Medical Cannabis for Chronic Pain: A Retrospective Review of Observational Data

MEDICAL CANNABIS FOR CHRONIC PAIN: A RETROSPECTIVE REVIEW OF OBSERVATIONAL DATA

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Lay Abstract

Many people live with long-term pain that negatively affects their daily lives. An increasing number of those who live with pain, particularly in North America, are using medical cannabis to reduce their symptoms. However, the evidence underlying the effectiveness of cannabis for chronic pain is limited. We accessed data from a mobile application called Strainprint® that collects data from people using medical cannabis to explore perceived effectiveness and patterns of usage. 741 individuals living with chronic pain recorded 83,622 sessions on the Strianprint app over a three-year period. Their average age was 39 years, and 63% were female. The majority (78%) used inhaled cannabis, and most sessions (65%) involved products with high levels of the psychotropic cannabinoid tetrahydrocannabinol (THC). Our adjusted linear regression model found that greater pain relief (on a 0-10 scale for pain) was associated with male sex, joint (vs. muscle) pain, and high THC (vs. high cannabidiol [CBD]) products. We also found significant interactions between the type of cannabis product and duration of use. Specifically, prolonged use of cannabis showed the greatest pain relief with balanced products (THC and CBD) vs. high CBD products. Many app users found that medical cannabis greatly reduced their chronic pain symptoms.

Abstract

Chronic pain is a debilitating condition that affects 1 in 5 adults globally. An increasing number of people living with chronic pain are using medical cannabis for symptom relief, however, the therapeutic potential of medical cannabis for treating chronic pain is debated. We conducted a retrospective cohort study examining cannabis use for the management of chronic pain using anonymous archival data obtained from the medicinal cannabis tracking app, Strainprint®. Multilevel models were used to analyze data from 741 users in which inhaled, and orally consumed cannabis was used to treat symptoms of chronic pain. In our adjusted model, greater pain relief was associated with male sex vs. female (-0.69 cm on a 10 cm visual analogue scale [VAS]; 95%CI -0.46 to -0.91 cm), joint pain vs. muscle-related pain (-0.05 cm; 95%CI -0.01 to -0.08 cm), and high THC vs. high cannabidiol [CBD]) products (-0.08 cm; 95%CI -0.01 to -0.14 cm); but no significant association with age (-0.008 cm; 95%CI 0.09 to -0.10 cm), nerve pain vs. muscle pain (-0.03 cm; 95%CI 0.02 to -0.08 cm), or the route of administration (inhaled vs. oral, -0.05 cm; 95%CI 0.002 to -0.1 cm). There was a significant interaction with duration of use and product type; specifically, greater pain relief was associated with prolonged use of balanced products (THC & CBD) vs. high CBD products (-0.009 cm; 95%CI -0.003 to -0.01 cm). Overall, medical cannabis provided large improvements in chronic pain symptoms.

Dedication

This work is dedicated to the memory of Douglas Lapp. See you on the dark side of the moon.

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2-AG - 2-Arachidonoylglycerol
ACMPR - Access to Cannabis for Medical Purposes Regulations
AEA - Anandamide
CBD - Cannabidiol
CB_1 - Cannabinoid receptor 1
CB_2 - Cannabinoid receptor 2
FAAH - Fatty acid amide hydrolase
MAGL - Monoacylglycerol lipase
MMAR - Marihuana Medical Access Regulations
MMPR - Marihuana for Medical Purposes Regulations
THC - Delta-9-tetrahydrocannabinol

Introduction

Burden of Chronic Pain

It is estimated that one in five adults suffer from chronic pain globally.[1] Pain may result from an injury or illness and has several etiologies. It can be acute, or it can last for a prolonged period. Pain lasting more than three months considered is chronic pain.[2] Chronic pain often persists for years and the way an individual experiences pain has been shown to vary, depending on factors such as age, gender, and mental health status.[3] The detrimental effects of chronic pain at the population level have made pain a well-known public health issue. The prevalence of chronic pain in Canada has ranged from 15.7 to 21% from the years 2000 to 2014.[4] As the age of the Canadian population rises, it is expected that the prevalence of chronic pain will increase in the coming years, adding stress to the already burdened Canadian healthcare system.[5]

Although chronic pain can arise as a symptom of a pre-existing condition, it has been recognized as a standalone disease by the World Health Organization and is included in the 11th version of the International Classification of Diseases.[5] Relative to acute pain, chronic pain can be more complex and difficult to manage.

Along with pain, individuals often must deal with comorbid mental health conditions such as anxiety and depression that stem from their pain. These additional mental health conditions that may co-occur with pain can exacerbate other health problems, resulting in negative outcomes such as social isolation and sleep disturbance.[6] Chronic pain can limit someone's ability to function as they normally would in society. Individuals living with chronic pain can experience detrimental impacts to their quality of life, social relationships, mobility,

productivity at work, and are at an increased risk of mental health disorders.[7] Pain is a personal experience and the way in which pain interferes with an individual's life varies from person to person.

Many times, pain is invisible to others but causes a heavy burden on the individual and the people close to them. The burden of chronic pain adds significant stress to the individual, their families, society, and the healthcare system. Many people use the healthcare system to seek help with their chronic pain which results in large costs to the Canadian healthcare system. The economic burden of chronic pain is significant in Canada and across the globe. Canadian estimates have put the direct cost of chronic pain at $6 billion per year.[8] Employed individuals living with chronic pain, on average lose 28.5 days per year due to their pain. The total economic cost to Canada in lost productivity is estimated to be $37 billion per year.[8] It is imperative for healthcare providers to optimize pain management so that individuals living with chronic pain are able to maintain their quality of life. In many cases, pain cannot be cured therefore, managing the pain becomes the best option for patients.

Chronic Pain Treatments

Typically, there is no single treatment that can cure chronic pain so modern treatments are focused on improving function and reducing suffering to provide a better quality of life. It is worth noting that chronic pain is heterogenous with pain arising from different mechanisms and pain pathways.[9] For example, endometriosis and arthritis can both cause chronic pain. However, the underlying mechanisms of the two diseases are different.

The biopsychosocial model of pain is helpful when trying to understand an individual's pain. The model views pain not only from the biological malfunction that is causing pain but incorporates other factors that influence an individual's pain such as their psychological and social well-being. Pain can be modulated by emotional state, level of social support and cultural factors.[6] This model allows clinicians and scientists to view the biological event that causes the pain and the subjective experience of that pain, in order to provide holistic treatment.[6]

It is not surprising that a multifaceted disease like chronic pain can require multimodal treatment. There are several therapies currently used to manage chronic pain. These therapies are delivered by a variety of healthcare providers and include pharmacological and non-pharmacological approaches. Some non-pharmacological approaches include exercise, acupuncture, electrical stimulation, surgery and cognitive behavioural therapy.[10] The list of non-pharmacological therapies is vast and some have shown efficacy; however, this thesis will not go into depth into the efficacy of the non-pharmacological approaches for the management of chronic pain. The focus will be on pharmacological approaches with a particular focus on medical cannabis.

When treating chronic pain, each circumstance is unique, what works for one person may not work for everyone. There are many guidelines available for healthcare providers prescribing pain medications for chronic pain, but some people require non-traditional treatment plans. These strategies will differ depending on the etiology of the pain; however, there are similarities between the recommended first, second, and third-line pharmacologic therapies across different countries. No drug is perfect. There will always be a balancing act between the benefits, risks,

and side effects when starting a patient on medication. Some classes of drugs are commonly used to treat several types of chronic pain. These drugs include non-steroidal anti-inflammatories, antidepressants, anticonvulsants, opioids, and topical drugs such as capsaicin.[9,11] The use of a specific drug is highly dependent on the origin, type of pain, and the advice of a healthcare practitioner. The type of drug used to treat chronic pain will vary depending on the cause of the pain, as some drugs work better in different circumstances.[9]

Defining Cannabis

The words medical cannabis can have many meanings depending on the context. Medical cannabis is often used interchangeably for a variety of products with different formulations and pharmacology. It is important to make a distinction between herbal cannabis, products refined from herbal cannabis, endocannabinoids, phytocannabinoids and synthetic cannabinoids. Cannabinoids are a class of molecules with structural similarity that bind to cannabinoid receptors. Cannabinoids can be produced by plants, synthetic or endogenous molecules produced by our bodies. Table 1 defines commonly used terms in this thesis.

Term	**Definition**	**Examples**
Phytocannabinoid	Cannabinoids that are produced by plants.	Tetrahydrocannabinol, Cannabidiol, Cannabichromene
Synthetic Cannabinoid	Man-made molecules that bind to cannabinoid receptors.	Nabilone, Dronabinol, WIN55212–2
Endocannabinoid	Molecules produced by the body that bind to cannabinoid receptors and elicit a cellular response.	2-Arachidonoylglycerol, Anandamide

Herbal Cannabis	Dried flowers from the cannabis plant.	Cannabis flowers, Cannabis, Marijuana
Medical Cannabis	Any product created from the cannabis plant that is used in a medical context.	Cannabis flowers, Cannabis extracts, Cannabis oil, tinctures, Sublingual sprays
Cannabis Concentrate	A product that is extracted from cannabis flowers for the purpose of concentrating the cannabinoids. Commonly packaged into cartridges for vape pens.	Hash, Wax, Bubble hash, Rosin, Butane hash oil

Table 1: Types of cannabis and cannabinoids.

The Endocannabinoid System

Herbal cannabis has been well known for its therapeutic properties for millennia. The first recorded use of cannabis dates to ancient China roughly 5000 years ago; however, the pharmacologically active constituents of cannabis remained unknown until recently.[12] The discovery of THC sparked the inquiry to find the endogenous system that THC was interacting with. After the discovery of THC in 1964, it took almost 30 years to identify the cannabinoid receptors in humans and their endogenous ligands.[13,14] The endocannabinoid system as we know it today is comprised of cannabinoid receptors, their endogenous ligands, and the enzymes responsible for their synthesis and degradation. This complex system is involved in many facets of our physiology including memory, learning, pain, nausea and vomiting, the immune system, and hunger.

