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Practical implications of cannabis as an alternative to opioids in pain management

Bachelor's Thesis

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CONTENTS

ABSTRACT

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Background: Prescription opioid use has been growing in many countries around the globe. The growth of opioid use, however, has not come without side-effects. Substance dependency, abuse and even death from opioid overdose are emerging concerns that have not so far been addressed sufficiently. At the same time more and more countries are decriminalizing cannabis and approving its use for pain management. Patients are seeking help from cannabis for various medical conditions and anecdotal evidence from patients' self-report rather than scientific evidence begs a question as to whether cannabis could serve as pain medication and be an alternative to prescription opioids.
Objective: To investigate existing scientific literature of cannabis use along with opioids and its effects to fathom its validity as an alternative to opioids.
Methods: Scoping literature review of publication concerning the use of medical cannabis in pain treatment along with or as substitute for opioids.
Results: 11 out of 13 studies reviewed observed varying degrees of pain relief using cannabis over opioids under certain specific conditions. Reduction in opioid consumption was observed in five studies while one study saw no significant impact on opioid consumption.
Conclusions: There appears to be some benefits in certain situations however cannabis certainly does not appear to be a drop-in replacement for opioids in chronic pain management. More research is required to determine accurately the conditions and types of pain that cannabis can efficiently manage. It is important to understand as a nurse how cannabis works and provide guidance to patients if they encounter such patients.

Keywords: cannabis substitute for opioids, cannabis pain management, cannabis opioid pain, opioid alternatives.

1 INTRODUCTION

Opioid prescription for pain and its fallout are a global trend, owing to pharmaceutical companies' persistent advertising and doctors willing to prescribe opioids without much consideration. Many in developed countries are seeing consequences surrounding their beloved ones and communities from opioid abuse. Countries afflicted by opioid crisis or addiction have seen their communities, schools and workplaces affected, their healthcare resources gradually exhausted and the young in a vulnerable position. This widely spread crisis calls for international solutions on a global level. (American Federation of Teachers 2018.)

The increased prescription rates has also led to rising trend in opioid related deaths (Marie, Arnstein, and Zimmer 2018). These developments along with the relaxation of laws pertaining to consumption of cannabis in certain regions have sparked new scientific interest in discovering whether cannabis could provide alternative chronic pain treatment options to supersede opioids.

Pain management is a critical part of adequate care provided in nursing. Ineffectively managed pain can have significantly harmful impacts on the patient physically and mentally and it remains an area that requires improvements in implementation on a global level (Glowacki 2015).

Pain causes not only just the sensation of pain, but also creates many other issues concomitantly such as reduced mobility and declined wellbeing, disturbed sleep, substantial economic impacts from the cost of pain medications, risk of addiction and even biological changes to the nervous system (Institute of Medicine (US) Committee on Advancing Pain Research, Care 2011.)

Pain can be categorized in two main groups as acute pain and chronic pain. Acute pain, characterized by sudden onset of pain, which is expected to last relatively a short time, can lead to the development of chronic pain. Acute pain usually recedes as the underlying cause is resolved. Acute pain can also be recurring or episodic without being chronic. Chronic pain, on the other hand, is regarded as pain that has been ongoing for a longer period at least for three to six months. It can incapacitate a person's ability to function and lead to an increased risk of mental issues such as depression and anxiety. Suffering from chronic pain is an ancillary cause of mental health issues (Institute of Medicine (US) Committee on Advancing Pain Research, Care 2011.)

The first instinct when considering the causes of chronic pain is to attribute its existence to an injury, an invasive surgery or pathophysiological conditions. However not all chronic pain has a clear cause and some illnesses such as chronic headaches, temporomandibular issues or fibromyalgia often have no attributable cause (Institute of Medicine (US) Committee on Advancing Pain Research, Care 2011).

Pain is created from the stimulation of peripheral nociceptors which release neurotransmitters and they subsequently trigger a signal that is transmitted via peripheral nerves to the dorsal root ganglion. From it the signal is injected into the spinothalamic tract through which it traverses to the thalamus producing the sensation of pain (Glowacki 2015.)

1.1 Opioid crisis – rising health concerns worldwide

A staggering number of Americans have seen their lives taken from overdoses of prescription opioid medications (POMs). As countermeasures, states are establishing policies in a bid to reduce POM-inflicted harms, prevent overdose, and seek alternative cures for pain, such as medical cannabis (Vyas, LeBaron, and Gilson 2018.)

The Centers for Disease Control and Prevention (CDC) report that prescription opioid for pain killers and heroin took a toll on more than 28,000 lives in 2014, the highest annual figure ever recorded until that year. However, this number has done little to inhibit opioid prescription and consumption patterns. The CDC estimates that the amount of prescription opioids sold in the U.S. is about four times greater, yet it has not made any remarkable difference in the amount of pain Americans live with (Reiman, Welty, and Solomon 2017.)

As of 2018, the US president declared a state of opioid crisis in the nation, calling it a public health emergency. Opioid abuse leads at least as many as a hundred to death daily, leaving the country the biggest costs ever (Mindock 2018.)

The institutionalized practice of overdosing opioid-based pain medication is the number one cause of accidental death in the United States. It appears to be necessary to find out alternative pain medication to opioids to address this matter. Cannabis can be an effective alternative option for pain, for it mitigates the chance of substance dependence and erases the risk of detrimental

overdose compared to opioid-based pain medications. Patients in their self-reports who use medical cannabis claim that cannabis is just as effective a way of pain management as opioids, if not more than opioid-based pain medications (Reiman, Welty, and Solomon 2017.)

1.1.1 Similarities in Canada

The opioid crisis is not an exception in the US neighbouring country, Canada. In an evidence synthesis article published by Belzak and Halverson (2018), both illegally obtained and prescription opioids claim eight deaths on a daily basis, a total of 2861 deaths in 2016 and 16 Canadian residents were hospitalized on a single day due to opioid-related incidents in the same year (Belzak and Halverson 2018). The opioid crisis is not just viewed as an individual's problem, but also as a national public health crisis affecting people of all walks of life and all backgrounds across the nation.

The current trend is in proportion to what has become a rampant use of prescription opioids in recent decades. Canada saw a more than 3000% increase in the quantity of prescription opioids sold to hospitals and pharmacies since the record began in the early 1980s. Almost one adult above the age 18 has been prescribed opioids, over 20 million prescriptions known to be dispensed in 2016, rendering Canada the second biggest opioid consumer country following the US (Belzak and Halverson 2018.)

Harms caused by prescription opioids and rates of prescription opioid abuse cases have been on the rise since 1999. Opioid prescription for nonmedical purposes was assessed to be the fourth most common after alcohol, tobacco and cannabis and an easier way to misuse than gaining access to heroin or cocaine (Belzak and Halverson 2018).

According to Canadian Tobacco, Alcohol and Drugs Survey (CTADS) in 2015, it found only 2% of people who reported misusing prescription opioids among the population that used a prescription opioid, but in a later online survey conducted by Health Canada in 2017 showed that not everyone of opioid users possessed a prescription. It also found out that the most common way of obtaining opioids without prescription was through family members while among other routes were, for example, a practice of double doctoring (patients seek many doctors to have them prescribe the same medication or different one with the same effect as the one they have previously been

prescribed), forgery, street market, thefts, robberies and online purchases, and this makes it challenging to estimate the exact rate of diversion from prescription opioid to misuse and could signify the numbers might be even greater (Belzak and Halverson 2018).

According to a Canadian government report published in 2019, there was a big surge in the percentage of opioid-inflicted deaths on the national level between January 2016 and June 2017. More than 13,900 deaths occurred between January 2016 and June 2019, with Western region being the most affected. Other regions have also seen increases in death rates and there were 17,050 hospital admissions due to opioid poisoning between January 2016 and March 2019 (Government of Canada 2020.)

1.1.2 Less severe trends in the UK

Some news articles have raised concern that the opioid crisis is spreading from the United States of America into Europe. Express (2019) reported in a sensational fashion that the United Kingdom saw an all-time high of more than 40,000 hospital admissions followed by opioid intoxication and the number of dispensed opioids jumped to 40,5 million, up by more than 20% in the previous year. Express went on saying the nation's pain-killer poison cases hit a new high, citing a 41% increase in fatalities due to painkillers from ten years prior to the publication of the article. A study by Cooper et al. (2017) supports this observation, noting that data published by Office for National Statistics did indeed show an increasing trend in opioid related fatalities from 2001 to 2011.

The trend is at least partially explained by similarly increasing number of opioid prescriptions during the same time span. In addition, the team pointed out that using mortality statistics as a sole indicator is not reliable, because such number does not consider other factors and underlying reasons that may lead to opioid overdose. Cooper et al. (2017) studied Clinical Practice Research Datalink (CPRD) data in between 2008-2012 and evaluated that of the 1 550 307 people who were prescribed opioids during the study timespan only 715 (0,05%) were later diagnosed with opioid use disorder and only 465 (0,03%) were incident cases in which the patient had at least 6 months or more of healthcare records preceding the start of the study which indicated no evidence of opioid use disorders. The results also indicated that incident cases per 10000 patient-years exposed to opioid pain management did not show a rising trend between 2008 and 2012.

