2021

Cannabis as a Prescription Opioid Substitute for Adults with Chronic Pain: A Systematic Literature Review

Lani Kranz
Minnesota State University, Mankato

Cannabis as a Prescription Opioid Substitute for Adults with Chronic Pain: A Systematic Literature Review

Lani Kranz

School of Nursing, Minnesota State University, Mankato

NURS 695: Alternate Plan Paper

Dr. Gwen Verchota

April 26, 2021

Abstract

Objective: To determine whether the use of cannabis improves pain control and/or reduces the amounts of opioids needed to control pain in adults with chronic pain.

Methods: A systematic literature review of research conducted from the past five years. Five databases were searched, resulting in 14 peer-reviewed articles relevant to the objective.

Results: The majority of the literature reviewed demonstrated the use of cannabis by adults with chronic pain resulted in better pain control and/or fewer opioids required to control pain in this population. The two articles which contradicted these findings only evaluated illicit, not medical, cannabis use by individuals with chronic pain.

Conclusions: Cannabis should be considered as an alternative or adjunct to opioid therapy in adults with chronic pain. Changes in patient and provider education about cannabis as a therapy for chronic pain are necessary. The classification of cannabis as a Schedule I controlled substance by the federal government complicates research, public perception, and patient access and should be re-evaluated. Further research is indicated in determining the specific types, strains, and methods of ingestion that are most effective in this population; the sub-types of pain that are improved with cannabis; what the adverse effects of cannabis use in this population are; and what barriers exist for providers in recommending cannabis as a treatment option. Evidence from RCTs, particularly comparing cannabis to opioids, is lacking yet difficult to obtain due to federal and ethical limitations.

Keywords: cannabis, marijuana, opioid(s), opiate(s), chronic pain, intractable pain, pain control, prescribed, prescription(s)

Cannabis as an Opiate Substitute for Adults with Chronic Pain:

A Systematic Literature Review

From 1999-2018, nearly 450,000 individuals died from an opioid overdose in the United States, including from the use of both prescription and illicit opioids (Centers for Disease Control and Prevention [CDC], 2020). In 2019 alone, almost 50,000 individuals died from opioid-involved overdoses in the United States (National Institutes of Health [NIH], 2021). Pharmaceutical companies assured health care providers that prescription opioids such as oxycodone were not addictive, leading to exponential increases in the prescribing of these medications for moderate and severe pain beginning in the late 1990s (CDC, 2020). Even after the CDC released new guidelines for providers in 2016 intended to reduce the number of opioids prescribed, 191 million opioid prescriptions were still written in 2017 (CDC, 2020). As public interest in reducing opioid prescriptions has increased, so have the number of states allowing the legal use of cannabis to treat a range of medical conditions, including chronic pain. Today, 31 of the 36 states with legalized cannabis use allow cannabis to be used to treat chronic pain, although the language and restrictions vary from state-to-state (Medical Marijuana Project [MMP], 2021). Fifteen states allow for adult use of cannabis for any reason, including recreationally and many individuals who purchase adult-use cannabis report using it to control pain (MMP, 2021). In the context of this newly expanded access to cannabis for pain control, the CDC's recommendation that providers consider other available options for treating chronic pain (Dowell et al., 2016) supports investigating the efficacy of cannabis in controlling chronic pain and evaluating its impact on opioid prescriptions for this population.

Background

CDC guidelines define 'chronic pain' as pain that has been present for greater than three months or past the time of normal tissue healing (Dowell et al., 2016). Data from the National Health Interview Survey indicated that in 2019, 20.4% of adults in the United States had chronic pain, and 7.4% of adults had 'high-impact' chronic pain frequently limiting life or work activities in the past 3 months (Zelaya et al., 2020). Chronic pain and high-impact chronic pain is associated with decreased quality of life; increased rates of depression, anxiety, and insomnia; lost work productivity and increased opioid use dependence (Zelaya et al., 2020). Survey data indicated that women, adults over the age of 65, and individuals living in rural communities were more likely to suffer from chronic pain than others (Zelaya et al., 2020).

Many patients affected by chronic pain are prescribed opioid analgesics. Of patients with chronic pain who are prescribed opioids, approximately 21-29% will misuse these opioids, 4-6% will transition to heroin use, and 8-12% will develop an opioid use disorder (NIH, 2021). In 2017, 1.7 million adults had a substance use disorder related to prescription opioid pain relievers (NIH, 2021). Repeated use of opioids over time increases the risk of developing an opioid use disorder (HHS, 2016). Even patients using opioids appropriately as prescribed are subject to a wide range of side effects including constipation, nausea, vomiting, sexual dysfunction, sedation, dizziness, physical dependence, withdrawal syndrome, and respiratory depression (Benyamin et al., 2008; Woodbury, 2015). Many patients develop tolerance to opioids over time and are prescribed increasingly larger doses. Some patients paradoxically experience increased pain on the higher doses of opioids, a phenomenon referred to as opioid-induced hyperalgesia (Woodbury, 2015). Contrary to public perception of opioids as the gold standard for pain relief, the CDC stated in its opioid prescribing guidelines for chronic pain that "Evidence on long-term

opioid therapy for chronic pain outside of end-of-life care remains limited, with insufficient evidence to determine long-term benefits versus no opioid therapy, though evidence suggests risk for serious harms that appears to be dose-dependent," (Dowell et al., 2016). The first recommendation from the CDC within these new guidelines is that "Nonpharmacologic therapy and *non-opioid* pharmacologic therapy are preferred for chronic pain…if opioids are used, they should be used in conjunction with nonpharmacologic and non-opioid pharmacologic therapy, as appropriate," (Dowell et al., 2016).