Our current knowledge of the endocannabinoid system begins with the two G-protein coupled receptors that were discovered in the 1990's. Cannabinoid receptors are most often found on presynaptic terminals. Both cannabinoid receptors interact with Gi proteins which

causes an inhibition of adenylate cyclase upon receptor activation, leading to decreases in cyclic adenosine monophosphate in the cell.[15] Activation of these receptors ultimately leads to decreases in neurotransmitter release in the presynaptic cell. The activation of cannabinoid receptor 1 (CB_1) results in hyperpolarization of the cell which is mediated by the opening of potassium channels and closing on calcium channels.[16] The CB_1 is densely distributed throughout central nervous system and less densely populated in the areas of the periphery such as skeletal muscle, liver, and pancreas.[12] The cannabinoid receptor 2 (CB_2) is found within the central nervous system in low levels of neuronal cells and non-neuronal cells. The greatest concentration of CB_2 is found within the periphery, mainly in immune cells.[17] Agonism of CB_2 on immune cells the periphery results in the inhibition of proinflammatory factors from the cell.[18]

The most prominent endocannabinoids are anandamide (AEA), noladin ether, and 2-arachidonoylglycerol (2-AG). Several other arachidonic ligands and peptides interact with the CB_1 and CB_2 but are less well known.[12] AEA is also an agonist of the transient receptor potential cation channel subfamily V member 1.[12] Endocannabinoids such as 2-AG and AEA are synthesized on demand from lipids derived from the phospholipid bilayer of the cell.[19] In the central nervous system endocannabinoids are synthesized in the postsynaptic cells and travel in retrograde to the cannabinoid receptors on the presynaptic cell.[18] 2-AG and AEA are both agonists at the CB_1 and CB_2 receptors.[19] Activation of CB_1 receptors may be excitatory or inhibitory depending on the type of presynaptic cell and its location within the greater neural circuitry. For example, if CB_1 on a GABAergic neuron is activated, it would result in an increase

in electrical activity in the postsynaptic cell. CB_1 receptors are ubiquitous in the brain and are common in pain pathways.[20]

When pain pathways are stimulated, endocannabinoids are synthesised and bind to cannabinoid receptors. The action of endogenous cannabinoids is short-lived as they are degraded quickly by the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) after uptake into the presynaptic cell. FAAH breaks down anandamide while MAGL is responsible for the breakdown of 2-AG.[19] Current research is targeting the inhibition of the enzymes, FAAH and MAGL, to increase tonic endocannabinoid levels for pain relief.[20] Thus far the work in this field has been unsuccessful at getting a therapeutic approved for use in humans. Most research has focused on the use of exogenous agonists to stimulate the endocannabinoid system for pain relief.

The phytocannabinoids produced by the cannabis plant – THC and CBD – are historically the most common molecules used to modulate the endocannabinoid receptors for pain relief. These molecules interact with the cannabinoid receptors in different ways. CBD is a promiscuous ligand as it interacts with several different receptors and does not seem to have a primary receptor that mediates its pharmacodynamic effects.[17] Currently the knowledge of CBD pharmacology is vague. Interestingly, CBD has low affinity at both cannabinoid receptors.[21] CBD may be a negative allosteric modulator of the CB_1 receptor.[17] The GPR55 receptor is another target of CBD. CBD binds well to GPR55 and acts as an antagonist at that receptor.[21] CBD is known to bind to transient receptor potential cation channels, serotonin receptors, calcium channels, and several orphan G-protein coupled receptors. It is a positive allosteric

modulator of the 5HT1a receptor and an agonist of the 5HT2a receptor.[21] Beyond g-protein coupled receptors and ion channels, CBD inhibits and stimulates several enzymes in humans.[21] Up to this point, it has been difficult to pinpoint the exact mechanism for CBD's pain-relieving effects. Even though CBD has a diverse pharmacodynamic profile, it has been shown to be safe to use with high tolerability in humans.

THC has been at the forefront of cannabis research since it's discovery in 1964, by Raphael Mechoulam.[13] Unlike CBD, the pharmacology of THC is well defined, and it has clear interactions with cannabinoid receptors. THC is a partial agonist at the CB_1 and CB_2 receptors.[17] THC also binds to a host of other receptors, including peroxisome proliferator-activated receptors, and transient receptor potential cation channels.[16] When THC binds to the CB_1, it mimics the effect of the endogenous ligands 2-AG and anandamide. The actions of THC provide pain relief by suppressing neuronal activity in pain pathways, thereby inhibiting the transmission of pain signals between neurons.[12] One of the largest problems with THC as a therapeutic is that it binds to all cannabinoid receptors in the central nervous system. Since CB_1 is found in several regions of the brain, there are many off-target effects. This means that instead of getting selective activation of cannabinoid receptors in only pain pathways, all brain regions that contain CB_1 receptors are affected. CB_1 receptors are found in regions of the brain responsible for appetite, motor function, memory, nausea, sleep, and anxiety. One of the most prominent side effects of THC use is euphoria. The psychoactive effects of THC are mediated through CB_1 receptor agonism.[16] Euphoria produced by THC is generally unwanted by medical users but is coveted by recreational users and is the primary reason why cannabis is such a popular recreational drug.

Cannabis for Chronic Non-Cancer Pain

There is a need to help identify which types of cannabis provide the best symptom relief for chronic pain patients. Specifically, what ratio or dose of THC and CBD, along with the best route of administration that will work best for treating patients with chronic non-cancer pain.[22] Pain consistently shows up as a primary symptom that patients are treating when they use medical cannabis. A Canadian survey of 628 individuals that used medical cannabis for therapeutic purposes showed there is a wide variety of conditions medical cannabis is used for. When asked for the primary condition for which they use medical cannabis, 82% of the sample said that pain was the primary reason.[23] Along with pain and sleep, other common conditions reported were anxiety, depression, appetite, nausea, and inflammation.

As the medical cannabis system in Canada expanded over the past 20 years, so did the supporting infrastructure. Clinics that specifically catered to medical cannabis patients opened and began collecting data on cannabis users. Data from these clinics provide insights into the symptoms and conditions that cannabis users are treating. A population of 10,269 authorized medical cannabis users from a group of clinics called Canadian Cannabis Clinics provides an example of the demographics of medical cannabis users in Ontario, Canada. The average age of patients in this population is 51 years old and 66% of them use medical cannabis for chronic pain.[24] Within that 66%, it was roughly split between general chronic pain (32.3%) and musculoskeletal pain (33.7%). Of those who had musculoskeletal pain, 34% of patients indicated that pain was being caused by osteoarthritis. Other studies have had similar findings.[23,25] Many of the patients in this sample also had moderate anxiety and depression.[24] The Canadian Alcohol and Drug Use Monitoring survey conducted in 2011 across all provinces found that 49.7% of

respondents used medical cannabis for a chronic pain condition. The other 50.3% of respondents indicated they use medical cannabis for several conditions including depression, anxiety, and insomnia.[26]

A study of medical cannabis users from dispensaries in the United States also found that many customers used cannabis for pain. 64% of this sample self-reported they were diagnosed by a medical professional with chronic pain. A larger proportion (91%) self-reported having chronic pain.[27] Customers with self-reported chronic pain found that medical cannabis helped manage their pain and improved their quality of life.[27] It is known that many patients turn to medical cannabis to help alleviate pain.[23]

The way in which cannabis relieves pain and improves quality of life is two-fold. Part of the benefit of cannabis is provided from a reduction in pain. While part of the subjective effect helps patients return to feeling normal. Patients report that cannabis can help to restore function, reduce pain, and improve sleep.[28] Pain is a destructive experience, it disrupts individual's from living a normal life. Cannabis is said to help distract patients from the experience of pain and bring back feelings of normalcy.[28] How this pain relief is achieved from a preclinical perspective is fairly well defined. However, when a healthcare provider authorizes cannabis use, they will look to the quality and depth of peer reviewed clinical evidence along with the safety data to come to a decision.

To date, systematic reviews and clinical guidelines have summarized how to best use medical cannabis to treat chronic pain. In Canada, the guideline from the College of Family

Physicians of Canada states that dried cannabis can be used to treat chronic pain only after patients have exhausted non-pharmacological therapies, pharmacological therapies, and synthetic cannabinoids such as nabilone.[29] Similar to the Canadian guidelines, the 2018 European Pain Federation guideline suggests that cannabis-based medicines which are extracts with defined THC and CBD concentrations should only be used to treat chronic neuropathic pain after first and second line treatments have been utilized.[30] A guideline that was specific to primary care strongly recommended against using medical cannabinoids to treat rheumatic pain. That guideline also recommended against using cannabinoids for neuropathic pain as a first or second line treatment due to a lack of evidence and high risk of harms.[31] The most recent guideline made a weak recommendation to offer a trial of non-inhaled medical cannabis or cannabinoids, in addition to standard care and management (if not sufficient to manage pain symptoms), for people living with chronic cancer or non-cancer pain.[32]

Most of the guidelines favor using medical cannabis as a third or fourth line therapy for those with chronic neuropathic pain and warn against using medical cannabis for other types of pain.[22,32,33] Reviews of guidelines suggest that there is a limited space in the clinical landscape for the use of medical cannabis for the treatment of chronic non-cancer pain. A recent guideline review concluded that cannabis is weakly recommended to be used to treat chronic non-cancer pain as a third or fourth line therapy.[22] Adverse events and lack of clinical evidence are commonly cited as reasons not to use cannabis to treat chronic pain.

Regardless of the state of peer-reviewed evidence, individuals with chronic pain are continuing to use medical cannabis to treat their pain. Not all aspects of cannabis use are

positive. Like any medication, there are side effects and adverse events, especially when target receptors are widely distributed in the central nervous system. A recent systematic review on the harms of using medical cannabis and cannabinoid found that serious adverse events are uncommon.[34] The same review did conclude that adverse events may be common; however, the certainty of evidence was low.[34] One of the main problems when using centrally active cannabinoids is the wide distribution of CB_1 receptors in the central nervous system. CB_1 receptors modulate appetite, motor function, pain perception, memory, and several other important bodily functions. This presents a challenge because stimulation of CB_1 receptors in non-pain pathways may result in unwanted side effects. The common side effects include euphoria, dizziness, drowsiness, and dry mouth. The therapeutic index of cannabis has been estimated to be 40,000:1, which makes it a safe substance.[35] Since CB_1 receptors are present in low amounts within the brainstem, cannabinoids do not depress respiratory activity as opioids do.[36] This is one positive aspect of starting a patient on a cannabinoid-based therapy.

Neuropathic Pain

Neuropathic pain is a type of pain that arises from damage to parts of the peripheral or central nervous system.[37] The origin of the damage can come from underlying disease, exposure to toxins, or physical trauma. For example, neuropathies can result from multiple sclerosis, HIV, stroke, shingles, and diabetes. Damage to the nervous system can cause loss of function to the affected nerves and result in pain. In some cases of neuropathic pain, the pain can present from an unknown etiology. Regardless of the origin of neuropathic pain, pain arising from nerve damage is complex, not well understood in humans, and generally difficult to treat. This type of pain can result in a hypersensitive response to a painful stimulus known as hyperalgesia. It can also occur when a non-painful stimulus causes pain. The worldwide prevalence of chronic

neuropathic pain is between 6% and 10%.[38,39] This type of pain can cause severe discomfort, disability, and reduce an individual's quality of life. There are currently several pharmacological treatment options for neuropathic pain. First line treatments include tricyclic antidepressants, gabapentin, pregabalin, serotonin, and noradrenaline reuptake inhibitors.[38] Other treatments include patches that release capsaicin or lidocaine. Opioids are used to treat neuropathic pain, but this treatment option is reserved for those who fail first line and second line therapies.[38]

Individuals with neuropathic pain often find their pain difficult to manage with conventional therapies which may lead them to using cannabinoid-based therapies for pain relief. There is not a single treatment that has proven to be effective for all people with chronic neuropathic pain. Therefore, if cannabis-based medicines can provide pain relief to a subset of individuals, research is necessary. Currently the Canadian Pain Society has recommended cannabis as a third line treatment for chronic neuropathic pain.[40] Several clinical studies have shown that medical cannabis does provide pain relief in different neuropathic pain states such as multiple sclerosis and HIV induced neuropathic pain.[34]

A recent systematic review compared several forms of medical cannabis, including oral mucosal spray, herbal cannabis, and nabilone against placebo and dihydrocodeine. The authors included randomized controlled double-blind trials with at least 10 participants in each arm and a minimum duration of two weeks. When all cannabis-based medicines were pooled and compared to placebo, they were superior to placebo in reducing pain intensity.[39] Although there was a suggestion that cannabis-based medicine may be effective for reducing pain intensity, the authors warned that the quality and clinical applicability of the evidence was generally low. There was

also an increased risk of short-term adverse events compared to placebo. When herbal cannabis was tested against placebo, no significant benefits were found compared to placebo.[39] The available evidence suggests that cannabis may provide pain relief for some people living with chronic neuropathic pain. One aspect of cannabis that the reviews on this subject have not assessed is the optimal ratio of THC and CBD in the products people are using to treat neuropathic pain.

