WHITEPAPER

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CHRONIC PAIN & CANNABIS

Cannabis, a Safer Alternative to Opioids

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FACTS: CANNABIS VS OPIOIDS

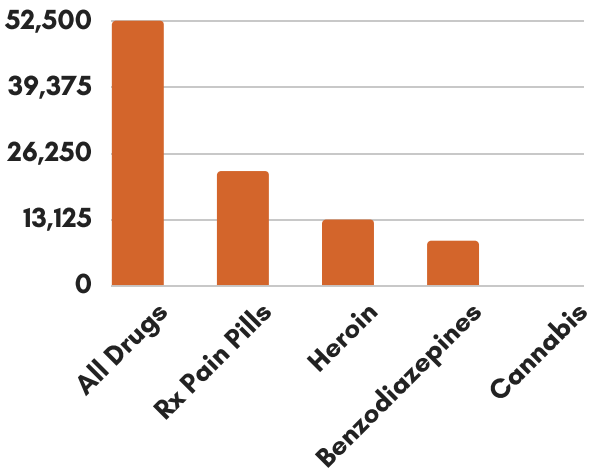
280%

INCREASE IN FATAL OPIOID OVERDOSES FROM 2002 - 2015 IN THE U.S.

-25%

AVG DECREASE IN RX OPIOID DEATHS IN STATES 2 YEARS AFTER IMPLEMENTATION OF MEDICAL MARIJUANA PROGRAMS

Fatal Drug Overdoses



For 2015, the National Institute on Drug Abuse reported fatal overdoses for Rx opioids (22,598), heroin (12,989), and benzodiazepines (8,791); there were NO reported fatal cannabis overdoses.

Cannabis is a hot button political issue. Policymakers regularly invoke the argument that cannabis will exacerbate the opioid epidemic, suggesting cannabis is a "gateway drug." However, the "gateway theory" has long been disproven. In fact, data suggests cannabis is an "exit drug" that often helps individuals get off of opioids (and other drugs).

Opioid Deaths Drop Significantly in States With Clinical Cannabis

In the years following implementation of clinical cannabis programs, states experienced significant drops in opioid related deaths:

Year 1: 19.9% drop in opioid deaths
Year 2: 25.2% drop in opioid deaths
Year 3: 23.6% drop in opioid deaths
Year 4: 20.2% drop in opioid deaths
Year 5: 33.7% drop in opioid deaths
Year 6: 33.3% drop in opioid deaths

Source: Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the U.S., 1999-2010

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Background

Treating chronic pain— one of the most prevalent and debilitating conditions in the world — presents burdensome challenges. In the U.S. alone, **117 million adults suffer from chronic pain**, **costing the U.S. an estimated $560 to $635 billion per year in** direct medical costs and lost productivity[1]. More significantly, North America faces an opioid epidemic unparalled in history. Opioid misuse and fatal overdoses have increased exponentially, with **52,404 fatal overdoses in 2015**[2]. With clinical cannabis gaining greater acceptance — legally and in public perception — could cannabis be part of the solution?

Legal medical cannabis is available to more than half of America and all of Canada. Given how widespread chronic pain is and how limited truly efficacious treatment options are, predictably, an increasing number of sufferers are turning to cannabis to treat their condition.

However, whether cannabis is right for you is a highly personal decision. What works for others, may not be appropriate for your situation. Likewise, deciding on whether cannabis should be an adjunctive therapy to your current treatment protocol or a replacement, is yet another consideration.

We have accumulated more evidence supporting a therapeutic role for cannabis to treat chronic pain than we have for most other conditions. Nonetheless, before you decide to use cannabis, it's important you develop a fundamental understanding of the dynamics of chronic pain, and how cannabis may (or may not) fit into your treatment program.In this paper, we put forth the case for why cannabis should play a role in chronic pain treatment.

Prevalence of Chronic Pain

20 percent of American adults report suffering from chronic pain, a staggering number that is only expected to increase over coming years. It may seem paradoxical that the prevalence of chronic pain would increase as medicine becomes more sophisticated, but oddly, our scientific advancements are actually part of the reason chronic pain conditions will continue to increase steadily.

1 Institute of Medicine. 2011. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: The National Academies Press. doi:https://doi.org/10.17226/13172

2 Rudd RA, Seth P, David F, Scholl L. Increases in Drug and Opioid-Involved Overdose Deaths — United States, 2010–2015. MMWR Morb Mortal Wkly Rep 2016;65:1445–1452. DOI: http://dx.doi.org/10.15585/mmwr.mm655051e1

The population is not only aging, but they're living longer. Moreover, conditions such as cancer, serious injuries, HIV, that were once a death sentence, are now treatable. And, while the patients survive, they're often left to deal with severe persistent neuropathic pain.