In the same study by Cooper et al. (2017) it is mentioned that with the healthcare system and opioid prescription practices of the US not comparable to those of European countries, it is hard to expect a similar crisis to happen outside of North America. Contrary to the US, little information is available about the links between opioid prescription and subsequent misuse cases or development of opioid use disorder in the UK. Similar arguments were made in a news article Yle (2019) by a Finnish doctor as she was saying an opioid epidemic on such a scale as in the US is not possible in Finland where doctors' remuneration is not commensurate with patients' satisfaction or how doctors cater to patients' desire for opioid prescription.

1.2 Opioid prescription on the rise in Finland

The use of strong opioid, Oxycodone, continued to grow remarkably in Finland. Figures released from Kela showed that the number of users had increased by thousands within a couple of years. In 2016, Oxycodone expenses were reimbursed to more than 37,000 people residing in Finland and according to a preliminary estimation, the number was expected to rise upto 45,000 by the end of 2018. Finland's Social Insurance Institute KELA stated in 2018 that it had reimbursed approximately 400,000 residents for opioid medication expenses annually (Helsingin Sanomat 2018.)

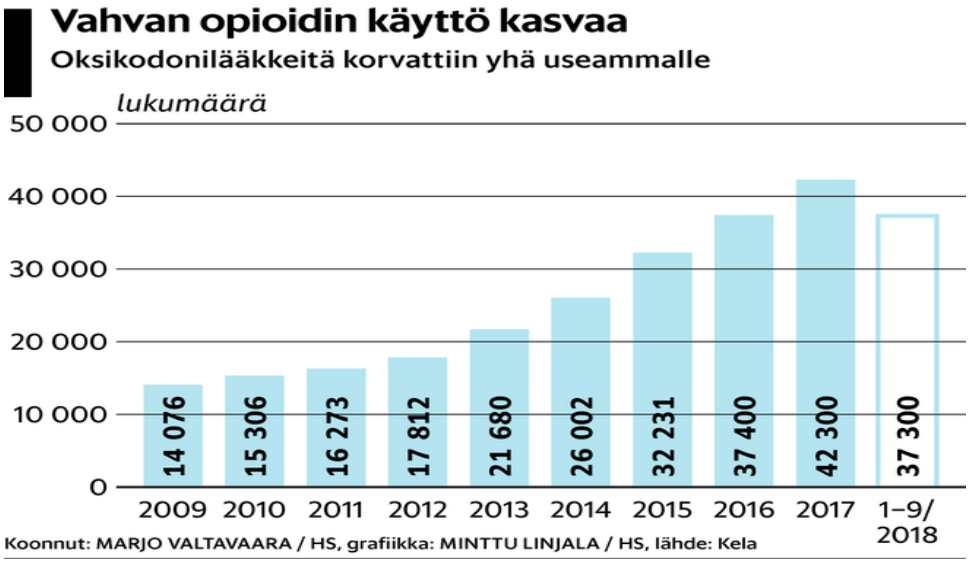

FIGURE 1. Increase in prescription opioid use in Finland (Helsingin Sanomat 2018).

In 2018 KELA was to send letters to some 7,000 doctors and dentists to order cautions in prescribing powerful opioids. The institution started to send similar letters as guidance on prescription from 1997 and in 2017 it had issued a warning to physicians against prescribing large amounts of Cocodamol, a compound analgesic containing codeine and paracetamol (Yle 2019.)

In 2019, KELA raised a voice of concern over an unprecedented rise in strongly addictive oxycodone purchases covered by health insurance. Oxycodone is sold under the brand name of Oxanest, Oxycontin and Oxynorm in the country. Health officials expressed their concerns that the country might see a similar opioid crisis as in the United States and the spike sent the officials on alert to fend off such a similar case (Yle 2019.)

1.2.1 The driving force behind the rise

This phenomenon was reflected in patients in substance abuse hospital, whose main problem was addiction to Oxycodone. The problem was iatrogenic, which originated from the use of prescription medication as far as Oxycodone was concerned. Oxycodone use continued as a mode of pain treatment even though continuation of the drug was not recommended anymore. Doctors at some point noticed that they should have discontinued it and then stopped the treatment, forcefully weaning patients off the analgesic as a result. Substance abuse patients under care were most

likely to be diagnosed with opioid use disorder (OUD). There were more amphetamine misusers than those of opioid but opioid withdrawal symptoms are known to be most intractable and persistent (Helsingin Sanomat 2018.)

The use of electronic prescription may have unnecessarily facilitated the renewing of prescription for opioids. Chronic pain treatment is demanding, and the results can be fruitless regardless of what mode of treatment chosen. This leads empathetic professionals to prescribing opioids with their patients in the grip of pain (Helsingin Sanomat 2018.)

The risk of medical opioid abuse accounts for about 20-30 % in long-term use, which means one in five people on long-term opioid treatment begins to misuse the analgesic otherwise than the original purposes. Nearly 200 people died annually in Finland from opioid-inflicted intoxication in recent years while pharmaceuticals make billions in opioid profits (Helsingin Sanomat 2018.)

1.3 Cannabis as pain medication

Medical cannabis is dried material obtained from cannabis plant that contains THC, cannabidiol and other cannabinoids. Medical cannabis and recreational cannabis may be alike in appearance. Therapeutic effects are dependent on THC concentration and the ratio of THC to cannabidiol due to cannabidiol's ability to counteract the effects of THC. The ratio can be tailored artificially to gain desired effects (Hill 2015.)

The interest in cannabis and cannabinoids to relieve chronic non-cancer pain is mounting, partly because of the issues regarding opioid based pain medication, which has been offering enough fodder for controversial debates over cannabis' medicinal properties. (Campbell et al. 2018) Many patients suffering musculoskeletal problems report using medical cannabis to abate chronic pain. If marijuana can provide an alternative to addictive analgesics in states where medical marijuana is legal, a positive outcome of medical cannabis laws may contribute to a reduction in harms associated with the use of more addictive and fatal opioids. Broader availability of medical cannabis may eventually offer a potential benefit of curtailing the use of highly addictive analgesics. (Powell, Pacula, and Jacobson 2018) Multiple studies suggest that using medical cannabis and opioids helped individuals suffering from intractable pain take less pain medications including opioids that led to less side effects. Reduction in opioid doses and experiencing less of undesirable effects

subsequently contributed to improved quality of life, decreased opioid-related fatalities and less hospital admissions due to addiction in states where legal access to medical cannabis was possible (Clem, Bigand, and Wilson 2020.)

Cannabis is a unique mode of treatment due to its incompatibly overlapping attributes when used medically and recreationally. Prescription opioids for medical conditions are often followed by severe addiction and abuse while the opposite is the case with medical cannabis. Cannabis users are likely to have first experienced recreational cannabis before they use it as a method of pain management. And despite such preceding experience, medical use of cannabis did not necessarily resulted in patients using cannabis recreationally, from which a fairly low chance of misusing it after treatment can be extrapolated. Findings show that only 7 or less than 3 % of participants reported continuously using cannabis after treatment (Lucas and Walsh 2017.)

1.4 Chemical composition and medicinal values of cannabis

There are more than five hundred chemical compounds in cannabis amongst which cannabinoids are one class of various chemical compounds and more than 100 different cannabinoids are believed to have been found. One of the most commonly known cannabinoids is delta-9-tetrahydrocannabinol (THC) that can induce psychosis and accounts for high feeling, triggering changes in perception, mood, emotion, cognition and motor function. Cannabidiol (CBD) is another type of cannabinoid that gained attention for Its non-psychoactive and medically useful properties in 2010s. (Russo 2011; UCLA Health 2019.) It is known to possess antianxiety and antipsychotic effects that counteract THC's effects and is used to help with various medical conditions such as anxiety, depression and psychosis (Hill 2015; United patients group 2014.)

1.4.1 Tetrahydrocannabinol (THC)

THC is the main psychoactive component in cannabis. It produces effects of relaxation, pain alleviation and appetite promotion as it binds to cannabinoid receptors. THC has medicinal benefits, thus is useful in treating many illnesses. It is known to contribute to reducing nausea and vomiting in chemotherapy patients and boosting appetite for AIDS patients who suffer decreased appetite. US Food and Drug Administration (FDA) approved two cannabinoids, dronabinol and nabilone, that are used for abovementioned conditions (Hill 2015; United patients group 2014.)

According to (Donvito et al. 2018) THC has been consistently proven to perform well in reducing a large variety of neuropathic pain states in humans. THC has been proven to produce pain-relieving and anti-hyperalgesic effects in animal samples and in an experiment performed on healthy adults or clinical pain samples. In an intradermal capsaicin-induced pain response test on 15 subjects by (Wallace et al. 2007) drew a result that smoked cannabis in different doses (low, medium or high and placebo) produced different effects on pain level, with medium dose contributing notably to pain relief, and high dose leading to a significant increase in pain level, in which the authors reached a conclusion that smoked cannabis is likely to possess a range of doses that produce therapeutic effects. Low dose did not make any remarkable differences in pain level and no effect was observed on hyperalgesia at any doses (Hill et al. 2017.)