Arthritic Pain (Joint Pain)

Arthritis is a group of diseases that affect the joints and the areas that surround the joints. In Canada, arthritis is a significant problem with approximately 6 million people living with the disease.[41] This number is expected to increase to 9 million by 2040.[41] The economic cost of arthritis in Canada is over 4.5 billion dollars per year with the majority of the cost being due to lost work.[42] There are two main forms of arthritis: osteoarthritis and inflammatory arthritis. Osteoarthritis is more common than inflammatory arthritis and it involves the degradation of cartilage in the joint that ultimately results in the breakdown of the bone. It affects 240 million people worldwide every year.[43] The primary cause of osteoarthritis is progressive wearing and tearing of joint tissue over the lifetime. It is not a simple disease, the development and progression of osteoarthritis is complex and is dependent on lifestyle and genetic factors. The etiology of osteoarthritis is very complex but can be summarized as dysfunctional joint metabolism, along with wear and tear over the lifetime resulting in physical destruction of the cartilage, ligaments, and bone in the joints. Female gender, older age, obesity, and prior joint trauma all increase the risk of getting osteoarthritis.[43]

The clinical presentation of osteoarthritis usually begins with pain or stiffness in the joints. Osteoarthritis most often develops in weight bearing areas such as knee or hip joints. Individuals with arthritis report having pain, lowered quality of life, and sleep difficulty. They also self-report having poor mental health relative to those without arthritis.[41] Overall, arthritis has a negative effect on one's life and inhibits people from carrying on regular lives. Treatments are available for those that suffer from pain or stiffness caused by osteoarthritis.

First line treatments often involve physical therapy and or exercise. These treatments are designed to promote weight loss, strengthen the supporting joint structures, and reduce the load on the affected joints. In terms of pharmacological treatment, non-steroidal anti-inflammatories are the first line of defense. These drugs can be applied orally or topically. The topical route of administration is less toxic and can provide direct relief of inflammation and pain to the affected joint. Non-steroidal anti-inflammatories have been shown to help reduce pain in knee osteoarthritis.[43] Second and third line treatments include gabapentin and certain opioids, such as tramadol.

Inflammatory Arthritis

Inflammatory arthritis is a group of diseases that includes rheumatoid arthritis, ankylosing spondylitis, and other inflammatory types of arthritis such as gout. The most common form of inflammatory arthritis is rheumatoid arthritis. Rheumatoid arthritis is a chronic disease that mainly affects the joints but can affect other organ systems. It is understood that an aberrant immune response in the joint develops over time. This development causes swelling and inflammation, which can eventually cause the destruction of the bone and cartilage in the joint.[44] It is believed the disease begins in genetically predisposed individuals that have exposure to

negative environmental and lifestyle events. Over time these factors play a role in the immune dysfunction that is seen in the joints of those with rheumatoid arthritis.[44] Exposure to environmental factors such as smoking, and poor socioeconomic status are risk factors for rheumatoid arthritis.[44]

The disease burden on the individual is significant. Those living with rheumatoid arthritis suffer from frequent pain, joint stiffness, and joint damage. Like osteoarthritis, pain is the primary complaint of those living with rheumatoid arthritis.[42] The pain that people experience is caused by chronic inflammation of the joint and damage to the joint environment over time. All of these symptoms result in reduced quality of life, decreased economic productivity, and an inability to participate in activities of daily living.[42,44] To help alleviate the burden of disease, patients have the option of several pharmacological therapies.

To effectively treat rheumatoid arthritis, patients are first treated with methotrexate and low-dose glucocorticoids to prevent the progression of the disease in the early stages of development.[44] Treatment needs to be initiated quickly to halt the progression of inflammation that could cause serious damage if left untreated. Non-steroidal anti-inflammatory drugs such as naproxen sodium and ibuprofen are also used to help combat symptoms. If first line treatments fail, there are several synthetic and biological disease modifying antirheumatic drugs available for patients. The primary goal of these therapies is to reduce inflammation. By reducing inflammation, the damage in the joints can be reduced. Cannabis has been shown to reduce inflammation and that is why some patients with osteoarthritis and rheumatoid arthritis may use cannabis for symptom relief.

Cannabis does not have a strong role to play in the prevention of arthritis; however, it may be used to manage pain and inflammation associated with the disease. The endocannabinoid system is involved in the regulation of pain and inflammation in humans through the modulation of the CB_1 and CB_2 receptors. The production of the endocannabinoids anandamide and 2AG is known to be upregulated during states of inflammation.[45] Regarding how this stimulation of the endocannabinoid system reduces inflammation, we have to look at the involvement of the CB_2 receptor. CB_2 receptors located on immune cells in the periphery mediate the release of pro-inflammatory molecules known to be involved in inflammatory arthritis.[45] When THC binds to CB_2 receptors, the release of pro-inflammatory cytokines is reduced, thereby suppressing inflammation.[19] Complimentary to the reduction of cytokine release, CB_2 receptors have also been to shown potential to reduce inflammation via several immune related mechanisms. They have been shown to inhibit T cells and macrophages from releasing inflammatory mediators and promoting the differentiation of osteoblasts.[45] This suggests a beneficial role of CB_2 receptor agonists in inflammatory arthritis. The role of CBD in arthritis is less well known than THC. CBD is a promiscuous ligand and does not with high affinity or produce a strong cellular response at cannabinoid receptors.[15] Some studies have shown that CBD is likely a negative allosteric modulator of cannabinoid receptors, but more work is required.[15,17]

Although the endocannabinoid system is involved in inflammation, much of the work has been done in preclinical models which do not always translate to high efficacy treatments in humans. There have been few clinical trials that have investigated if people with arthritis can benefit from medical cannabis. One such trial reviewed the efficacy of Sativex for pain caused by rheumatoid arthritis in a randomized controlled trial of 58 patients. This trial found that

Sativex provided small amounts of pain relief along with improvements in sleep quality.[46] There were adverse events such as dizziness and dry-mouth but overall Sativex was well tolerated. Currently there is a paucity of clinical evidence to support the use of cannabinoids in the treatment of rheumatoid arthritis.

The landscape of clinical trials targeting the endocannabinoid system for osteoarthritis is like that of rheumatoid arthritis. One randomized controlled trial investigated the efficacy of a FAAH inhibitor in patients with osteoarthritis of the knee. The FAAH inhibitor was well tolerated but the trial was stopped early due to a lack of efficacy.[47] A systematic review suggested that there is not enough evidence to use cannabinoids for the treatment on rheumatic diseases.[48] The current state of clinical evidence for the use of cannabinoids to reduce pain in arthritis is lacking. There is even less data available on the use of herbal cannabis for the treatment of pain from arthritis.

At the moment, there is not a strong case for prescribing cannabinoids for the relief of pain from osteoarthritis or inflammatory arthritis. There is some clinical evidence that suggests cannabinoids will relieve pain, but the substantial lack of clinical evidence suggests that there should be more research done on the efficacy of cannabinoid-based treatments before their use is supported by physicians.[49,50] There is a gap in the evidence due to limited randomized controlled trials.

Cannabis is commonly used by people with arthritis even though there is a lack of clinical evidence supporting its benefit. A study of 200 patients with osteoarthritis of the knee and hip found that 24% of patients in the study population used CBD for pain relief.[51] Similarly

in a group of 10,269 Canadian medical cannabis users, 33.7% of the sample was using cannabis to treat pain from osteoarthritis.[24] High rates of medical cannabis use in this population may be the reason why organizations like the Arthritis Society of Canada dedicated several pages on their website for medical cannabis information. The Arthritis Society of Canada was also one of the first health charities to fund medical cannabis research in Canada. Large proportions of people use cannabis for arthritis in observational studies but not many clinical trials have been completed that specifically address cannabis use for arthritis. There is a disconnect between the amount of people using cannabis for arthritis and strong clinical evidence for its use. Future studies may help elucidate if medical cannabis is truly effective for arthritis patients.

Muscle Pain

Myofascial pain which is commonly referred to as muscle pain is a diverse and unique type of pain. Prominent conditions such as fibromyalgia fall under this category of pain. The subjective effects of muscle pain can be described as feelings that are aching, feelings of tenderness, and diffuse pain.[52] This type of pain differs from the subjective experience of cutaneous pain, which is more localized in a specific area and gives a sharper pain relative to muscle pain. Muscle pain can be highly variable between individuals in terms of its duration, localization, and intensity.[52] This type of pain can also cause referred pain, which is when pressure on a sensitive point will cause pain in a different part of the body. People with muscle pain also experience allodynia, which is when a non-painful stimulus results in an individual experiencing pain.

Fibromyalgia is a chronic pain syndrome that involves widespread muscle pain across the body lasting for more than three months.[53] This disease can appear alone or as a comorbidity of another disease. The estimates of the prevalence of fibromyalgia can differ depending on the

diagnostic criteria used to assess the disease. Between 2-4% of the population are affected by fibromyalgia but it is experienced more often in people that have existing inflammatory conditions such as rheumatoid arthritis or lupus.[53] The symptoms of fibromyalgia are widespread and complex, often involving many areas of the body. People with the disease not only experience widespread pain that is described as "hurting all over their body", they often experience fatigue, mood disorder, and sleep disturbance.[53] Due to this persistent pain, it is common for people afflicted with fibromyalgia to utilize healthcare at a high rate and lose economic productivity. Currently, the exact cause of fibromyalgia is still unknown.[53]

There is a genetic predisposition to fibromyalgia along with environmental factors that contribute to disease development and risk factors such as female sex.[53] Besides the genetic risk factors, the current opinion is that people with fibromyalgia have aberrant pain regulation mechanisms which cause their symptoms. Specifically, these irregularities cause an amplification of pain while also inhibiting pain inhibition across pain pathways.[54] These irregular pain processing mechanisms occur both in the central and peripheral nervous system.[55] It is believed that the nervous system of someone with fibromyalgia is sensitized to pain and over time these changes become engrained, causing chronic pain. Disturbances in the immune system may also contribute to symptoms. Just as the body's pain response is dysregulated, the immune system is also out of balance, causing increased inflammation in people with fibromyalgia.[55] To begin treating the pain, there are several non-pharmacological therapies available. If the pain is not sufficiently treated there are drugs available that may help with pain relief.

