

**A PETITION TO ADD
OPIOID REPLACEMENT & OPIOID USE DISORDER
TO THE ACCEPTED LIST OF CONDITIONS FOR
MEDICAL MARIJUANA IN DELAWARE**

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1.0	10/10/2018	Initial Submission
1.1	12/5/2018	Amendment <ul style="list-style-type: none">- Addressed concerns published by DHHS in their Medical Review (dated 10/20/2018)- Inclusion of additional clinical and physiological evidence

CONTENTS

1	Declaration of Intent	7
2	Executive Summary	7
3	Extent to which the condition is generally accepted as a valid, existing debilitating medical condition	8
3.1	Opioids	8
3.1.1	<i>CDC Guidelines Do Not Recommend Opioids for Long Term Pain Mgmt (2016)</i>	8
3.2	What is Opioid Use Disorder?	8
3.3	Opioid overdoses	9
3.3.1	<i>Risk factors for opioid overdose</i>	9
3.3.2	<i>People at higher risk of opioid overdose</i>	10
3.3.3	<i>People likely to witness an opioid overdose</i>	10
3.3.4	<i>Additional Statistics</i>	10
4	Extent to which the condition causes severe suffering, or otherwise severely impairs the patient's ability to carry on activities of daily living	11
4.1	Opiate Overdose Crisis in America	11
4.2	Opioid-Related Overdose Deaths In Delaware	11
4.2.1	<i>Monthly overdose deaths Increasing in Delaware (2018)</i>	11
4.3	Opioid Pain Reliever Prescriptions	12
4.4	Neonatal Abstinence Syndrome (NAS)	12
4.5	HIV Prevalence and HIV Diagnoses Attributed to Injection Drug Use (IDU)	12
5	The Extent that conventional treatments cause or add to the suffering of those afflicted with Opioid Use Disorder	14
5.1	Methadone	14
5.1.1	<i>Methadone Poisoning</i>	14
5.1.2	<i>Methadone's Negative Side Effects</i>	14
5.2	Suboxone	15

5.2.1	<i>High Risk for Addiction</i>	15
5.3	Naloxone	16
5.3.1	<i>Health risks</i>	16
5.3.2	<i>Skyrocketing Cost</i>	17
6	The Extent to which cannabis can be replace opioids in the treatment of chronic pain	18
6.1	Drug derived from marijuana has triggered the first federal shift on cannabis in half a century, and experts predict an avalanche effect (2018).....	18
6.2	An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. (2017).....	18
6.3	Medical cannabis and mental health: A guided systematic review (2017)	18
6.4	Cannabis as a Substitute for Opioid-Based Pain Medication (2017)	19
6.5	Substituting cannabis for prescription drugs, alcohol and other substances among medical cannabis patients: The impact of contextual factors (2016).....	19
6.6	CDC Guidelines Do Not Recommend Prescribing Opioids for Chronic Pain (2016).....	20
6.7	Medical Marijuana and Chronic Pain: a Review of Basic Science and Clinical Evidence (2015).....	21
6.8	Cannabis is the least risky recreational drug (2015).....	21
6.9	Cannabis for the Management of Pain: Assessment of Safety Study (2015)	21
6.10	Marijuana is the least Addictive Drug (2014).....	22
6.11	Zero People Have Fatally Overdosed On Marijuana (2014).....	23
6.12	The medicinal use of cannabis and cannabinoids—An international cross-sectional survey on administration forms. (2013).....	23
6.13	Cannabis as a substitute for alcohol and other drugs: A dispensary-based survey of substitution effect in Canadian medical cannabis patients. (2013)	24
6.14	Smoked cannabis for chronic neuropathic pain: A randomized controlled trial (2010).....	24
6.15	Marijuana use and the risk of lung and upper digestive tract cancers: Results of a population-based case–control study. (2006).....	25
7	The Extent that cannabis can be effective as an opioid reduction strategy for those patients already using opioids	27
7.1	Emerging Evidence for Cannabis' Role in Opioid Use Disorder (2018).....	27
7.2	Rationale for Cannabis-based interventions for the Opioid Epidemic (2017).....	27

- 7.3 Legalized medical cannabis lowers opioid use (2018) 28
- 7.4 Medical Marijuana Cuts Use of Prescription Drugs (2018) 28
- 7.5 States with medical marijuana laws had about 6 percent fewer opioid prescriptions among Medicaid patients compared with states without such laws (2018) 28
- 7.6 Rationale for cannabis-based interventions in the opioid overdose crisis (2017)..... 29
- 7.7 Cannabis as a Substitute for Opioid-Based Pain Medication (2017) 29
- 7.8 Marijuana Addiction Treatment for Opioid Dependency (2016)..... 29
- 7.9 Among veterans, opioid prescription requests down in step with rise in medical pot (2016)..... 30
- 7.10 Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain (2016)..... 30
- 7.11 After Medical Marijuana Legalized, Medicare Prescriptions Drop For Many Drugs (2016) 31
- 7.12 Fewer Pills prescribed in medical pot states (2016)..... 31
- 7.13 The Prescription Opioid and Heroin Crisis: A Public Health Approach to an Epidemic of Addiction. (2015)..... 32
- 7.14 Access to legal dispensaries linked to significant decrease in both prescription painkiller abuse, and in overdose deaths from prescription painkillers (2015) 32
- 7.15 Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010 (2014)..... 33
- 7.16 Therapeutic Benefits of Cannabis: A Patient Survey (2014)..... 34
- 7.17 Prescription drug overdose deaths lower in states with legal medical marijuana (2014)..... 34
- 7.18 Cannabis in palliative medicine: improving care and reducing opioid-related morbidity (2011)..... 34
- 7.19 Exploring the relationship between perceived inter-dose opioid withdrawal and patient characteristics in methadone maintenance treatment. (2009)..... 35
- 7.20 Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances (2009)..... 35
- 8 The Extent to which Cannabis can relieve the symptoms of Withdrawal & Cravings 36**
- 8.1 Cannabis Is an Exit Drug for Major Addictions, Not a Gateway to New Ones (2017)..... 36
- 8.2 Antidepressant-like and anxiolytic-like effects of cannabidiol: a chemical compound of Cannabis sativa. (2014) .. 36
- 8.3 Therapeutic Benefits of Cannabis: A Patient Survey (2014). 38
- 8.4 The endocannabinoid system and the brain (2013) 38
- 8.5 Cannabis for therapeutic purposes: Patient characteristics, access, and reasons for use. (2013)..... 38

8.6	Anxiogenic-like effects of chronic cannabidiol administration in rats (2012).	39
8.7	Medicinal use of cannabis in the United States: historical perspectives, current trends, and future directions (2009)39	
8.8	Effects of cannabidiol (CBD) on regional cerebral blood flow (2004).....	40
8.9	Unresponsiveness to Cannabinoids and Reduced Addictive Effects of Opiates in CB1 Receptor Knockout Mice (1999)40	
9	The Extent to which Cannabis is effective as an adjunct therapy to medication assisted treatment in order to increase treatment success rates.....	41
9.1	When opioids are used in combination with cannabis, marijuana can boost an opioid's effectiveness without requiring higher dosages (2018)	41
9.2	Cannabis as a substitute for prescription drugs – a cross-sectional study. (2017).....	41
9.3	Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients (2017).....	42
9.4	Cannabis breaks the cycle of pleasure and reward being programmed by opiates (2018).....	42
9.5	Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain (2016).....	43
9.6	Impact of cannabis use during stabilization on methadone maintenance treatment. (2013)	43
9.7	Cannabinoid-opioid interaction in chronic pain (2011)	43
9.8	Intermittent marijuana use is associated with improved retention in naltrexone treatment for opiate-dependence. (2009)44	
9.9	Self-efficacy, social support and service integration at medical cannabis facilities in the San Francisco Bay area of California. Health Soc Care Community (2008)	44
9.10	Cannabis in painful HIV-associated sensory neuropathy: A randomized placebo-controlled trial (2007)	44
9.11	Synergistic interactions between cannabinoid and opioid analgesics (2004).....	45
9.12	The role of endogenous opioids in enhancing the antinociception produced by the combination of delta 9-tetrahydrocannabinol and morphine in the spinal cord (1996)	45
9.13	Synergistic interactions of endogenous opioids and cannabinoid systems. (1999)	46
9.14	Antinociceptive activity of intrathecally administered cannabinoids alone, and in combination with morphine, in mice (1992)	47
10	The Extent to which a legal precedent exists to Add Opioid Replacement and Opioid Use Disorder as a qualifying condition.....	48

10.1 New York State Adds Opioid Replacement Now a Qualifying Condition for Medical Marijuana (July 2018)..... 48

10.2 Pennsylvania Adds Opiate Use Disorder as a Qualifying Condition (May 2018)..... 48

10.3 New Jersey Adds Opiate Use Disorder as a Qualifying Condition (March 2018) 49

11 Letters of Support from Licensed Medical Professionals..... 50

1 DECLARATION OF INTENT

As a private citizen, I am petitioning the State of Delaware to add Opioid Use Disorder and/or Opioid Replacement to the list of qualifying conditions for Medical Marijuana. This petition compiles over 60 pieces of clinical and non-clinical evidence including peer reviewed journals citing key scientific outcomes and physiological results in animals & humans that demonstrate how cannabis can ease opioid withdrawal symptoms, reduce opioid consumption, ameliorate opioid cravings, prevent opioid relapse, improve OUD treatment retention, and reduce overdose deaths.

2 EXECUTIVE SUMMARY

Delaware's approach to the opioid epidemic so far has focused on funding new treatment centers and subsidizing overdose medications. Funding new treatment centers doesn't break the cycle of addiction, and subsidizing overdose medications does nothing to deter users from using then abusing opioids in the first place.

Addiction isn't something you can attack with more pills or tougher enforcement. If we have learned anything from the failed war on drugs, we learned that wars cannot be fought against things, wars are fought against people. It is impossible to win a war on an idea without first educating the participants. To that end, the clinical and non-clinical evidence included in this petition has been organized into 4 sections. Each section provides supporting evidence to the extent that patients with Opioid Use Disorder can benefit from medical cannabis...

- 1) As a opioid replacement prior to opioid introduction in the treatment of chronic pain
- 2) As an adjunct therapy to medication assisted treatment in order to increase treatment success rates.
- 3) As an adjunct therapy that provides relief from withdrawal symptoms & cravings
- 4) As an opioid reduction strategy for patients already using opioids, as well as those suffering from Opioid Use Disorder

The argument in favor of recognizing medical cannabis as a substitute for opioids in the treatment of chronic pain is informed by science, common sense, and simple compassion: if patients never start using opioids, there is no risk their use might progress to dependence or overdose. Three states including New York, Pennsylvania and New Jersey have already added either Opiate Replacement or Opiate Use Disorder as qualifying condition for medical cannabis.

More clinical studies have been performed on cannabis than most legal medications approved by the FDA. A quick search for "marijuana" or "cannabinoids" in the PubMed database yields tens of thousands of studies. This research provides clear evidence of marijuana's minimal risks and versatile uses. By contrast, an analysis of 200 FDA-approved drugs showing that almost a third of those were passed based on a single study. Cannabis works as an alternative to these drugs because, unlike other commonly used drugs, cannabinoids are excreted at a low rate so even abrupt cessation of cannabis use is not associated with rapid declines in plasma that would precipitate severe or abrupt withdrawal symptoms. Studies have also shown cannabis can blunt cravings in individuals with opioid dependence following a period of abstinence. Cannabis' greatest potential to positively impact the opioid epidemic may be due to its promising role as a first line analgesic in lieu of or in addition to opioids.

In short, this growing body of research supports the medical use of cannabis for Opioid Use Disorder and creates an evidence-based rationale for governments, health care providers, and academic researchers to implement cannabis-based interventions as part of a new multi-dimensional approach to addressing in the opioid crisis. Like all consumers of health care, addicts would be better served by expanding treatment options available to them rather than forcing patients to use whichever program or prescription has the best reputation. Doing anything less would be a disservice to all Delawareans.

3 EXTENT TO WHICH THE CONDITION IS GENERALLY ACCEPTED AS A VALID, EXISTING DEBILITATING MEDICAL CONDITION

3.1 OPIOIDS

http://www.who.int/substance_abuse/information-sheet/en/

Opioids are substances derived from the opium poppy, or synthetic analogues with similar effects. Examples are morphine, heroin, tramadol, oxycodone and methadone. Opioids have the potential to cause substance dependence that is characterized by a strong desire to take opioids, impaired control over opioid use, persistent opioid use despite harmful consequences, a higher priority given to opioid use than to other activities and obligations, increased tolerance, and a physical withdrawal reaction when opioids are discontinued. Dependence on prescription opioids includes iatrogenic dependence following the treatment of chronic pain, and dependence following the diversion and theft of prescription opioids from patients, medical facilities, pharmacies and the manufacturing and distribution chains.

