medical marijuana may relieve the suffering related to opioid use disorder when it is used in conjunction with MAT.

As for the final factor, which is whether there were letters from physicians or other licensed health care professionals knowledgeable about the condition supporting the inclusion of opioid use disorder under the MMP, I find that the petitions were submitted with support from medical professionals.

Based upon the above analysis, I find that the condition of opioid use disorder is "debilitating" and that medical marijuana is more likely than not to be potentially beneficial to treat or alleviate the debilitating effect of this condition when it is used in conjunction with MAT. As such, I find that opioid use disorder, as a standalone condition, should be added to the MMP.

Appendix 2: “Synergistic Interactions between Cannabinoid and opioid analgesics”

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Abstract

Cannabinoids and opioids both produce analgesia through a G-protein-coupled mechanism that blocks the release of pain-propagating neurotransmitters in the brain and spinal cord. However, high doses of these drugs, which may be required to treat chronic, severe pain, are accompanied by undesirable side effects. Thus, a search for a better analgesic strategy led to the discovery that delta 9-tetrahydrocannabinol (THC), the major psychoactive constituent of marijuana, enhances the potency of opioids such as morphine in animal models. In addition, studies have determined that the analgesic effect of THC is, at least in part, mediated through delta and kappa opioid receptors, indicating an intimate connection between cannabinoid and opioid signaling pathways in the modulation of pain perception. A host of behavioral and molecular experiments have been performed to elucidate the role of opioid receptors in cannabinoid-induced analgesia, and some of these findings are presented below. The aim of such studies is to develop a novel analgesic regimen using low dose combinations of cannabinoids and opioids to effectively treat acute and chronic pain, especially pain that may be resistant to opioids alone.

Keywords: Cannabinoid; Opioid; Synergy; Analgesia

Introduction

It is widely known that opioids and cannabinoids share several pharmacological effects, including antinociception, hypothermia, inhibition of locomotor activity, hypotension and sedation (Manzaneres et al., 1999; Massi et al., 2001). Opioids such as morphine are commonly prescribed analgesics for chronic or persistent pain, but the analgesic benefits of cannabinoids such as delta 9-tetrahydrocannabinol (THC), the major psychoactive constituent of marijuana, have not been well explored in

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humans, aside from anecdotal reports. Early studies indicated that oral doses of THC were no more effective than codeine for pain, and produced a significant amount of dysphoric side effects (Noyes et al., 1975; Campbell et al., 2001). Thus it was believed that THC could only produce analgesia at doses that were high enough to cause other behavioral side effects. However, THC and other synthetic cannabinoid compounds have proven to demonstrate potent analgesic effects up to 10 times that of morphine in animal models of acute and neuropathic pain via parenteral or systemic administration (Johnson et al., 1981; Lichtman and Martin, 1997; Fuentes et al., 1999; Fox et al., 2001). The first evidence that the antinociceptive effects of THC could be separated from its adverse behavioral effects was published in 1994, when Smith and colleagues demonstrated that a kappa opioid receptor antagonist, nor-binaltorphimine (norBNI), blocked only the antinociceptive effect of THC in rodents with no effect on hypothermia, hypoactivity or catalepsy (Smith et al., 1994; Welch and Eades, 1999).

For many years, studies have indicated that cannabinoids can enhance the antinociceptive properties of opioids. The effects of morphine have been found to be enhanced by crude cannabis extract (Ghosh and Bhattacharya, 1979) and by orally administered Δ^6-THC and Δ^9-THC (Mechoulam et al., 1984). Evidence in recent years studying the synergy between opioids and cannabinoids has suggested that cross-talk between these two signaling pathways shows promise for combination pain therapy as well as novel treatments for opioid addiction and abuse. A combination of low dose analgesics devoid of undesirable side effects would be ideal to replace high dose analgesics that cause unnecessary sedation, respiratory depression and constipation.