The available treatments are a mix of medications used to treat neuropathic pain as well as inflammatory pain seen in diseases such as arthritis. The treatment of fibromyalgia is done using the biopsychosocial approach with a combination of exercise, cognitive behavioural theory

and drugs for symptom relief.[53] First line therapies include tricyclic antidepressants such as amitriptyline.[56] Pain is also managed with serotonin-norepinephrine reuptake inhibitors, gabapentinoids, and non-steroidal anti-inflammatory drugs. Lastly, in cases of refractory pain, opioids may be used.[53] Even with these therapies available, patients still struggle to manage their pain due to the complexity of treating pain caused by fibromyalgia. Some patients have turned to cannabis for its pain relieving and anti-inflammatory effects to treat pain arising from fibromyalgia.

Some observational and retrospective studies have found that patients may benefit from medical cannabis treatment and concluded the treatment was safe and tolerable.[57,58,59] However, it is important to consider that the products used across these studies are heterogenous. Observational and retrospective studies also have their own methodological limitations. Higher quality evidence from randomized controlled trials using cannabinoids for the treatment of fibromyalgia are almost non-existent. Due to the lack of clinical trials, cannabis-based medicines are not currently recommended for treating fibromyalgia. There is a lack of strong clinical evidence but some people with fibromyalgia do use medical cannabis and there is preclinical data that suggest cannabis may be an effective treatment option.[55]

There have been limited randomized controlled trials that evaluate the efficacy of cannabinoids for treating pain due to fibromyalgia. The first trial evaluated nabilone to treat pain associated with fibromyalgia and found that patients reported reductions in pain.[60] A second trial found that nabilone also improved patient's sleep quality.[61] In the aforementioned trials, nabilone was well tolerated. This is not sufficient evidence to recommend cannabinoids for pain relief and more research is needed. Herbal cannabis has not been evaluated as a treatment in a randomized

controlled trial and neither has CBD.[55] Further high quality clinical trials may help define the role of cannabinoid based therapies in the treatment of pain resulting from fibromyalgia.

Medical Cannabis in Canada

The medical cannabis system in Canada has evolved significantly since its inception in 2001, when the Marihuana Medical Access Regulations (MMAR) came into effect. At the time, medical cannabis users had the option of purchasing cannabis from a single government producer or growing their own cannabis. Over time there were changes made to the MMAR which gradually allowed Canadians better access to medical cannabis. In 2014, the marihuana medical access regulations were replaced with the marihuana for medical purposes regulations (MMPR). These new regulations allowed for the formation of a commercial industry to supply cannabis to Canadians. At that time, companies deemed licenced producers provided medical cannabis for all medical cannabis users in Canada. Licensed producers supplied dried flower, cannabis oil, and fresh cannabis to medical users. Strict regulation by Health Canada ensured that patients were receiving a safe supply of cannabis products. Only two years after the inception of the MMPR, it was deemed unconstitutional because it denied patients reasonable access to cannabis.

The regulations changed once again in 2016 when the MMPR was replaced with the Access to Cannabis for Medical Purposes Regulations (ACMPR). Now every Canadian has the option to either grow their own cannabis or purchase cannabis grown by a licensed producer. The option to grow your own cannabis helped patients who were accustomed to doing so. It also helped those who were unable to afford the high cost of purchasing cannabis from a licensed

producer. Under the ACMPR, Health Canada was responsible for licensing and policing the commercial cannabis producers while also overseeing personal medical cannabis production for individuals wanting to produce their own cannabis at home. Once cannabis was legalized for recreational use on October 17, 2018, the Cannabis Act replaced the ACMPR.[62] Currently in Canada, an individual can obtain a medical document from their healthcare provider that allows them to either grow their own cannabis, designate a grower, or purchase cannabis from a federally licenced cannabis producer.

Over time, more and more patients have been given access to medical cannabis in Canada. Near the beginning of the medical cannabis program under the MMAR, there were only around 200 active regitrations.[23] The number of registrations has grown substantially since the introduction of the MMPR in 2014. Just as the amount of medical cannabis users was growing, so was the number of companies producing cannabis. As more companies were formed, the quantity and variety of medical cannabis products expanded rapidly. Although advertising was highly regulated, the financial incentive for cannabis producers pushed them to grow their client base which may have accelerated the number of registrations in Canada. In early 2014 there were only 7,914 medical cannabis registrations in Canada.[63] As of September 2020, 43,211 individuals were registered to grow cannabis for medical purposes in Canada with a total of 377,024 registrations for medical use.[62] One interesting facet of the medical cannabis program is how much cannabis medical patients are authorized. Medical documents in Canada authorize patients to a specific amount of cannabis per day. On average, Canadian medical patients are authorized to purchase two grams per day from a federally licenced cannabis producer. For those patients

that are authorized for personal production of cannabis, their average daily authorization is 36.2 grams per day.[62]

After the introduction of the Cannabis Act in Canada, the government needed a comprehensive way to collect data around cannabis use in Canada. In 2017, the Canadian Cannabis Survey was developed and has been conducted annually since its introduction. The survey collects information on what kind of cannabis people are using, the amounts and the source of their purchase. The report covers both medical and recreational use. Medical use was defined as using cannabis for the purpose of treating symptoms of a disease or directly treating a disease.[64] There were 10,822 responses from Canadians across every province and territory in the 2020 survey. 14.84% of survey respondents self-reported using cannabis for medical purposes. Of those, 905 (8.36%) respondents completed a section of the survey that was specific to medical cannabis use.

The survey asked about several types of products used within the last year, including dried flower, cannabis oil, edibles, concentrates, topicals, and beverages. The most consumed products were dried flower, cannabis oil, and edibles. 54% of people said that they had used dried flower within the last year while 48% and 33% of people used cannabis oil and edibles respectively.[64] The amounts of self-reported use were similar to the average amounts authorized to medical cannabis patients. Those using dried flower reported using 1.8 gram per day and the average daily amount of cannabis authorized for medical use is two grams per day.[62,64]

It was interesting to note that within the medical use subset, 76% of respondents used medical cannabis without documentation from a healthcare provider. As our sample is pulled from the general population, we may expect that the users of the Strainprint app are using cannabis for medical purposes without the permission or guidance of a healthcare provider. Most self-reported medical users in the Canadian Cannabis Survey reported daily or almost daily use with 43% of respondents using cannabis at least 5 days per week.[62]

Patient Perspectives on Medical Cannabis

Patients using medical cannabis can have a complicated journey when trying to find the optimal treatment. Patients still struggle to find the right type of cannabis for their condition and are often left to use trial and error to find a product that works for their symptoms.[65] The options are even less straightforward if a patient decides to use herbal cannabis to treat their symptoms. In addition to the array of products to try, patients also have several ways to consume cannabis available to them. Over time, they may build a preference to a specific way of consuming cannabis, but this may also require trial and error to find what is effective. Adding to this difficulty, cannabis has a negative stigma associated with its use, even among medical users.

Observational studies have provided insight into the experience of being a medical cannabis user.[27,65] Since using medical cannabis can be a unique experience relative to consuming a standard pharmaceutical treatment, there are several nuances to their experience. A survey of dispensary customers in the United States identified several positive and negative themes surrounding patient perspectives of medical cannabis use.[27] The respondents elaborated on positive and negative aspects of medical cannabis use when asked what they liked most and least about the experience of using medical cannabis. When asked about the route of

administration, inhaled methods such as joints or vaporization were most common, followed by edibles and tinctures.[27] The most common positive aspects were the health benefits. Pain relief was the most common positive sub theme reported. When these medical cannabis users were describing how cannabis helped with their pain, common themes involved the dulling of the pain or changes in how they experience pain. Some dispensary customers reported that cannabis relieves pain while others mentioned that medical cannabis helps them tolerate their pain better.[27] Second to pain relief, sleep improvement was noted as a benefit.

High cost of products, respiratory irritation, and societal views of their cannabis use were reported as negative aspects of using medical cannabis.[27] The most common negative theme reported was the high cost of medical cannabis products.[27] This may be a jurisdictional problem because the participant's insurance did not cover their medical cannabis use. Next to the high cost, negative physical effects were the second most prominent theme. These included negative respiratory effects, unwanted increases in appetite and foggy cognition after use.[27] The negative stigma associated with cannabis use was the third most common theme. Participants felt that their cannabis use was frowned upon by society and in some instances their healthcare providers.[27] This negative stigma can be common for medical cannabis users.

A cross-sectional online survey conducted in 2015 assessed the stigma associated with medical cannabis use that is experienced by Canadian medical cannabis users. The majority of users found that their family and friends were supportive of their use, while their physicians were less supportive.[66] The study also noted that 80% of their sample reported hiding their cannabis use at one point with avoiding judgement and privacy being the main reasons for hiding their

medical cannabis use.[66] Canadian medical cannabis users have reported significant stigma surrounding their cannabis use from friends, family and healthcare practitioners.[67] Although the medical use of cannabis has been legal in Canada for 20 years, cannabis users still face stigma for using cannabis as a medicine. There are several factors at play that perpetuate stigma around cannabis use. Since cannabis has been illegal for decades in almost every country across the globe, people associate its use with an illegal activity. Even though the medical use is legal, for some users it does not negate the stigma associated with using an illegal substance.[67] Medical cannabis users reported family and healthcare providers assuming that their cannabis use is illegitimate and they were faking a medical issue only to gain access to cannabis.[67] Over time this stigma may fade, however, it is likely to take decades because it requires a cultural overhaul of how cannabis is viewed in society.

Healthcare Practitioner Perspectives on Medical Cannabis

Globally there is a lack of education for healthcare professionals explaining how to prescribe medical cannabis as a therapeutic.[68] Even in countries with legalized medical cannabis, trainees felt that they were not prepared to provide guidance for patients.[68] This lack of medical education surrounding medical cannabis can be detrimental for patients because healthcare providers may not be well equip to provide evidence-based information for patients seeking cannabis for therapeutic purposes. Furthermore, it has been found that trainees in medical fields use non-scientific sources of information found online rather than being provided with this information in a standardized educational format.[68,69] In places where medical cannabis is available, it is common that healthcare providers are responsible for providing or giving access

to cannabis.[69] Generally, healthcare providers are gatekeepers to medical cannabis however, their knowledge about how to properly prescribe cannabis is limited.

It is interesting to note that healthcare providers in medicine, nursing, and pharmacy are somewhat supportive of providing medical cannabis.[69] Saying that, there is a difference between being supportive of a patient using medical cannabis and actually providing medical cannabis. A provider may support a patient's decision to use medical cannabis but may not authorize the patient to use cannabis. Part of the reason why providers may not be willing to prescribe medical cannabis may be because they lack clinical knowledge. A recent systematic review found that healthcare providers had poor self-perceived clinical knowledge and believed they required further education about medical cannabis use.[69] Healthcare providers may be cautious to prescribe medical cannabis because of this lack of knowledge.