3.1.1 CDC GUIDELINES DO NOT RECOMMEND OPIOIDS FOR LONG TERM PAIN MGMT (2016)

The Center for Disease Control Guidelines for prescribing opioids for chronic pain states explicitly there is no evidence of long term use of opioids for Chronic Pain.

https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fmmwr%2Fvolumes%2F65%2Frr%2Frr6501e1er.htm

No evidence shows a long-term benefit of opioids in pain and function versus no opioids for chronic pain with outcomes examined at least 1 year later (with most placebo-controlled randomized trials ≤6 weeks in duration).

Extensive evidence shows the possible harms of opioids (including opioid use disorder, overdose, and motor vehicle injury).

Extensive evidence suggests some benefits of nonpharmacologic and nonopioid pharmacologic treatments compared with long-term opioid therapy, with less harm.

*Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. **Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient.** If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.*

3.2 WHAT IS OPIOID USE DISORDER?

https://en.wikipedia.org/wiki/Opioid_use_disorder

Opioid use disorder is a problematic pattern of opioid use that causes significant impairment or distress. Symptoms of the disorder include a strong desire to use opioids, increased tolerance to opioids, failure to fulfill obligations, trouble reducing use, and withdrawal syndrome with discontinuation. Opioid withdrawal symptoms may include nausea, muscle

aches, diarrhea, trouble sleeping, or a low mood. Addiction and dependence are components of a substance use disorder. Complications may include opioid overdose, suicide, HIV/AIDS, hepatitis C, marriage problems, or unemployment.

Opioids include substances such as heroin, morphine, fentanyl, codeine, oxycodone, and hydrocodone. In the United States, a majority of heroin users begin by using prescription opioids. These can be bought illegally or prescribed. Diagnosis may be based on criteria by the American Psychiatric Association in the DSM-5. If more than two of eleven criteria are present during a year the diagnosis is said to be present. Individuals with an opioid use disorders are often treated with opioid replacement therapy using methadone or buprenorphine.

In 2013, opioid use disorders affected about 0.4% of people.^[4] As of 2015, it was estimated that about 16 million people worldwide have been affected at one point in their lives.^[15] Onset is often in young adulthood.^[4] Males are affected more often than females. It resulted in 122,000 deaths worldwide in 2015, up from 18,000 deaths in 1990. In the United States during 2016, there were more than 42,000 deaths due to opioid overdose, of which more than 15,000 were the result of heroin use.^[17]

3.3 OPIOID OVERDOSES

http://www.who.int/substance_abuse/information-sheet/en/

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 pain¹. In the United States of America alone in 2016, there were an estimated 63 632 deaths due to drug overdose, which is a 21% increase from previous years. This was largely due to a rise in deaths associated with prescription opioids. This group of opioids (excluding methadone) was implicated in 19 413 deaths in the country, more than double the number in 2015.

3.3.1 RISK FACTORS FOR OPIOID OVERDOSE

People dependent on opioids are the group most likely to suffer an overdose. The incidence of fatal opioid overdose among opioid-dependent individuals is estimated at 0.65% per year. Non-fatal overdoses are several times more common than fatal opioid overdoses. About 45% of drug users experience nonfatal overdose and about 70% witness drug overdose (including fatal) during their lifetime.

Risk factors for overdoses with prescribed opioids include a history of substance use disorders, high prescribed dosage (over 100mg of morphine or equivalent daily), male gender, older age, multiple prescriptions including benzodiazepines, mental health conditions and lower socioeconomic status.

3.3.2 PEOPLE AT HIGHER RISK OF OPIOID OVERDOSE

- people with opioid dependence, in particular following reduced tolerance (following detoxification, release from incarceration, cessation of treatment);
- people who inject opioids;
- people who use prescription opioids, in particular those taking higher doses;
- people who use opioids in combination with other sedating substances;
- people who use opioids and have medical conditions such as HIV, liver or lung disease or suffer from depression;
- household members of people in possession of opioids (including prescription opioids).

3.3.3 PEOPLE LIKELY TO WITNESS AN OPIOID OVERDOSE

- people at risk of an opioid overdose, their friends and families;
- people whose work brings them into contact with people who overdose (health-care workers, police, emergency service workers, people providing accommodation to people who use drugs, peer education and outreach workers).

3.3.4 ADDITIONAL STATISTICS

- Roughly 21 to 29 percent of patients prescribed opioids for chronic pain misuse them.⁶
- Between 8 and 12 percent develop an opioid use disorder.
- An estimated 4 to 6 percent who misuse prescription opioids transition to [heroin](#).
- About 80 percent of people who use heroin first misused prescription opioids.
- Opioid overdoses increased 30 percent from July 2016 through September 2017 in 52 areas in 45 states.
- The Midwestern region saw opioid overdoses increase 70 percent from July 2016 through September 2017.
- Opioid overdoses in large cities increase by 54 percent in 16 states.¹

4 EXTENT TO WHICH THE CONDITION CAUSES SEVERE SUFFERING, OR OTHERWISE SEVERELY IMPAIRS THE PATIENT'S ABILITY TO CARRY ON ACTIVITIES OF DAILY LIVING

4.1 OPIATE OVERDOSE CRISIS IN AMERICA

<https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis>

Every day, more than 115 people in the United States die after overdosing on opioids.¹ The misuse of and addiction to opioids—including [prescription pain relievers](#), [heroin](#), and synthetic opioids such as [fentanyl](#)—is a serious national crisis that affects public health as well as social and economic welfare. The Centers for Disease Control and Prevention estimates that the total "economic burden" of prescription opioid misuse alone in the United States is \$78.5 billion a year, including the costs of healthcare, lost productivity, addiction treatment, and criminal justice involvement.²

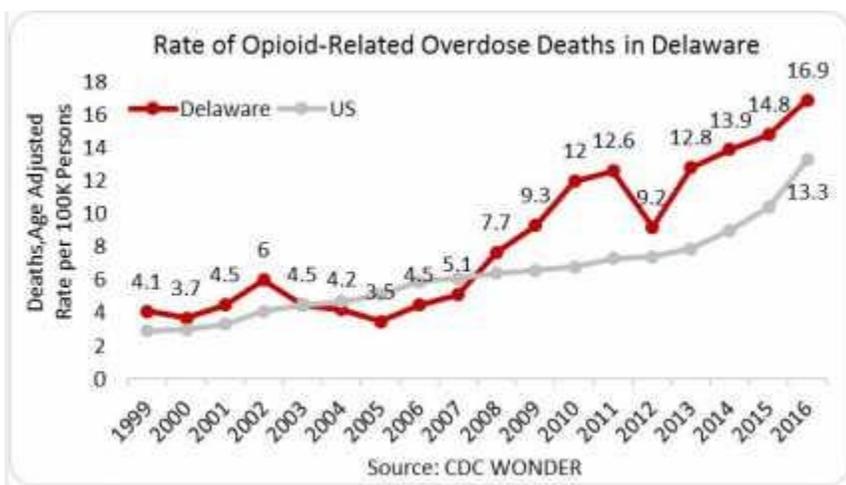
In the late 1990s, pharmaceutical companies reassured the medical community that patients would not become addicted to prescription opioid pain relievers, and healthcare providers began to prescribe them at greater rates. This subsequently led to widespread diversion and misuse of these medications before it became clear that these medications could indeed be highly addictive. Opioid overdose rates began to increase.

In 2015, more than 33,000 Americans died as a result of an opioid overdose, including prescription opioids, heroin, and illicitly manufactured fentanyl, a powerful synthetic opioid.¹ That same year, an estimated 2 million people in the United States suffered from substance use disorders related to prescription opioid pain relievers, and 591,000 suffered from a heroin use disorder (not mutually exclusive).

4.2 OPIOID-RELATED OVERDOSE DEATHS IN DELAWARE

<https://www.drugabuse.gov/drugs-abuse/opioids/opioid-summaries-by-state/delaware-opioid-summary>

In 2016, there were 154 opioid-related overdose deaths in Delaware—a rate of 16.9 deaths per 100,000 persons and more than the national rate of 13.3 deaths per 100,000 persons.



4.2.1 MONTHLY OVERDOSE DEATHS INCREASING IN DELAWARE (2018)

<https://why.org/articles/monthly-overdose-deaths-break-record-in-delaware/>

The opioid overdose epidemic is arguably the worst public health crisis in U.S. history. At the time of this publication, more people are dying than at the peak of the AIDS epidemic, and for the first time, drug overdoses outnumber automobile and handgun deaths.

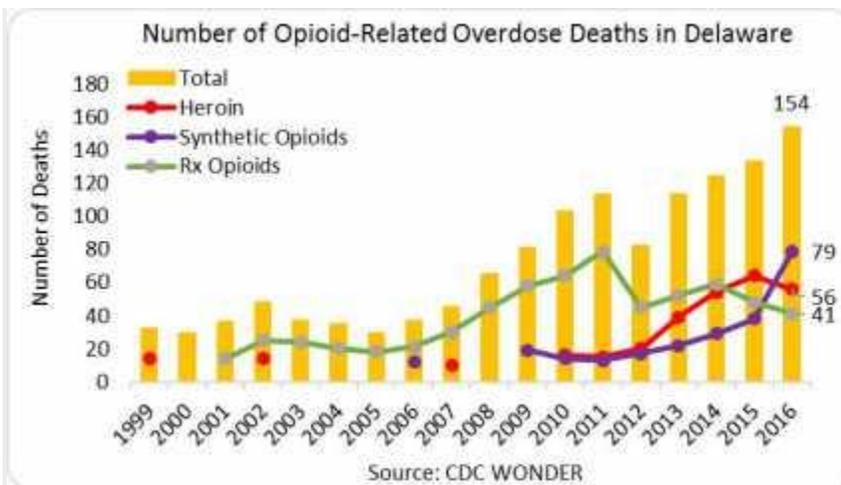
More people died in August of suspected drug overdoses in a single month than ever before in Delaware, according to the Department of Health and Social Services.

Last month, 39 fatal overdoses were reported, eclipsing the previous record of 27 that occurred in April.

Twenty-seven of the August deaths were in New Castle County, nine in Kent County and three in Sussex County.

4.3 OPIOID PAIN RELIEVER PRESCRIPTIONS

In 2015, providers in Delaware wrote 768,974 prescriptions for opioid pain relievers or 80 prescriptions for every 100 persons. This was a 7.1 percent decline since 2013—compared to the average U.S. rate of 71 opioid prescriptions per 100 persons.



4.4 NEONATAL ABSTINENCE SYNDROME (NAS)

This issue has become a public health crisis with devastating consequences including increases in opioid misuse and related overdoses, as well as the rising incidence of neonatal abstinence syndrome due to opioid use and misuse during pregnancy.

According to hospital discharge data, during 2010 to 2013 in Delaware, 639 cases of NAS were identified with an incidence of 15.6 cases per 1,000 births. The incidence of NAS increased 56 percent, from 11.9 cases per 1,000 births in 2010 to 18.5 cases per 1,000 births in 2013. Delaware's 2012 and 2013 NAS rates (17.8 and 18.5 cases per 1,000 births, respectively) were 3 times that of the 2012 average U.S. rate (5.8 cases per 1,000 births).

4.5 HIV PREVALENCE AND HIV DIAGNOSES ATTRIBUTED TO INJECTION DRUG USE (IDU)

The increase in injection drug use has also contributed to the spread of infectious diseases including HIV and hepatitis C.

- **U.S. Incidence:** In 2015, 9.1 percent (3,594) of the 39,513 new diagnoses of HIV in the United States were attributed to IDU. Among new cases, 8.2 percent (2,614) of cases among men and 13.2 percent (980) of cases among women were transmitted via IDU ([CDC](#)).
- **U.S. Prevalence:** In 2014, 955,081 Americans were living with a diagnosed HIV infection—a rate of 299.5 per 100,000 persons. Of these, 18.1 percent (131,056) of males and 22.6 percent (52,013) of females were living with HIV attributed to IDU ([CDC](#)).
- **State Incidence:** Of the new HIV cases in 2015, 109 occurred in Delaware, with 4.7 percent¹ of new cases in males and 8.7 percent of new cases in females attributed to IDU.
- **State Prevalence:** In 2014, an estimated 3,213 persons were living with a diagnosed HIV infection in Delaware—a rate of 407 per 100,000 persons. Of these, 25.7 percent¹ of males and 26.3 percent of females were living with HIV attributed to IDU.
- Hepatitis C (HCV) Prevalence and HCV Diagnoses Attributed to Injection Drug Use
- **U.S. Incidence:** In 2015, there were 181,871 reported cases of chronic HCV and 33,900 estimated cases of acute HCV² ([CDC](#)). Where data were available, 64.2 percent of acute cases reported IDU ([CDC](#)).
- **U.S. Prevalence:** An estimated 3.5 million Americans are living with HCV, including approximately 2.7 million living with chronic infections ([CDC](#)).
- **State Incidence:** In 2015, Delaware reported 31 cases of chronic HCV and 4 cases of acute HCV (0.4 per 100,000 persons) ([CDC](#)).
- **State Prevalence:** Current state prevalence data are not available. As of 2010, an estimated 13,600 (1,970 per 100,000) persons were living with HCV in Delaware.