Enhancement studies

Spinal administration of various cannabinoids with morphine produces a greater-than-additive effect with respect to antinociception in mice as measured by the tail–flick radiant heat test (Welch and Stevens, 1992; Smith and Martin, 1992; Smith et al., 1994). THC at i.t. doses that are marginally active in the tail–flick test significantly shift the dose–response curve of morphine to the left, indicating an increase in antinociceptive potency (a 4- to 12-fold shift). Similar shifts in morphine potency are also seen with 11-hydroxy-THC, Δ^8-THC, and levonantradol (Welch and Stevens, 1992). The enhancement of morphine by cannabinoids is not universal; studies have shown that there are two categories of cannabinoid/opioid interactions–supraspinal and spinal components. Some cannabinoids have been found to enhance morphine in the brain while others act predominantly in the spinal cord, as seen from a comparison of i.t. and i.c.v. administration (Welch et al., 1995). THC enhances the effects of morphine in the spinal cord, whereas the synthetic cannabinoid CP 55,940 does not enhance spinally administered morphine but shifts the morphine dose–response curve nearly 10-fold after i.c.v. administration (Welch and Stevens, 1992; Welch et al., 1995). CP 55,940 also increases morphine antinociception by about 45% when administered i.p. (Massi et al., 2001). Anandamide, an endogenous cannabinoid, does not enhance opioid antinociception, most likely due to its rapid breakdown by lipid-hydrolyzing enzymes (Pugh et al., 1996; Welch, 1997; Fowler et al., 2001).

A synergy also exists in the opposite direction; that is, morphine can enhance the antinociception induced by THC. Reche and colleagues report that an ineffective dose of morphine i.p. shifted the dose–response curve of THC i.v. to the left in a significant fashion (Reche et al., 1996). Parenteral administration of morphine and THC also increases the efficacy of morphine (Smith et al., 1998).

Table 1
ED_{50} values (mg/kg) and potency ratios for various opioids in combination with vehicle or THC (20 mg/kg) in the tail–flick test for antinociception

Drugs	*ED50*		Potency ratio
	vehicle	THC	
morphine	28.8 (20.2–41)	13.1 (8.8–19.5)	2.2
codeine	139.9 (75.2–260.5)	5.9 (1.4–24.9)	25.8
oxymorphone	2.6 (1.7–3.9)	0.5 (0.3–0.8)	5.0
hydromorphone	5.6 (3.2–9.7)	0.4 (0.2–0.8)	12.6
methadone	12.0 (8.1–17.9)	2.7 (1.4–5.2)	4.1
LAAM	8.0 (6.4–10.1)	2.6 (1.7–3.9)	2.5
heroin	26.1 (12.7–53.4)	5.4 (1.7–16.9)	4.1
meperidine	86.2 (52.8–140.6)	11.1 (4.2–29.4)	8.9
fentanyl	6.1[a]	0.5 (0.3–0.8)	ND[b]
pentazocine	625.9[a]	838.6[a]	ND[b]

Mice were injected with vehicle (1:1:18; emulphor, ethanol, saline) or THC (20 mg/kg) p.o. 10–30 min prior to p.o. opioid treatment, and tested 10–30 min later in the tail–flick test. Dose–response curves were generated for each opioid, with at least 4 doses (n=6 for each dose) per curve. ED_{50} values and 95% confidence limits were determined along with potency ratios between opioid plus vehicle and opioid plus THC.
Reprinted from Cichewicz et al., 1999.
[a] Estimated ED_{50} from an extrapolated curve.
[b] ND = not determined; showed no % MPE above 50%.

Altogether, these data examining the behavioral interaction between THC and morphine suggest a greater-than-additive analgesic effect when given in combination.

THC and morphine administration by any combination of routes (i.t., i.c.v., s.c., p.o.) significantly enhances the potency of morphine in mice (Smith et al., 1998). Further studies confirm that a non-antinociceptive oral dose of THC (20 mg/kg) can enhance the potency of an acute oral dose of morphine, codeine, oxycodone and other opioid analgesics (Cichewicz et al., 1999; see Table 1). Most recently, a full isobolographic evaluation of the synergy between oral THC and morphine or codeine has been published (Cichewicz and McCarthy, 2003). Using this type of evaluation, a graph is constructed which compares the effects of actual experimental dose pairs with a *line of additivity*; i.e. the line which contains all points describing the effects predicted from a solely additive relationship. The combinations of THC and morphine or codeine tested all fell below this line and thus demonstrated synergy. Isobolographic analysis provides the best evidence that two drugs produce a greater-than-additive effect because the doses are varied in the combination. Oral synergy is particularly relevant to clinical settings because of the ease of administration to patients, and thus these combinations show promise as novel drug therapies for pain.