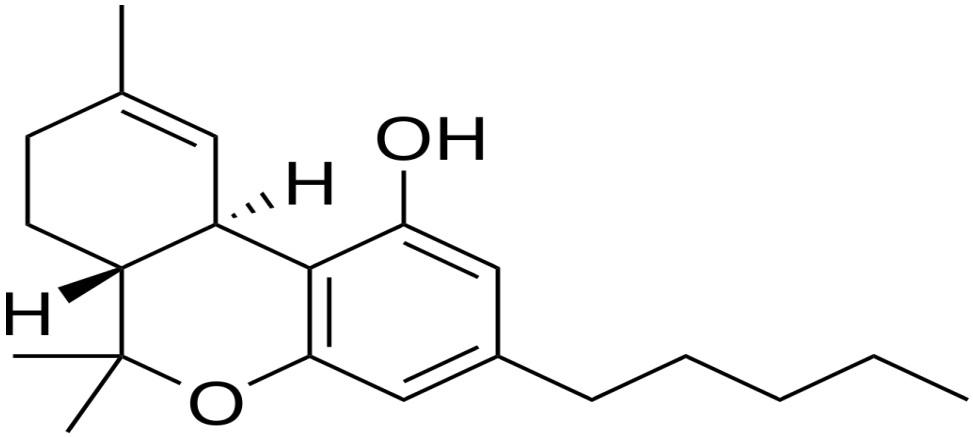

FIGURE 2. Chemical composition of THC.

1.4.2 Cannabidiol (CBD)

CBD is the primary non-psychoactive phytocannabinoid found in the cannabis sativa plant. It accounts for about 40 % of the plant extract. The absence of the psychotomimetic and psychotropic effects found in the other main plant compound THC inspired investigation into pharmacological properties of CBD and it has been revealed that CBD is a potential treatment regimen for various non-psychiatric and psychiatric illnesses such as anxiety, depression and psychosis. Extensive investigations into the pharmacological effects of CBD, however, have failed to explain clearly the mechanisms involved in these effects (Campos et al. 2012.)

In 2018, the US Food and Drug Administration (FDA) approved the use of CBD-based medical cannabis for treatment of difficult epilepsy episodes. Cannabidiol on the other hand has limited research on its pain-relieving effects and further research is needed for more definitive conclusions (Donvito et al. 2018.)

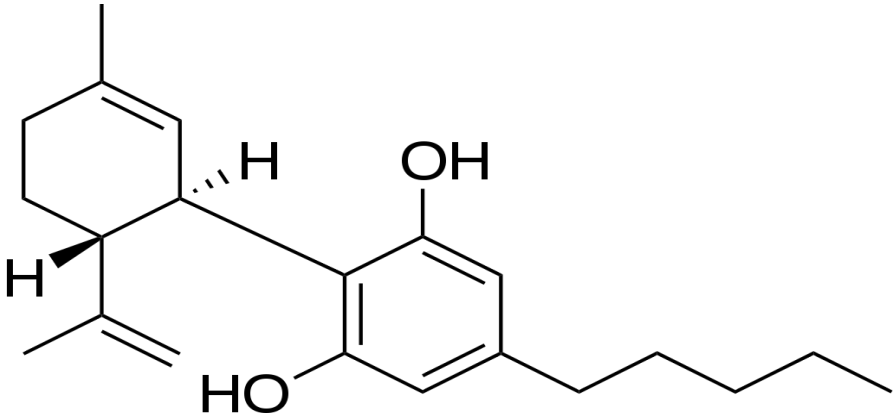

FIGURE 3. Chemical composition of CBD.

1.4.3 Cannabinol (CBN)

THC exposition to light and oxygen creates cannabinol (CBN). It produces mildly psychoactive effects and is a cannabinoid that is a metabolite of THC. it is usually found in small quantities in live, generally older cannabis plants. At least 7 cannabinols have been identified (ElSohly and Slade 2005). According to Karniol et al. (1975) CBN is likely to amplify the effects of THC. Reportedly CBN has anti-epileptic, anti-spasmodic, anti-depressant, and intraocular pressure relieving effects. It can also help prevent convulsions and sedate patients undergoing pain. Other promising implications of CBN are for glaucoma, inflammation and insomnia. CBN, so-called natural aspirin or non-narcotic analgesic is believed to be three times more potent. Taking the lustre off the medicinal values of CBN is, however, its giddy and groggy physiological side effects (United patients group 2014.)

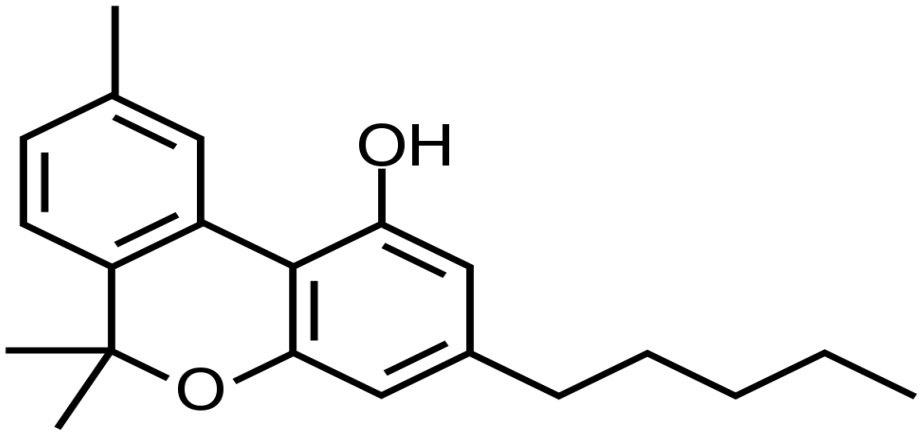

FIGURE 4. Chemical composition of CBN.

1.4.4 Tetrahydrocannabinolic Acid A (THCA-A)

Tetrahydrocannabinolic acid A is the acidic form that turns into tetrahydrocannabinol. Through biosynthesis THCA-A accumulates in the flower and leaf part of cannabis plant, accounting for 90 % of the whole THC in the plant. Decarboxylation of THCA-A during storage, fermentation, baking, smoking and vaporizing forms THC and THCA-A can further separate into cannabinol by adjusting temperature, level of light, and auto-oxydation. THCA-A does not cause psychotropic effects in humans and the term THCA is commonly used to refer to other acidic THC derivatives without distinction (Moreno-Sanz 2016.)

Several investigations indicate that THCA-A interacts with a few molecular targets and yields pharmacologically notable results such as anti-inflammatory, immunomodulatory, neuroprotective, and antineoplastic effects. Some in vivo studies conducted with this compound in rodent samples also reveal that it triggers pharmacological actions, explained by engaging in interaction with CB1 receptors (Moreno-Sanz 2016.)

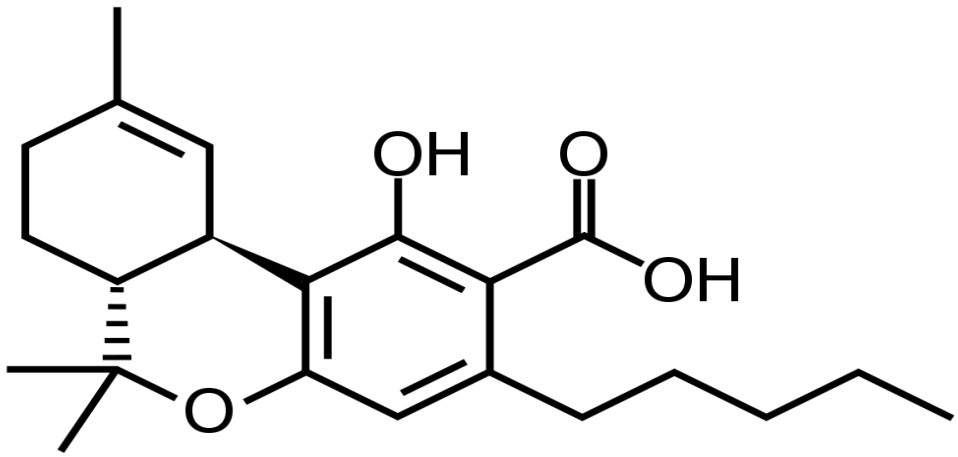

FIGURE 5. Chemical composition of THCA-A.

1.4.5 Cannabichromene (CBC)

Cannabichromene is a natural, non-psychotropic cannabinoid among many others that abound in the cannabis plant. It is especially rich in freshly harvested dry bud and known to be the second most abundant compound. Despite its abundance, little has been explored about this compound. According to reports, CBC induced prolonged hexobarbital hypnosis in mice and rodents. Researchers observed activity related to anti-inflammatory, analgesic, antimicrobial and antidepressant effects. CBC caused no observable effects similar to those of THC when consumed intravenously by Rhesus monkeys or smoked by humans (Izzo et al. 2012.)

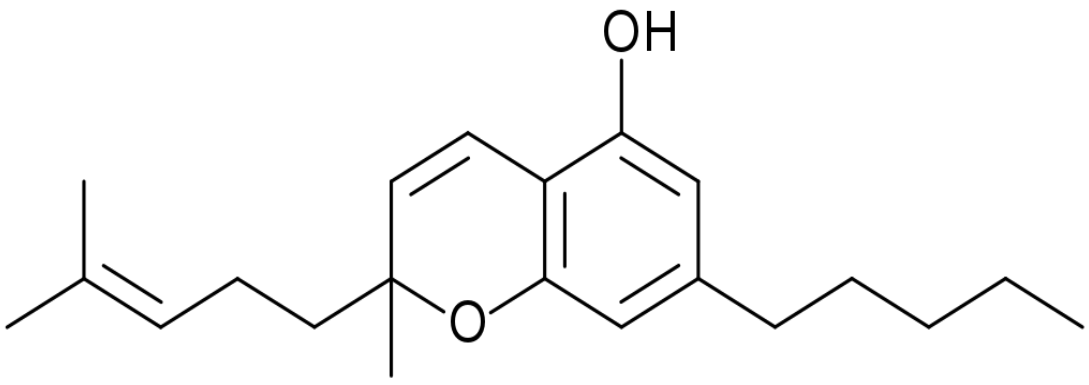

FIGURE 6. Chemical composition of CBC.