5 THE EXTENT THAT CONVENTIONAL TREATMENTS CAUSE OR ADD TO THE SUFFERING OF THOSE AFFLICTED WITH OPIOID USE DISORDER

One of the biggest challenges in Medication Assisted treatment is the abuse of medications prescribed to treat cravings. Some users face such intense cravings that they begin to abuse the treatment medication itself, which defeats the purpose of the pharmacotherapy.

5.1 METHADONE

<https://www.northpointrecovery.com/blog/methadone-scary-truth/>

Since 1947, methadone has been approved for use in the United States as treatment for opioid addiction. Methadone is the most commonly-prescribed first-line treatment for OAT, and maintenance clinics around the country dispense dosages to many thousands of suffering and opioid addicts, giving them a fighting chance to recover.

But as important a medication as methadone is, it is not without its problems:

5.1.1 METHADONE POISONING

Even though methadone is dispensed as a way to reduce harm associated with addiction to other opioids, it is itself a highly-addictive and powerful opioid –*up to five times stronger than morphine*.

- In 2011, **4418** people died in the United States because of methadone poisoning.
- That number represents **26%** of ALL opioid poisoning deaths.
- In 1999, the number of methadone deaths was **only 790**.
- In 2006, the FDA released a caution about the medication, saying, “*Methadone use for pain control may result in death*”.

5.1.2 METHADONE’S NEGATIVE SIDE EFFECTS

As with any medication, the positives of methadone – *harm reduction* – must be weighed against the negatives:

- Methadone has a high potential for abuse. This is why OAT dosages are so highly regulated and dispensed by clinics.
- It is possible to become dependent upon and addicted to methadone.
- Methadone is dispensed over the long-term. It is not unusual for a person to be on a methadone maintenance plan for over a year, and some individuals must take methadone for an even longer, indefinite period.
- A person can take methadone and still continue to use illicit opioids.
- While structure IS important to addicts, the rigid protocol of some methadone clinics can cause patients to feel that they have no control over their own lives and no input about their own treatment.
- Methadone will show up on employment drug screens, making it difficult for methadone patients to get or keep a job.
- Having to travel to the methadone clinic every day can be problematic for those patients who either have jobs or do not have a car.
- Require daily attendance at the methadone clinic can prohibit overnight travel.
- The clinical environment can result in lowered self-esteem.

- Methadone can interact dangerously with several other medications, particularly with benzodiazepines such as Klonopin, Xanax, or Valium.
- Drinking alcohol after taking methadone can be potentially fatal.
- Menstrual Problems
- Decreased Libido/Impotence/Difficulty in Achieving Orgasm

For many people, the adverse side effects of methadone can be unpleasant enough to spur them into discontinuing the maintenance program:

- Breathing Difficulties
- Low Blood Pressure
- Chest Pain
- Constipation/Urinary Problems
- Nausea/Vomiting/Diarrhea/Stomach Pains
- Profuse Sweating/Intolerance to Heat
- Red, Flushed Appearance
- Weakness/Dizziness/Fainting
- Exhaustion/Chronic Fatigue
- Sleep disturbances – Extreme Insomnia or Difficulty Staying Asleep
- Headache/Confusion
- Swelling of the Extremities
- Mood Swings – Anxiety, Agitation, Disorientation
- Blurred Vision
- Loss of Appetite/Anorexia
- Itching/Skin Rash

5.2 SUBOXONE

<https://www.linkedin.com/pulse/truth-suboxone-detox-drug-your-next-addiction-fried-cap-icadc-chc>

Suboxone is classified as a semi-synthetic opioid and largely used to reduce the painful and difficult withdrawal symptoms associated with heroin and other opiate dependence. In a monitored, medical detox setting, Suboxone is often prescribed as a taper which brings an individual through heroin or opiate withdrawal in a much more comfortable way than “cold turkey.”

Suboxone is just the brand name. The active ingredient in the drug is buprenorphine, which is also found in Subutex, Norspan, Zubslov, Butrans, and Buprenex. Although Suboxone can be a welcome relief to individuals who desire to quit using drugs such as heroin, morphine, and prescription painkillers, much controversy surrounds the drug due to its use in lengthy (and even life-long) maintenance programs keeping patients using the drug far longer than medically necessary.

5.2.1 HIGH RISK FOR ADDICTION

<https://drugabuse.com/library/the-effects-of-suboxone-use/>

Because Suboxone contains an opioid, it can lead to dependence. This means your body has come to depend on it to feel well and you will feel uncomfortable when you stop using it.

One of the key signs of Suboxone dependence is that you start to suffer from withdrawal after ceasing use of the drug. Because it is a long-acting opioid, early withdrawal might not begin until up to 36 hours from the last use.⁹

Withdrawal symptoms can mimic the flu, but they can last for more than a week. It is a sign that the opioid and its ultimately toxic influences are finally relinquishing their grip on a wide range of the body's systems and functioning.

Suboxone dependence often requires a medically monitored detox period to keep the user comfortable and help protect them from relapsing to alleviate their

Although some say the euphoric effects pale in comparison to other drugs, it is still classified as an opiate, with a high potential for physical dependency if consumed on a regular basis for an extended period of time.

Because the opioid receptors of the brain are used to binding with a chemical that tells them when to release dopamine, withdrawal begins when this chemical is absent. This is true for any opiate. Suboxone Maintenance

Suboxone maintenance can be a threat to recovery. Much like the methadone maintenance programs, Suboxone is becoming increasingly used by many doctors. The rationale behind this may be that it is safer to be taking prescribed Suboxone on a daily basis than it is to be out scoring harder drugs. But in reality, it is trading one bandage for another and the user is still dependent on a substance to make it through the day.

A New York Times investigation into Suboxone found that its manufacturer, Reckitt Benckiser, has employed aggressive tactics to locate physicians interested in rolling the painkiller market over into Suboxone-lifers. And, they push any studies that support the concept of maintenance and ignore those that support short-term use. I know this might seem crazy to anyone in the recovery community, but much of the general medical population still believes that an individual with a history of painkiller abuse can never be drug-free. I have had doctors tell em that opioid users have zero chance of success without a maintenance program. This flies in the face of the science and data collected over many decades.

5.3 NALOXONE

<https://www.ncbi.nlm.nih.gov/pubmed/17367258>

Naloxone is a non-selective, short-acting opioid receptor antagonist that has a long clinical history of successful use and is presently considered a safe drug over a wide dose range (up to 10 mg). In opioid-dependent patients, naloxone is used in the treatment of opioid-overdose-induced respiratory depression, in (ultra)rapid detoxification and in combination with buprenorphine for maintenance therapy (to prevent intravenous abuse).

5.3.1 HEALTH RISKS

Risks related to naloxone use in opioid-dependent patients are: i) the induction of an acute withdrawal syndrome (the occurrence of vomiting and aspiration is potentially life threatening); ii) the effect of naloxone may wear off prematurely when used for treatment of opioid-induced respiratory depression; and iii) in patients treated for severe pain with an opioid, high-dose naloxone and/or rapidly infused naloxone may cause catecholamine release and consequently

pulmonary edema and cardiac arrhythmias. These risks warrant the cautious use of naloxone and adequate monitoring of the cardiorespiratory status of the patient after naloxone administration where indicated.

5.3.2 SKYROCKETING COST

<https://www.businessinsider.com/price-of-naloxone-narcan-skyrocketing-2016-7>

All five pharmaceutical companies that produce naloxone have seen price hikes in recent years or, for the newer entrants such as Adapt, priced their product far above the industry average several years ago.

Frequently referred to as an "antidote" for opioid overdoses, naloxone has seen drastic price increases in recent years, according to information provided by [Truven Health Analytics](#), a healthcare-analytics company. A popular injectable version of the drug has gone from \$0.92 a dose to more than \$15 a dose over the last decade. An auto-injector version is up to more than \$2,000 a dose.

"We're not talking about a limited commodity. Naloxone is a medicine that is almost as cheap as sterile sodium chloride — salt water," Dan Bigg, the executive director of the Chicago Recovery Alliance, an outreach organization that has been providing naloxone to drug users for nearly 20 years, told Business Insider.

"At the same time this epidemic is killing tens of thousands of Americans a year, we're seeing the price of naloxone go up by 1000% or more," McCaskill wrote. "Maybe there's a great reason for the price increases, but given the heart-breaking gravity of this epidemic and the need for this drug, I think we have to demand some answers."

6 THE EXTENT TO WHICH CANNABIS CAN BE REPLACE OPIOIDS IN THE TREATMENT OF CHRONIC PAIN

6.1 DRUG DERIVED FROM MARIJUANA HAS TRIGGERED THE FIRST FEDERAL SHIFT ON CANNABIS IN HALF A CENTURY, AND EXPERTS PREDICT AN AVALANCHE EFFECT (2018)

<https://www.businessinsider.com/marijuana-epilepsy-drug-approved-dea-cbd-2018-9>

This is the first time in 46 years that the Drug Enforcement Administration has shifted its stance on cannabis.

When the FDA approved Epidiolex in June, it triggered a 90-day countdown clock for the DEA to change its stance on marijuana.

"We don't have a choice on that," the DEA's public-affairs officer, Barbara Carreno, told Business Insider just after Epidiolex's approval. CBD, she said, "absolutely has to become [Schedule 2, 3, 4, or 5](#)."

That's not exactly what happened. Instead of rescheduling CBD, the agency chose to reschedule drugs containing CBD that the FDA has already approved; those drugs will now be classified as Schedule 5. But at the moment, the only drug that fits the description is Epidiolex.

6.2 AN UPDATE ON SAFETY AND SIDE EFFECTS OF CANNABIDIOL: A REVIEW OF CLINICAL DATA AND RELEVANT ANIMAL STUDIES. (2017)

<https://www.liebertpub.com/doi/10.1089/can.2016.0034>

Results: *In general, the often described favorable safety profile of CBD in humans was confirmed and extended by the reviewed research. The majority of studies were performed for treatment of epilepsy and psychotic disorders. Here, the most commonly reported side effects were tiredness, diarrhea, and changes of appetite/weight. In comparison with other drugs, used for the treatment of these medical conditions, CBD has a better side effect profile. This could improve patients' compliance and adherence to treatment. CBD is often used as adjunct therapy. Therefore, more clinical research is warranted on CBD action on hepatic enzymes, drug transporters, and interactions with other drugs and to see if this mainly leads to positive or negative effects, for example, reducing the needed clobazam doses in epilepsy and therefore clobazam's side effects.*

6.3 MEDICAL CANNABIS AND MENTAL HEALTH: A GUIDED SYSTEMATIC REVIEW (2017)

<https://www.ncbi.nlm.nih.gov/pubmed/27816801>

This review considers the potential influences of the use of cannabis for therapeutic purposes (CTP) on areas of interest to mental health professionals, with foci on adult psychopathology and assessment. We identified 31 articles relating to the use of CTP and mental health, and 29 review articles on cannabis use and mental health that did not focus on use for therapeutic purposes. Results reflect the prominence of mental health conditions among the reasons for CTP use, and the relative dearth of high-quality evidence related to CTP in this context, thereby highlighting the need for further research into the harms and benefits of medical cannabis relative to other therapeutic options. Preliminary evidence suggests that CTP may have potential for the treatment of PTSD, and as a substitute for problematic use of other substances. Extrapolation from reviews of non-therapeutic cannabis use suggests that the use of CTP may be problematic among individuals with psychotic disorders. The clinical implications of CTP use among individuals with mood disorders are unclear. With regard to assessment, evidence suggests that CTP use does not increase risk of harm to self or others.

6.4 CANNABIS AS A SUBSTITUTE FOR OPIOID-BASED PAIN MEDICATION (2017)

<https://www.liebertpub.com/doi/10.1089/can.2017.0012>

Ninety-seven percent of the samples “strongly agreed/agreed” that they are able to decrease the amount of opiates they consume when they also use cannabis, and 81% “strongly agreed/agreed” that taking cannabis by itself was more effective at treating their condition than taking cannabis with opioids. Results were similar for those using cannabis with nonopioid-based pain medications.

Discussion: Thirty-four percent of the sample reported using opioid-based pain medication in the past 6 months. Respondents overwhelmingly reported that cannabis provided relief on par with their other medications, but without the unwanted side effects. Ninety-seven percent of the samples “strongly agreed/agreed” that they are able to decrease the amount of opiates they consume when they also use cannabis, and 81% “strongly agreed/agreed” that taking cannabis by itself was more effective at treating their condition than taking cannabis with opioids. Results were similar for those using cannabis with nonopioid-based pain medications.

Conclusion: Future research should track clinical outcomes where cannabis is offered as a viable substitute for pain treatment and examine the outcomes of using cannabis as a medication assisted treatment for opioid dependence.

6.5 SUBSTITUTING CANNABIS FOR PRESCRIPTION DRUGS, ALCOHOL AND OTHER SUBSTANCES AMONG MEDICAL CANNABIS PATIENTS: THE IMPACT OF CONTEXTUAL FACTORS (2016)

<https://www.ncbi.nlm.nih.gov/pubmed/26364922>

The medical use of cannabis may play a harm reduction role in the context of use of these substances, and may have implications for abstinence-based substance use treatment approaches.