Endogenous opioids and opioid receptors

THC administered i.t. has been shown to release endogenous opioids which stimulate both delta and kappa opioid receptors (Welch, 1993; Smith et al., 1994; Pugh et al., 1996). This has been substantiated by the findings that dynorphin antisera and nor-BNI block THC-induced antinociception (Welch, 1993; Smith et al., 1994; Pugh et al., 1996; Reche et al., 1996). Furthermore, the discovery of a bi-directional

cross-tolerance of THC and CP 55,940 to kappa agonists in the tail–flick test (Smith et al., 1994) confirms that cannabinoids interact with kappa opioids. It is believed that the synergistic effect with THC and morphine results from the initial release of dynorphin A by THC and the subsequent breakdown of dynorphin A to smaller dynorphin fragments and leucine–enkephalin metabolites (Pugh et al., 1996; Mason et al., 1999). A time correlation between antinociception and increased dynorphin levels suggest that these endogenous opioids interact with the delta and kappa opioid receptors to mediate the antinociceptive effect of THC (Mason et al., 1999; Welch and Eades, 1999). In fact, Corchero and colleagues report that five-day treatment with THC produces increases in both prodynorphin and proenkephalin gene expression in rat spinal cord (Corchero et al., 1997), while other studies demonstrate that THC-induced analgesia is reduced in prodynorphin knockout animals (Zimmer et al., 2001). Simultaneous stimulation of the mu receptor by morphine with these other opioid receptors may account for the greater-than-additive antinociceptive effect seen with THC and morphine. Leucine–enkephalin and DPDPE, a specific delta opioid receptor agonist, both increase the analgesic potency of mu opioid receptor agonists (Vaught et al., 1982; Horan et al., 1992). In addition, others have shown a functional relationship between kappa and mu, and heterodimerization between delta and mu, suggesting a link between opioid receptors (Pan et al., 1997; Gutstein et al., 1998; Gomes et al., 2000).

Antagonist studies with cannabinoid receptors implicate the CB1 and mu receptors in the enhancement of morphine by THC. SR141716A, the CB1-specific receptor antagonist, blocks active doses of THC but has no effect on morphine alone (Smith et al., 1998), demonstrating that SR141716A selectively antagonizes THC. Furthermore, the enhanced antinociception due to a combination of a low oral dose of THC and a low oral dose of morphine is blocked by SR141716A (Smith et al., 1998). Naloxone also blocks the synergistic antinociception produced by low oral doses of THC and morphine or codeine, indicating the involvement of the mu receptor. However, oral synergy is not blocked by norBNI, contrary to what was seen in the spinal cord (Cichewicz et al., 1999). Taken together with the above spinal findings, it seems that all three of the major opioid receptor subtypes are involved in some part in the enhancement of opioids by THC, depending on route of administration.

Cannabinoid and opioid receptors are both members of the G-protein-coupled receptor family, activating pertussis toxin-sensitive G_i/G_o proteins. Recent work has examined agonist-stimulated GTP binding in both of these receptor systems, using cellular and molecular paradigms. In COS-7 cells transfected with cannabinoid and opioid receptors, a combination of these drugs failed to induce an additive increase in [^{35}S]GTPγS binding, suggesting that these receptors share a common pool of G_i/G_o proteins (Shapira et al., 2000). However, in neuroblastoma cells that endogenously express delta opioid and cannabinoid receptors, etorphine and desacetyllevonantradol (DALN) produce an additive stimulation of binding, indicating that the receptors draw from separate G protein pools (Shapira et al., 2000). Thus, cells which typically contain these receptors likely contain different mechanisms than those into which foreign receptors are introduced, pointing to the importance of models that accurately depict human systems. The enhancement of opioid analgesic effect by cannabinoids in rodent models suggests that the receptors involved do not share the same pool of G proteins.