The relatively high risk-benefit ratio of using opioids for chronic pain requires primary care providers to re-evaluate options for controlling pain in this population. In early 2016 when the CDC published its recommendations on the prescription of opioids for providers, only 25 states and the District of Colombia provided for the legal use of medical cannabis (Medical Marijuana Project, 2021). Today, 31 states include a provision for the legal use of medical cannabis for severe or chronic pain. Even though most states now allow for legalized medical cannabis to control chronic pain, cannabis remains a Schedule I controlled substance under Federal Law, placing it in the same class as drugs deemed to have no medical benefit and a high risk of abuse such as heroin and LSD. Prescription opioids, by contrast, are classified as Schedule II-V drugs which confers some medical benefit at the expense of varying risks of abused. Despite its Schedule I classification, 15 states currently allow for legalized recreational use of cannabis by adults. Many adults in these states purchase cannabis from recreational dispensaries to be used medicinally, akin to purchasing ibuprofen over the counter instead of obtaining a prescription for ibuprofen due to ease of access.

Cannabis, also known as 'marijuana', refers to the leafy plants *Cannabis sativa* and *Cannabis indica*. Cannabis grows naturally in much of the world and has been used for various

medicinal purposes for thousands of years (Borgelt et al., 2013). The United States Pharmacopeia included it as a medical compound from 1851 until it was removed in 1942, five years after it was criminalized, despite objections from the American Medical Association (Borgelt et al., 2013). Cannabis contains a mixture of chemicals known as cannabinoids. Examples of cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the cannabinoid typically found in the greatest quantity in cannabis and is known to be psychoactive. It binds to two types of cannabinoid receptors (C1 and C2) in the brain. It is thought that analgesia created by THC's binding to the endocannabinoid system in the brain may be the result of several different mechanisms including modulation of neuronal activity, effects on descending pain pathways, and inhibition of prostaglandin synthesis (Borgelt et al., 2013). The mechanism by which CBD works is not completely known, but it is known that it does not bind to the C1 or C2 receptors like THC and is hypothesized to counteract some of the psychogenic effects of THC (Borgelt et al., 2013).

There are currently no cannabis products that have been approved for medical use by the U.S. Food and Drug Administration (Food and Drug Administration [FDA], 2021). Dronabinol and nabilone are oral medications containing synthetically derived THC that are FDA-approved prescription medications for nausea and vomiting related to chemotherapy. Dronabinol has also been approved for anorexia and wasting from AIDS, due to its appetite-enhancing effect. The only other related product that is FDA-approved is Epidolex, a purified form of CBD (without THC), indicated for specific severe seizures in children (FDA, 2021). None of these products are FDA-approved for the treatment of acute or chronic pain (FDA, 2021). Although research has been done on the above cannabinoids as to their efficacy in relieving pain, for the purpose of this review we will limit further discussion exclusively to include only cannabis.

The juxtaposition of the federal classification of cannabis as a Schedule I controlled substance and the increasing availability of legalized medical cannabis as an option for treatment of chronic pain merits investigation into whether evidence supports its use for this purpose. Primary care providers, including nurse practitioners, see many patients presenting with chronic pain in their day-to-day practice. Primary care providers also serve as stewards of public health who are being urged to assist in the opioid crisis by re-evaluating their prescribing practices relating to opioids. A review of pertinent literature will aim to answer the clinical question: *In adults with chronic pain, does the use of cannabis improve pain control and reduce the amounts of opioids required to control pain*? The intent of this review is to provide primary care providers, including nurse practitioners, with evidence-based recommendations for their patients presenting with chronic pain regarding treatment with medical cannabis.

Methods

Databases and Search Strategies

An extensive literature search was completed between the dates of 10/15/2020 and 11/20/20. Both PubMed and EBSCO Host Databases were included. Within EBSCO Host, the Academic Search Premier database, CINAHL Plus with Full-Text database, Cochrane Central Register of Controlled Trials database and the Cochrane Database of Systemic Reviews were selected for the searches. The searches were restricted to full-text journal articles in the English Language from the past five years. Specific search restrictions for each database and the general subjects covered by each database are included in Table 1 of the appendix.

Details on the search terms used and resulting hits in each database are included in Table 2 of the appendix. Titles of articles which were included in searches with less than 25 hits were

scanned and duplicate titles were eliminated. Of the 28 individual articles remaining, the titles and abstracts were reviewed to see if the article met inclusion or exclusion criteria.