Concerns of adverse mental, physical, or societal harms of using medical cannabis are apparent when healthcare practitioners were asked about their concerns with providing medical cannabis. They are primarily concerned with adverse psychiatric drug interaction and other potential drug-drug interactions.[69] Some healthcare providers are also worried that patients seek medical cannabis under the guise of medical use while their true intentions are to use cannabis recreationally.[67,69] Although many of these concerns are valid, it is interesting that healthcare providers are concerned while their self-perceived knowledge about the clinical utility of medical cannabis is low.

Historically in Canada, medical education has not had a strong focus on medical cannabis. A survey of physicians completed by the Canadian Medical Association in 2012 reported that 80% of the respondents would like more information in the form of clinical guidelines. They would also like to understand the best therapeutic indications for medical cannabis use.[23] Canadian medical students also reported a need for more education surrounding the use of medical cannabis in clinical practice.[70] They have acknowledged there are gaps in medical education about medical cannabis, specifically regarding building a treatment plan.[70] There is clearly a lack of medical education about medical cannabis and physicians require more training to be comfortable prescribing cannabis for their patients.

A qualitative study of Canadian family physicians found that many are not comfortable authorizing or prescribing medical cannabis.[71] The reasoning for the discomfort was multifaceted. The physicians that were interviewed were concerned about adverse effects and were unsure about how to build a treatment plan. Overall, these physicians were concerned that there is limited peer reviewed evidence for the use of medical cannabis.[71] An interesting piece of information that came out of this study was the physician's attitude towards cannabis clinics. Some family physicians believed that cannabis clinics are providing patients with cannabis without properly assessing and advising the patient's suitability for medical cannabis.[71] It is important to note that this study did not claim to represent all of physicians in Canada, as some physicians may commonly incorporate cannabis in their clinical practice, and may be more willing to authorize medical cannabis.

Real-World Cannabis Use

Randomized placebo-controlled trials are the gold standard for evaluating the efficacy of a drug for a particular condition. Although physicians rely on randomized controlled trials to make clinical decisions, those types of trials are not incredibly well suited to assess the effects of a heterogeneous product with several routes of administration such as medical cannabis. Since there is such a wide variety of products available to medical cannabis users, it is common for them to move between several varieties of cannabis. This poses an additional challenge for researchers trying to evaluate the effectiveness of a medication. Looking for different ways besides randomized controlled trials may provide physicians and patients with complementary information regarding how cannabis is used to treat chronic pain.

Real-world use may provide a different perspective on how a drug is used outside of the clinical trial setting. The U.S. Food and Drug Administration describes real-world evidence as "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials".[72] Real-world data can be generated from a variety of sources including disease registries, patient generated data, electronic health records, and wearable devices. The data and conclusions garnered from real-world studies can be used to help design further trials. They can also be used to generate evidence about the effectiveness and safety of a drug when it is used in a large population. Generating real-world evidence does come with limitations. In our case, the data cannot be used to draw a causal inference for the effectiveness of the products in our dataset and it lacks a control group. However, it will help us better understand usage patterns, and which products provide better subjective symptom relief.
It is nearly impossible to design a clinical trial that assesses the vast amounts of products that medical cannabis patients use. Whereas a real-world dataset provides a big picture view on the

usage trajectory of hundreds of medical cannabis users over several years. These types of studies have been done in the past for cannabis products, but they are relatively new.

Releaf and Strainprint are prominent mobile applications developed to help medical cannabis users track and better understand which cannabis products provide greatest symptom relief. These applications are part of a growing trend in which patients are using mobile health applications.[73] There are several categories of these applications, each with different functionality and use cases. Some offer wellness and disease management, self-diagnosis, medication reminders, and patient portals as a few examples. Mobile health applications are becoming more prominent year by year, and the mobile health application market is predicted to grow at a compound annual growth rate of 17.7% over the next seven years.[74] In 2020, a total of 47,140 mobile health applications were available on the google play store and this number is expected only to grow in coming years.[74] These applications offer a secure way to grow vast amounts of real-world data.

Mobile health applications made for medical cannabis users' function as medication and disease management software. The value they provide to patients lies within their ability to make it fast and easy for people to keep track of how well their medications are managing their disease symptoms. They allow patients to easily gain insight into what works best for managing a particular condition. Cannabinoids, and specifically herbal cannabis are good candidates for evaluation in a real-world setting via data generated from mobile health applications.
When researchers are trying to evaluate medical cannabis, it becomes more difficult to evaluate because there is a large variety of cannabinoids that interact with the body's receptors in

different ways. On top of the complexity of cannabinoid pharmacodynamics, there are several routes of administration commonly used including smoked, oral ingestion, sublingual sprays, and dermal application. Herbal cannabis is the most challenging to evaluate because it is the most heterogeneous product category in terms of ingestion methods and concentrations of biologically active ingredients. Some work has been done to date by researchers evaluating data generated from the Strainprint and Releaf applications in large populations of medical cannabis users.

A study conducted with data generated from the Releaf application over a two-year period tracked the sessions of 3,341 cannabis users. During each of these sessions, users consumed cannabis and self-reported the severity of their symptoms before and after cannabis consumption. A wide variety of symptoms were tracked across the 19,910 sessions completed and there was an average symptom improvement of 3.5 points on an 11-point scale.[75] Most users consumed dried flower products and the authors found that dried flower products with higher levels of THC gave users more symptom relief while no association was found between CBD concentration and symptom relief.[75]

A second study was published with data from the Releaf application with similar findings that specifically focused on cannabis and pain. This dataset included 2987 users, tracking 20,513 sessions. Five categories of pain were measured including nerve, musculoskeletal, headache, gastrointestinal, and non-specific pain. Users reported a 3.1-point reduction of pain on average across all pain categories on an 11-point visual analogue scale.[76] This study also concluded that the users found the most relief when using dried flower products with higher THC content.[76] However, this finding was specific to musculoskeletal, non-specific, and headache pain. Products

with <10% THC were found to provide the lowest levels of symptom relief. Product testing in the United States may not be as strictly regulated as those in Canada because the United States lacks a national policy that regulates product testing. Conversely, many products in the Strainprint dataset are legally available products in Canada.

The Strainprint® application is different than Releaf because it draws most of its data from Canadian cannabis producers. Due to standardized potency testing required in Canada, it can be expected that the levels of cannabinoids in the application are true to the product. Several studies have been published using Strainprint data for conditions such as headache, post-traumatic stress disorder, anxiety, and pain. The studies published with data about cannabis use for pain relief have reported positive results. A recent study found people with muscle, joint, and nerve pain reported that 84% of all sessions conducted on the app results in decreased pain after cannabis use.[77] Users with joint pain reported the greatest pain reduction out of the three types of pain. Men also found greater pain reductions compared to the women. Self-reported data from the Relief and Strainprint applications suggest that there is potential for cannabis to provide short term pain relief for a variety of pain types. We are expecting similar results to the previously published Strainprint studies because we are using a similar dataset as previous researchers. More research is needed to further the understanding of the patterns of medical cannabis use and which factors are important for pain reduction.

Research Questions

1. Do individuals with chronic pain using medical cannabis in a real-world setting find reductions in their chronic pain symptoms?
2. How many individuals have an important reduction of pain (1cm on a 10cm VAS)?

Methods

Strainprint Application

We conducted a retrospective cohort study examining cannabis use for the management of chronic pain symptoms using anonymous archival data obtained from the medicinal cannabis tracking app, Strainprint. The app allows users to track and monitor changes in their symptoms as a function of different doses, strains, and forms of cannabis. It engages users through a loyalty rewards system where they earn points for tracking sessions of cannabis use.

Through Strainprint, users can record medical conditions, symptoms being treated, methods of ingestion, doses, emotive effects, plus pre- and post- medication symptom ratings, and cannabis product ingredients by batch, for each tracked session. Upon initial use of the app, individuals are prompted to enter basic demographic information, such as year and month of birth and sex, plus the conditions and symptoms that they will treat. When individuals are ready to track their medication session, they open the app prior to using cannabis and select the relevant symptom they wish to treat from a dropdown list of their previously chosen symptoms. Users are then taken through a set of steps where they are first prompted to rate the severity of their symptom on a 0-10-point numeric rating scale (0- LEAST severe; 10- very severe) prior to medication. Next, individuals select the cannabis they are using by product name and batch.

Strainprint pre-populates the app with lab-verified chemical ingredients by batch for all medical cannabis products sold by licensed producers in Canada. Users then select the product form (flower, oil, capsule, edible, vape pen, concentrate), route of administration (vape, oil, smoke, edible, pill, tincture, spray, concentrate, dab bubble, dab portable, oral, topical,

transdermal) and dose (drops, mg, ml, puffs) for that specific session. After an onset period that is defined by the chosen route of administration (eg. 10 minutes for smoke, 60 minutes for pill or edible, 8 hours for sleep), users are prompted with a push notification to complete their session by rating their symptom severity post-medication on the same 10-point numeric scale.

Strainprint also provides individuals with a complete history of their usage, along with product recommendations based on other user experiences with the same symptoms. As part of Strainprint's terms of service, individuals agree to share their anonymous information for research and other purposes. For the current study, we examined the data of individuals who used medicinal cannabis to manage the severity of chronic pain symptoms within the condition of chronic pain. Specific variables for this study were determined prior to data extraction and the information was subsequently provided by Strainprint stripped of identifiers.

Strainprint Staff Data Cleaning

Strainprint cleaned and organized their data prior to sending to our group. Their staff removed users from the United States with products that do not have their certificate of analysis that verifies the chemical composition of the product. They are able to determine who is gaming the application by adding fake sessions only to get points to redeem for merchandise. Users who log hundreds or thousands of sessions, with the same product, same dose, and the same effectiveness are examples of gaming. The Strainprint staff indicated that these users are a relatively small portion of the total user base, amounting to roughly 5% of the dataset. In total, 88 users were removed by Strainprint prior to sending the data, accounting for 15,546 individual sessions.

Discrepancies with certain products and their routes of administration were found. For example, a dried flower product would have an oral ingestion method, or an oil product would have an inhaled ingestion method. After discussion with Strainprint staff we removed the sessions with incongruent products and routes of administration. The data was extensively searched by looking through each route of administration by searching the "strain type" and "ingestion method" variables. The initial goal of these exclusions was to remove all the sessions in which the dosage of the product may have been incorrect. This also ensures any incorrect entries that had products with mismatched routes of administration would also be removed. In total, there were 3697 sessions removed.

Eligibility Criteria

Data in the Strainprint app was selected from February 2017 to November 2020. Patients who used any type of medical cannabis (THC, CBD or combination of THC and CBD; phytocannabinoid or synthetic cannabinoid) for moderate to severe chronic non-cancer pain (including joint, muscle or nerve pain) were eligible, regardless of age, sex, or comorbidity. We only included inhaled or ingested medical cannabis (table 2). Patients who used medical cannabis for acute pain or for less than 30 days were excluded. Individuals with less than 30 days of use were excluded to avoid people that were using medical cannabis to treat acute pain. Patients with no or mild pain (i.e. baseline pain score < 4 on a 0-10 pain scale) were also excluded. We also excluded the patients with missing age or sex information.