Opioid and cannabinoid receptors are co-distributed in areas of the dorsal horn of the spinal cord (Welch and Stevens, 1992; Hohmann et al., 1999; Salio et al., 2001) as well as areas of the brain controlling nociceptive responses, such as the periaqueductal gray (PAG), raphe nuclei and central-medial thalamic nuclei (Mansour et al., 1988; Herkenham et al., 1991; Lichtman et al., 1996). Studies show that cannabinoids exhibit a similar binding distribution in the brain to that of morphine (Kuhar et al., 1973; Mailleux and Vanderhaeghen, 1992). Furthermore, the blockade of THC-induced Fos

immunoreactivity by naloxone in the ventral tegmental area, hypothalamus and PAG suggests that these areas are important in cannabinoid-opioid interactions (Allen et al., 2003). In fact, Meng and colleagues demonstrate that analgesia produced by cannabinoids and opioids involve similar brainstem circuitry through modulation of rostal ventromedial medulla neuronal activity (Meng et al., 1998). Thus the spinal blockade of pain transmission becomes greater-than-additive as both opioid and cannabinoid receptor types are activated in the dorsal horn. Simultaneous activation of brain receptors could then disinhibit interneurons regulating endogenous opioid release, further contributing to the antinociceptive effect.

Cannabinoid-opioid interactions not only underlie synergy in acute analgesia, but persist after chronic drug administration. Up-regulation of opioid receptor protein in the spinal cord that we observe in chronic combination-treated animals (Cichewicz et al., 2001) may underlie the retention of efficacy of the drug combination. In addition, the CB1 receptor and mu opioid receptor have been found to be co-localized in areas important for the expression of morphine abstinence—nucleus accumbens, septum, striatum, PAG and amygdaloid nucleus (Navarro et al., 2001). Thus, THC might alter the expression of morphine antinociceptive tolerance and/or dependence. After short-term treatment in mice with low doses of THC and morphine in combination, there is an avoidance of tolerance to the opioid without compromising the antinociceptive effect (Cichewicz and Welch, 2003). Chronic interactions between opioids and cannabinoids have also been examined at the cellular level. Prolonged exposure to DALN failed to result in a downregulation of delta opioid receptors in HEK-293 cells co-transfected with CB1 and delta receptors (Shapira et al., 2003). These results support behavioral data which suggest that cannabinoids like THC can alter the expression of morphine tolerance. Thus, not only does THC increase the acute analgesic effect of morphine, but may also be useful long-term to provide pain relief in opioid-tolerant subjects.

Clinical implications

In conclusion, the research presented here marks a potential use for low doses of THC to enhance the potency of opioid drugs. The wealth of research examining endogenous opioid tone and receptor function points to the involvement of the opioid system in the analgesic effects produced by THC. THC is a schedule II drug currently marketed for oral administration as dronabinol (Marinol®), and is primarily used as an appetite stimulant in AIDS-wasting patients and as an anti-emetic for cancer chemotherapy (Nelson et al., 1994; Timpone et al., 1997; Beal et al., 1997); however, THC has not been approved for analgesic use due to lack of consistent data. Recent clinical reports support the use of cannabinoids and opioids for peripheral inflammatory pain (Sawynok, 2003) but debate the effectiveness of cannabinoids for chronic cancer-related pain due to adverse side effects (Campbell et al., 2001). However, other studies emphasize the frequency of cannabis use among chronic pain patients and provide statistics that support analgesic benefits of marijuana (Ware et al., 2003). While high doses of THC are analgesic, they can be accompanied by anxiety, headache, dry mouth, euphoria, and tachycardia. Low doses of oral THC have no analgesic effects, and in mice, no behavioral changes such as ataxia, aggressiveness or loss of righting reflex have been observed. Thus, these low doses could safely be administered in combination with opioids such as morphine without increasing detrimental side effects. Since continued administration of morphine can lead to tolerance and morphine-resistant pain, an adjunct to morphine may be the key to prolong appropriate treatment. The administration of low doses of

THC in conjunction with low doses of morphine seems to be an alternative regimen that reduces the need to escalate opioid dose while increasing opioid potency.

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