Inclusion and Exclusion Criteria

To most effectively answer the clinical question posed above, pre-determined inclusion criteria required that the article either: a) examined the effects of cannabis consumption on chronic pain, b) examined the relationship between cannabis use and prescription opioid use in patients with chronic pain, or c) examined the relationship between cannabis use and the amounts of opioids prescribed by providers. Exclusion criteria included a) illicit or non-prescription use of opioids as a variable, or no specification as to whether the opioid was prescribed, b) a study population that included individuals < 18 years of age, c) no inclusion of cannabis or its use in the study, d) investigation of cannabis or opioid misuse, e) opinion articles, f) study or policy proposals. Table 3 of the appendix details specific application of inclusion and exclusion criteria to each of the 28 articles. Of these, 14 met criteria for inclusion in the final literature review.

Literature Review Process

The full text of the selected 14 articles was reviewed and analyzed to extrapolate what populations were being studied, what variables were being investigated, what instruments were utilized, pertinent clinical findings, implications for practice, and the level of evidence involved. Table 4 of the appendix summarizes each of these 14 articles in detail.

Methodological Assessment

Several databases were searched using multiple relevant search terms in various combinations, producing articles which all helped answer the clinical question posed above. However, this literature review was subject to certain limitations. In wishing to retrieve the most

recent data, the search timeframe was limited to articles published within the last five years. This may have resulting in missing other pertinent research, albeit older, that could support or refute the conclusions. Initially, the review was going to be limited to only medicinal cannabis, but in reading some of the articles it was apparent there were subsets of individuals who would either qualify for medical cannabis but lived in one of the 15 states where recreational cannabis was legal and purchased it at the recreational dispensaries instead or those that self-substituted illicit cannabis for prescription opioids. Hence, the criteria for cannabis to be strictly 'medical' was eliminated. Searching more databases may have yielded more articles, as would have not limiting the search to full text only. This review was completed by one author and having a second author validate the above searches, articles, and inclusion/exclusion criteria would better control for potential bias and enhance the validity of the findings, consistent with established standards for systematic reviews.

Literature Review

Study Characteristics

Most of the studies evaluated were cross-sectional cohort studies or secondary data analyses of cross-sectional cohort studies. One study was a quasi-experimental difference-within-differences study, one was a historical cohort study, one study was a secondary data analysis of a prospective cohort study, and one study was a case report (n=1). Three studies were qualitative in nature, describing the experience of individuals with chronic pain and cannabis. Due to the design of the studies retrieved, the highest level of evidence found was the inclusion of several cross-sectional studies that were Level IV (Melnyk & Fineout-Overholt, 2015). All the studies reviewed would be considered Level IV, except for the three qualitative studies and the individual case report, all of which were Level VI (Melnyk & Fineout-Overholt, 2015). One

relevant systemic review and meta-analysis on cannabinoids (Level I) was found while searching the Minnesota Department of Health website for additional resources (Whiting et al., 2015). However, because this meta-analysis and systemic review explored all cannabinoids and not just cannabis, only the information included on the studies involving cannabis was considered so the overall meta-analysis was not applicable.

Types of Research

While conducting the literature review, it became apparent that the clinical question posed above could be broken down into two related components. Eight of the articles examined whether cannabis helped control pain in individuals with chronic pain. Thirteen of the articles examined whether cannabis use impacted the amount of prescription opioids that were either used or prescribed for adults. All eight articles which examined whether cannabis helped control pain also examined whether cannabis use was related to prescription opioid use, so there was overlap among these eight articles. One qualitative article did not fit directly into either of the above divisions but provided complementary insight into decreased opioid prescriptions driving the desire to utilize medical cannabis for a group of adults with chronic pain and was retained for this reason.

Populations Studied

The populations studied ranged in number from a case study of an individual with acute on chronic pain (Meng et al., 2016) to a secondary data analysis of 4,840,562 individual records of commercially insured adults, of which a subgroup of adults with chronic pain that represented approximately 30% of that number were included (Shah et al., 2019). Eight of the cross-sectional quantitative studies had an $n>1000$, while the three qualitative studies had $n=15$ (Sinha et al., 2019), $n=21$ (Gill & Young, 2019), and $n=200$ (Zaller et al., 2015).

The populations studied fall into four categories: 1) Cannabis users whose reasons for using were studied, 2) adults with chronic pain who were using cannabis and prescription opioids together, 3) Medicare patients with chronic pain, and 4) Medicaid patients with opioid prescriptions. One study only included adults with chronic pain from sickle-cell anemia (Sinha et al., 2019), and two studies included only adults with HIV and chronic pain (Merlin et al., 2019, Sohler et al., 2018). The single case study focused on an adult male who had diagnoses of acute and chronic pain with long-standing opioid use (Meng et al., 2016).