1.4.6 Medical properties of cannflavin A and B

Cannflavins are flavonoids or chemical compounds found in cannabis sativa plant. Cannflavins A (shown in FIGURE 7) and B (shown in FIGURE 8) were first found in 1985 and known to possess anti-inflammatory properties that were approximately 30 times more potent than acetylsalicylic acid, aka Aspirin when measured gram-for-gram. Deeper investigations into these molecules, however, have been mothballed for years partially due to stringent regulations on cannabis (Akhtar 2019.)

A research team in University of Guelph has discovered how these pain-relieving molecules are created in the cannabis through a combination of biochemistry and genomics, signaling a potential to invent a novel way to effective pain relief without suffering the risk of dependency of other conventional pain medications. These molecules strike the inflammation at its source and their non-psychoactiveness has much to recommend it as ideal alternative painkillers (Akhtar 2019.)

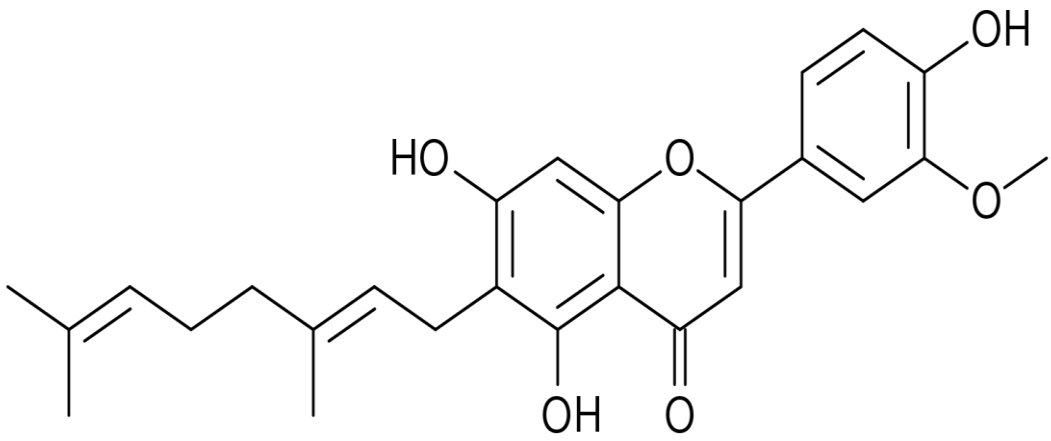

FIGURE 7. Chemical structure of Cannflavin A.

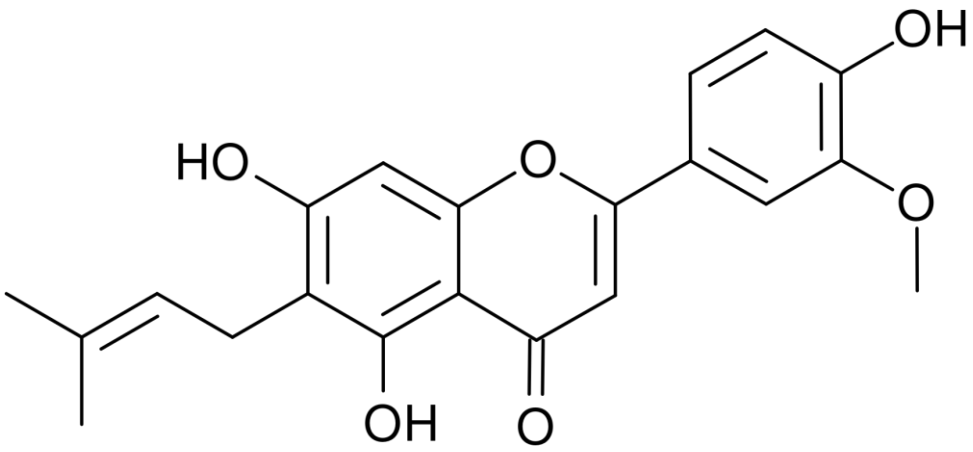

FIGURE 8. Chemical structure of Cannflavin B.

1.5 Endocannabinoid system (ECS) and cannabinoid pharmacology

Cannabis has served as a food, a fibre, and a medicine and even been used in religious rituals since the ancient times but explorations of endocannabinoids and actions elicited from them are at a nascent stage and just expanding (Gerdeman and Schechter 2010). The endocannabinoid system, or endogenous cannabinoid system is a cell-signalling physiological system that consists of intercellular molecules naturally produced in the body, their receptors and enzymes that degrade endocannabinoids' function. The name ECS gained its name when exogenous cannabinoids present in the cannabis plant were identified. It exists and is active both in the brain and the whole body, playing important physiological roles while contributing to general health and well-being (Alger 2013; Healthline 2019.)

Endocannabinoids are molecules produced in our body analogous to cannabinoids in the cannabis plant. Endocannabinoids have existed not just in humans but in other life forms, way before the cannabis plant emerged in evolutionary history. Despite irrelevance to cannabis plant, these natural molecules are named after the plant. Two main endocannabinoids were identified by Mechoulam as arachidonate-based anandamide (AEA) and 2-arachidonoylglyerol (2-AG) that activate cannabinoid receptors CB1 mainly found in the brain (basal ganglia, cerebellum, hippocampus, association cortices). Lower distribution of CB1 is present in spinal, peripheral nervous tissue and in a few non-nervous tissues. CB2 is present outside the CNS, especially involved in the immune system, which may contribute to cannabinoids' pain and inflammation alleviation. (Gerdeman and

Schechter 2010; Healthline 2019) AEA is known to be a partial agonist of CB1 but hardly reactive with CB2, while 2-AG works as an agonist at both the receptors (Zou and Kumar 2018.) Upon receiving certain electrochemical or excitatory signals, cells produce and release these two compounds in response. For instance, in the brain, a presynaptic neuron delivers electrical signals toward the postsynaptic neuron, then it in turn generates and sends out endocannabinoids from the cell membrane (Gerdeman and Schechter 2010; Healthline 2019.)

Endocannabinoids bind to their receptors by traveling the opposite direction of normal neurotransmitters, from which they gained their nickname as 'retrograde messengers'. Conventionally, electric signals that travel through the axon trigger neurotransmitters release from the axon terminal of a presynaptic cell to bind to receptors on the postsynaptic neuron. The reverse is true for endocannabinoids, as they travel to the end of the presynaptic neuron where they find and bind to CB1 receptors. This temporarily ceases the release of other neurotransmitters from the axon terminal such as L-glutamate, GABA, noradrenaline, dopamine, serotonin and acetylcholine, which results in decreased neuronal activity, thereby protecting cells from overstimulation (Gerdeman and Schechter 2010; Manzanares, Julian, and Carrascosa 2006.)

Endocannabinoids can also work in the opposite way as endocannabinoids target inhibitory neurons, which leads to increased neuronal activity. In other words, endocannabinoids constantly control and adjust synaptic inputs, causing either restraint of over-excitation (inhibition) or restraint of inhibition (disinhibition). This dampening and boosting effects at the synaptic cleft are referred to as synaptic plasticity, a critical mechanism by which humans think, feel, learn and remember things (Gerdeman and Schechter 2010; Manzanares, Julian, and Carrascosa 2006.)

According to Zou and Kumar (2018), multiple studies show pain relief properties of cannabinoids in treating different types of pain. The endocannabinoid system plays a part in physiological pain sensation process. Both preclinical and clinical studies shed light on the role of endocannabinoids when medicinally applied in inflammatory and neuropathic pain. Evidence supports that not only CB1 but also CB2 with TRPV1 is involved in pain regulation that cannabinoids mediate. Phytocannabinoids such as CBD as an example of chronic pain modulator have entered the limelight for their antinociceptive function and medical feasibility in neurological problems. This could explain why some view cannabis as a promising future medicine due to its ability to mimic endocannabinoids, a remarkable effect of cannabinoids as cannabis receptor agonists.

Cannabis has more than 60 active cannabinoids that interact with the cannabinoid receptors. Just like endocannabinoids, receptor activation by these exogenous cannabinoids binding results in suppression of the release of neurotransmitters from such as acetylcholine, dopamine and glutamate, affecting y-aminobutyric acid, N-methyl-D-aspartate, opioid and serotonin receptors. It causes physiological responses such as euphoria, psychosis, memory and cognition impairment, declined locomotor ability, promotion of appetite, antiemetic effects, pain relief, antispasmodic effects and sleep promotion. Locations of receptors, with CB1 primarily in the brain and CB2 in the immune system, elucidate partially cannabis pain relief and anti-inflammatory properties (Hill 2015.)

CB1 receptors expressed on nociceptive sensory neurons block the pain signals and cannabinoid receptor ligands modulate neuronal activity and pain thresholds so long as they act on CB1 receptors. There are suggestions that mast cells also express CB1 receptors and they might be involved in anti-inflammatory actions. A few types of inflammatory cells and immunocompetent cells express CB2 receptors. CB2 receptors are in general known for their immunologic responses but they also play a part in antinociception. CB2 activation by either endocannabinoid from the tissue cell or exogenous cannabinoids from the plant inhibits the release of inflammatory mediators from the immune cell, thereby eliciting antinociceptive effect in conditions like inflammation-induced pain and neuropathic pain. One putative mechanism of this is diminished mast cell degranulation and less neutrophil accumulation, both accredited to the cause of increased pain sensitivity (Gerdeman and Schechter 2010; Manzanares, Julian, and Carrascosa 2006.)