What Is Chronic Pain?

Those who live with pain on a near daily basis often describe it as "debilitating," "exhausting," and "intolerable." Describing it easy, but defining it is more difficult. The Association for the Study of Pain (IASP) offers a useful definition: "[Chronic pain] is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

Broadly speaking, if you have pain that persists for more than three months and has not been relieved by medical or surgical care, you may have a chronic pain condition. Chronic pain is a condition characterized by generalized muscle or nerve pain, that continues well beyond reasonable expectations of recovery; it affects 100 million Americans — approximately two out of five adults.

Types of Pain

- **Nociceptive** - Caused by tissue damage or inflammation, it is usually described usually described as sharp, aching, or throbbing pain. It is often attributed to other conditions.

- **Neuropathic** - Caused by nervous system damage or malfunction. Sufferers commonly describe the pain as causing numbness or a burning sensation. Because nerves connect the spinal cord to the rest of the body and facilitate communication between internal organs, muscles, and skin, the pain can affect many parts of the body. It is often attributed to poor diet, infections, alcohol abuse, or autoimmunity dysfunction, which can interfere with pathways and induce a pain response.

What Causes Chronic Pain?

With so many possible causes, the precise cause of chronic pain can be hard to pinpoint. While pain may start with a disease or injury, it can persist because of stress, emotional problems, improper treatment, or persistent abnormal pain signals in the body. Chronic pain can even occur without any previous injury, illness or known cause.

There are also a number of specific diseases associated with chronic pain, including shingles, diabetes, blood vessel problems, HIV, and most types of cancer. While treatment may cure one of these diseases, it's common for chronic pain symptoms to persist.

Anyone can develop chronic pain, although it most commonly affects older adults and people with health conditions like diabetes, arthritis, or back problems. Treatment may bring the disease under control, or even cure it completely, but the chronic pain continues. Similarly, simply because a pain-inducing disease can not be cured, does not mean the pain cannot be mitigated. Effective pain management requires ongoing attention in conjunction with a qualified medical professional.

Associated Conditions & Diseases

Chronic pain is also often associated with other conditions and diseases, including:

- Fibromyalgia
- Osteoarthritis & rheumatoid arthritis
- HIV/AIDS
- Cancer
- Spinal diseases
- Complex regional pain syndrome (CRPS)
- Recurrent headache, including migraines
- Painful neurological disorders resulting from damage to the nerves

Common Comorbid Issues

Chronic pain can also cause numerous other issues, including:

- Immobility, followed by wasting of muscle and joints
- Immune system issues that can cause increased vulnerability to disease
- Insomnia and sleep disturbances
- Depressed appetite and poor diet
- Dependence on medications
- Isolation from friends and family and job performance issues
- Fear and anxiety
- Depression which can become severe leading to a higher risk of suicide

What Treatments Are Available to Treat Chronic Pain?

- Antidepressants
- Anticonvulsant analgesic
- Nonsteroidal
- Anti-inflammatory drugs
- Opioids

These treatments can be effective for many patients, however, there can be a downside. Some patients report intolerable side effects. Others report they are only nominally effective or become less effective over time (e.g. the efficacy of opioids decreases significantly within 90 days). Reported side effects include:

- Constipation with opioids
- Gastrointestinal issues
- Cardiovascular damage from NSAIDs

Because of unpredictable efficacy, potentially intolerable side effects, and risk of addiction, an increasing number of patients are turning to cannabis. While cannabis may be effective for many patients, like all drugs, it's not necessarily appropriate for all patients.

Before considering cannabis, you should speak with a clinician who is knowledgeable on all forms of chronic pain treatments (pharmacological and nonpharmacological), and is not biased towards a single treatment (there is no panacea that is works for everyone).

How Can Cannabis Help Treat Chronic Pain?

The study of cannabis is continually evolving and we are constantly gaining a better understanding of why cannabis can be an effective treatment for a variety conditions, particularly chronic pain conditions. Exo-cannabinoids — including synthetic and botanical preparations — act on the body's endocannabinoid system (ECS). The ECS, which scientists only discovered two decades ago, is one of the body's most important physiological systems.

Dr. Donald Abrams, a professor and Chief of Hematology & Oncology at San Francisco General Hospital, notes there is a convincing body of evidence showing cannabis "is effective in a number of neuropathic pain syndromes," and that cannabinoids may not only play a role in symptom management, but also provide preventative benefits.