Research Synthesis

Population of Interest

Most of the studies reviewed explicitly limited the population under investigation to adults with chronic pain. Recall that chronic pain is considered by the CDC to be pain that has been present for greater than three months or past the time of normal tissue healing (Dowell et al., 2016), and that in 2019 one-fifth of the US population suffered from chronic pain (Zelaya et al., 2020). The individuals who were classified as having chronic pain for the purposes of these studies had a variety of underlying diagnoses, ranging from individuals with chronic low back pain (Vigil et al., 2017) to individuals affected by sickle cell disease (Sinha et al., 2019) and HIV (Merlin et al., 2019; Sohler et al., 2018). Some of the studies inferred chronic pain from patients having prescriptions for opioids (Ishida et al., 2019; Wen & Hockenberry, 2018). The variety of conditions which could cause chronic pain are numerous and are not differentiated in most of the studies reviewed. The Minnesota Department of Health, for example, lists 24 primary symptoms experienced by individuals certified for intractable pain who participated in the medical cannabis program between Aug 1, 2016 and December 31, 2016 and notes that 15.3% of patients enrolled in the program were concurrently certified for at least one additional condition (Minnesota

Department of Health [MDH], n.d.a). However, all the studies either involved adults with a diagnosis of chronic pain, adults who self-identified as having chronic pain, or adults who were taking cannabis or prescription opioids for pain.

Types of Cannabis

This review was limited to cannabis, however, within the definition of cannabis is a high degree of variability regarding THC: CBD ratio, strain, method of ingestion, and whether the cannabis is used legally or illegally. Only one study investigated which types and strains were most favored by individuals with chronic pain. Baron et al. (2018) reported that individuals with chronic pain preferred hybrid (37%), indica (25.4%) and sativa (20.2%) types, all of which have a high ratio of THC: CBD. By contrast, the CBD dominant types were only preferred by 8.2% of the chronic pain patients, and balanced types containing equal ratios of CBD and THC were also preferred by 8.2% (Baron et al., 2018). The preferred cannabis strains out of the 42 options reported by the chronic pain subset were OG Shark (hybrid type), CBD House Blend (CBD dominant type), and Pink Kush (hybrid type) (Baron et al., 2018). These patients were all participants in one of Canada's national medical marijuana programs, Tilray, and the results highlight how many options exist for users of "medical cannabis."

The propensity toward high THC: Low CBD ratio is consistent with data from the state of Minnesota's medical cannabis program. For the first five months that intractable pain was certified as a qualifying condition, 57% of purchases were for "very high" THC: CBD products (MDH, n.d.a). This was followed by 33% of purchases being for products with a balanced (1:1) THC: CBD ratio (MDH, n.d.a). Notably, several of the other studies included evaluated recreational or illicit cannabis use, where the specific type or strain would likely be unknown.

The same data set from the MDH also included information on the method of how medical cannabis was ingested. 54% of purchases were for inhaled cannabis, 39% were for oral cannabis, with only 6% for oromucosal and 0.6% for topical preparations (MDH, n.d.a). A survey of 200 adults using medical cannabis at a Rhode Island dispensary revealed the vast majority smoked (74%) or used vaporized preparations (17%) (Zaller et al., 2015). Nine of the other studies explicitly noted differences in the method of use.

Some of the studies evaluated the use of cannabis in a non-medical context. This included illicit use (Campbell et al., 2018, Ishida et al., 2019, Meng et al., 2019, Sohler et al., 2018) and use of cannabis in Colorado at an adult-use dispensary without a prescription (Bachhuber et al., 2019). The remainder of the studies evaluated only medical cannabis in their analyses.

Control of Pain

Of the eight studies which examined the relationship between cannabis use and chronic pain, six found that cannabis use improved pain control and two found that cannabis use had no positive effect on pain control. Cannabis use was evaluated both in the context of medical (prescribed) and recreational (adult) use, as some patients reported using cannabis which was not medically prescribed for symptom control.

Bachhuber et al. (2019) surveyed 1,000 adults purchasing cannabis at a recreational dispensary in Colorado. Recreational use of cannabis is legal for adults in Colorado. Of the adults surveyed, 65% reported taking cannabis for pain relief and 74% reported taking cannabis to help with sleep (Bachhuber et al., 2019). Within the cannabis users taking cannabis for pain, 80% rated it as very or extremely helpful in controlling their pain (Bachhuber et al., 2019). Difficulty sleeping can be a consequence of chronic pain, and of the users reporting taking cannabis to promote sleep, 83% found it to be very or extremely helpful for sleep.

Adults who were prescribed medical cannabis were questioned as to their underlying conditions at a dispensary in Rhode Island (Zaller et al., 2015). The most common reason for use among the 200 patients surveyed was chronic pain management, with 69% of patients reporting experiencing chronic pain at baseline (Zaller et al., 2015). 85% of these patients reported that medical cannabis resulted in feeling "much better" (Zaller et al., 2015)

Of 21 individuals surveyed through a medical cannabis delivery service in California, 10 reported using it for chronic pain (Gill & Young, 2019). One theme that emerged during their interviews was that cannabis was often used due to clinical failure, defined as the inability of other medical treatments to control their pain, or to control symptoms such as insomnia that other treatments did not help with (Gill & Young, 2019). Another theme endorsed by this cohort was the lack of side effects from using cannabis for pain control compared to other treatments, including opioids (Gill & Young, 2019). In the case study of a 57-year-old man who suffered from a complex pain syndrome and then received a liver transplant, his pre-transplant VAS global pain scores were rated as 5-6/10 with scheduled prescription opioids to control pain. Post-operatively his VAS pain scores were 5-8/10, requiring escalating doses of opioids. After adding medical cannabis to his pain management profile, his VAS scores averaged 4/10 five months post-operatively, while on a lower average dose of opioids than pre-operatively (Meng, 2016). A dramatic reduction in his neuropathic pain scores (hot-burning 1/10, pain caused by light touch 3/10) and continuous pain descriptors (throbbing, gnawing) were noted (Meng, 2016), although his intermittent pain descriptors (shooting, stabbing, splitting, and sharp) did not change and he had developed new neuropathic pain descriptors (numbness, tingling) that were not present prior to his post-operative discharge. He also reported the cannabis helped with sleep, nausea, and general malaise (Meng et al., 2015).