2 PURPOSE, OBJECTIVE AND RESEARCH QUESTIONS

The purpose of the thesis is to describe the medical use of cannabis as a substitute for prescription opioids in pain management and to answer the research questions outlined below:

1. What outcomes can be expected when using medical cannabis along with opioids?
2. How can medical cannabis possibly substitute opioids in chronic pain management?

3 RESEARCH METHODS

In thesis writing, a research methodology is discussed, and it explains what was done and how the research was conducted so readers can evaluate how reliable and valid the research is. The methods section should include the following according to McCombes (2019):

- The type of research
- How data was collected
- How data were analysed
- Tools or materials used in the research
- Rationale for the methods chosen

3.1 Research type

Scoping review has been chosen as a type of research in this thesis to comprehensively collate and form a synthesis of evidence and knowledge about relevant studies to research questions devised for this thesis. A scoping review appeared to be suitable considering the scale of a bachelor's thesis, to evaluate the level of scientific consensus that might exist with the current state of research on the topic. The research questions have been designed to enable investigations into potential use of medical cannabis in areas where opioid pain relief is currently dominating.

In a systematic literature review the main aim is to discover and study published research concerning one or more well-formed research questions. The question aims to answer typically a very empirical question (Fink 2010) by following strict guidelines to assess the literature and conduct the study (Grant and Booth 2009).

In a similar manner a scoping review is built upon well-formed research questions but does not put as much emphasis on strict evaluation of the source material as a systematic review does. This kind of review is often employed to do a preliminary assessment of the scale of source materials and notifies those in authority to make policy whether a more sophisticated systematic review of

the literature is required. Scoping review possesses similar characteristics as systematic review in that it aims to be systematic, easy to understand and reproducible (Grant and Booth 2009.)

3.2 Data aggregation and search keywords

Data was collected primarily using literature aggregators Mendeley and Google Scholar. Search results were selected according to search criteria for further screening. The selected results were categorized into loosely defined groups based on their titles such as cannabis in medication, cannabis vs opioids, and history and theory.

The primary search terms used involve cannabis, primary cannabis compounds and opioids.

TABLE 1. Search terms and the total number of results retrieved by aggregator sources.

Search terms	Mendeley results	Google Scholar results
Cannabis + opioids + pain	568	~30000
CBD + pain	2208	~39000
THC + pain	1455	~107000
Cannabis + pain + alternative	545	~40000

Due to the dynamic nature of these search engines the number of results was relatively high especially on Google Scholar. For the purposes of a scoping review the algorithms tended to show the most relevant results at the top of the search results. Majority of the literature obtained using these engines did not evaluate medical cannabis performance relative to opioids and were therefore out of the scope of this thesis.

3.2.1 Selection Criteria

Selection criteria is used to include source materials into the literature review as well as to exclude source materials that do not meet the requisite conditions set in this section. Inclusion criteria were selected to find answers to the research questions while exclusion criteria were selected to limit the scope of materials that best suit the purposes of the thesis.

TABLE 2. Selection criteria of the literature review.

Inclusion criteria	Exclusion criteria
Discusses using cannabis for pain management as a substitute for opioids	Qualitative literature
Discusses using cannabis for pain management as an adjunct to opioids	Focuses solely on precise acute pain management
Discusses using cannabis to treat pain management-related opioid use disorder	Literature published before 1999
	Not written in English or Finnish

3.2.2 Search strategy

A search strategy is defined to explain how and what methods will be used to discover the source materials for the literature review. Research materials that match the selection criteria are most likely to be found from online database resources. Therefore, the search focuses on a broad range of databases using search terms such as:

- cannabis pain management
- opioid pain management
- opioid alternatives
- cannabis opioid pain

Source materials found from database are initially reviewed based on their titles. After collecting all qualifying materials that can be found using the search terms described above, they are further processed by reviewing their abstract. The suitability and appropriateness of the source materials in relation to the selection criteria should be possible to fully assess from the abstract.

In addition to databases, a few books can be screened and acquired if they are deemed qualified as references.

3.2.3 Data analysis and research synthesis

Data analysis is the step where the selected literature is studied in closer details for relevant information that allows synthesizing results. The focus of analyzing is discovering themes which are important in the selected literature. Data analysis forms the backbone of composing a structured synthesis. The synthesis consists of summary of the included literature where the author shows that they have gained an understanding of the contents of the reviewed material. Polit and Beck (2012) emphasize the point that the review must not simply summarize nor paraphrase the assessed literature. It is also noted that the review should remain objective and that it must not ignore the evidence that appears to be against the research questions or the hypothesis of the thesis (Polit and Beck 2012.)

A research synthesis is a process that identifies and unites what each literature review represents. H. Cooper, Hedges, and Valentine (2009) mention that the two main factors which define the research synthesis are the focus and the goals of the literature review. Literature reviews typically focus on one or more of four major areas concerning the material that is being reviewed: the findings, the methods, the theories or the applications. The goals of literature reviews most frequently aim for research synthesis to combine research which is regarded relevant to a common topic. This involves mustering up generalizations, examining and attempting to resolve conflicts in the studied research and in general evaluating the individual publications in a bigger picture. An attempt is made to find major issues surrounding the covered publications for further research in the future (H. Cooper, Hedges, and Valentine 2009.)

3.2.4 Ethical considerations

Ethical considerations are important in all modern-day research. Historically ethics of research were set in motion by the Nuremberg Code in 1947 which listed 10 key points for permissible medical experiments, with the first point being that participation to medical experiments should have voluntary consent of the participant. The Nuremberg Code served as a baseline for the Declaration of Helsinki in 1964 which has since become the foundation of ethical considerations in humans research (Polit and Beck 2012, 150-152.)

The first ethical consideration that often comes to mind is naturally physical harm. Polit and Beck (2012, 150) give examples of cases up until 80s where patients in medical research deliberately were not given appropriate treatment to study consequences of untreated disease. While this kind of research is blatantly unethical, Polonsky and Waller (2014, 53-54) lists three major areas where inadvertent ethical harms can occur to research subjects: psychological, financial and social.

A research could cause psychological harm to research subjects. An example would be a research that infringes upon the privacy of research subjects or causes unnecessary psychological distress to the research subject, for example by interviewing subjects who are emotionally vulnerable to the interview topic (Polonsky and Waller 2014, 53-54).

A second example of unintentional ethical issue would be a research that leads to financial harm. Financial harm can come in many forms such as unexpected expenses that fall upon the research subject due to the research. It could also come as a form of income loss, for example, if the employer of the research subject received identifiable information related to the research, it could lead to termination of employment (Polonsky and Waller 2014, 53-54.) Finally Polonsky and Waller (2014, 53-54) lists social harm, where personal information that the research subject would prefer to keep confidential leaks through the research into the social circle of the research subject.

The general principles of research ethics may vary to some degree regionally, however one universal aspect of research ethics is protecting the research subject (Polit and Beck 2012, 152-167). The research subject must have the right to self-determination on their involvement in the research, the researcher must do their best to avoid harm to the research subject and the research subject's anonymity and privacy must be protected. In addition to general principles, research ethics involving Finnish medical science research is governed by the Medical Research Act and Decree (Finlex 2019).

3.3 Rationale for the search methods

Initially an attempt was made to discover materials using licensed databases that OUA provides access to but because it did not lead to a sufficient amount of research literature that compares

medical cannabis performance to opioids in pain relief, it was challenging to find suitable materials utilizing them. Instead using research aggregators such as Mendeley and Google Scholar has led to discovering a larger selection of literature to include in this thesis, which enabled embarking on this literature review to materialize.

4 IMPLEMENTATION

The literature review began with data aggregation which yielded 60 results, selected by the title and considering the exclusion criteria of publication years and language. Further evaluation of abstract removed a significant number of candidates, including 10 that were qualitative by nature. The remaining 19 were thoroughly read and after judging that all the criteria were met 13 publications remained.

TABLE 3. Total number of publications considered in each selection step

Step	Results (change)
Keyword search (with year and language constraints)	60
Abstract assessment	19 (-41)
Full text assessment	13 (-6)

4.1 Selected literature

A total of 13 publications passed the final full text assessment. These publications have been illustrated in APPENDIX 1.

5 REVIEW

The review process aimed to identify common themes, research outcomes and sources of unreliabilities among the studies. These features were then categorized under major topics which are presented in this section. The major categories were methodology, effectiveness, impact on pain levels, implications on health and quality of life, implications on opioid use and reliability considerations.

5.1 Methodology

Seven of the studies selected in this literature review collected their data either partially or completely online of which five were based on data that was collected utilizing private resources. In total the study had six studies that were based on public institutions or other public sources as opposed to being associated with private businesses or corporations. Fanelli et al. (2017) had excellent dataset coverage available due to conducting their research in Italy where registration and consent for research are prerequisite for medical cannabis prescription. The study samples were, however, not representative of general population.

Both Fanelli et al. (2017) and Clem, Bigand, and Wilson (2020) had samples which consisted primarily of older Caucasian women. This is simply because the homogenous group is most dominant in patients suffering from chronic pain in the regions where the research was conducted. Cooke, Chavez, and Freisthler (2020) on the other hand had a sample of relatively younger average age of 35 years.