The endocannabinoid system is responsible for a number of physiological functions related to health, including pain modulation and inflammation. The ECS, through two receptors, CB1 and CB2, help modulate a variety of functions, including:

- **CB1:** Appetite, immune function, muscle control, pain, cognition, and reward
- **CB2:** Immune function, cell proliferation, inflammation, and pain

"I believe that the reason we and all animal species have the complex system of cannabinoid receptors and endocannabinoids is to help us modulate the experience of pain," notes Dr. Abrams. "It is no wonder, therefore, that the plant cannabinoids also seem to have a significant analgesic activity. We have studied the effectiveness of cannabis in painful nerve damage (neuropathy) as well as in combination with opiates. From my own oncology practice I am impressed that cancer patients are able to decrease their use of narcotic analgesics when adding in cannabis medicines."

When you ingest cannabis, cannabinoids such as THC and CBD, can act on the endocannabinoid system's receptors and periphery to provide anti-inflammatory and analgesic effects.

How Effective Are Cannabinoids in Treating Chronic Pain?

Over 200 studies have been conducted evaluating the efficacy of cannabis and cannabinoid-derived formulations to treat chronic pain conditions. Harvard professor and addiction psychiatrist, Dr. Kevin Hill, reviewed 28 well-designed studies including: six chronic pain trials of 325 patients; five neuropathic pain trials that included 396 patients; and, 12 multiple sclerosis trials that included 1600 patients. Hill concluded, "[The] use of marijuana for chronic pain, neuropathic pain, and spasticity due to multiple sclerosis is supported by high-quality evidence."[1]

Summary of Key Findings:

- **Six out of six general chronic pain studies** demonstrated significant improvement in symptoms.

- **Five out of five neuropathic pain studies** found a significant improvement in symptoms. (Three out of five studies investigated "smoked" cannabis, while two examined an oral spray preparation).

Canadian researchers came to similar conclusions in their 2011 Review Study of 18 trials, identifying 15 trials that demonstrated efficacy in treating chronic non-cancer pain. Of the 18 studies, 15 investigated neuropathic pain, while five (overlapping studies) examined other types of pain (one in fibromyalgia; one in rheumatoid arthritis; and, one as an adjunct to opioids in patients with mixed chronic pain; and, two in mixed chronic pain).[2]

They noted several trials reported significant improvements in sleep, with no serious side effects. Further, the studies found just a few adverse effects which were mild to moderate and well tolerated.

1 Hill, Kevin P. "Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems." Jama 313.24 (2015): 2474. Web. <https://www.ncbi.nlm.nih.gov/pubmed/26103031>.

2 Lynch, Mary E., and Fiona Campbell. "Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials." British Journal of Clinical Pharmacology 72.5 (2011): 735-44. Web. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3243008/>.

Can Cannabis Help Patients Eliminate (Or Reduce) Opioid Use?

In recent years, North America has been ravaged by an ever-growing epidemic: opioid abuse. Since Purdue Pharma brought OxyContin to the market in the mid 1990s, prescriptions have increased four-fold.

"Cannabis can play an important role in pain relief – with or without opiates. Given the epidemic level of opioid overdoses, it is evident that more physicians should consider prescribing cannabis as part of their therapeutic protocol. Not to, would be irresponsible, unscientific, and unethical."
— Dr. Michael Hart

Following the increase in prescriptions, rates of heroin addiction and the number of opioid-related overdoses have skyrocketed. While the government has (belatedly) tried to solve the epidemic by clamping down on "pill mills," and revising recom-mended opioid prescription protocols, the actions have elicited unintended conse-quences. Many individuals who developed a dependency on prescription narcotics found access to OxyContin more difficult, and turned to heroin for a cheaper, more easily accessible, and a more potent "high."

Data from the Centers for Disease Control (CDC) illustrate how dire the situation is[1]:

- **Fatal opioid overdoses increased 280%** between 2002 and 2015, propo-rotional to the increase in doctor prescribed opioids.
- **Two-thirds of all U.S. opioid overdose deaths** involve a prescription opi-oid.
- **22,598 people died** from overdoses involving prescription opioids in 2015.

1 Centers for Disease Control and Prevention. Centers for Disease Control and Prevention, 16 Dec. 2016. Web. 23 Feb. 2017.

Opioids Are a Gateway Drug. Cannabis Is an Exit Drug.

Evidence demonstrates how opioids are often a gateway to heroin, with **four out of five heroin addicts** reporting have become opioid addicted starting with prescription narcotics, like Vicodin and OxyContin[1].