Results

Substituting cannabis for one or more of alcohol, illicit drugs or prescription drugs was reported by 87% (n = 410) of respondents, with 80.3% reporting substitution for prescription drugs, 51.7% for alcohol, and 32.6% for illicit substances. Respondents who reported substituting cannabis for prescription drugs were more likely to report difficulty affording sufficient quantities of cannabis, and patients under 40 years of age were more likely to substitute cannabis for all three classes of substance than older patients.

Discussion and Conclusions

The finding that cannabis was substituted for all three classes of substances suggests that the medical use of cannabis may play a harm reduction role in the context of use of these substances, and may have implications for abstinence-based substance use treatment approaches. Further research should seek to differentiate between biomedical substitution for prescription pharmaceuticals and psychoactive drug substitution, and to elucidate the mechanisms behind both.

6.6 CDC GUIDELINES DO NOT RECOMMEND PRESCRIBING OPIOIDS FOR CHRONIC PAIN (2016)

https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fmmwr%2Fvolumes%2F65%2Frr%2Frr6501e1er.htm

The Center for Disease Control Guidelines for prescribing opioids for chronic pain states explicitly there is no evidence of long term use of opioids for Chronic Pain.

No evidence shows a long-term benefit of opioids in pain and function versus no opioids for chronic pain with outcomes examined at least 1 year later (with most placebo-controlled randomized trials ≤ 6 weeks in duration).

Extensive evidence shows the possible harms of opioids (including opioid use disorder, overdose, and motor vehicle injury).

Extensive evidence suggests some benefits of nonpharmacologic and nonopioid pharmacologic treatments compared with long-term opioid therapy, with less harm.

Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be

combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.

6.7 MEDICAL MARIJUANA AND CHRONIC PAIN: A REVIEW OF BASIC SCIENCE AND CLINICAL EVIDENCE (2015)

<https://www.ncbi.nlm.nih.gov/pubmed/26325482>

Evidence to support the use of cannabinoids for some cancer, neuropathic, spasticity, acute pain, and chronic pain conditions.

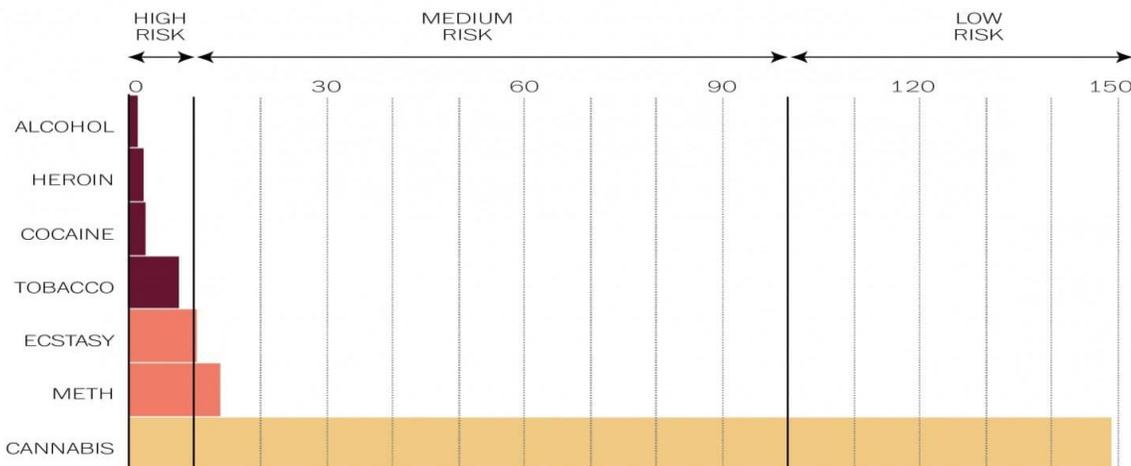
Cannabinoid compounds include phytocannabinoids, endocannabinoids, and synthetics. The two primary phytocannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), with CB1 receptors in the brain and peripheral tissue and CB2 receptors in the immune and hematopoietic systems. The route of delivery of cannabis is important as the bioavailability and metabolism are very different for smoking versus oral/sublingual routes. Gold standard clinical trials are limited; however, some studies have thus far shown evidence to support the use of cannabinoids for some cancer, neuropathic, spasticity, acute pain, and chronic pain conditions.

6.8 CANNABIS IS THE LEAST RISKY RECREATIONAL DRUG (2015)

https://www.washingtonpost.com/news/wonk/wp/2015/02/23/marijuana-may-be-even-safer-than-previously-thought-researchers-say/?noredirect=on&utm_term=.f7f8662547ff

By a wide margin, cannabis is the least risky recreational drug

Ratio between toxic dose and typical human intake



WASHINGTONPOST.COM/WONKBLOG

Source: "Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach"

6.9 CANNABIS FOR THE MANAGEMENT OF PAIN: ASSESSMENT OF SAFETY STUDY (2015)

[https://www.jpain.org/article/S1526-5900\(15\)00837-8/fulltext](https://www.jpain.org/article/S1526-5900(15)00837-8/fulltext)

Cannabis can be effective as part of a carefully monitored pain management program when conventional treatments have been considered medically inappropriate or inadequate.

To our knowledge, this is the first cohort study of the long-term safety of medical cannabis use ever conducted...

We found no impact of medical cannabis use on measures of hematological, biochemical, liver, renal, and endocrine function among 78 patients followed over 1 year.

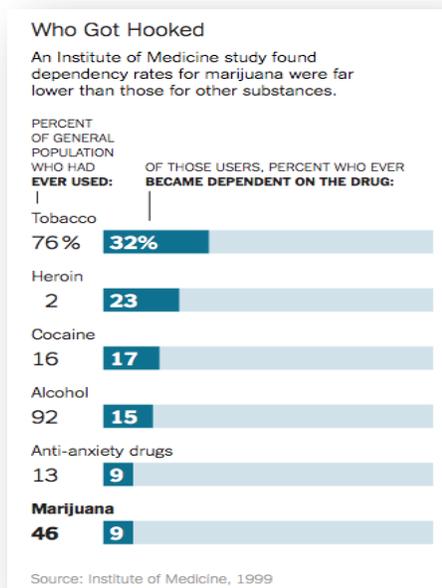
With respect to secondary efficacy measures, we noted significant improvements in pain intensity and the physical dimension of quality of life over 1 year among the cannabis users compared with controls; there was also significant improvement among cannabis users in measures of the sensory component of pain, symptom distress, and total mood disturbance compared with controls. These findings, although not the primary outcomes of the study, are nevertheless important in considering the overall risk-benefit ratio of medical use of cannabis.

Despite these limitations, this study improves our knowledge about the safety of medical cannabis. Caution should be exercised in interpreting these results for all medical cannabis use as patients in this study used a standardized, quality-controlled herbal cannabis product with a reliable THC potency of 12.5%.

In conclusion, this study suggests that the AEs of medical cannabis are modest and comparable quantitatively and qualitatively with prescription cannabinoids. The results suggest that cannabis at average doses of 2.5 g/d in current cannabis users may be safe as part of a carefully monitored pain management program when conventional treatments have been considered medically inappropriate or inadequate.

6.10 MARIJUANA IS THE LEAST ADDICTIVE DRUG (2014)

<https://www.nytimes.com/2014/07/31/opinion/what-science-says-about-marijuana.html>



6.11 ZERO PEOPLE HAVE FATALLY OVERDOSED ON MARIJUANA (2014)

http://www.huffingtonpost.com/entry/marijuana-deaths-2014_us_56816417e4b06fa68880a217

The rate of absolutely zero deaths from a marijuana overdose remained steady from last year, according to figures released this month by the Centers for Disease Control. But while Americans aren't dying as a result of marijuana overdoses, the same can't be said for a range of other substances, both legal and illicit.

6.12 THE MEDICINAL USE OF CANNABIS AND CANNABINOIDS—AN INTERNATIONAL CROSS-SECTIONAL SURVEY ON ADMINISTRATION FORMS. (2013)

<https://www.ncbi.nlm.nih.gov/pubmed/24175484>

Cannabinoids, including tetrahydrocannabinol and Cannabidiol, are the most important active constituents of the cannabis plant. Over recent years, cannabinoid-based medicines (CBMs) have become increasingly available to patients in many countries, both as pharmaceutical products and as herbal cannabis (marijuana). While there seems to be a demand for multiple cannabinoid-based therapeutic products, specifically for symptomatic amelioration in chronic diseases, therapeutic effects of different CBMs have only been directly compared in a few clinical studies. The survey presented here was performed by the International Association for Cannabinoid Medicines (IACM), and is meant to contribute to the understanding of cannabinoid-based medicine by asking patients who used cannabis or cannabinoids detailed questions about their experiences with different methods of intake. The survey was completed

by 953 participants from 31 countries, making this the largest international survey on a wide variety of users of cannabinoid-based medicine performed so far.

6.13 CANNABIS AS A SUBSTITUTE FOR ALCOHOL AND OTHER DRUGS: A DISPENSARY-BASED SURVEY OF SUBSTITUTION EFFECT IN CANADIAN MEDICAL CANNABIS PATIENTS. (2013)

<https://www.tandfonline.com/doi/full/10.3109/16066359.2012.733465>

Cannabis substitution for problematic substance use is justified by clinical and nonclinical evidence.

Results: Over 41% state that they use cannabis as a substitute for alcohol (n = 158), 36.1% use cannabis as a substitute for illicit substances (n = 137), and 67.8% use cannabis as a substitute for prescription drugs (n = 259). The three main reasons cited for cannabis-related substitution are “less withdrawal” (67.7%), “fewer side-effects” (60.4%), and “better symptom management” suggesting that many patients may have already identified cannabis as an effective and potentially safer adjunct or alternative to their prescription drug regimen.

Discussion: With 75.5% (n = 305) of respondents citing that they substitute cannabis for at least one other substance, and in consideration of the growing number of studies with similar findings and the credible biological mechanisms behind these results, randomized clinical trials on cannabis substitution for problematic substance use appear justified.

6.14 SMOKED CANNABIS FOR CHRONIC NEUROPATHIC PAIN: A RANDOMIZED CONTROLLED TRIAL (2010)

<http://www.cmaj.ca/content/182/14/E694>

Cannabis sativa has been used to treat pain since the third millennium BC. 5 An endogenous pain-processing system has been identified, mediated by endogenous cannabinoid ligands acting on specific cannabinoid receptors. 6 These findings, coupled with anecdotal evidence of the analgesic effects of smoked cannabis, 7 support a reconsideration of cannabinoid agents as analgesics.

Results: We recruited 23 participants (mean age 45.4 [standard deviation 12.3] years, 12 women [52%]), of whom 21 completed the trial. The average daily pain intensity, measured on the 11-point numeric rating scale, was lower on the prespecified primary contrast of 9.4% v. 0% tetrahydrocannabinol (5.4 v. 6.1, respectively; difference = 0.7, 95% confidence interval [CI] 0.02–1.4). Preparations with intermediate potency yielded intermediate but nonsignificant degrees of relief. Participants receiving 9.4% tetrahydrocannabinol reported improved ability to fall asleep (easier, p = 0.001; faster, p < 0.001; more drowsy, p = 0.003) and improved quality of sleep (less wakefulness, p = 0.01) relative to 0% tetrahydrocannabinol. We found no differences in mood or quality of life. The most common drug-related adverse events during the period

when participants received 9.4% tetrahydrocannabinol were headache, dry eyes, burning sensation in areas of neuropathic pain, dizziness, numbness and cough.

Conclusion: A single inhalation of 25 mg of 9.4% tetrahydrocannabinol herbal cannabis three times daily for five days reduced the intensity of pain, improved sleep and was well tolerated. Further long-term safety and efficacy studies are indicated. (International Standard Randomized Controlled Trial Register no. ISRCTN68314063)

Chronic neuropathic pain has a prevalence of 1%–2%, 1 and treatment options are limited. 2 Pharmacotherapy includes anticonvulsants, antidepressants, opioids and local anesthetics, 3, 4 but responses vary and side effects limit compliance.

Cannabis sativa has been used to treat pain since the third millennium BC. 5 An endogenous pain-processing system has been identified, mediated by endogenous cannabinoid ligands acting on specific cannabinoid receptors. 6 These findings, coupled with anecdotal evidence of the analgesic effects of smoked cannabis, 7 support a reconsideration of cannabinoid agents as analgesics.