POINT study was a large-scale Australian study researching pain and opioids in treatment consisting of 1514 pain treatment patients and it followed their opioid use and pain outcomes over four years. Two publications used this study as their dataset. Campbell et al (2018) investigated whether cannabis use can reduce opioid dose requirements in managing chronic non-cancer pain and Degenhardt et al. (2015) researched the levels of pain relief achieved using cannabis in various circumstances.

5.2 Effectiveness as pain medication

All studies in the literature review made at least some mention of effectiveness of medical cannabis for pain relief. Effectiveness in the context of this section refers to how likely medical cannabis is to achieve pain relief in the study patient. Evaluating this between different studies is not straightforward, since methods, dosages, combined use of other pain relief methods and pain types vary. Drawing some rough generalizations however is possible. For example the study by Campbell et al (2018) discovered no link of cannabis reducing pain and therefore the effectiveness from perspective of their study was zero. Three researches indicated an effectiveness level of approximately 50 %, meaning that half of the research subjects did achieve some degree of pain reduction.

Takakuwa et al. (2020) performed a retrospective cohort study whether cannabis could serve as an alternative or adjuvant treatment option for opioid users suffering from back pain over ten years on average. The final sample size of 61 patients was taken to the study and their opioid use lasted on average three years, the use of morphine was 21 mg on a daily basis and cannabis use was 1.45 g per day. While the research itself did not take any stance on effectiveness, it concluded that 48 % were able to reduce their opioid use, indicating cannabis' effectiveness in pain relief (Takakuwa et al. 2020.)

Similar observation was made in a cross-sectional study by Corroon, Mischley, and Sexton (2017), but with a slightly lower percentage of patients who substituted cannabis for prescription medications. 2774 individuals of an accidental sampling recruited through SNS and cannabis dispensaries in the state of Washington answered to an online anonymous questionnaire whether they were able to see medicinal benefits from cannabis. In the survey, respondents reported using cannabis at least once in the last three months. Of those 46% answered they had substituted cannabis for prescription medications, with the most common classes substituted being narcotics or opioids by 35.8%, anxiolytics or benzodiazepines by 13.6% and antidepressants by 12.7% (Corroon, Mischley, and Sexton 2017.)

The results of the two aforementioend studies were followed by similar results from Italy, illustrated in FIGURE 9. Cannabis was prescribed to 89.2% of subjects without excluding their preceding pain treatment. 76.2% participants continued cannabis treatment while 23.8% stopped. Approximately 49% of participants reported improvement while 26% reported that they saw nothing of factual

improvement nor worsening condition. Patients from these groups opted to continue the therapy. On the other hand patients that discontinued the therapy accounted for approximately 15% of the total sample who reported side effects as the reason for suspending the therapy. In addition therapy was discontinued by 7% of the patients, disatisfied with the outcome and 1% due to worsening condition. As for the remaining 2%, the data lacked (Fanelli et al. 2017.)

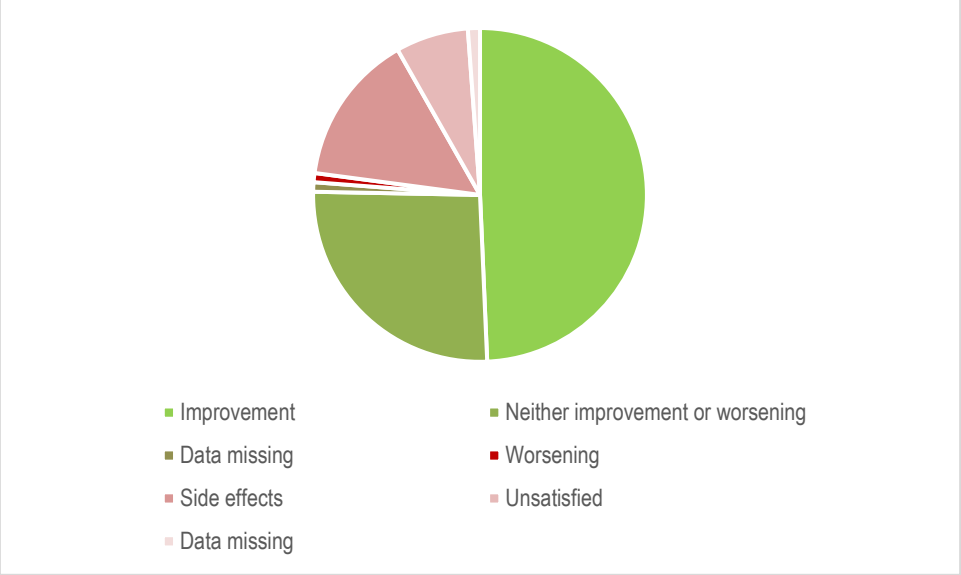

FIGURE 9. Proportions of treatment outcomes: Green shades represent participants who continued cannabis therapy and red shades account for those who discontinued (Fanelli et al. 2017).

According to findings from the Pain and Opioids IN Treatment (POINT) including 1514 people residing in Australia on prescribed opioids for chronic non-cancer pain condition revealed that 237 people (16%) tried cannabis and 34 out of the number experienced a 100% pain relief efficacy while 10 reported experiencing full pain relief from other medications. Among those who achieved 100% pain relief using cannabis, four reported complete regression in pain as well when using other medications. In other words, full pain alleviation was more viable using cannabis than opioids among those who used cannabis. Average pain relief achievement with cannabis in this sample group was 70% whilst 50% saw improvements with opioids (Degenhardt et al. 2015).

The rest of the studies observed pain relief but drew no conclusions on the accuracy on individual level meaning they looked mainly in the mean changes in the whole study population. Evidently the efficiency of pain relief appears to highly depend on individuals and unknown variables. But there are indications in the studies mentioned above that efficiency could be about 50 %.

For example the cross-sectional study conducted by Clem, Bigand, and Wilson (2020) investigated cannabis use motivation in the context of opioid based pain relief and opioid dependence and addiction management. Participants from the two groups commonly mentioned recreational or social occasion and pain management as their main reasons for cannabis use and no distinctive difference in other reasons for cannabis use was observed among these populations. 63% of the sample named pain as their motivation source of using cannabis and this figure does not show big differences between the two populations.

5.2.1 Effectiveness on specific pain types

The observation in the previous section that cannabis is effective to some but not all patients could be due to its effectiveness being significantly dependent on the type of the pain. Pain could be categorized for example by location, intensity and root cause such as neurological pain or pain due to an injury. Generally, patients participating in the studies had a wide range of pain related symptoms. Some studies report on specific types of pain although there was no study that focused primarily on discovering specific pain types where cannabis-based pain relief could be most effective.

Boehnke, Litinas, and Clauw (2016) observed in their study, where they targeted medical cannabis users for chronic pain, the effectiveness was most significant in the survey population group that had the least amount of perceived pain and also in the survey group that had the least centralized pain. Centralized pain in the context of the study meant pain related to the central nervous system as opposed to localized pain. The study hypothesized that their findings would be contrary, which meant patients would achieve greater pain relief with centralized pain.

Pain relief in cancer pain, rather a broad concept, was reported by two studies. In both studies the observed pain relief effectiveness was in line with the general trend of other studies. First of the studies was a retrospective cohort study of cancer patients under palliative care, in which a total of 83 patients were divided into two groups - one using solely opioid and the other using both opioid and cannabis. It found out that there was a difference observed in morphine equivalent daily dose (MEDD) between these two. Over a six-month period, there was about 25% increase in MEDD in the patients group that received treatment using opioid alone and only 7.5% in the combination

group and this observation was attributed possibly to cannabis use through which neurotransmitter release and neuropathic pain mechanism were inhibited. However the data did not mention whether the type of pain was neuropathic and the result of this study was not robust enough, according to the author, to corroborate the hypothesis (Pritchard et al. 2020.)

In addition, in the study by Abuhasira et al. (2018), 60,8% of study populatoin reported cancer as one of the reasons for their treatment. The study achieved perhaps the largest effectiveness of all evaluated studies in this review where a reduction from high levels of pain was observed in 88.7% of the study subjects for the six months of pain treatment.

Finally, back pain was a specific type of pain that was studied in one of the studies. The results of the study showed that roughly half of the patients had positive outcomes in pain treatment using cannabis (Takakuwa et al. 2020.)

5.3 Pain levels

Pain intensity can be described using a numeric rating scale of 0-10 or simply verbally using descriptive words such as low, moderate and high. While most studies evaluated changes in perceived pain in descriptive words, only one study graded pain levels using a numeric scale and compared them before and after the cannabis treatment period.

The study reviewed how pain levels shifted in patients receiving treatment using medical cannabis using the 11-point numerical scale. Subjects were asked to estimate their pain before starting the treatment and after completing a six-month treatment. The pain level was described on a numeric scale ranging from 0 (no pain) to 10 (maximum pain). Majority of patients reported their pain level to be intense from 7 to 10 prior to treatment. Post-treatment result revealed that there was a big shift in pain level, with majority reporting it to be either low or medium on a scale of 1 to 6. Even a full recovery was achieved in some patients (Abuhasira et al. 2018.)

Other studies mainly focused on comparing whether the research subjects saw some benefit with cannabis use in pain management, thus refrained from drawing conclusions on the effects on pain reduction. This nevertheless indicates that cannabis does provide significant pain relief to subjects, but it would be premature to draw statistically significant conclusions based on only a single study.