In contrast, according to a Veterans Administration study, states with medical marijuana programs had (on average) a 25% lower opioid fatality rate compared to states without legal clinical cannabis. More impressive: states experienced significant drops in opioid-related deaths in the years following implementation of clinical cannabis programs that strengthened over time, supporting the argument that cannabis is an "exit drug," not a "gateway drug."

- **Year 1: −19.9%** drop in opioid-related deaths
- **Year 2: −25.2%** drop in opioid-related deaths
- **Year 3: −23.6%** drop in opioid-related deaths
- **Year 4: −20.2%** drop in opioid-related deaths
- **Year 5: −33.7%** drop in opioid-related deaths
- **Year 6: −33.3%** drop in opioid-related deaths

The evidence clearly suggests that cannabis may be an effective alternative to opioids, providing patients with relief, while reducing opioid-related fatalities. The CDC argues that the opioid prescribing is fueling the epidemic; it would be a sensible strategy to encourage physicians to consider cannabis as an alternative (or, adjunct) to opioid-based treatment programs.

Cannabis Helps Pain Patients Decrease Opioid Use

According to Dr. Abrams, "In my clinical practice I have seen many patients decrease their dose of narcotics or wean off them altogether with the addition of cannabis to their regimen. Pain relief, with or without opiates, is another area where cannabis may be quite useful."

1 Abuse, National Institute on Drug. "Prescription opioid use is a risk factor for heroin use." NIDA. N.p., n.d. Web. 23 Feb. 2017.

Cannabis & The "Synergistic Effect"

Evidence suggests opioids are only effective for acute pain, and many patients find they must progressively increase their dosage to achieve the same effect; within a short period of time, their pain isn't responsive to opioid treatment. On the other hand, there is evidence that cannabis (or, more specifically, cannabinoids) may act synergistically with opioids, allowing patients to lower dosage of opioids while achieving comparable pain relief.

Cannabinoids appear to be synergistic with opioids in producing analgesia." Based on preclinical research, Dr. Abrams conducted a small study to investigate cannabis as an opioid potentiator. His team found that vaporized cannabis didn't affect morphine or oxycodone blood levels, but they observed synergistic pain relief.

After the addition of vaporized cannabis, patients realized a 27% decrease in pain. Abrams and his team concluded vaporized cannabis "augments the analgesic effects of opioids without significantly altering plasma opioid levels."

According to Dr. Abrams, evidence from studies on animal models, suggest, "Can

"We have studied the effectiveness of cannabis in painful nerve damage (neuropathy) as well as in combination with opiates. From my own oncology practice I am impressed that cancer patients are able to decrease their use of narcotic analgesics when adding in cannabis medicines."

— Dr. Donald Abrams
Chief of Hematology & Oncology - San Francisco General Hospital

Other studies support the role of cannabis as part of a strategy to reduce opioid use. A University of Michigan March 2016 Study provided evidence that cannabis may be superior to opioids and provide a valuable harm reduction strategy[1].

Noting that while opioids are commonly used to treat patients with chronic pain, "there is little evidence that they are effective for long term [chronic pain] treatment. "

1 Boehnke, Kevin F., Evangelos Litinas, and Daniel J. Clauw. "Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain." The Journal of Pain 17.6 (2016): 739-44. Web.

Cannabis Can Be An Effective Adjunct to Pain Therapy

The University of Michigan study, published in the Journal of Pain, provides compelling data that cannabis is effective as an adjunct to therapy:

- **Patients Reduce Opioid Intake**: Cannabis use was associated with **64% lower opioid use** in patients with chronic pain.
- **Improved Quality of Life**: Cannabis use was associated with better quality of life in patients with chronic pain.
- **Fewer Side Effects**: Cannabis use was associated with fewer medication side effects and medications used.
- **Fewer Fatal Opioid Overdoses**: Previous studies reported strong associations between passage of medical cannabis laws and a decrease in opioid overdose statewide.

Dr. Daniel Clauw, one of the study's researchers and a professor of pain management anesthesiology at the University of Michigan Medical School, commented:

"We are learning that the higher the dose of opioids people are taking, the higher the risk of death from overdose. This magnitude of reduction in our study is significant enough to affect an individual's risk of accidental death from overdose."

Case Study: Kevin Ameling, A Real World Success Story

Kevin Ameling is a "real-world" success story. A chronic pain patient from Colorado, in 2007, Ameling was severely injured in a fall. It didn't take long after his doctor prescribed him a combination of prescription drugs that included Clonazepam, Tramadol, Lexapro, and OxyContin for him to develop a dependency.

As his chronic pain progressed, Ameling found the drugs to be less effective, particularly the OxyContin. A resident of Colorado where clinical cannabis (and "adult use") is legal, he became a medical marijuana patient.