Out of 9,003 respondents answering a survey about individual perceptions and use of cannabis, 486 adults reported using both cannabis and regular use of prescription opioids for pain within the last year (Ishida et al., 2019). The most common reason for substitution of opioids for cannabis by this subgroup were better control of pain (36%), fewer side effects (32%) and fewer withdrawal symptoms (26%) (Ishida et al., 2019). While these individuals did not have a specific diagnosis of chronic pain, their regular use of prescription opioids for pain would imply that they experienced some degree of chronic pain. Survey responses by 37 chronic pain patients enrolled in the New Mexico Cannabis Program (MCP) who were regular users of medical cannabis indicated that they experienced a statistically significant reduction ($p<0.001$) in pain levels from pre-enrollment to one year post enrollment with a mean change of -3.4 on a pain scale from 0-10 (Vigil et al., 2017). These patients all were being treated for musculoskeletal pain, with back pain as the predominant condition (Vigil et al., 2017). On a follow up survey completed by 23 out of the 37 patients to assess quality-of-life indicators, most patients surveyed also reported improvements in activity levels, social life, ability to concentrate, and overall quality-of-life (Vigil et al., 2017). None of the 23 respondents believed that using cannabis as a treatment for pain had negative effects on any of the quality-of-life indicators (Vigil et al., 2017).

A systematic review and meta-analysis of cannabinoids for medical use was not found during the literature search, likely because the topic was the broader class of cannabinoids and not limited to cannabis (Whiting et al., 2015). However, this information was discovered in researching the Minnesota Department of Health website for information on the state's medical cannabis program. Although the findings of the systematic review and meta-analysis demonstrated that there was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain (Whiting et al., 2015), for the purpose of this literature review only the

data from the single study involving cannabis was reviewed. This study showed pain was improved for chronic pain patients who used cannabis. Compared to the other studies included in the meta-analysis that used cannabinoids other than cannabis, the study involving cannabis showed the highest degree of improvement following use (Whiting et al., 2015). This was measured as the average number of patients reporting a reduction in pain >30% (*OR*, 3.43[95% CI, 1.03-11.48]) compared to placebo (*n*=50) (Whiting et al., 2015).

As explained above, the Minnesota Department of Health website was searched to find information on the medical cannabis program in Minnesota. Chronic pain was added as a qualifying condition for medical cannabis in Minnesota in 2020, and prior to that, intractable pain had been a qualifying condition since 2016 (MDH, 2019a). Intractable pain was previously defined by state law as pain "whose cause cannot be removed and, according to generally accepted medical practice, the full range of pain management treatments appropriate for the patient have been used without adequate result or with intolerable side effects," (MDH, n.d.b). The expansion of medical cannabis to include chronic pain has only been in effect since August 1, 2020, so no data is yet available on the experiences of this population. However, state health commissioner Jan Malcolm stated:

> Minnesota's medical cannabis program tracks patient experiences so we can learn about the real-world benefits and downsides of using medical cannabis for various conditions. The generally positive experience patients have had using medical cannabis to treat intractable pain prompted us to add chronic pain as a qualifying condition. (MDH, 2019a)

.

Between the time intractable pain was added as a condition in August 2016 and when the most recent survey data was available in June 2017, 29% of the 4060 patients receiving cannabis for intractable pain experienced a > 30% decrease in pain from baseline within the first four

months in the program, and 36% of these who experienced a > 30% decrease in pain were able to maintain that level after 4 months, or 11% were able to achieve and maintain a >30% decrease in pain for 4 months or longer (MDH, 2019b). However, for other related symptoms, intractable pain patients who reported moderate or severe symptoms of anxiety, lack of appetite, depression, disturbed sleep, fatigue, nausea, and vomiting saw much greater increases in experiencing a 30% improvement in these symptoms for 4 months or longer (MDH, 2019b). Thirty-four percent had > 30% improvement in anxiety, 34% maintained improvement of appetite, 37% for depression, 32% saw continued improvement of insomnia, 23% of fatigue, 40% for nausea and 50% for vomiting (MDH, 2019b). When intractable pain patients were administered the PEG scale to assess Pain Intensity, Enjoyment, and General Activity, 22% of patients experienced and maintained some degree of improvement in their composite score for greater than four months (MDH, 2019b). For each subset of the PEG scale, 17% of intractable pain patients experienced and maintained some improvement in pain intensity, 25% experienced and maintained some improvement in life enjoyment experience, and 26% experienced and maintained some improvement in general activity interference (MDH, 2019b).