The original dataset included 1593 participants with 103,206 sessions. Among those, 830 patients who had less than 30 days of cannabis and one patient with baseline pain score <4 on a

0-10 pain scale were excluded. We also excluded 14 patients with missing age or sex information and seven patients with errors in routes of administration. Finally, 741 participants with a total of 83,622 sessions proved eligible. The flow diagram can be found in appendix C.

Route of Administration	Collapsed Strain Type	Collapsed Ingestion Methods
Inhaled (puffs)	Concentrate, flower, vape pen	Concentrate, dab bubbler, dab portable, Vape, Smoked
Oral (mg)	Oil	Oil
Sublingual (mg)	Tincture, Oil	Tincture

Table 2: Route of administration condensed into three categories.

Dosage Calculations

In previously published studies using Strainprint data, the number of puffs was used as the dose.[78,79,80] Initially dose was going to be included as a factor in our analysis. However, after looking through the data, we decided against using dose as a factor in the analysis. Firstly, there is large variability in the total volume of a single puff of inhaled cannabis. Some studies found average puff volumes of cannabis smoke from a joint ranged between 36ml – 55ml.[81,82] Additionally, there are several methods used to smoke cannabis, including joints, pipes, and bongs. Each of these methods produce different amounts of smoke and some include filtering the smoke through water. There is also variability when individuals vaporize cannabis. A study explored the total amount of THC that could be recovered from cannabis vapor. Of the five commercially available vaporizers, the THC levels in the vapour ranged from 51%- 81%.[83] For these reasons, we did not convert puffs to milligrams of THC or CBD and excluded dose as a factor in the analysis.

Product Labelling

The dataset included a wide variety of cannabis products. There were 1461 products in the dataset. To describe and categorize the products, they were grouped into three categories

based on the ratio of THC to CBD in the product. The decision to label products by their chemotype was made to avoid the pitfalls of the self-reported dose. The chemotype of a cannabis plant can be determined by the cannabinoid concentrations in the flower. There are five recognized chemotypes of cannabis, three of which were present in the dataset. Chemotype I, II, and III, which are high THC with little or no CBD, balanced ratio of THC and CBD, and high CBD with little THC respectively.[84] The chemotypes of cannabis are dictated by the presence of the two enzymes, CBDA synthase and THCA synthase.[84] These enzymes are coded in two codominant alleles. If both alleles for THCA are present, then the plant is chemotype I with high THC. If the plant expresses one of each, then the resulting chemotype will have roughly equal amounts of CBD and THC. In the third case when only the CBD synthase alleles are expressed, the plant will produce mainly CBD. Most commercially available medical and recreational cannabis products fall into one of these categories and it is easy for patients and medical providers to find these products when purchasing cannabis in Canada.

When it comes to a standardized classification of THC dominant, balanced, or CBD dominant variety of cannabis, there is no gold standard ratio that defines a chemotype. One study determined a variety to be THC dominant when there was 0% CBD with any amount of THC or a THC/CBD ratio of ≥5:1.[85] CBD dominant varieties has a THC/CBD ratio of ≤1:5 and balanced varieties had a THC/CBD ratio between >1:5 and ≤ 2:1.[85] Another study that used a large state-wide dataset that included the chemical testing of all commercially available cannabis products in the state-licensed laboratories. They found that the samples fell into three main chemotypes. Type I (high THC, low CBD), type II (balanced THC and CBD) and type III (high CBD and low THC).[86] Chemotype I was defined as a THC:CBD ratio of 5:1 or greater. If a product has a

THC:CBD ratio of 1:5 or lower it was defined as a chemotype III variety. Any product with a ratio less than 5:1 and greater than 1:5 was defined as a chemotype II variety.[86]

To classify the products in the dataset, the method from Jikomes & Zoorob, 2018 was chosen. The problem with using this method is that the chemotype does not correlate directly with the ingested dose of cannabis. If a product is labeled "high THC", it does not mean that an individual consumed a large amount of that product. Conversely, a product could have a low amount of THC and a person could consume a large amount of the product, resulting in a high dose of THC.

Chemotype	**THC/CBD Ratio**
High THC (Chemotype I)	5:1 or greater
Balanced THC/CBD (Chemotype II)	Less than 5:1 and greater than 1:5
High CBD (Chemotype III)	1:5 or lower

Table 3: Cannabis chemotypes defined by the ratio of THC to CBD.

Multilevel Models

Multilevel modelling is appropriate to use in this circumstance because there is both between and within subject variability. There may be differences between individual participants but also differences in a single participant's sessions over time. A simpler linear regression would not be able to account for the variability in the data. A multilevel linear mixed effects model was run for the primary analysis. Linear mixed model allows examining change in pain score by considering both within- and between-subject variability despite differences in the number of observations across individuals. It estimates time-variant slope variables at the within-subject level that are then used to predict change at the between-subject level. Thus, linear mixed models were used to examine the associations of age at baseline, sex, chronic pain symptoms, chemotype, route of administration, and duration of medical cannabis with the change of pain

score after treatment. These models included fixed effect terms for age at baseline (for every 10-year increase), sex (female vs. males), and chronic pain symptoms. Among those, chronic pain symptoms (joint pain, nerve pain and muscle pain) were entered as a dummy variable. To further control for possible interactions between the type of cannabis and time, an interaction term was included as cannabis*duration. All cannabis use related variables and outcome (pain change scores) were modeled as functions of time/sessions at the within-subjects level, and the slopes of these regressions (i.e., regression coefficients) were used to test for the between-subjects level effects. An unstructured covariance matrix for perceived stress improved the fit statistics (Akaike's Information Criterion, Bayesian Information Criterion) the most. The model was used to predict changes in pain symptom severity over time. Negative coefficients indicate reduction in pain. Statistical analysis was performed with Stata 15.1 (StataCorp LP, College Station, TX, USA).

Results

Participant Characteristics

There were 741 users included in the final analysis that had a combined 83,622 sessions. The median (IQR) age was 38 (31-46) years. The age of the app users ranged from 18 to 76 years old. Approximately two thirds of the users were female (62.62%). All users had self-reported chronic pain with one or more symptoms of muscle, nerve, or joint pain. Sessions treating joint pain accounted for 40.9% of the total sessions. Muscle pain made up 40.3% of the sessions and nerve pain was the least common symptom, comprising 18.8% of the total sessions.

Characteristic	**Mean (SD)**	**Range**
Age	38.9 (11.1)	18 to 76

Table 4: Age of Strainprint app users.

Characteristic	N (%)
App Users	741
Male	277 (37.38)
Female	464 (62.62)
Sessions	83,622
Nerve Pain	15,684 (18.8)
Joint Pain	34,202 (40.9)
Muscle Pain	33,736 (40.3)

Table 5: Sex and pain symptoms.

Product Characteristics

The dataset contained 1461 unique products. Inhaled products were the most common in our dataset with dried flower products accounting for the vast majority. In total, 78% of all products were consumed by inhalation. Of that 78%, 44.6% of the products were consumed by vaping and 32% were consumed by smoking. Concentrates, which include the ingestion methods of concentrate, dab bubbler, and dab portable were the least common inhaled products combining for 1.44% of the total sessions. Next to inhaled products, orally consumed oils were the second most common product in the dataset.

Orally ingested products were composed solely of liquid oils. These products contain cannabinoids that are mixed with an oil, such as a medium chain triglyceride. They are meant to be directly consumed or mixed with food before oral consumption. These oils accounted for 21% of the total sessions. The least common route of administration was sublingual. Sublingual products comprised 0.8% of the total sessions. These products were either oils that were dropped under the tongue, or tincture products specifically designed to be consumed sublingually.

Route of Administration	Number of Sessions	%
Oral		21.2
Oil	17698	21.2
Sublingual		0.8
Tincture	43	0.051
Oil	606	0.724
Inhaled		78.036
Vape	37,303	44.6
Smoke	26,738	32.0
Concentrate	1,104	1.3
Dab Bubbler	100	0.1
Dab Portable	30	0.036

Table 6: Product type and consumption methods.

The products were divided into three chemotypes based on cannabinoid content. In 64.8% of the sessions, users were consuming high THC products. Sessions with high CBD products were the least common, making up 14.6% of the total sessions. Products with a balanced THC/CBD ratio were used in 20.6% of all sessions.

Cannabis Chemotype	Number of Sessions
Total Sessions	83,622
High CBD	12,206/83,622 (14.6%)
Balanced THC/CBD	17,252/83,622 (20.6%)
High THC	54,164/83,622 (64.8%)

Table 7: Sessions by cannabis chemotype.

Cannabis Consumption Characteristics

Users had a median (IQR) of 24 (9-93) sessions. The median (IQR) number of days on the Strainprint app was 214 (85-490) days; however, there was a wide range of duration with some users, some only having one session and others using the app for over 3 years. There is a wide variety of legally available products in Canada, and it was common for users to switch between products over time. It took a median (IQR) 2 (1-3) sessions to switch to a different product. A switch was defined as the user changing the product, they used from one session to

another. The median amount of time users switched products was 2 (0-11) over the course of their recorded cannabis use. There was a large range of switches recorded with some users never switching products and others switching over 1000 times.

Usage Characteristic	**Median (IQR)**	**Range**
Average Sessions	24 (9-93)	1 to 4921
Treatment Durations (days)	214 (85-490)	1 to 1304
Number of Products Switches	2 (0-11)	0 to 1245
Number of Sessions Between each Switch	2 (1-3)	1 to 1228

Table 8: Product use behaviour.

Effect on Pain Symptoms

Symptom severity was measured on a scale of 0-10, where 10 represented worse symptoms. For each session, a change score was generated by subtracting the initial symptom severity from the symptom severity after cannabis use. Since some users have multiple sessions per day, the average change score for each day of cannabis use was taken to calculate the daily average change score for all users. The median (IQR) change in pain scores across all symptom categories was -3.0 (-4.5 to -2.0).

Linear Mixed Effect Model

Factors		**Beta Coef.**	**95% CI**	**P-value.**
Age	every 10-year decrease	-0.008	-0.10 to 0.09	0.87
Sex	Female	reference		

	Male	-0.69	-0.91 to -0.46	**<0.001**
Symptom	Muscle pain	reference		
	Joint pain	-0.05	-0.08 to -0.01	**0.01**
	Nerve pain	-0.03	-0.08 to 0.02	0.21
Chemotype	High CBD	reference		
	Balanced THC/CBD	-0.01	-0.08 to 0.06	0.82
	High THC	-0.08	-0.14 to -0.01	**0.02**
Route of Administration	Inhaled	reference		
	Digested	-0.05	-0.10 to 0.002	0.06
Duration of treatment (months)	every 1-month increase	0.0003	-0.004 to 0.005	0.91
Cannabis*Duration	High CBD at shorter term	reference		
	Balanced THC/CBD at longer term	-0.009	-0.01 to -0.003	**0.002**
	High THC at longer term	-0.005	-0.01 to 0.001	0.06

Table 9: Linear mixed effect model for pain reduction.