Cannabis helped him reduce reliance on on prescription drugs, allowing him to cut his dosages significantly:

- **Clonazepam**: 3 mg to .5mg
- **Lexapro**: 30 mg to 5 mg
- **Tramadol**: 300 mg to 75 mg
- **OxyContin**: Reduced daily intake by more than 50% (and, reports being able to skip doses)

"I was well aware of the dangers associated with benzodiazepines and opioids, and didn't want to be a statistic. OxyContin became less effective and I didn't want to up my dosage," recounts Ameling.

"By using cannabis as an adjunct to my therapy, I was able to cut back on all my medications. Most impressively, while reducing my OxyContin intake, it didn't become less effective, and in fact, I believe cannabis allows OxyContin to be maintain efficacy far longer than typical."

Ameling noted everyone responds differently, but for him, "low dose edibles work much better than smoking. In fact, smoking seems to worsen my symptoms, while edibles clearly improve them."

Do Chronic Pain Patients Risk Developing a Cannabis Use Disorder?

Any drug that elicits feelings of reward has addictive potential. Cannabis is no exception. Approximately 9 percent of people who try cannabis will develop a diagnosable use-disorder. However, evidence suggests cannabis is safer and has the lowest risk of mortality than alcohol, tobacco and many other popular drugs.

A National Institute on Drug Abuse (NIDA) study of 8,000 people between the ages of 15 and 64 compared the risk of developing a dependency of popular substances after trying the substance at least once[1]:

- **Cannabis**: 9 percent
- **Alcohol**: 15 percent
- **Cocaine**: 17 percent
- **Heroin**: 23 percent
- **Nicotine**: 32 percent

Further, in contrast to commonly prescribed opioids that are responsible for over 40 fatal overdose deaths per day in the U.S., the toxicity of cannabis is so low that reported fatal overdoses are virtually non-existent.[2]

Nonetheless, given the fact that chronic pain is persistent condition in which treatment is ongoing and can last a lifetime, it's reasonable to be concerned about developing a dependency on cannabis. The few studies conducted suggest there is some risk, but comparatively low.

Israeli researchers conducted a study of 888 individuals receiving treatment for chronic pain[3]. 99.4% were treated with prescription opioids or medical marijuana. The prevalence of problematic use — as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) — was as follows:

- **52.6% of opioid users** met the DSM-IV criteria for use-disorder
- **21.2% of medical marijuana** users met the DSM-IV criteria for use disorder

1 Amsterdam, Jan Van, Antoon Opperhuizen, Maarten Koeter, and Wim Van Den Brink. "Ranking the Harm of Alcohol, Tobacco and Illicit Drugs for the Individual and the Population." European Addiction Research 16.4 (2010): 202-07. Web.
2 "Prescription Opioid Overdose Data." Centers for Disease Control and Prevention. Centers for Disease Control and Prevention, 16 Dec. 2016. Web. 23 Feb. 2017.
3 Problematic Use of Prescription Opioids and Medicinal Cannabis Among Patients Suffering from Chronic Pain

Addiction Potential: Cannabis vs Opioids

Clearly, the risk for opioids is higher, but 21.2% is more than double the rate of dependency among individuals who've reported having tried cannabis at least once in their lives. The findings suggest that while the risk of developing cannabis dependence is significantly less compared to opioids, patients should be mindful of their usage patterns, while maintaining an open and honest dialogue with their physician.

Notably, the study found risk of problematic use of opioids and cannabis was greater in individuals using medications over a longer period of time; were dealing with comorbid issues of depression and anxiety; or, using alcohol or other drugs.

Further, problematic use of opioids was associated with higher self-reported levels of pain, while problematic use of cannabis was more common among individuals using larger quantities of medical marijuana.

Another study conducted by the Veteran's Health Administration in conjunction with the University of Michigan and University of Pennsylvania, considered the question, "are medical cannabis users with chronic pain at greater risk of developing a dependency than users with other conditions (e.g., anxiety, insomnia, and muscle spasms)?" Given the fact chronic pain patients constitute up to 90% of medical marijuana patients in many states, the results were encouraging[1]:

- Individuals who used cannabis to manage chronic pain **experienced fewer cannabis use problems** than those who did not use it for pain;

- Among those who used cannabis for pain, average pain level in the past week **was not associated** with cannabis use problems.

Another interesting finding in the study was that individuals who were using cannabis to treat chronic pain preferred indica over sativa strains. Further, patients expressing a preference for indica demonstrated fewer cannabis use problems than users who preferred hybrids.

The authors concluded that patients using cannabis to treat chronic pain may be at lower risk for developing cannabis use problems compared to patients who used cannabis to treat other conditions.