A separate report was compiled by the Minnesota Department of Health (n.d.a) that summarized the experience of intractable pain patients enrolled in the Medical Cannabis Program (MCP) during the first five months that intractable pain was a qualifying condition in Minnesota from August 1, 2016 to December 31, 2016. A total of 2,290 patients were enrolled in the MCP for intractable pain during this timeframe (MDH, n.d.a). Fifty-four percent of patients responded to initial baseline surveys and follow-up surveys six months after certification (MDH, n.d.a). The patient self-reported PEG and symptom scores in this report mirrored the results described above which included an additional six months of data (MDH, n.d.a). However, a

"very high or high" level of benefit from medical cannabis was reported by 61% of patients responding. Only 10% of patients believed they experienced "little or no benefit" from the medical cannabis. Though a decrease in pain severity was the benefit mentioned most often by patients (64%), improvement in sleep, reductions in anxiety, reduction of other medications and associated side effects improved mobility and function and improvement of other indicators of quality of life were all mentioned as secondary benefits of medical cannabis (MDH, n.d.a).

This MDH report (n.d.a) also surveyed all the health care practitioners caring for intractable pain patients enrolled in the MCP, of which 40% responded. They reported that 41% of the 489 patients they cared for in the MCP program had a >30% reduction in their pain score 6 months after enrolling in the MCP (MDH, n.d.a) using the same pain scoring system prior to enrollment in the MCP and at six months afterwards. Forty-three percent of providers believed their patients experienced a "very-high or high" level of benefit from the medical cannabis, with only 24% believing their patients experienced "little or no" benefit.

In contrast to the above studies and reports, a four-year prospective study in Australia (The Pain and Opioids In Treatment [POINT] study) found that in a sample of 1,514 non-cancer, chronic pain patients who were prescribed opioids, those who reported using cannabis had greater pain and lower self-efficacy in managing pain scores, and found no evidence that cannabis use reduced pain severity (Campbell et al., 2018). Likewise, Merlin et al. (2019) found that in a sample of 433 people living with HIV and chronic pain, the 120 who reported also using non-medical cannabis in the past three months did not experience a change in their pain severity with increasing or decreasing their cannabis use during the timeframe. Individuals who had used marijuana in the past three months were also more likely to report symptoms of anxiety and depression (Merlin et al., 2019). The most common pain locations for this cohort were low back

and hands/feet (Merlin et al., 2019). Both the Campbell et al. (2018) and Merlin et al. (2019) studies investigated non-medical cannabis use, as cannabis was illegal for all purposes, including medical, in Australia during the years the POINT study took place. Using cannabis for medical purposes was explicitly excluded from the Merlin et al. (2019) study.

Use of Opioids

Like the results for whether cannabis improved pain control or not, 11 of the 13 studies found the use of cannabis resulted in decreased amounts of opioids used or prescribed to control pain. Two studies found no such relationship between the cannabis and opioids. These 13 studies were designed to either allow patients to self-report cannabis use and concurrent prescription use or to compare the amount of opioid prescribing in states without medical cannabis laws to states providing for medical cannabis for chronic pain.

Bachhuber et al. (2019) found in their survey of 1,000 adult-use cannabis customers at a dispensary in Colorado that among the 65% of those who reported using cannabis for pain relief, 88% of those prescribed opioids for pain had either decreased or stopped using opioids since initiating the use of cannabis. In their survey of medical cannabis users at a dispensary in Rhode Island, Zaller et al., (2015) found that 55% of the 200 users studied had substituted medical cannabis for prescription pain relievers, including opioids. Of those endorsing substitution, 92% reported fewer unwanted side-effects from medical cannabis compared to traditional prescription pain medications, including opioids (Zaller et al., 2015). Gill and Young (2018) found in their interviews with patients using a mobile medical cannabis delivery service in California that seven out of the ten individuals who were prescribed cannabis for chronic pain had stopped using their prescription pain relievers completely. All the medications referenced were opioids, with ibuprofen as the only exception (Gill & Young, 2018). Six of these patients stopped using

prescription analgesics due to the undesirable side effect profile and one patient had become addicted to their prescription pain reliever and decided to stop (Gill & Young, 2018). Themes that emerged during their interviews included a distrust of the medical field, including physicians and pharmaceutical drugs, and use of cannabis to treat addiction to prescription opioids (Gill & Young, 2018).

In a survey of 2,032 patients enrolled in Tilray, one of Canada's nationally run Medical Cannabis Programs, chronic pain was the primary diagnosis for 29.4% of the patients (Baron et al., 2018). Of this subset of chronic pain patients, 53% reported substituting cannabis for prescription drugs, with opioids representing 73% of the medications substituted (Baron et al., 2018). Lucas et al. (2019) analyzed responses from the entire cohort of 2,032 patients, regardless of primary diagnosis, and found that the most common substitution of cannabis was for prescription drugs (69%), and of those prescription drugs, 35% were opioids. Within the patients (n=610) who reported substituting cannabis for prescription opioids, 59% had stopped using opioids entirely (Lucas et al., 2019).