Oral cannabinoids such as tetrahydrocannabinol, cannabidiol and nabilone have, alone and in combination, shown efficacy in central 8,9 and peripheral 10 neuropathic pain, rheumatoid arthritis 11 and fibromyalgia. 12

6.15 MARIJUANA USE AND THE RISK OF LUNG AND UPPER DIGESTIVE TRACT CANCERS: RESULTS OF A POPULATION-BASED CASE—CONTROL STUDY. (2006)

<http://cebp.aacrjournals.org/content/15/10/1829>

A major limitation of previous studies was the relative lack of subjects with use >10 joint-years, which limited their power to detect effects. In contrast, we had ample numbers of such users for oral and lung cancers. Nonetheless, and contrary to our expectations, we found no positive associations between marijuana use and lung or UAT cancers. Although we observed positive dose-response relations of marijuana use to oral and laryngeal cancers in the crude analyses, the trend was no longer observed when adjusting for potential confounders, especially cigarette smoking. In fact, we observed ORs <1 for all cancers except for oral cancer, and a consistent monotonic association was not apparent for any outcome. Similar findings were found when the analyses were restricted to subjects who never smoked cigarettes. The 95% confidence intervals for the adjusted ORs did not extend far above 1 (e.g., were under 2 for marijuana and lung cancer), which suggests that associations of marijuana use with the study cancers are not strong and may be below detectable limits for this type of study.

Despite several lines of evidence suggesting the biological plausibility of marijuana use being carcinogenic ([1](#)), it is possible that marijuana use does not increase cancer risk, as suggested in the recent commentary by Melamede ([26](#)). Although the adjusted ORs <1 may be chance findings, they were observed for all non-reference exposure categories with all outcomes except oral cancer. Although purely speculative, it is possible that such inverse associations may reflect a protective effect of marijuana. There is recent evidence from cell culture systems and animal models that 9-tetrahydrocannabinol, the principal psychoactive ingredient in marijuana, and other cannabinoids may inhibit the growth of some tumors by modulating key signaling pathways leading to growth arrest and cell death, as well as by inhibiting tumor angiogenesis ([27-29](#)). These antitumoral associations have been observed for several types of malignancies including brain, prostate, thyroid, lung, and breast.

7 THE EXTENT THAT CANNABIS CAN BE EFFECTIVE AS AN OPIOID REDUCTION STRATEGY FOR THOSE PATIENTS ALREADY USING OPIOIDS

7.1 EMERGING EVIDENCE FOR CANNABIS' ROLE IN OPIOID USE DISORDER (2018)

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6135562/#B167>

Many of the barriers that prevent people from accessing traditional OUD treatment do not apply to cannabis therapy, and access to cannabis medicine is rapidly growing as more U.S. states roll back prohibition.

Patients, healthcare providers, and regulating bodies would all greatly benefit from additional evidence that fills in massive gaps in the knowledge base about the utility of cannabis for OUD treatment: dosing, cannabinoid content and ratios, bioavailability, contraindications, misuse liability, route of administration, and many other questions remain. Even the clinical work that has been conducted thus far may have little validity in the modern landscape of legalized cannabis; all federally-funded cannabis research in the United States is conducted using a single source of cannabis (NIDA drug supply), which is notoriously low in potency and quality, and does not resemble the staggering phytochemical variability in whole-plant cannabis products in regulated state markets.³⁶ These barriers to research funding and access to “real world” cannabis for clinical research directly contribute to our inability to address the opioid epidemic with what appears to be a safe and efficacious tool.

7.2 RATIONALE FOR CANNABIS-BASED INTERVENTIONS FOR THE OPIOID EPIDEMIC (2017)

The following was published in the Harm Reduction Journal in 2017.

<https://harmreductionjournal.biomedcentral.com/articles/10.1186/s12954-017-0183-9>

*This paper presents an evidence-based rationale for cannabis-based interventions in the opioid overdose crisis informed by research on **substitution effect**, proposing three important windows of opportunity for cannabis for therapeutic purposes (CTP) to play a role in reducing opioid use and interrupting the cycle towards opioid use disorder:*

- 1) prior to opioid introduction in the treatment of chronic pain;*
 - 2) As an opioid reduction strategy for those patients already using opioids; and*
 - 3) As an adjunct therapy to methadone or Suboxone treatment in order to increase treatment success rates.*
-

There is a growing amount of evidence that increasing adult access to both medical and recreational cannabis has significant positive impacts on public health and safety, largely as a result of substitution effect.

Epidemiological research has found that medical cannabis programs are associated with a reduction in the use of opioids and associated morbidity and mortality. Bachhuber et al. [8] report that U.S. states with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate compared to states without medical cannabis laws, and a 2016 study found that the number of Medicare prescriptions to seniors in medical cannabis states dropped for drugs that treat pain, depression, anxiety, nausea, psychoses, seizures and sleep disorders [9]. For pain, the annual number of annual doses prescribed per physician fell by 1826 doses. More recently, a retrospective survey of Michigan patients concluded that medical cannabis use was associated with a 64% decrease in opioid use (n = 118), decreased side effects of medications, and an improved quality of life [10], and a large survey of 2897 medical cannabis patients in California found that 30% of the sample (n = 841) reported using opioid-based pain medications, 97% of which “strongly agreed/agreed” that they were able to decrease their opioid use when using medical cannabis [11].

7.3 LEGALIZED MEDICAL CANNABIS LOWERS OPIOID USE (2018)

<https://www.sciencedaily.com/releases/2018/04/180402202236.htm>

In states with medical cannabis dispensaries, the researchers observed a 14.4 percent reduction in use of prescription opioids and nearly a 7 percent reduction in opiate prescriptions filled in states with home-cultivation-only medical cannabis laws...Our findings suggest quite clearly that medical cannabis could be one useful tool in the policy arsenal that can be used to diminish the harm of prescription opioids, and that's worthy of serious consideration," David Bradford said.

7.4 MEDICAL MARIJUANA CUTS USE OF PRESCRIPTION DRUGS (2018)

<https://drugabuse.com/study-medical-marijuana-cuts-use-of-prescription-drugs/>

The study was conducted at Depaul and Rush universities and consisted of thirty participants at an average age of 45 years old. At the conclusion of the study, participants said marijuana worked faster to relieve their pain than other prescription medication and had fewer side effects.

7.5 STATES WITH MEDICAL MARIJUANA LAWS HAD ABOUT 6 PERCENT FEWER OPIOID PRESCRIPTIONS AMONG MEDICAID PATIENTS COMPARED WITH STATES WITHOUT SUCH LAWS (2018)

<https://www.nbcnews.com/storyline/legal-pot/amid-opioid-crisis-researchers-aim-put-medical-marijuana-test-n904276>

Some research has been encouraging. In one of two five-year studies published in April in the Journal of the American Medical Association's [JAMA Internal Medicine](#), researchers found that states with medical marijuana laws had about 6 percent fewer opioid prescriptions among Medicaid patients compared with states without such laws. The second study, which looked at Medicare Part D patients, found a drop of 8.5 percent in such prescriptions in the medical marijuana states.

7.6 RATIONALE FOR CANNABIS-BASED INTERVENTIONS IN THE OPIOID OVERDOSE CRISIS (2017)

<https://harmreductionjournal.biomedcentral.com/articles/10.1186/s12954-017-0183-9>

Additionally, cannabis that is high in cannabidiol (CBD) and low in tetrahydrocannabinol (THC) may reduce potential harms to vulnerable populations. CBD is a relatively safe, non-impairing cannabinoid that has been shown to have many therapeutic effects relevant to the opioid crisis, including the reduction of heroin-seeking behavior in mice [39], and positive effects on mental health conditions like anxiety, depression, psychosis and bi-polar disorder [37, 40]

In other words, the existence of vulnerable populations should not result in abandoning or otherwise withholding this treatment option from others who might benefit from CTP, particularly in the treatment of chronic pain.

7.7 CANNABIS AS A SUBSTITUTE FOR OPIOID-BASED PAIN MEDICATION (2017)

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5569620/>

Thirty-four percent of the sample reported using opioid-based pain medication in the past 6 months. Respondents overwhelmingly reported that cannabis provided relief on par with their other medications, but without the unwanted side effects. Ninety-seven percent of the samples “strongly agreed/agreed” that they are able to decrease the amount of opiates they consume when they also use cannabis, and 81% “strongly agreed/agreed” that taking cannabis by itself was more effective at treating their condition than taking cannabis with opioids. Results were similar for those using cannabis with nonopioid-based pain medications.

7.8 MARIJUANA ADDICTION TREATMENT FOR OPIOID DEPENDENCY (2016)

<https://www.inquisitr.com/3773040/marijuana-addiction-treatment-for-opioid-dependency/>

Marijuana addiction treatment for opioid dependency is prescribed to combat withdrawal symptoms and other physical issues that reduce a patient's quality of life. Chronic pain, nausea,

tremors, and anxiety have all been treated successfully in a clear majority of patients with medicinal marijuana. The treatment is not new.

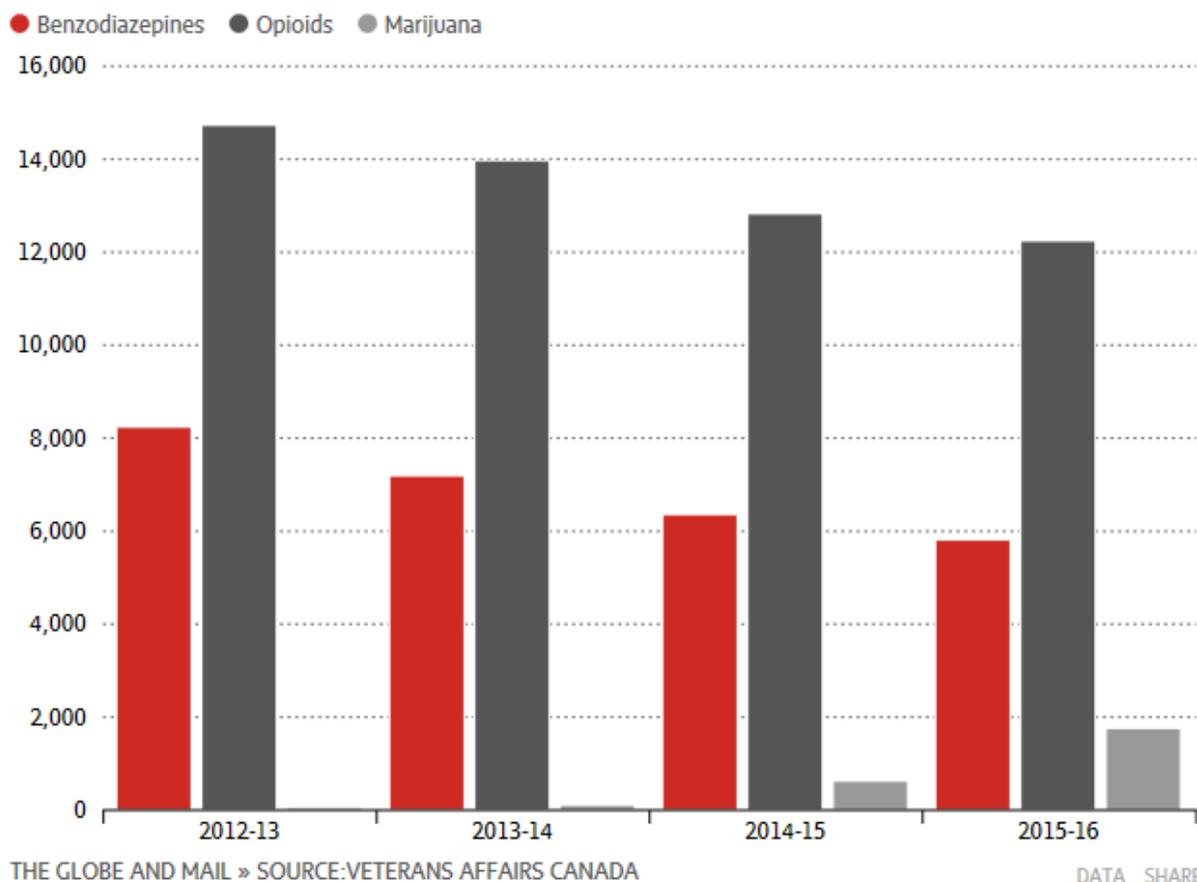
In 1931, *Time Magazine* [addressed the issue](#) in an article stating that “in spite of the legends, no case of physical, mental or moral degeneration has ever been traced exclusively to marijuana... doctors have recently been experimenting with the drug as an aid in curing opium addiction.”

7.9 AMONG VETERANS, OPIOID PRESCRIPTION REQUESTS DOWN IN STEP WITH RISE IN MEDICAL POT (2016)

<http://www.theglobeandmail.com/news/national/among-veterans-opioid-prescription-requests-down-in-step-with-rise-in-medical-pot/article30285591/>

Since 2008, the number of Canadians taking prescription sedatives – including benzodiazepines, but also sleep aids such as zopiclone – has remained steady at roughly 10 per cent, according to a bulletin issued last July by the government-funded Canadian Centre on Substance Abuse. While illicit opioid use has skyrocketed in recent years, the number of Canadians prescribed to this class of heavy painkillers has dropped from about 21 per cent in 2008 to 15 per cent in 2013, according to that same bulletin, which provides the latest data available.