1 Cohen, Nicole L., Adrienne J. Heinz, Mark Ilgen, and Marcel O. Bonn-Miller. "Pain, Cannabis Species, and Cannabis Use Disorders." Journal of Studies on Alcohol and Drugs 77.3 (2016): 515-20. Web.

Harm Reduction: The Substitution Effect

Interview With Amanda Reiman, PhD

Amanda Reiman, PhD has long been not only a tireless advocate for clinical cannabis, but a recognized expert in the fields of Substance Abuse treatment and Social Work. A lecturer at UC, Berkeley and the California Policy Manager for the Drug Policy Alliance (DPA), Amanda earned her Master of Social Work at the University of Illinois at Chicago and her PhD at UC, Berkeley.

Over her career, she has conducted extensive research and lead studies on dispensaries, patients, and cannabis as a substitute treatment for addiction. She's advised numerous cities and states on how to create sound medical marijuana policy. Her work has been particularly influential shaping our understanding of "substitution therapy" and "the substitution effect."

"Substitution Therapy" and the "Substitution Effect"

Substitution therapy: Also known as "replacement therapy," substitution therapy is a strategy aimed at harm reduction, by replacing a harmful substance with a less harmful substance. The most widely known (and embraced) substitution therapy is the replacement of heroin with methadone or Suboxone (a combination of buprenorphine and naloxone). Both of these drugs are opioids, but longer acting, less euphoric, and less harmful than heroin.

The benefits of substitution therapy can be significant, both for society and the dependent individual. The strategy is associated with reducing criminal behavior and drug overdoses, while improving the long-term physical and emotional health of the patient.

While research strongly supports the efficacy of substitution therapy, most strategies focus on total abstinence. While substitution therapy has gained traction over the years in combating the heroin epidemic, unfortunately, most government approaches to reducing drug abuse ignore the evidence supporting cannabis as a component of public health policy, and cannabis substitution therapy remains (unnecessarily) controversial.

That substitution therapy isn't more widely embraced is unfortunate. We must be honest about the facts: there is no single treatment that works for everyone; recovering opioid (and alcohol) users have an incredibly high relapse rate; and, the U.S. and Canada face the worst opioid epidemic in history. The evidence suggests cannabis-based substitution therapy could be a highly useful tool in our arsenal.

Substitution Effect: Similarly, the "substitution effect" is a phenomenon observed as state medical marijuana programs have expanded over the last two decades. In one of Amanda's studies, her team found that nearly three quarters of medical cannabis consumers were using cannabis as a substitute for alcohol, prescription drugs, or other illicit drugs (like heroin or benzodiazepines). Furthermore, another study found when states enacted medical marijuana programs, they experienced (on average) a 25% reduction fatal opioid-related drug overdoses and a significant reduction in alcohol abuse.

In a recent interview with Amanda, she shared important insights on the cannabis and its relevance to the opioid epidemic facing the U.S.

What is the history of substitution therapy?

One of the first known cases in the modern era of cannabis substitution was observed by Dr. Todd Mikuriya. He's a psychiatrist from California who was one of the first doctors to engage with recommending medical cannabis. One of the things he noticed was that when he had patients who had alcohol issues and were having trouble controlling their alcohol use, cannabis made that easier for them. It reduced their alcoholism-related symptoms. It made their decision to moderate their drinking a lot easier. It lessened the withdrawal symptoms that they may have from reducing or eliminating their alcohol use.

Why isn't substitution therapy more accepted or embraced?

We have such intolerance in this country for anything but abstinence-based treatment for drug dependence. Much of the research on substitution therapy -- not just with cannabis, but with methadone Suboxone, other substitutes for things like opiates -- is difficult to come by. The reason being, it goes against this kind of moral guidebook of what it means to be sober, what it means to be clean, and what it means to be in recovery. So a lot of this research has come from the bottom up, meaning that it's individuals who are seeking out the substitution behavior as a life-saving measure and then reporting its effectiveness to the doctors and others in their lives. And, this is very much true when looking at cannabis substitution.

Based on the data, it certainly seems to make a lot of sense.

It absolutely makes sense and if we were talking about anything else besides an illicit substance, I think it would be a no brainer. You know what I mean? If we had some kind of evidence that showed that states that offer free gym memberships saw a 25% reduction in obesity related illness, you would have legislators out there saying, "Well everyone should do that. Why aren't we giving more people free gym memberships? This is something that could really help people," but because it's cannabis, people really have a hard time accepting it.

Some people say, "It's going too far to replace one potentially addictive substance -- even though far less addictive -- with another. How would you respond to that criticism?