* Negative values represent greater pain reduction and 0-10 numeric rating scale for pain.

Age and Sex

As age increased by decade, there was less pain reduction; however, this amount of change was very small with 0.008-point pain reduction on a 0-10 pain scale (95% CI -0.10 to 0.09) and insignificant p = 0.87. Out of all the factors, male sex was associated with the greatest reduction in pain. Compared to female patients, males who used medical cannabis achieved greater pain relief [beta coef. -0.69 (95% CI -0.91 to -0.46), p <0.001].

Symptoms

People who used medical cannabis for joint pain had statistically significant but small pain reduction compared to those with muscle pain [beta coef. -0.05 (95% CI -0.08 to -0.01), p = 0.01]. There was no significant difference in pain relief between patients with nerve pain and muscle pain [beta coef -0.03, 95% CI -0.08 to 0.02, p = 0.21].

Type of Cannabis and Interactions

High THC and balanced THC/CBD products provided marginally better symptom relief than high CBD products. Products with high THC were superior for pain relief relative to high CBD products [beta coef. = -0.08 (95% CI -0.14 to -0.01) p = 0.02]. Balanced THC/CBD products were not independently superior to high CBD products [beta coef = -0.01, 95% CI -0.08 to 0.06, p = 0.82]. The route of administration did not have a significant impact on pain reduction [beta coef = -0.05, 95% CI -0.10 to 0.002, p = 0.06]. Over longer durations, balanced THC/CBD products provided minimally better pain reduction relative to high CBD products [beta coef. = -0.009 (95% CI -0.01 to -0.003), p = 0.002].

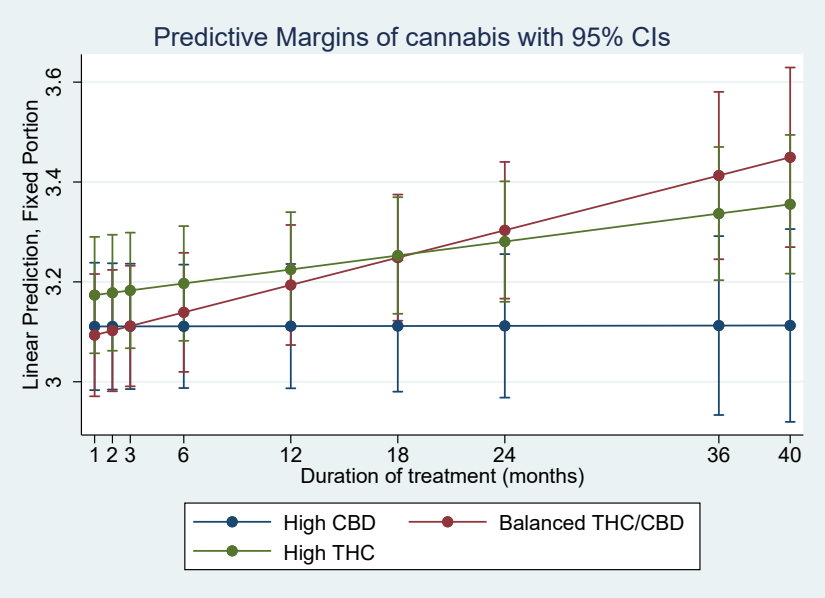

Figure 1: Predictive margins for three types of cannabis and duration of treatment (months).

Discussion

This study assessed medical cannabis use on a large scale over several years in a real-world chronic pain population. When looking at change scores in Strainprint data, it appears that medical cannabis can provide large and clinically significant reduction in chronic pain symptoms, however, in the final adjusted model these differences were negligible. The results of this study revealed that medical cannabis users have large and clinically significant reductions in pain symptoms from using medical cannabis to treat chronic pain. These findings are aligned with previous reports of real-world cannabis use.[76,77] The reductions in pain observed in this study were much larger than clinical trials have found.[87] The most recent clinical guideline gave weak recommendations for the use of non-inhaled medical cannabis for chronic pain due to the close balance between benefits and harms along with high variability in patient preferences.[32]

The results provide an understanding of how medical cannabis users have adapted to using a non-conventional medicine to treat symptoms of chronic pain. It is evident that many

people that use medical cannabis are using it to treat pain.[88] Randomized controlled trials are effective for comparing a few products for a few symptoms. However, they fail to account for the diversity of products available to medical users and the multiple routes of administration medical cannabis can be consumed by.

The individuals in our dataset showed similarities to chronic pain populations. 62.6% of our sample was female. The higher proportion of females is consistent with previous reports, as chronic pain is more prevalent in females.[5] This finding supports the reliability of the self-reported pain diagnosis in our dataset. A study done with Strainprint data looking at a broad range of symptoms also had a high proportion (58.7%) of females, so there may also be more females using this application than males.[89]

This study found that males have greater reductions in chronic pain symptoms relative to females. Currently, the state of the evidence on sex dependant differences in pain reduction after the administration of cannabinoids is limited. Preclinical evidence has shown that female rodents have greater reductions in pain after treatment with cannabinoids relative to male rodents.[90,91] However, in clinical studies, these observations have not been repeated. One study that looked at pain responses after the administration of a cold-pressor test found that men had decreased pain sensitivity after they consumed THC while women had no decrease.[91] The same study found that men and women had similar and significant increases in pain tolerance.[91] The data from our study is similar to previous clinical research but it diverges from some preclinical evidence. Another study that used Strainprint data found that men had greater reduction in pain symptoms

compared to women.[77] Whether men or women benefit more from using medical cannabis for pain is still unknown. Further research needs to be conducted to address this gap in the literature.

Our results found that age had little effect on pain reduction. There was a slight trend for older participants to have less pain reduction than younger participants; however, the change was small and insignificant with a beta coefficient -0.008 (95% CI -0.10 to 0.09) p = 0.87. It was expected that our sample would be older because chronic pain is more common in older adults than it is in younger adults.[5] Compared to a sample of over 10,000 medical cannabis users from Ontario, Canada of which 66% used cannabis for pain, our sample was on average 10 years younger, with a median (IQR) age of 38 (31-46) years.[24] Our sample may be younger than most chronic pain populations because younger people may be more apt to use a digital application to track their cannabis use relative to an older population.

The way that individuals consumed cannabis in our dataset was variable. It was rare that an individual would stick with one product consistently, as many users switched products often. The median (IQR) number of sessions before some would switch products was 2 (1-3). A likely explanation for this behaviour was that a product was not relieving pain, so they decided to try something else that would provide superior symptom relief. Not all products offered by licensed producers in Canada are in stock indefinitely. If a product were discontinued, the person would be forced to switch products. A study of authorized Canadian medical cannabis users found that over a 12-month period, 86% of 585 patients changed the type of product they were using.[92]

Additionally, any product such as cannabis that offers a wide variety of choices, may have product branding influence the consumer's decision to select one product over another. Medical cannabis users have been shown to select products not only based on the name of the cultivar, but also labels such as indica or sativa.[93] Therefore, they may try the same cultivar from a different producer. They also may switch between products to get a desired increase or decrease in cannabinoid content.[93] Differences in the quality of the cannabis may also affect their choice. Experienced cannabis users understand if a product is dry, visually unappealing, or has an unpleasant flavour profile. Cannabis users have been known to select cannabis based on the aforementioned traits of the product.[93] Cannabis users will also take price into account when purchasing a product.[94] If the price of a product fluctuates, they may also switch products.

If someone does have chronic pain, there would be an urge to quickly find a product that helps, and this is another reason why people may want to switch often. Researchers have postulated that medical cannabis users use multiple products and different routes of administration to relieve different symptoms.[95] The authors termed this practice "dose layering". For physicians working with a patient, they should understand that switching products may be common in this population. They may have to work with patients to try and find products that work using trial and error.

Route of Administration

Strainprint users frequently used inhaled routes of administration to consume products. In our study, 78% of all sessions used inhaled products, with vaping (44.6%) and smoking (32%) being the two most common inhaled methods. Concentrates, which include the ingestion methods of concentrate, dab bubbler, and dab portable were the least common inhaled products.

This data is consistent with previous reports of medical cannabis users' preferred consumption methods, as vaping and smoking are common methods of consumption for both medical and recreational cannabis users.[93,95] Although smoking and vaporization are common methods of consumption, it is interesting to note that it is not always the case.

A study of physician authorization patterns in Quebec, Canada, found that oils were the most commonly authorized products.[92] This study mainly consisted of patients using cannabis for pain as their primary complaint. Since we do not know if our users had been prescribed cannabis by a physician, their product choices may not have been influenced by a healthcare provider. Healthcare providers may be more likely to prescribe orally consumed products due to the harmful effects of smoking cannabis on the lungs. Strainprint users may not have had an advising physician, as cannabis can be legally obtained without a medical authorization in Canada. The lack of physician oversight, paired with the lower price and higher abundance of dried cannabis products may be why inhaled routes of administration were common in our dataset.

Oils and sublingual tinctures were consumed in 22% of all sessions. The dominant form of orally consumed products were oils which made up 21.2% of the total sessions. Oils are a common way of ingesting medical cannabis and have the added benefit of a long duration of action relative to inhaled products. When inhaled products were compared to orally consumed products, neither route of administration significantly helped to reduce pain. Since there was no difference in pain reduction between the two methods and smoking cannabis can result in damaging the respiratory system, it may be recommended that cannabis should be consumed

orally. Oral administration does not have a negative effect on the respiratory system and has the added benefit of prolonged action relative to inhaled cannabis. A recent systematic review determined that non-inhaled medical cannabis use provides small to very-small improvements in pain relief, furthering the case for using orally consumed products.[87]

Chemotype

Although we do not know why the users chose to use certain products, it was evident that many sessions involved products higher in THC and lower in CBD. In 64.8% of all sessions, high THC products were used. Products with a THC ratio of 5:1 or more was the most popular in this chronic pain population. THC has been shown to inhibit the transmission of pain signals and a study previously done with real world data also found that cannabis users frequently select high THC products.[12,89] When medical cannabis users were surveyed about their top reasons for selecting a product, high THC was the second most important factor.[93]

We found that products with higher ratios of THC/CBD provided improved pain relief and products with low THC/CBD ratios provided less relief; however, the differences were trivial. Studies with similar real-world data have found similar and conflicting results. One study found that a product with higher amounts of THC was the greatest predictor of pain relief.[76] The same study also had similar results to ours in regard to the therapeutic effect of CBD, where CBD potency did not predict pain relief. We also noted products with balanced THC/CBD ratios also provided superior pain relief relative to high CBD products over time. We can speculate this because products high in CBD were less effective than products high in THC, so the THC in the balanced products may be responsible for the pain reduction. It may also be that both CBD and

THC are providing some level of pain relief. Over time, products with a balanced ratio of THC/CBD provided better pain relief than high CBD products whereas products with low ratios of THC/CBD (1:5 or lower) provided less pain relief.