Prescriptions for Canadian veterans



7.10 MEDICAL CANNABIS USE IS ASSOCIATED WITH DECREASED OPIATE MEDICATION USE IN A RETROSPECTIVE CROSS-SECTIONAL SURVEY OF PATIENTS WITH CHRONIC PAIN (2016)

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.

7.11 AFTER MEDICAL MARIJUANA LEGALIZED, MEDICARE PRESCRIPTIONS DROP FOR MANY DRUGS (2016)

<https://www.npr.org/sections/health-shots/2016/07/06/484977159/after-medical-marijuana-legalized-medicare-prescriptions-drop-for-many-drugs>

If the trend bears out, it could have other public health ramifications. In states that legalized medical uses of marijuana, painkiller prescriptions dropped — on average, the study found, by about 1,800 daily doses filled each year per doctor. That tracks with research on the subject.

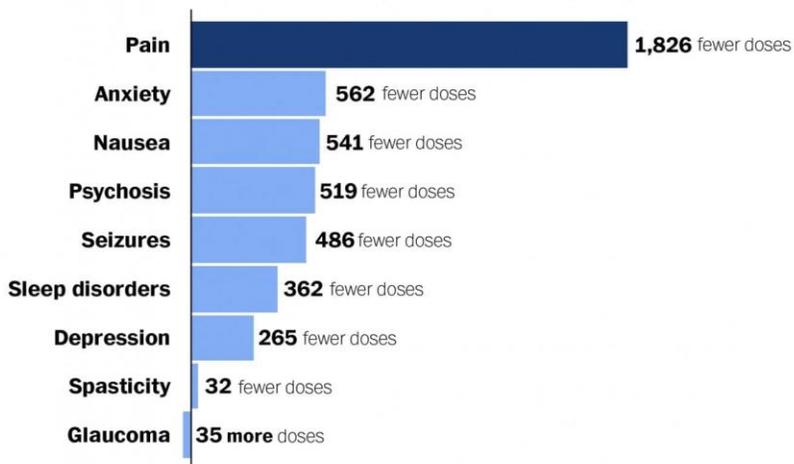
Marijuana is unlike other drugs, such as opioids, overdoses of which can be fatal, said Deepak D'Souza, a professor of psychiatry at Yale School of Medicine, who has researched marijuana. "That doesn't happen with marijuana," he added.

7.12 FEWER PILLS PRESCRIBED IN MEDICAL POT STATES (2016)

https://www.washingtonpost.com/news/wonk/wp/2016/07/13/one-striking-chart-shows-why-pharma-companies-are-fighting-legal-marijuana/?noredirect=on&utm_term=.145dee32494d

Fewer pills prescribed in medical pot states

Difference between annual drug doses prescribed per physician in medical marijuana states, and in states without medical marijuana laws, by drug category



WAPO.ST/WONKBLOG

Source: Bradford and Bradford, Health Affairs, July 2016

7.13 THE PRESCRIPTION OPIOID AND HEROIN CRISIS: A PUBLIC HEALTH APPROACH TO AN EPIDEMIC OF ADDICTION. (2015)

<https://www.ncbi.nlm.nih.gov/pubmed/25581144>

Public health authorities have described, with growing alarm, an unprecedented increase in morbidity and mortality associated with use of opioid pain relievers (OPRs). Efforts to address the opioid crisis have focused mainly on reducing nonmedical OPR use. Too often overlooked, however, is the need for preventing and treating opioid addiction, which occurs in both medical and nonmedical OPR users. Overprescribing of OPRs has led to a sharp increase in the prevalence of opioid addiction, which in turn has been associated with a rise in overdose deaths and heroin use. A multifaceted public health approach that utilizes primary, secondary, and tertiary opioid addiction prevention strategies is required to effectively reduce opioid-related morbidity and mortality. We describe the scope of this public health crisis, its historical context, contributing factors, and lines of evidence indicating the role of addiction in exacerbating morbidity and mortality, and we provide a framework for interventions to address the epidemic of opioid addiction.

7.14 ACCESS TO LEGAL DISPENSARIES LINKED TO SIGNIFICANT DECREASE IN BOTH PRESCRIPTION PAINKILLER ABUSE, AND IN OVERDOSE DEATHS FROM PRESCRIPTION PAINKILLERS (2015)

https://www.washingtonpost.com/news/wonk/wp/2015/07/14/how-medical-marijuana-could-literally-save-lives/?utm_term=.4f491243cd5b

The researchers on the NBER paper, however, found that access to state-sanctioned medical marijuana dispensaries is linked to a significant decrease in both prescription painkiller abuse, and in overdose deaths from prescription painkillers. The study authors examined admissions to substance abuse treatment programs for opiate addiction as well as opiate overdose deaths in states that do and do not have medical marijuana laws.

They found that the presence of marijuana dispensaries was associated with a 15 to 35 percent decrease in substance abuse admissions. Opiate overdose deaths decreased by a similar amount. "Our findings suggest that providing broader access to medical marijuana may have the potential benefit of reducing abuse of highly addictive painkillers," the researchers conclude.

This paper builds on [previous work](#) showing that "states with medical marijuana laws on the books saw 24.8 percent fewer deaths from painkiller overdoses compared to states that didn't have such laws." But the new paper's findings are more robust -- it uses more data, and the authors drew on a broader range of statistical methods to test the validity of their data.

7.15 MEDICAL CANNABIS LAWS AND OPIOID ANALGESIC OVERDOSE MORTALITY IN THE UNITED STATES, 1999-2010 (2014)

<https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/1898878>

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.*

7.16 THERAPEUTIC BENEFITS OF CANNABIS: A PATIENT SURVEY (2014)

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3998228/>

Other reported therapeutic benefits included relief from stress/anxiety (50% of respondents), relief of insomnia (45%), improved appetite (12%), decreased nausea (10%), increased focus/concentration (9%), and relief from depression (7%). Several patients wrote notes (see below) relating that cannabis helped them to decrease or discontinue medications for pain, anxiety, and insomnia. Other reported benefits did not extend to 5% or more of respondents. Six patients (6%) wrote brief notes relating how cannabis helped them to decrease or to discontinue other medications.

Comments included the following: "Medical cannabis replaced my need for oxycodone. Now I don't need them at all." "I do not need Xanax anymore." "In the last two years I have been able to drop meds for anxiety, sleep, and depression." "I've cut back 18 pills on my morphine dosage."

CONCLUSIONS:

More research needs to be pursued to discover degrees of efficacy in other areas of promise such as in treating anxiety, depression, bipolar disorder, autism, nausea, vomiting, muscle spasms, seizures, and many neurologic disorders. Patients deserve to have cannabis released from its current federal prohibition so that scientific research can proceed and so that physicians can prescribe cannabis with the same freedom accorded any other safe and effective medications.

7.17 PRESCRIPTION DRUG OVERDOSE DEATHS LOWER IN STATES WITH LEGAL MEDICAL MARIJUANA (2014)

<https://hub.jhu.edu/2014/08/26/medical-marijuana-prescription-drugs/>

In states where it is legal to use medical marijuana to manage chronic pain and other conditions, the annual number of deaths from prescription drug overdose is 25 percent lower than in states where medical marijuana remains illegal, new research suggests.

7.18 CANNABIS IN PALLIATIVE MEDICINE: IMPROVING CARE AND REDUCING OPIOID-RELATED MORBIDITY (2011)

<http://www.ncbi.nlm.nih.gov/pubmed/21444324>

"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.”

7.19 EXPLORING THE RELATIONSHIP BETWEEN PERCEIVED INTER-DOSE OPIOID WITHDRAWAL AND PATIENT CHARACTERISTICS IN METHADONE MAINTENANCE TREATMENT. (2009)

<https://www.ncbi.nlm.nih.gov/pubmed/19713051>

Physical opioid withdrawal is an important factor in understanding patient satisfaction with MMT. However, patient characteristics, such as level of psychological distress and negative mood, may also need to be considered because of their relationship with perceived inter-dose opioid withdrawal symptoms and patient satisfaction.

7.20 CANNABIDIOL, A NONPSYCHOTROPIC COMPONENT OF CANNABIS, INHIBITS CUE-INDUCED HEROIN SEEKING AND NORMALIZES DISCRETE MESOLIMBIC NEURONAL DISTURBANCES (2009)

<https://www.ncbi.nlm.nih.gov/pubmed/19940171>

The findings highlight the unique contributions of distinct cannabis constituents to addiction vulnerability and suggest that CBD may be a potential treatment for heroin craving and relapse.

There remains debate regarding the impact of cannabis on neuropsychiatric disorders. Here, we examined the effects of cannabidiol (CBD), a nonpsychoactive constituent of cannabis, on heroin self-administration and drug-seeking behavior using an experimental rat model. CBD (5-20 mg/kg) did not alter stable intake of heroin self-administration, extinction behavior, or drug seeking induced by a heroin prime injection. Instead, it specifically attenuated heroin-seeking behavior reinstated by exposure to a conditioned stimulus cue. CBD had a protracted effect with significance evident after 24 h and even 2 weeks after administration. The behavioral effects were paralleled by neurobiological alterations in the glutamatergic and endocannabinoid systems. Discrete disturbances of AMPA GluR1 and cannabinoid type-1 receptor expression observed in the nucleus accumbens associated with stimulus cue-induced heroin seeking were normalized by CBD treatment. The findings highlight the unique contributions of distinct cannabis constituents to addiction vulnerability and suggest that CBD may be a potential treatment for heroin craving and relapse.

8 THE EXTENT TO WHICH CANNABIS CAN RELIEVE THE SYMPTOMS OF WITHDRAWAL & CRAVINGS

8.1 CANNABIS IS AN EXIT DRUG FOR MAJOR ADDICTIONS, NOT A GATEWAY TO NEW ONES (2017)

<https://www.alternet.org/drugs/evidence-overwhelming-cannabis-exit-drug-major-addictions-not-gateway-new-ones>

For example, in jurisdictions where marijuana use is legally regulated, researchers have reported year-over-year declines in opioid-related abuse and mortality. According to data published in the Journal of the American Medical Association, deaths attributable to both prescription opiates and heroin fell by 20 percent shortly after marijuana legalization and by 33 percent within six years. Overall, the study's investigators concluded, "States with medical cannabis laws had a 24.8 percent lower mean annual opioid overdose mortality rate compared with states without medical cannabis laws." Data published this past April in the journal Drug and Alcohol Dependence also reports a dramatic decline in opioid pain reliever related hospitalizations following legalization.

Patients' use of other prescription drugs has also been shown to fall in states where marijuana is legally accessible. Newly published data from both the United States and Canada finds that patients curb their use of anti-depressants, anti-anxiety drugs and sleep aids after initiating cannabis use—a reality that is quantified in their spending habits. According to researchers at the University of Georgia's Department of Public Policy, Medicare recipients residing in medical marijuana states spent millions less on prescription drugs as compared to patients with similar ailments in non-legal states. Patients' spending on Medicaid related services is also significantly lower in cannabis-friendly states.

8.2 ANTIDEPRESSANT-LIKE AND ANXIOLYTIC-LIKE EFFECTS OF CANNABIDIOL: A CHEMICAL COMPOUND OF CANNABIS SATIVA. (2014)

<https://www.ncbi.nlm.nih.gov/pubmed/24923339>

Anxiety and depression are pathologies that affect human beings in many aspects of life, including social life, productivity and health.

Cannabidiol (CBD) is a constituent non-psychotomimetic of Cannabis sativa with great psychiatric potential, including uses as an antidepressant-like and anxiolytic-like compound. The aim of this study is to review studies of animal models using CBD as an anxiolytic-like and

antidepressant-like compound. Studies involving animal models, performing a variety of experiments on the above-mentioned disorders, such as the forced swimming test (FST), elevated plus maze (EPM) and Vogel conflict test (VCT), suggest that CBD exhibited an anti-anxiety and antidepressant effects in animal models discussed. Experiments with CBD demonstrated non-activation of neuroreceptors CB1 and CB2. Most of the studies demonstrated a good interaction between CBD and the 5-HT1A neuro-receptor.

8.3 THERAPEUTIC BENEFITS OF CANNABIS: A PATIENT SURVEY (2014).

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3998228/>

Other reported therapeutic benefits included relief from stress/anxiety (50% of respondents), relief of insomnia (45%), improved appetite (12%), decreased nausea (10%), increased focus/concentration (9%), and relief from depression (7%). Several patients wrote notes (see below) relating that cannabis helped them to decrease or discontinue medications for pain, anxiety, and insomnia. Other reported benefits did not extend to 5% or more of respondents.

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Comments included the following: "Medical cannabis replaced my need for oxycodone. Now I don't need them at all." "I do not need Xanax anymore." "In the last two years I have been able to drop meds for anxiety, sleep, and depression." "I've cut back 18 pills on my morphine dosage."