I think we have to look at what we're trying to accomplish. Because opiates have a high risk of fatal overdose. Accidental overdose is now the number one cause of accidental death in the United States, surpassing traffic accidents. So we know this is a risk. I think we really have to look at it as a life or death situation and if we have an individual that is taking a potentially lethal substance and we can transition them to a non-lethal substance, that's a win, right? Let's start there because then we're eliminating the potential of death, which is good. Once we do that we can start to work with them on other issues that may be related to harmful substance use but harmful substance use on opiates looks a whole lot different than harmful substances use on cannabis.

Right, and we currently do employ drug substitution strategies. There's Suboxone and methadone are used as replacement, substitution therapy.

Right, but methadone is still addictive and it can be difficult to withdraw from methadone. I think one of the reasons we're okay with methadone is because we feel it doesn't give the same high as the heroin so we're like, "Well, you know, as long as they're not getting high, we don't really care if they're dependent on this." I think that's also been a roadblock for cannabis because cannabis does not present the same dependence potential as those other substances but it does have euphoria attached to it and in this country we are totally okay with people taking a drug to go from feeling bad to feeling nothing but we've never been okay with people taking a drug to go from feeling nothing to feeling good unless it's alcohol.

Final Considerations for Patients

Chronic pain sufferers have turned to cannabis for years, long before more than half of the U.S. legalized medical marijuana. Encouragingly, over recent years, research is starting to catch up — although far more is needed — and, an ever-increasing body of evidence validates what medical marijuana chronic pain patients have known for years. While the evidence is compelling — particularly for treatment of neuropathic pain — it's important for patients to recognize that strains can vary considerably in chemical composition.

Moreover, choice of delivery device influences outcomes. It may take a little trial and error before you find the most effective strain and preferred form of administration. Most importantly, if you are currently using opioids, it would be unwise to radically change your treatment protocol without professional medical supervision. Withdrawal from opioids can be severe!

- **Administration Method:** Keep in mind that method of administration is important. An edible will have a different effect than vaporizing. Vaporizing will elicit different effects from a tincture. And, of course, prescription formulation.

- **Strain Preferences**: A 2016 study published in the Journal of Studies in Drugs and Alcohol found that pain patients preferred indica-dominant strains over sativa.

- **Trial & Error**: While anecdotally, many patients report a preference for edibles, everyone is different, so you may want to experiment with different methods until you find what works best.

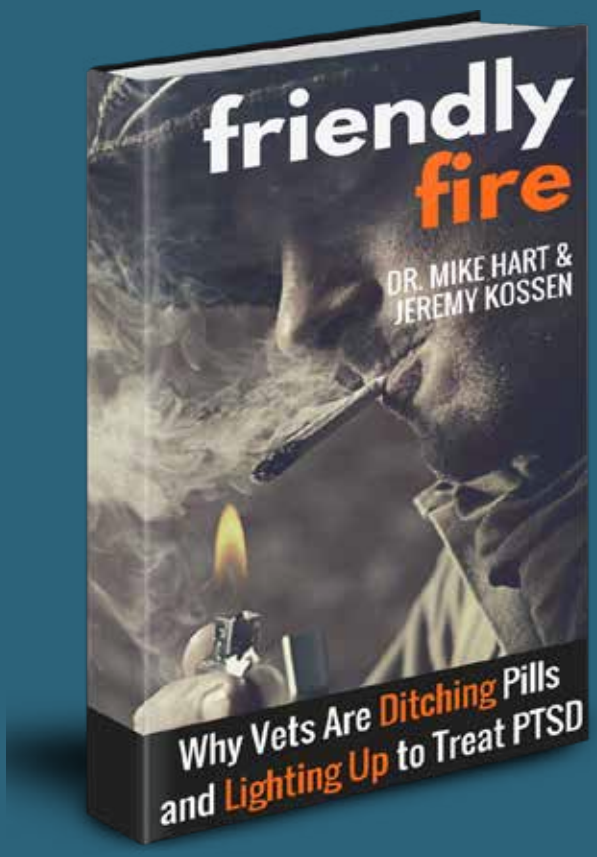
- **Exercise Caution**: If you're currently taking prescription opioids, exercise caution as withdrawal from opioids can be severe. Protocol changes should be monitored by a physician.

- **Everyone Responds Differently**: Different strains will elicit different effects that are THC and CBD dose-dependent Further, differing ratios of THC will impact the effect. Similar to how people respond differently to the same drug, people will have different experiences that may be affected by the diverse composition among strains.

COMING SOON

GET A COMPLIMENTARY COPY (FIRST 100 PEOPLE)...