5.4 Implications on health and quality of life

Pain can directly affect the quality of life for example by reducing mobility and indirectly forcing patients to withdraw from their social life. In addition, pain medication can create undesirable side effects that undermine the quality of life of the patient. Four studies included in the literature review drew conclusions directly about the quality of life implications or indirectly by analyzing side effects associated with pain medications. In addition, one study drew conclusions about the effects of medical cannabis use on health. These studies showed that medical cannabis use may have influenced patients' quality of life in a positive way by reducing pain level and side effects from using other pain medications.

In the study by Boehnke, Litinas, and Clauw (2016) 64% of survey participants reported reduced opioid consumption and 45% reported that their quality of life had increased. The team observed that the reduction of opioid use was most significant in the survey population that had the least amount of perceived pain and likewise least significant in the survey population that had the highest amount of perceived pain. For the lowest pain quartile opioid use was reduced by 79% and for the highest quartile the reduction was -48%. The team concluded that the greatest improvement in quality of life using medical cannabis was achieved by those who had least centralized pain (Boehnke, Litinas, and Clauw 2016.)

In the second study participants saw improvement in quality of life. At the start of the experiment only 20.7% of patients described their quality of life as good or very good and after a six-month treatment period it had increased to 58.6%. Overall, the treatment was viewed by the patients as fruitful by 708 out of 1198 participants. The study did not assess reasons why quality of life improved (Abuhasira et al. 2018.)

Similarly as for side effects, Boehnke, Litinas, and Clauw (2016) noted that a substantial reduction of side effects caused by other medication after starting consumption of medical cannabis. The reduction of side effects can be viewed as an indirect improvement on quality of life even though the term was not explicitly mentioned or evaluated in other studies.

One reason patients chose medical cannabis was that the priority often was to remove symptoms rather than to cure the source of them. This was discovered in a comprehensive survey of patients in Canada who obtained cannabis from a federally authorized licensed source within the Marihuana

for Medical purposes Regulation (MMPR) which was conducted by 271 (90%) out of 301 participants answering 107 questions regarding demographics, consumption patterns and self-reported efficacy from cannabis substitution (Lucas and Walsh 2017.)

The findings pointed out the importance of differentiating the main conditions cannabis is originally prescribed for from the particular symptoms ease they experience. With respect to conditions, pain-inflicting conditions were dominant, answered by 53% or 144 of participants while chronic pain was the number one symptom by 73%, or 197 participants. Cannabis was deemed very effective in symptom attenuation by 95% or 257 users saying it often or always did remove symptoms. In addition cannabis was used as opioid substitute in 80% of the cases, for the reason that it inflicted less undesirable side effects upon users or users found it safer, experiencing better removal of symptoms (Lucas and Walsh 2017.)

In a later study by Lucas, Baron, and Jikomes (2019) patients obtaining cannabis from a federally authorized licensed producer in Canada received a cross-sectional survey of 239 questions through e-mail to understand their cannabis use patterns and to evaluate its anecdotal evidence based impact on dependence on prescription medications, illegal substances, alchohol and tobacco in January 2017, with 2032 surveys completed.

The reasons of substitution for prescription medications were ranked in order of dominance, one regarded as most dominant and critical being the belief that cannabis use can dispense with opioids safely by 51.2%, followed by less adverse side-effects, 39.7%, more effective symptom management, 19.5%, less withdrawal symptoms, 11.4%, feasibility of gaining access to cannabis relative to opioids, 3% and lastly the public perception of cannabis as less stigmatizing than prescription medications, 2.4%. The authors expected a possibility that medical cannabis could contribute to mitigating opioid withdrawal conditions and yield better results in opioid replacement therapy for those undergoing treatment for opioid use disorder, which in turn led to positive health impacts on opioid crisis (Lucas, Baron, and Jikomes 2019.)

Participants substituted cannabis most commonly for prescription drugs by 69.1% or 953, of which opioids made up for 35.3%. Patients self-reported that opioid replacement led to a complete cessasion of opioid use by 59.3%. A further 18.4% of participants said they managed to reduce opioid doses by three fourth. Those whose opioid use was replaced with cannabis showed tendency to more cannabis consumption, a total of 1.71 g in a day compared to a sum of 1.46 g by

those who did not substitute cannabis for opioids (Lucas, Baron, and Jikomes 2019.) 1.71 g of cannabis is within the range of median daily dose of medical cannabis by users according to a report published by Oakville Massage & Wellness Clinic (2017).

Finally a study by (Cooke, Chavez, and Freisthler 2020.) drew conclusions on health implications of medical cannabis use for different levels of pain intensity. The team did not observe any significant relation between cannabis use and changes in health for patients with low pain level with their frequency remaining at less than three times a day. On the contrary, a significant relation was found for patients with high pain levels. Patients in high pain category inclined to consume cannabis three times or more on a daily basis and their health condition tended to deteriorate proportionally. The pain level did not correlate to daily use of cannabis but it affected frequency of use. These results could indicate that cannabis use for patients reporting high pain levels may be counterproductive (Cooke, Chavez, and Freisthler 2020.)

5.5 Changes in opioid consumption patterns

As mentioned earlier, highly addictive opioid use can lead to accidental deaths, addiction and increased hospitalizations, leaving the society a big burden. While the effectiveness of long-term opioid use for chronic pain is being questioned, patients self report substituting cannabis for opioid and changes subsequently brought upon in their opioid use patterns is worth noting.

Seven studies discussed how medical cannabis affected opioid consumption patterns of patients who initiated medical cannabis treatment. Of those six studies revealed that patients were able to reduce opioid consumption and in two of them even a case of complete suspension of opioid use after shifting to cannabis was mentioned, which implies a possibility to decrease harm associated with opioid use. Only one study found no changes in opioid use, saying that the use of cannabis led to no increase, decrease nor cessation of opioid medication.

Reduction was observed in a study conducted by Reiman, Welty, and Solomon (2017) using survey sent via e-mail to patients using cannabis for medical purposes in California found out that pain was their primary condition and main reason to rely on cannabis. In the past six months prior to the study approximately one third of the respondents reported using opioid-based medications and of those who did almost two thirds used them with cannabis. There was a consensus among

respondents who had been using opioid-based pain medications at the time of survey or in the previous six months that they managed to reduce the amount of opioids they take when they combined them with cannabis and that using cannabis per se was even more helpful in treating pain than using both. More than 70% answered positively to a question if cannabis produced the same level of efficacy as their opioid-based medications did and 92% actually preferred cannabis to opioids while 93% strongly believed that they would be more inclined to vote for cannabis for their condition if it was more easily obtainable (Reiman, Welty, and Solomon 2017.)

Almost two thirds of respondents reported using a non-opioid based pain medication for their condition at the time of survey or in the past six months and seventy-six reported using cannabis along with a non-opioid based pain medication at the time or in the past six months. Of the respondents, almost all (96%) argued that cannabis consumption dispensed with the need for as much non-opioid based pain medication as they need when they solely relied on it. 92% claimed that cannabis yielded better efficacy for their condition compared to the conventional method of using only nonopioid-based pain medication (Reiman, Welty, and Solomon 2017.)

Cannabis preference over non-opioids was predominantly observed among 9% of respondents and the opioid-based pain medication group showed similarity by the same token, with 93% saying they would probably opt for cannabis as a substitute if it was easier to obtain (Reiman, Welty, and Solomon 2017.)

Similar phenomenon was observed in a study by (Boehnke, Litinas, and Clauw 2016), in which remarkable reductions of opioids or other classes of pain medications were reported by study participants. 65% of the study population was using opioids before initiation of cannabis but the percentage dropped to 18% after they commenced cannabis use (Boehnke, Litinas, and Clauw 2016.)

Lucas and Walsh (2017) implied cannabis could possibly play a crucial part in slashing prescription drug abuse and its invariably concomitant health burdens. Cannabis was substituted for prescription medications, alcohol, tobacco or nicotine and illegal substances by 71% of study subjects, with 63% accounting for substitution for prescription medications, 25% for alcohol, 12% for tobacco or nicotine and 3% for ilicit drugs. Participants were told to name up to three medications which they substituted cannabis for. 59% of those who mentioned prescription medications as their reason to substitute cannabis for reported substituting cannabis for one class of medications,

followed by 33% for two classes and 8% for three classes, with the most common substitution being for opioids (Lucas and Walsh 2017.)

Similar results were reported in a later study by Lucas, Baron, and Jikomes (2019). The results of the study were covered in the section on quality of life implications; the summary was that 51.2% of the study population substituted medical cannabis for opioids.

Cannabis substitution for various prescription medications was also mentioned in another study by Corroon, Mischley, and Sexton (2017) that implies reduction in opioid consumption. In the study, 1248 participants reported substituting cannabis for approximately two prescription medications. Narcotics or opioids were no other than the most common classes of medications superseded by medical cannabis by 35.8%, about 2.5 times higher the substitution for anxiolytics or benzodiazepines by 13.6 % (Corroon, Mischley, and Sexton 2017.)

According to Takakuwa et al. (2020) not only chronic opioid users but also irregular opioid users succeeded in reducing daily opioid intake after cannabis pain management initiation. It turned out to be that those chronically dependent on opioids were noticably prone to use larger amounts of cannabis to achieve pain relief. Those who stopped using opioids took a higer average dose of 1.4 g a day than those who still used opioids, whose average daily cannabis intake was 0.64g. Therefore, combined use of opioids and cannabis for alleviating pain and possibly other concurrent symptoms such as muscle spasm, anxiety, depression and poor sleep may have offered a sufficient level of pain relief in a synergistic manner and helped participants reduce doses of prescription opioids (Takakuwa et al. 2020.)