Symptom Reductions

Strainprint users reported large reductions in the pain symptom of joint, muscle and nerve pain. The median (IQR) reduction in pain reported was -3.0 (-4.5 to -2.0). Previous studies using Strainprint data have reported similar findings. A recent study looking at the same symptoms found that in more than 84% of all sessions Strainprint users reported a reduction in pain symptoms.[77] Another study using data from a similar application to Strainprint, called Releaf, found the average reduction in pain was roughly 3 points on a 0-10 scale.[76] These reductions in negative symptoms are remarkably consistent across studies that track medical cannabis use via a mobile application, no matter the symptom. Other Strainprint studies have found similar reductions in negative symptoms such as headache, migraine, and post-traumatic stress disorder.[79,80]

When these results are contrasted with results from clinical trials, it seems that people are finding a higher degree of pain relief in real-world studies compared to clinical trials. There could be several reasons for this finding. Perhaps in real-world studies, patients eventually find a product that works well for them, through trial and error. Whereas in a clinical trial they are stuck with a single product during the trial period that may only work well for a portion of the trial participants. It is also possible that individuals that do not benefit from medical cannabis choose to stop using the app, therefore biasing the sample to people that derive benefit from medical cannabis. In addition, observational studies do not disentangle specific and non-specific

effects, and a recent systematic review of randomized trials found that 52% of patients randomized to placebo reported important improvement in pain relief.[87]

Limitations

There are several limitations to this study. First, all the data used in the study is self-reported and users may not accurately report the product or dose they used. There is also a financial incentive for Strainprint users to complete sessions, as they are rewarded with Strainprint points. Once users accumulate enough points, they can redeem those points for goods such as clothing and electronics. This may influence users to complete sessions only to redeem points, thereby corrupting the data. Although Strainprint did remove users that may have been gaming the system, it is possible that not all these users were removed.

Another limitation is the lack of a clinical diagnosis of chronic pain. Without the insight of the clinician, we may not know how many users in the dataset truly qualify for a chronic pain diagnosis. This limitation has implications for the accuracy of the results. There may have been people that were using cannabis for recreational and medicinal purposes. Without the diagnosis of chronic pain, we cannot say that all users were consuming cannabis only for pain relief. The lack of a control group was another significant limitation that could have introduced expectancy effects. It is also not known if users were consuming cannabis prior to tracking their sessions on the application. Some people may have been heavy cannabis users and built tolerance while others may have never tried cannabis before. It is possible that more experienced users have learned which products provide better symptom relief. In addition, because the dose information was not accurate, we could not run any dose-response relationship to explore the optimal dose of THC or CBD.

Since we found that most users report reductions in pain, it may be possible that the users that find benefit from cannabis, continue to use the application, while those that do not benefit, stop using the application. Therefore, our user base may be skewed toward people that only benefit from using medical cannabis. 830 app users were excluded from the analysis because they had less than 30 days of cannabis use. There are several reasons for app users having less than 30 days of use. Negative side effects such as dizziness and drowsiness are common when using medical cannabis.[87] It is possible that people that experience negative side effects and stop recording their cannabis use.

Another limitation of the study is the lack of basic demographic factors that could have been used as covariates in the analysis. The data did not include demographics such as socio-economic status, education, disability, and ethnicity. Additionally, we lacked measures of quality of life, function, and mental health. Having these measures would have allowed us to determine the impact of cannabis use on additional outcomes that are important to patients other than pain relief.

Conclusion and Future Directions

People suffering from chronic pain may choose medical cannabis to alleviate their symptoms.[88] Previous systematic reviews and guidelines have recommended medical cannabis as a third line therapeutic for chronic neuropathic pain that may provide small reductions in chronic pain.[22,33] A 2021 guideline provided a weak recommendation for the use of non-inhaled medical cannabis for the management of chronic pain, due to the close balance between benefits and harms.[32] Our analysis showed that there were large improvements in chronic pain symptoms, and

these reductions in pain would likely be significant to patients. The findings from this study indicated that medical cannabis may provide reductions in pain, however, the reductions in pain symptoms were much larger than in previous randomized controlled trials.

Many studies done on real-world cannabis use have found that users are reporting benefits for treating a wide range of symptoms.[75,76,77] There is a strong signal coming from self-reported, real-world cannabis use that is not reflected in the results of randomized controlled trials. It is nearly impossible for a randomized controlled trial to account for the diversity of cannabis-based medicines used for multiple chronic pain conditions. HIPAA, PIPEDA, and PHIPA compliant applications such as Strainprint are important for conducting real-world studies. They provide researchers with secure access to large scale datasets that can be used to run complementary studies to randomized controlled trials. These studies will become more common as researchers gain access to large datasets such as the one provided by Strainprint. Real-world data generated from these studies provides a different perspective on how medical cannabis is used outside the rigid format of a clinical trial. Real-world data may not be the best for comparing the efficacy of a substance against a placebo or active comparator. They may be more valuable for determining why certain products are chosen over others and which dosages and routes of administration are common. These learnings can then be used to inform the design of future randomized controlled trials or clinical practice.

A significant limitation of this study was lack of diagnosed chronic pain. It would be ideal if there was an option to differentiate between users that are using medically or recreationally. Going forward, applications such as Strainprint that are privacy compliant should

try to incorporate electronic health records that indicate whether a user has a clinical diagnosis. This would allow researchers to separate medical and recreational users to make more accurate conclusions. If future applications can integrate electronic health records, it would be possible to include data about comorbidities that could also make a more robust analysis.

We have seen that medical cannabis users change the products they consume often when they have many products available to them. Although we cannot determine whether these product changes are directed by a healthcare provider or made by the person themselves, medical cannabis users often change the product they use with several potential reasons for switching. Further research should focus on the reasons why these changes are being made and what can be done to mitigate the number of changes. Reducing the amount of product switching may help medical cannabis users spend less time and money finding a product that works for them. It would also be interesting to know if medical cannabis users change products often in areas where there are limited medical cannabis products. This study did not uncover why products were selected over others. It is important to know in future studies how patients and their physicians come to find and try certain products over others for chronic pain. There is also much work to do in determining optimal dosing regimes and routes of administration that work best for chronic pain. Real-world studies such as this one may be useful in informing future designs of clinical trials to answer these research questions.

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Appendix

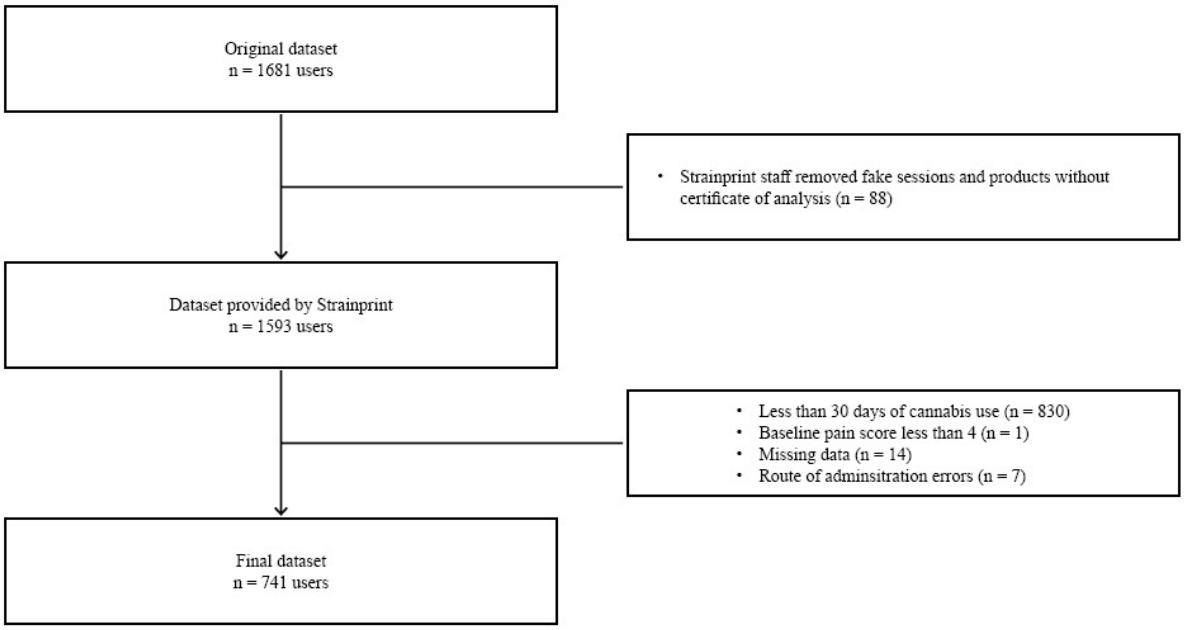
Appendix A

	Model 2			
	Coef.	**[95% Conf. Interval]**		**P-value.**
Age (every 10-year increase)	-0.008	-0.10	0.09	0.87
Sex (Female vs. Male)	0.69	-0.46	0.91	<0.001
Symptom				
Muscle pain vs. Joint pain	-0.05	-0.08	-0.01	0.01
Nerve pain vs. Joint pain	-0.01	-0.06	0.04	0.57
Type of cannabis				
Balanced THC/CBD vs. High CBD	0.01	-0.06	0.08	0.82
High THC vs. High CBD	0.08	0.01	0.14	**0.02**
Mode (Inhaled vs. digested)	-0.05	0.06	-0.10	0.06
Duration of treatment (months)	-0.0003	-0.005	0.004	0.91
Cannabis*duration				
Balanced THC/CBD	0.009	0.003	3.04	**0.002**
High THC	0.005	0.003	1.92	0.06
Sex#cannabis				
Female#Balanced THC/CBD				
Female#High THC				
AIC	125934			

Appendix B

	Model 3			
	Coef.	**[95% Conf. Interval]**		**P-value.**
Age (every 10-year increase)	-0.009	-0.10	0.09	0.86
Sex (Female vs. Male)	-0.76	0.51	1.00	<0.001
Symptom				
Muscle pain vs. Joint pain	-0.04	-0.08	-0.009	0.01
Nerve pain vs. Joint pain	-0.02	-0.07	0.03	0.52
Type of cannabis				
Balanced THC/CBD vs. High CBD	0.13	0.07	0.19	<0.001
High THC vs. High CBD	0.12	0.06	0.18	<0.001
Mode (Inhaled vs. digested)	-0.05	-0.10	0.003	0.07
Duration of treatment (months)	0.005	0.003	0.007	<0.001
Cannabis*duration				
Balanced THC/CBD				
High THC				
Sex#cannabis				
Female#Balanced THC/CBD	-0.19	-0.31	-0.07	0.002
Female#High THC	-0.05	-0.16	0.06	0.35
AIC	125930			

Appendix C


Original dataset
n = 1681 users
Strainprint staff removed fake sessions and products without certificate of analysis (n = 88)
Dataset provided by Strainprint
n = 1593 users
Less than 30 days of cannabis use (n = 830)
Baseline pain score less than 4 (n = 1)
Missing data (n = 14)
Route of adminsitration errors (n = 7)
Final dataset
n = 741 users