These findings are consistent with the Ishida et al. (2019) study: Among the 486 users of both prescription opioids for pain and cannabis, 41% reported a decrease or cessation in prescription opioid use. The case study of a 57-year-old man suffering from complex generalized abdominal pain prior to liver transplantation illustrated a dramatic reduction in his post-operative opioid requirements once medical cannabis was added to his pain regimen six-weeks post-operatively (Meng et al., 2015). His pre-operative hydromorphone requirements ranged between 2 mg-8 mg/day, and at six week post-operatively, he was taking approximately 20-30 mg of hydromorphone/day and unable to resume work as an engineer because he was too drowsy from the opioids (Meng et al., 2015). Medical cannabis was added to his pain regimen at that point,

and by 12 weeks post-operatively he was weaned down to 6 mg of hydrocodone/day while still taking the cannabis (Meng et al., 2015). He was also able to resume working because he was no longer too drowsy to function. In a secondary data analysis of 790 HIV-positive individuals, half of whom reported chronic pain, Sohler et al. (2018) found that only illicit cannabis was significantly (*OR* 0.57, CI 95%: 0.38-0.87) related to lower odds of prescription opioid use when compared to cigarettes, alcohol, and other illicit drugs.

Wen and Hockenberry's (2018) review of Medicaid data from 2011 (the first year that state reporting of Medicaid managed prescription data became mandatory) to 2016 (when the CDC issued new recommendations restricting opioid prescribing) compared the data from states with legalized medical and/or recreational (adult-use) cannabis to those without laws for either medical or adult-use cannabis. Wen and Hockenberry (2018) demonstrated that states with medical cannabis laws had a 5.88% lower rated of opioid prescribing (95% CI, -11.55% to -0.21%) and states with legalized adult-use marijuana laws had a 6.38% lower rate of opioid prescribing (95% CI, -12.20% to -0.56%). This study was not explicitly limited to chronic pain patients but only evaluated opioids that had been prescribed specifically for pain.

The findings for this Medicaid population are consistent with the review of data from 4,840,562 commercially insured individuals between 2006 and 2014 comparing prescription opioid use in states with and without legal access to medical cannabis (Shah et al., 2019). Shah et al. (2019) found that in states where medical cannabis was legal, there was a modestly lower rate of acute, chronic, and high-risk opioid use compared to states without legalized medical cannabis. Acute opioid use was defined as at least one opioid prescription in the past year, chronic opioid use was defined as least 90 days of opioid use within 180 days, with no more than a 30-day gap in prescriptions, and high-risk opioid use was defined as a) at least one day of

overlap between opioid and benzodiazepine prescriptions, or b) maximum daily dose > 120 milligrams of morphine equivalents (MME), or c) diagnosis of a substance use disorder in the same year as the opioid prescription (Shah et al., 2019). A subgroup analysis of individuals with at least one non-cancer chronic pain diagnosis also showed lower risks of opioid use in states with legalized medical cannabis: Opioid use (Diff (95%) CI: 1.230% (1.200%-1.260%); *OR* (95% CI): 0.94 (0.92-0.05); chronic opioid use (Diff (95%) CI: 0.279% (0.275%-0.284%); *OR* (95% CI): 0.94 (0.91-0.97); high-risk opioid use (Diff (95%) CI: 0.431% (0.423%-0.440%); *OR* (95% CI): 0.91 (0.88-0.94) (Shah et al., 2019). A falsification test was also performed, finding no relationship between the states with medical cannabis use laws and usage of antihypertensive or antilipidemic drugs (Shah et al., 2019), contrary to the findings for prescription opioids.

Within the state of New Mexico, a preliminary cohort study compared 37 chronic pain patients that were enrolled in the state's Medical Cannabis Program (MCP) to 29 chronic pain patients using prescription opioids who did not enroll in the MCP (Vigil et al., 2017). After 21 months of observing the Prescription Monitoring Program (PMP) records of opioid prescribing for these patients, MCP enrollment was associated with 17.27 higher odds of opioid prescription cessation (CI 1.89-157.36, p=0.012), 5.12 higher odds of decreasing daily prescription opioid doses (CI 1.56-16.88, p=0.007) and a 47-percentage point decrease in daily opioid doses compared to a mean change of positive 10.4 percentage points in the non MCP group (Vigil et al., 2017). Monthly trends for the MCP patients were negative over time (-0.64 mg IV morphine, CI -1.10 to -0.18, p=0.008) but not statistically significant for the non MCP group (Vigil et al., 2017).