Cannabis users with opioid use disorder (OUD) were more inclined to cite opioid-related abstinance syndrome as their motive with approximately 33% of OUD participants relying on cannabis for withdrawal symptoms and only 9% of persistent pain population using cannabis for the same reason (Clem, Bigand, and Wilson 2020.)

5.6 Reliability of data and results

Scientific literature can contain issues with reliability of data or results. Data reliability issues can arise from situations such as poorly formulated survey questions or having a sample that is not sufficiently representative of the study population. Generally, authors should disclose any conflicts of interests they may have in their study whether these conflicts are intentional or unintentional. Additionally, there can be underlying unreliability that the authors did not consider or notice themselves while conducting the study.

Six authors in the literature review noted issues with reliability in their data or identified limitations due to their data. Boehnke, Litinas, and Clauw (2016) pointed out that multiple relevant outcomes from their cross-sectional study relied on patient's ability to recall relevant data from the past. While this is to be expected in a retrospective study, the issue that arises is the accuracy of their memory. In the study subjects were using medical cannabis for a median of four years, which certainly raises a question whether their memory dating back four years is reliable.

Two of these studies had samples that were not representative of general population although they were representative of the study population (in their respective regions) that mostly requires medical attention due to chronic pain. Clem, Bigand, and Wilson (2020) identified this as unreliable in the study while Fanelli et al. (2017) classified it as a limitation.

In the case of the study by Campbell et al. (2018) the data were collected anonymously from patients' anecdotal reports and the authors were concerned that due to the illegal nature of cannabis there could have been underreported cases of cannabis use.

Fifth author introduced also a case where interesting hypotheses were discovered during the study, but the study itself did not contain sufficient resources to produce conclusions (Pritchard et al. 2020). Finally (Lucas, Baron, and Jikomes 2019) identified possible unreliability due to their sample consisting of active medical cannabis users. According to the authors this could lead to selection bias and patients who are more likely to report on the positive effects of medical cannabis. The authors also announced that they had conflicts of interest associated with their study authors as did Abuhasira et al. (2018). Additionally it is worth noting that Abuhasira et al. (2018) conducted their research in a similar setting, with the sample from a medical cannabis clinic, but did not disclose any possible unreliability with their data.

Finally Reiman, Welty, and Solomon (2017) also had a sample from existing medical cannabis users database, which could also lead to selection bias, but the authors did not comment on this in any way.

In addition, this study did not necessarily contain a representative cross-section of the literature concerning the topic at hand. This is partially due to the nature of a scoping review that does not seek to systematically assess all available literature but also partially due to the fact that there appears to be a lot of new literature published during 2019-2020 period, signifying a trend in increasing frequency of relevant publications. Therefore, there could already be new key findings that did not make it into this review. The review relied heavily on the search result ranking algorithms of Mendeley and Google Scholar which may have introduced a selection bias.

6 RESULTS

Among thirteen research papers reviewed were seven that indicated potential use of medical cannabis in either pain management or opioid withdrawal symptom management, two that found no evidence of therapeutic value of cannabis as medication and four studies which remained inconclusive. The purpose of this thesis was to find answers to the research questions as to what results can be expected from combined use of cannabis and opioids and how medical cannabis can substitute for opioids in chronic pain management.

6.1 Outcomes using medical cannabis along with opioids

Based on the review, the most commonly reported outcomes of cannabis use in chronic pain management were reduction in pain (reported in 11 studies) and opioid consumption (reported in 6 studies), improved quality of life (reported in 2 studies) and even to complete cessation of opioid use (reported in 2 studies).

However, not every user of medical cannabis can expect these kinds of positive outcomes. Approximately half of the study subjects saw benefits from cannabis but according to one study, subjects with severe pain experienced their health condition declining due to their higher doses of cannabis.

6.2 Substitution of opioids in chronic pain management

Majority of the studies indicated that cannabis can partially be substituted for opioids for the purpose of chronic pain relief, but no study asserted it with full certainty. Considering this result and the outcomes mentioned above the use of cannabis as a substitute for opioids in chronic pain management and opioid use disorder symptom treatment could yield positive outcomes in certain situations. However, due to a few of aforementioned reports indicating that cannabis had no benefit further academic scrutiny is required to not only determine why cannabis may or may not be useful

selectively in patients under certain medical conditions but also to boost the robustness of positive findings that already exist.

7 CONCLUSIONS

Reported medical cannabis treatment outcomes were mostly positive and neutral, with negative outcomes being a minority. Viable as medical cannabis may appear as an alternative, it does not guarantee its effectiveness on an individual basis. It looks evident, however, that cannabis-based medicines may hold promising and intriguing possibilities in the future should diverse researches are to be conducted on cannabinoids and physiology of cannabinoid receptors.

Considering the state of the world, there obviously appears to be an urgent need to come up with alternatives for pain relief that can surpass or supplement opioids, as consequences of opioid use can be grave and it does not necessarily provide pain relief sufficiently. It is imperative that nurses understand alternative options that can wean patients off opioid use and their motivation to turn to cannabis. Should they encounter patients who state they prefer cannabis over opioids, they should take account of patients' right to self-determination instead of discouraging the use of illicit substance simply because of its legal status.

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LITERATURE INCLUDED IN THE REVIEW APPENDIX 1

Year, Authors	Purpose	Source materials	Methods	Key findings
2016 Boehnke, Litinas, and Clauw	To examine whether medical cannabis for chronic pain changed individual opioid use patterns.	Online survey was sent to 244 medical cannabis users with chronic pain.	Cross-sectional retrospective survey.	Cannabis reduced pain, increased quality of life and lowered opioid consumption.
2017 Reiman, Welty, and Solomon	To examine the use of cannabis as a substitute for opioid-based pain medication.	E-mail survey data were collected from 2897 medical cannabis patients.	Cross-sectional survey.	Cannabis reduced pain and lowered opioid consumption.
2017 Lucas and Walsh	To explore how medical cannabis is used to substitute for other pain medications by patients.	Registered patients who purchase cannabis from a federally authorized licenced producer were invited to answer an online survey.	Cross-sectional survey.	Cannabis reduced both pain and side effects from other medications and lowered opioid consumption.

2018 Abuhasira et al.	To assess the characteristics of the elderly using medical cannabis, its safety and efficacy.	2736 patients aged above 65 who initiated medical cannabis treatment answered to initial questionnaire.	Prospective study.	Cannabis reduced cancer pain and increased quality of life.
2015 Degenhardt et al.	To inspect patterns and correlates of cannabis use in people prescribed opioids for chronic non-cancer pain.	Data on cannabis use, ICD-10 cannabis use disorder and cannabis use for pain were collected from 1514 people who had been prescribed opioids.	Cohort study	Reduction of pain was observed while using cannabis.
2017 Fanelli et al.	To evaluate routes of administration, types of cannabis products utilized, dosing and effectiveness and safety of the treatment.	Anonymized data from registered patients upon their permission	Retrospective case series analysis	Cannabis reduced pain, however approximately 50% saw no benefit.

2020 Takakuwa et al.	To determine if cannabis can serve as an alternative or adjunct treatment for occasional and chronic prescription opioid users.	Utilized data collected from the active database of patients records with lower back pain.	Retrospective cohort study.	Cannabis reduced pain and lowered opioid consumption. Approximately 50% saw no benefit.
2017 Corroon, Mischley, and Sexton	To survey cannabis users to determine whether they intentionally substituted cannabis for prescription drugs.	Subjects were surveyed via online questionnaire anonymously who had been self-selected or recruited through social media and cannabis dispensaries.	Cross-sectional study.	Cannabis reduced pain and lowered opioid consumption. Approximately 50% saw no benefit.
2020 Pritchard et al.	To evaluate cannabis effect on opioid use in cancer patients undergoing palliative care.	Consists of a sample of 159 patients, data was collected from the palliative care clinic at a medical centre and from the electronic medical records.	Retrospective cohort study.	Cannabis reduced cancer pain.

2019 Lucas, Baron, and Jikomes	To have a broad understanding of cannabis use from Canadian medical cannabis patients.	A 239-question survey was sent to federally authorized medical cannabis patients registered with Tilray, resulting in 2032 complete surveys.	Cross-sectional survey.	Cannabis reduced both pain and side effects from other medications. It also reduced opioid consumption.
2020 Clem, Bigand, and Wilson	To determine whether motivations for cannabis use differ between adults prescribed opioids for persistent pain vs those receiving opioids as medication-assisted treatment for opioid use disorder.	150 OUD patients and 150 persistent pain patients were recruited from two outpatient opioid treatment program and three pain clinics in Washington state and answered a survey on measures of pain, depression, anxiety, self-efficacy and cannabis use.	Cross-sectional survey.	Cannabis reduced pain.

2020 Cooke, Chavez, and Freisthler	To examine whether levels of chronic pain were associated with cannabis consumption patterns.	Utilized the survey data collected from medical cannabis dispensary patients in Los Angeles, California.	Cross-sectional survey.	No significant relation between cannabis use and health status in low-moderate pain. Counterproductive in high pain.
2018 Campbell et al	To examine links between cannabis use, opioid use and pain outcomes over a four-year period.	Consists of 1514 people living with chronic non-cancer pain, using The Pain and Opioids IN Treatment (POINT) study.	National cohort study.	Cannabis provided no pain reduction and there was no increase, decrease or discontinuation of opioids observed.