8.4 THE ENDOCANNABINOID SYSTEM AND THE BRAIN (2013)

<http://www.ncbi.nlm.nih.gov/pubmed/22804774?dopt=Abstract>

The historical use of cannabis to treat anxiety disorders goes back possibly thousands of years. The use of cannabis in the treatment of anxiety disorders was first described by ancient Indian medical literature, which said that cannabis helped its user to be "delivered from all worries and care"

In 1563, Garcia de Orta, a Portuguese physician, herbalist, and naturalist, published Colóquios dos simples e drogas da India, the earliest book on the medicinal plants of India. The publication claimed that cannabis helped patients suffering from anxiety to be "delivered from all worries and care."

8.5 CANNABIS FOR THERAPEUTIC PURPOSES: PATIENT CHARACTERISTICS, ACCESS, AND REASONS FOR USE. (2013)

<https://www.ncbi.nlm.nih.gov/pubmed/24095000>

RESULTS:

Patients reported using cannabis to treat multiple symptoms, with sleep, pain, and anxiety being the most common. Cannabis was perceived to provide effective symptoms relief across medical conditions. Patterns of use were also consistent across medical conditions. Notable differences were observed with regard to modes of access.

CONCLUSION:

Across medical conditions respondents reported using cannabis to effectively address diverse symptoms. Results indicate a substantial disconnect between the therapeutic use of cannabis and research on the risks and benefits of such use; particularly with regard to the anxiolytic and sedative use of cannabis. Authorized and unauthorized users exhibited few meaningful differences with regard to medical conditions and patterns of use, but faced substantial differences regarding access.

8.6 ANXIOTIC-LIKE EFFECTS OF CHRONIC CANNABIDIOL ADMINISTRATION IN RATS (2012).

<http://www.ncbi.nlm.nih.gov/pubmed/22083592>

Chronic administration of CBD produced an anxiogenic-like effect in clear opposition to the acute anxiolytic profile previously reported. In addition, CBD decreased the expression of proteins that have been shown to be enhanced by chronic treatment with antidepressant/anxiolytic drugs.

More research needs to be pursued to discover degrees of efficacy in other areas of promise such as in treating anxiety, depression, bipolar disorder, autism, nausea, vomiting, muscle spasms, seizures, and many neurologic disorders. Patients deserve to have cannabis released from its current federal prohibition so that scientific research can proceed and so that physicians can prescribe cannabis with the same freedom accorded any other safe and effective medications.

8.7 MEDICINAL USE OF CANNABIS IN THE UNITED STATES: HISTORICAL PERSPECTIVES, CURRENT TRENDS, AND FUTURE DIRECTIONS (2009)

<https://www.ncbi.nlm.nih.gov/pubmed/19662925>

Cannabis (marijuana) has been used for medicinal purposes for millennia, said to be first noted by the Chinese in c. 2737 BCE. Medicinal cannabis arrived in the United States much later, burdened with a remarkably checkered, yet colorful, history. Despite early robust use, after the advent of opioids and aspirin, medicinal cannabis use faded. The past few decades have seen renewed interest in medicinal cannabis, with the National Institutes of Health, the Institute of Medicine, and the American College of Physicians, all issuing statements of support for further research and development.

The recently discovered endocannabinoid system has greatly increased our understanding of the actions of exogenous cannabis. Endocannabinoids appear to control pain, muscle tone, mood state, appetite, and inflammation, among other effects. Cannabis contains more than 100 different cannabinoids and has the capacity for analgesia through neuromodulation in

ascending and descending pain pathways, neuroprotection, and anti-inflammatory mechanisms.

8.8 EFFECTS OF CANNABIDIOL (CBD) ON REGIONAL CEREBRAL BLOOD FLOW (2004).

<https://www.ncbi.nlm.nih.gov/pubmed/14583744>

CBD significantly decreased subjective anxiety and increased mental sedation, while placebo did not induce significant changes. Assessment of brain regions where anxiolytic effects of CBD were predicted a priori revealed two voxel clusters of significantly decreased ECD uptake in the CBD relative to the placebo condition ($p < 0.001$, uncorrected for multiple comparisons). These included a medial temporal cluster encompassing the left amygdala-hippocampal complex, extending into the hypothalamus, and a second cluster in the left posterior cingulate gyrus. There was also a cluster of greater activity with CBD than placebo in the left parahippocampal gyrus ($p < 0.001$). These results suggest that CBD has anxiolytic properties, and that these effects are mediated by an action on limbic and paralimbic brain areas.

8.9 UNRESPONSIVENESS TO CANNABINOIDS AND REDUCED ADDICTIVE EFFECTS OF OPIATES IN CB1 RECEPTOR KNOCKOUT MICE (1999)

<HTTP://SCIENCE.SCIENCEMAG.ORG/CONTENT/283/5400/401>

These observations suggest that the CB1 receptor is involved in the motivational properties of opiates and in the development of physical dependence and extend the concept of an interconnected role of CB1 and opiate receptors in the brain areas mediating addictive behavior.

The function of the central cannabinoid receptor (CB1) was investigated by invalidating its gene. Mutant mice did not respond to cannabinoid drugs, demonstrating the exclusive role of the CB1 receptor in mediating analgesia, reinforcement, hypothermia, hypolocomotion, and hypotension. The acute effects of opiates were unaffected, but the reinforcing properties of morphine and the severity of the withdrawal syndrome were strongly reduced.

9 THE EXTENT TO WHICH CANNABIS IS EFFECTIVE AS AN ADJUNCT THERAPY TO MEDICATION ASSISTED TREATMENT IN ORDER TO INCREASE TREATMENT SUCCESS RATES.

9.1 WHEN OPIOIDS ARE USED IN COMBINATION WITH CANNABIS, MARIJUANA CAN BOOST AN OPIOID'S EFFECTIVENESS WITHOUT REQUIRING HIGHER DOSAGES (2018)

<https://www.cnn.com/2018/04/29/health/medical-marijuana-opioids/index.html>

Sulak's review of the medical literature resulted in the same conclusion. He points out that when opioids are used in combination with cannabis in animals, marijuana can boost an opioid's effectiveness without requiring higher dosages.

Slinker is now a patient of Sulak's integrative health practice. Instead of taking 25 pills a day, she supplements smoking a gram of marijuana every three or four weeks with marijuana tinctures, oils and vapor. She also uses a drug called naltrexone to help with her autoimmune-related issues.

She credits her life now to cannabis and wants others to know about it. "I want people to know that they have options. Do not be afraid to tell your doctor that you do not want these chemicals in your body," she said.

9.2 CANNABIS AS A SUBSTITUTE FOR PRESCRIPTION DRUGS – A CROSS-SECTIONAL STUDY. (2017)

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5422566/>

Results

A total of 1,248 (46%) respondents reported using cannabis as a substitute for prescription drugs. The most common classes of drugs substituted were narcotics/opioids (35.8%), anxiolytics/benzodiazepines (13.6%) and antidepressants (12.7%). A total of 2,473 substitutions were reported or approximately two drug substitutions per affirmative respondent. The odds of reporting substituting were 4.59 (95% confidence interval [CI], 3.87–5.43) greater among medical cannabis users compared with non-medical users and 1.66 (95% CI, 1.27–2.16) greater among those reporting use for managing the comorbidities of pain, anxiety and depression. A slightly higher percentage of those who reported substituting resided in states where medical cannabis was legal at the time of the survey (47% vs. 45%, $p=0.58$), but this difference was not statistically significant.

Discussion

These patient-reported outcomes support prior research that individuals are using cannabis as a substitute for prescription drugs, particularly, narcotics/opioids, and independent of whether they identify themselves as medical or non-medical users. This is especially true if they suffer from pain, anxiety and depression. Additionally, this study suggests that state laws allowing access to, and use of, medical cannabis may not be influencing individual decision-making in this area.

9.3 MEDICAL CANNABIS ACCESS, USE, AND SUBSTITUTION FOR PRESCRIPTION OPIOIDS AND OTHER SUBSTANCES: A SURVEY OF AUTHORIZED MEDICAL CANNABIS PATIENTS (2017)

<https://www.ncbi.nlm.nih.gov/pubmed/28189912?dopt=Abstract>

RESULTS:

Cannabis is perceived to be an effective treatment for diverse conditions, with pain and mental health the most prominent. Findings include high self-reported use of cannabis as a substitute for prescription drugs (63%), particularly pharmaceutical opioids (30%), benzodiazepines (16%), and antidepressants (12%). Patients also reported substituting cannabis for alcohol (25%), cigarettes/tobacco (12%), and illicit drugs (3%). A significant percentage of patients (42%) reported accessing cannabis from illegal/unregulated sources in addition to access via LPs, and over half (55%) were charged to receive a medical recommendation to use cannabis, with nearly 25% paying \$300 or more.

CONCLUSION:

The finding that patients report its use as a substitute for prescription drugs supports prior research on medical cannabis users; however, this study is the first to specify the classes of prescription drugs for which cannabis it is used as a substitute, and to match this substitution to specific diagnostic categories.

9.4 CANNABIS BREAKS THE CYCLE OF PLEASURE AND REWARD BEING PROGRAMMED BY OPIATES (2018)

<https://nypost.com/2018/03/05/weed-is-helping-me-quit-opioids/>

“Cannabis breaks the cycle of pleasure and reward being programmed by opiates,” says Dr. Bonni Goldstein, a cannabis-focused M.D., as well as owner and medical director of Canna-Centers Wellness & Education in Southern California. A 2016 study by investigators at Scripps Research institute in La Jolla, Calif., and Icahn School of Medicine at Mount Sinai in NYC,

reports that the class of neurotransmitters activated in the brain by marijuana “modulates the rewarding effects of addictive drugs.”

“The cannabinoid receptors are located in areas of the brain that control pleasure and reward. If there is a dysfunction in that part of the brain, causing the driving force for addiction, cannabis tells the cells to stop seeking drugs,” says Goldstein. “It breaks the drug-seeking message.”

9.5 MEDICAL CANNABIS USE IS ASSOCIATED WITH DECREASED OPIATE MEDICATION USE IN A RETROSPECTIVE CROSS-SECTIONAL SURVEY OF PATIENTS WITH CHRONIC PAIN (2016)

[10.1016/j.jpain.2016.03.002](https://doi.org/10.1016/j.jpain.2016.03.002).

[View Article](#)

[PubMed](#)

[Google Scholar](#)

[https://www.jpain.org/article/S1526-5900\(16\)00567-8/fulltext](https://www.jpain.org/article/S1526-5900(16)00567-8/fulltext)

9.6 IMPACT OF CANNABIS USE DURING STABILIZATION ON METHADONE MAINTENANCE TREATMENT. (2013)

<https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1521-0391.2013.12044.x>

Objective rates of cannabis use were high during methadone induction, dropping significantly following dose stabilization. History of cannabis use correlated with cannabis use during MMT but did not negatively impact the methadone induction process. Pilot data also suggested that objective ratings of opiate withdrawal decrease in MMT patients using cannabis during stabilization.

9.7 CANNABINOID-OPIOID INTERACTION IN CHRONIC PAIN (2011)

<https://www.ncbi.nlm.nih.gov/pubmed/22048225>

Vaporized cannabis augments the analgesic effects of opioids without significantly altering plasma opioid levels. The combination may allow for opioid treatment at lower doses with fewer side effects.

Cannabinoids and opioids share several pharmacologic properties and may act synergistically. The potential pharmacokinetics and the safety of the combination in humans are unknown. We therefore undertook a study to answer these questions. Twenty-one individuals with chronic pain, on a regimen of twice-daily doses of sustained-release morphine or oxycodone were enrolled in the study and admitted for a 5-day inpatient stay. Participants were asked to inhale

vaporized cannabis in the evening of day 1, three times a day on days 2-4, and in the morning of day 5. Blood sampling was performed at 12-h intervals on days 1 and 5. The extent of chronic pain was also assessed daily. Pharmacokinetic investigations revealed no significant change in the area under the plasma concentration-time curves for either morphine or oxycodone after exposure to cannabis. Pain was significantly decreased (average 27%, 95% confidence interval (CI) 9, 46) after the addition of vaporized cannabis. We therefore concluded that vaporized cannabis augments the analgesic effects of opioids without significantly altering plasma opioid levels. The combination may allow for opioid treatment at lower doses with fewer side effects.

9.8 INTERMITTENT MARIJUANA USE IS ASSOCIATED WITH IMPROVED RETENTION IN NALTREXONE TREATMENT FOR OPIATE-DEPENDENCE. (2009)

<https://www.ncbi.nlm.nih.gov/pubmed/19444734>

Intermittent cannabis use was also associated with greater adherence to naltrexone pill-taking. Treatment interacted with cannabis use level, such that intensive behavioral therapy appeared to moderate the adverse prognosis in the consistent cannabis use group. The association between moderate cannabis use and improved retention on naltrexone treatment was replicated. Experimental studies are needed to directly test the hypothesis that cannabinoid agonists exert a beneficial pharmacological effect on naltrexone maintenance and to understand the mechanism.