"FRIENDLY FIRE: WHY VETS ARE DITCHING PILLS AND LIGHTING UP TO TREAT PTSD"



Authors Jeremy Kossen and Dr. Mike Hart explain why so many vets are abandoning pills in favor of cannabis to treat PTSD, insomnia, chronic pain, and other ailments. Backed with the most current research, Kossen and Hart lay out a compelling argument for why cannabis may be our most effective weapon in combating the current opioid and prescription drug epidemic.

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You can read his health & science articles on Leafly, the most popular cannabis website in the world.

Follow Jeremy on Twitter: **@JeremyKossen**

DR. MIKE HART

Dr. Mike Hart is a Canadian physician and author. In his clinical practice, he focuses on the veteran population. He's treated several thousand vets for PTSD, chronic pain and other conditions. Integrating clinical cannabis, mindfulness exercises, and lifestyle changes into his practice, he's helped more than 1000 vets kick their dependency on opioids, alcohol and other drugs.

Follow Mike on Twitter: **@DrMikeHart**

ZANA HEALTHLAB

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We're continually producing (and curating) original content created by clinical cannabis experts:

- **Clinical Cannabis Guidance**: General and condition-specific (insomnia, chronic pain, PTSD, etc.)
- **Free Downloadable Resources**: "How-To's," treatment and guidance checklists, eBooks, videos, podcasts, and more
- **Exclusive Discounts**: Subscribers get Zana Medical program and product discount
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RESEARCH

Cannabis & Opioids

Cannabinoid-opioid interaction in chronic pain.
University of California, San Francisco. Donald Abrams, MD; et, al.

Cannabis as an adjunct or substitute for opiates in the treatment of chronic pain.
Research Affiliate, Centre for Addictions Research of BC. Philippe Lucas

Pain, Cannabis Species, and Cannabis Use Disorders.
National Center for PTSD, VA Marcel Bonn-Miller; et, al.

Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain.
University of Michigan, Medical School. Kevin F. Boehnke, MD; et, al.

Problematic Use of Prescription Opioids and Medicinal Cannabis Among Patients Suffering from Chronic Pain.
Department of Psychology, Ariel University, Ariel, Israel. D. Feingold, MD; et, al.

Cannabis as an "Exit Drug"

Medical cannabis and mental health: A guided systematic review
Marijuana could help treat drug addiction, mental health
Walsh, Zach, Raul Gonzalez, et al. Clinical Psychology Review 51 (2017): 15-29.

Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients
International Journal of Drug Policy 42 (2017). Lucas, Philippe, and Zach Walsh.

Cannabis as a substitute for alcohol and other drugs
Harm Reduction Journal (2009). Amanda Reiman, PhD.

Cannabis as a substitute for alcohol and other drugs: A dispensary-based survey
Addiction Research & Theory (2013) Lucas, Philippe, Amanda Reiman, Mitch Earley-wine, et al. Addiction Research & Theory 21.5 (2012): 435-42. Web.

"Cannabis as a Substitute for Alcohol: A Harm-Reduction Approach."
Journal of Cannabis Therapeutics 4.1 (2004): 79-93. Mikuriya, Tod H.

Cannabis & Pain Management

Using Medical Cannabis in an Oncology Practice.
UCSF Osher Center for Integrative Medicine. Donald I. Abrams, MD.

Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials.
Department Anesthesia, Psychiatry, Dalhousie University, Halifax, Canada. Mary Lynch, MD; et, al.

Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review.
Harvard Medical School. Kevin Hill, MD.

Cannabinoids in the management of difficult to treat pain.
Ethan Russo, MD.

Modulation of neuropathic-pain-related behaviour by the spinal endocannabinoid/endovanilloid system.
Department of Pain Pharmacology, Polish Academy of Sciences. Barbara Przewlocka, Katarzyna Starowicz, Ph.D.

Role of the Cannabinoid System in Pain Control and Therapeutic Implications for the Management of Acute and Chronic Pain Episodes.
J Manzanares, MD; et, al.

The Endocannabinoid System as a Potential Therapeutic Target for Pain Modulation.
Department of Medical Pharmacology, Trakya University Faculty of Medicine, Edirne, Turkey. Ahmet Ulugöl, MD.

The Role of Cannabinoids in Pain Management.
Department of Psychological Brain Sciences, Indiana University. Andrea Hohmann, Ph.D., Ethan Russo, MD.

The Analgesic Potential of Cannabinoids.
Division of Hematology, Oncology and Transplantation and the Vascular Biology Center, University of Minnesota. Pankaj Gupta, MD; et, al.