9.9 SELF-EFFICACY, SOCIAL SUPPORT AND SERVICE INTEGRATION AT MEDICAL CANNABIS FACILITIES IN THE SAN FRANCISCO BAY AREA OF CALIFORNIA. HEALTH SOC CARE COMMUNITY (2008)

<https://www.ncbi.nlm.nih.gov/pubmed/18181813>

Results show that medical cannabis patients have created a system of dispensing medical cannabis that also includes services such as counselling, entertainment and support groups - all important components of coping with chronic illness. Furthermore, patients tend to be male, over 35, identify with more than one ethnicity, and earn less than US\$20 000 annually. Levels of satisfaction with facility care were fairly high, and higher than nationally reported satisfaction with health care in the USA. Facilities tended to follow a social model of cannabis care, including allowing patients to use medicine on site and offering social services. This approach has implications for the creation and maintenance of a continuum of care among bottom-up social and health services agencies.

9.10 CANNABIS IN PAINFUL HIV-ASSOCIATED SENSORY NEUROPATHY: A RANDOMIZED PLACEBO-CONTROLLED TRIAL (2007)

RESULTS:

Fifty patients completed the entire trial. Smoked cannabis reduced daily pain by 34% (median reduction; IQR = -71, -16) vs 17% (IQR = -29, 8) with placebo ($p = 0.03$). Greater than 30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group ($p = 0.04$). The first cannabis cigarette reduced chronic pain by a median of 72% vs 15% with placebo ($p < 0.001$). Cannabis reduced experimentally induced hyperalgesia to both brush and von Frey hair stimuli ($p < \text{or} = 0.05$) but appeared to have little effect on the painfulness of noxious heat stimulation. No serious adverse events were reported.

CONCLUSION:

Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated sensory neuropathy. The findings are comparable to oral drugs used for chronic neuropathic pain.

9.11 SYNERGISTIC INTERACTIONS BETWEEN CANNABINOID AND OPIOID ANALGESICS (2004)

<https://www.ncbi.nlm.nih.gov/pubmed/14706563>

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.

9.12 THE ROLE OF ENDOGENOUS OPIOIDS IN ENHANCING THE ANTINOCICEPTION PRODUCED BY THE COMBINATION OF DELTA 9-TETRAHYDROCANNABINOL AND MORPHINE IN THE SPINAL CORD (1996)

<https://www.ncbi.nlm.nih.gov/pubmed/8930163>

We have shown previously that intrathecal (i.t.) administration of the combination of delta 9-tetrahydrocannabinol (THC) and morphine results in a greater than additive antinociceptive effect. Similarly, pretreating mice with subthreshold doses of the kappa agonist, Dynorphin A (1-8), produced a parallel, leftward shift of the morphine dose-response curve, shifting the ED50 of morphine from 0.32 to 0.04 micrograms/mouse. A cocktail of enzyme inhibitors used to prevent the metabolism of Dynorphin A (1-8) into the delta receptor agonist, [Leu5]-enkephalin, attenuated the enhancement of morphine-induced antinociception by delta 9-THC. The enhanced antinociceptive effect observed after i.t. administration of the combination of delta 9-THC and morphine was also attenuated with antisera to Dynorphin A (1-8) (10 micrograms/ mouse) and Dynorphin A (1-13) (10 micrograms/mouse). Antisera to Dynorphin A (1-8) and Dynorphin A (1-17) blocked the antinociceptive effects of delta 9-THC (50 micrograms i.t.) without producing any significant alteration in the hypothermic and cataleptic effects or hypomotility produced by delta 9-THC. The antinociception produced by the combination of delta 9-THC and morphine was blocked by the kappa antagonist, nor-binaltorphimine (2 micrograms/ mouse), as well as the delta antagonist, naltrindole (5 micrograms/ mouse). Thus, the antinociception of morphine, which is mediated predominately by mu receptors, may be enhanced by delta 9-THC through the activation of kappa and delta receptors.

9.13 Synergistic interactions of endogenous opioids and cannabinoid systems. (1999)

<http://www.ncbi.nlm.nih.gov/pubmed/10612710>

*Cannabinoids and opioids are distinct drug classes historically used in combination to treat pain. Delta(9)-THC, an active constituent in marijuana, releases endogenous dynorphin A and leucine enkephalin in the production of analgesia. The endocannabinoid, anandamide (AEA), fails to release dynorphin A. The synthetic cannabinoid, CP55,940, releases dynorphin B. Neither AEA nor CP55,940 enhance morphine analgesia. The CB1 antagonist, SR141716A, differentially blocks Delta(9)-THC versus AEA. Tolerance to Delta(9)-THC, but not AEA, involves a decrease in the release of dynorphin A. Our preclinical studies indicate that Delta(9)-THC and morphine can be useful in low dose combination as an analgesic. Such is not observed with AEA or CP55,940. We hypothesize the existence of a new CB receptor differentially linked to endogenous opioid systems based upon data showing the stereoselectivity of endogenous opioid release. **Such a receptor, due to the release of endogenous opioids, may have significant impact upon the clinical development of cannabinoid/opioid combinations for the treatment of a variety of types of pain in humans.***

9.14 ANTINOCICEPTIVE ACTIVITY OF INTRATHECALLY ADMINISTERED CANNABINOIDS ALONE, AND IN COMBINATION WITH MORPHINE, IN MICE (1992)

<http://www.ncbi.nlm.nih.gov/pubmed/1320680>.

The antinociceptive effects of various cannabinoids, alone and in combination with opiates, were evaluated in antinociceptive tests in mice. The cannabinoids tested produce marked antinociceptive effects after i.t. administration to mice. The rank order of potency for the drugs using the tail-flick test was levonantradol greater than CP-55,940 = CP-56,667 greater than 11-hydroxy-delta 9-THC greater than delta 9-THC greater than delta 8-THC; dextronantradol was inactive at a dose of 25 micrograms/mouse. Respective ED50 values in the tail-flick test were 0.4, 12.3, 4.2, 15, 45 and 72 micrograms/mouse. Although pretreatment with morphine somewhat enhanced the effects of delta 9-THC, pretreatment of the mice with naloxone (1 mg/kg s.c. or 1 micrograms/mouse i.t.) failed to block the antinociceptive effects of the cannabinoids, indicating that the cannabinoid-induced antinociception does not occur due to direct interaction with the opiate receptor. Pretreatment of mice with 3.13 micrograms/mouse and 6.25 micrograms/mouse of delta 9-THC shifted the ED50 of morphine to 0.15 and 0.05 micrograms/mouse, respectively (a 4- and a 12-fold shift). The shifts in the dose-response curve of the morphine were parallel. Naloxone administration (1 mg/kg s.c.) completely blocked the antinociceptive effects of the combination of 6.25 micrograms of delta 9-THC with morphine. The AD50 for naloxone blockade of the drug combination was 0.24 (0.06-0.94) mg/kg s.c. and the pA2 was 7.7 (6.7-8.9). The pA2 for naloxone blockade of the dimethylsulfoxide-morphine combination was 6.9 (5.7-8.1).

10 THE EXTENT TO WHICH A LEGAL PRECEDENT EXISTS TO ADD OPIOID REPLACEMENT AND OPIOID USE DISORDER AS A QUALIFYING CONDITION

10.1 NEW YORK STATE ADDS OPIOID REPLACEMENT NOW A QUALIFYING CONDITION FOR MEDICAL MARIJUANA (JULY 2018)

https://www.health.ny.gov/press/releases/2018/2018-07-12_opioid_replacement.htm

Effective immediately, registered practitioners may certify patients to use medical marijuana as a replacement for opioids, provided that the precise underlying condition for which an opioid would otherwise be prescribed is stated on the patient's certification. This allows patients with severe pain that doesn't meet the definition of chronic pain to use medical marijuana as a replacement for opioids.

In addition, the regulation adds opioid use disorder as an associated condition. This allows patients with opioid use disorder who are enrolled in a certified treatment program to use medical marijuana as an opioid replacement.

10.2 PENNSYLVANIA ADDS OPIATE USE DISORDER AS A QUALIFYING CONDITION (MAY 2018)

On Monday, May 14, 2018, Pennsylvania became the first state to add opioid addiction to its list of approved conditions for medicinal cannabis. In a [press release from Pennsylvania Governor Tom Wolf](#) it was stated that the Department of Health developed temporary regulations to implement the recommendations of the Medical Marijuana Advisory Board. These temporary regulations took effect on May 17, 2018.

<https://www.governor.pa.gov/wolf-administration-approves-eight-universities-certified-medical-marijuana-academic-clinical-research-centers/>

In light of the current opioid crisis and issues with accessibility of treatments for opioid use disorders, it is time for us to look for alternative treatments that can increase access. Medical marijuana is one potential treatment alternative, which is more readily available to individuals in need across the country. It is estimated that sixty percent of Americans live in a state with at least some form of legal medical marijuana and nearly 21% live in states with legal recreational marijuana. We know that there are close interactions between cannabinoid system and the opioid system. These shared pharmacological properties may help to explain why we have already seen decreased admissions for opioid-related treatment and dramatically reduced rates of opioid overdoses in states with medical marijuana laws. Opioid users may find cannabis to be an appealing alternative to opioids.

Subjective reports of medical marijuana patients in the US and Canada make a stronger case as to why some find marijuana as a helpful substitution treatment. (In this context,

“substitution” means when someone uses one substance intentionally in place of another substance associated with more harms and negative consequences.) A study with 350 medical marijuana patients in California found that 26% of respondents reported they used marijuana as a substitute for illicit drugs and 65.8% for prescription drugs. When asked why they preferred marijuana as a substitution, the most common reasons included fewer harmful side effects, helpfulness in managing their symptoms, lower likelihood of withdrawal, and better availability. A study with 404 medical marijuana patients in Canada found similar results; 36.1% of respondents reported marijuana was a substitute for illicit drugs and 67.8% for prescription drugs. The commonly reported reasons for substitution were the same as in the aforementioned US study. Given these results, there is reason to believe that there are already individuals using medical marijuana as a substitute for opioids and other drugs.

Pennsylvania is the first state to add opioid-use disorder separately as an approved condition for medical marijuana patients.

10.3 NEW JERSEY ADDS OPIATE USE DISORDER AS A QUALIFYING CONDITION (MARCH 2018)

https://www.nj.com/marijuana/2018/03/might_you_qualify_for_medical_marijuana_in_nj_here.html

These conditions were immediately added Tuesday:

Anxiety;

Migraines;

Tourette's syndrome;

*Chronic pain related to musculoskeletal disorders, which include rheumatoid arthritis, lupus, and fibromyalgia and **opioid use disorder**;*

Chronic pain affecting of "visceral origin," which includes pancreatitis, irritable bowel syndrome and bowel dysfunction.

A medical marijuana advisory panel comprised of physicians, pharmacists and other health professionals recommended adding the new conditions last fall.

Health Commissioner Shereef Elhanal would be able to expand the list at his discretion in the future, Murphy said.

11 LETTERS OF SUPPORT FROM LICENSED MEDICAL PROFESSIONALS



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Dear Sir/Mam,

I have been asked to provide comment in relation to the appropriateness of utilizing cannabis in the treatment of opioid use disorder. Cannabis has shown to be useful in the treatment of opioid use disorder through several separate mechanisms. I will expand upon these physiological mechanisms in further detail.

The primary mechanism for cannabis treating opioid use disorders would be through receptor site competition. In other words, the receptor sites throughout the nervous system that interact with opioids also show an affinity for cannabinoids. Therefore, these receptor sites can also be acted upon by cannabis, resulting in a reduction in the severity of acute withdrawal symptoms & chronic opioid seeking behavior at the receptor site.

In addition to reducing the severity of withdrawal symptoms, cannabis is useful for the treatment of the variety of symptoms that may remain. Some such examples would be the reduction of nausea commonly associated with detoxification from opiates. Cannabis has shown to ameliorate the anxiety and depression that is common for individuals as they seek to rectify their opiate use disorder. Cannabis is also deemed beneficial to those struggling with insomnia, which is a relatively consistent side effect of ceasing opioid use in an opioid dependent individual.

Reduction in pain is perhaps one of the most impactful ways that cannabis has been shown to help those suffering from opioid use disorder. This application has several facets. First, we must examine the initial use of opioid based medications. Studies have shown that many cases of opioid use disorder can be traced to opioid based treatment regimens involving legitimate medical conditions. As such, treatment outcomes of the subsequent opioid use disorder are improved when the underlying medical condition is simultaneously treated. Cannabis has many analgesic applications, and therefore proves to be effective treatment for a myriad of painful conditions. As such, cannabis is additionally shown to be beneficial for the treatment of pain that customarily accompanies opiate withdrawal.

Several JAMA published studies support the positive impact that cannabis therapy has shown in the treatment of opioid use disorder. Multiple regression analysis results from 2010-15 show a reduction of 2.11 million opioid based daily doses each year billed to Medicare Part D per average state with a medical cannabis law in place. More impressive are the findings that states with a medical cannabis law have seen a 24.8% lower mean annual opioid overdose mortality rate. This is a figure that we simply cannot afford to ignore.

In closing, cannabis is a relatively safe, non-toxic, medically supported treatment method for opioid use disorder. Therefore, I recommend that opioid use disorder be added to the qualifying conditions for medical cannabis in Delaware.

Sincerely,

James S. Warson MD