Again, the Minnesota State Department of Health website was reviewed for information that may not have been discovered during the literature search. The only data found that

examines the effect of medical cannabis on prescription opioid use is found in the report on the first five months that intractable pain was included as a qualifying condition in Minnesota (MDH, n.d.a). Of the 586 responses received from health care practitioners caring for these patients, 221 indicated that opioid use was reduced six months after enrolling in the medical cannabis program. Three hundred and fifty-three patients were known to be taking opioids at baseline from self-reporting, so if only those patients are considered, 221/353, or 63% were able to reduce or stop using opioids after six months of cannabis (MDH, n.d.a). Of the 221 patients who had a decrease in opioid use, 58% reduced their use of at least one opioid by 50% or more during the six-month period (MDH, n.d.a). A review of resources on the MDH website revealed a relevant article (Bradford et al., 2018) that did not appear in the database searches, possibly because the full text was not available within the databases searched. Bradford et al. (2018) completed a longitudinal analysis of daily doses of prescription opioids filled in Medicare Part D from 2010-2015 and compared states with medical cannabis laws (MCL) to those without MCL. States with active medical cannabis dispensaries saw 3.742 million fewer daily doses per year of opioids filled (CI 95%, -6.289 to -1.194) out of an average of 23.08 million daily doses per year. Results varied between types of opioid, with statistically significant negative associations for hydrocodone and morphine in states with MCL (Bradford et al., 2018).

An alternative perspective was explored in the qualitative study exploring the experiences of adults living with chronic pain related to sickle cell disease after the implementation of the CDC recommendations for restricted opioid prescribing. Fifteen adults interviewed felt that the new restrictions had limited their access to, and amounts of, opioids prescribed to control their chronic pain (Sinha et al., 2019). They reported wishing to discuss other options for pain control, specifically cannabis, with their provider but felt their provider neglected to discuss adequate

pain control or comprehensive care with them (Sinha et al., 2019). The patients cited difficulty obtaining adequate amounts of opioids, intolerable side effects associated with opioids, and a desire to be "off" opioids as their reasons for wanting to explore medical cannabis (Sinha et al., 2019). These are patients who would likely intentionally decrease their opioid use in favor of using medical cannabis, but they lacked direction from their provider on how to explore this as an option.

Like the investigation into the relationship between cannabis use and pain control, the same two studies that found cannabis did not improve pain control also found no association between using cannabis and the amounts of opioids prescribed for chronic pain patients. The POINT study, conducted in Australia on 1,514 patients with chronic pain taking prescription opioids found no evidence that cannabis use reduced the use of prescribed opiates or resulted in increased rates of opioid discontinuation (Campbell et al., 2018). Merlin et al. (2019) concluded in their study of 433 individuals living with chronic pain and HIV that cannabis use was not associated with either higher rates of opioid cessation or lower odds of opioid initiation. As mentioned in the preceding section, both studies explicitly investigated recreational cannabis use, which was illegal at the time of the POINT study in Australia.

Gaps in Literature

The most prominent areas where the literature was lacking information was a) on the specific strains, types, strength, and method of ingestion of cannabis, b) explicit detail on the types of pain experienced by individuals experiencing chronic pain, and c) head-to-head comparisons effectiveness of cannabis vs. opioids is in clinical trials. Only one study investigated which strains of cannabis are preferred by those with chronic pain (Baron et al., 2018); this same study noted that of the larger sample surveyed, 42 different strains were

mentioned, giving people many options when it comes to selecting cannabis. Only the single case study investigated which types of pain were improved after adding cannabis (Meng et al., 2016) by using descriptors such as "burning," "stabbing," etc. 'Pain' can refer to many types of unpleasant feelings and it would be beneficial to understand what types of pain are improved by cannabis. None of the studies compared the effectiveness of cannabis to opioids in head-to-head clinical trials. The federal classification of cannabis as a Schedule 1 substance presents legal and logistical difficulties in accomplishing this at the present time. The Minnesota Department of Health also notes in their evaluation of cannabis-related studies that because most intractable, or chronic, pain patients are experiencing pain prior to starting cannabis, it is usually only studied as an adjunct treatment (MDH, n.d,a). Regardless, if feasible to study, this information would be helpful for both practitioners and patients in understanding what their best options may be for pain control.

Discussion

In the middle of the opioid crisis, researching alternatives to treat pain, particularly chronic pain, is of utmost importance to all primary care providers, including nurse practitioners. The literature reviewed for this article supports the consideration of cannabis for the treatment of chronic pain, both for its value in relieving pain with relatively few side effects and for its role in potentially lowering opioid requirements. Chronic pain is multifaceted and can be debilitating. Nearly all studies reviewed showed that for some adults with chronic pain, control of their pain improved with the use of cannabis. The only two studies which did not show improvement in pain for adults with chronic pain after using cannabis considered cannabis use that was illegal in one study (Campbell et al., 2018), and either illegal or recreational in the other study, but specifically not prescribed medically (Merlin et al., 2019). It is important to consider that the use

of cannabis and its effects on pain could be underreported in these two studies due to its legal status at the time.

In addition to improving pain for patients with chronic pain, it was evident in the literature that for some individuals, cannabis also help improve other related symptoms such as insomnia (Bachhuber et al., 2019; Gill & Young, 2019; MDH, n.d.b), nausea and malaise (Meng et al., 2016), depression (Sinha et al., 2019), concentration (Meng et al., 2016; Vigil et al., 2017) and anxiety (MDH, n.d.b; Sinha et al., 2016). In contrast, Campbell et al. (2018) demonstrated in the POINT study that patients using illicit cannabis and prescription opioids had higher generalized anxiety severity scores than patients taking prescription opioids who did not use illicit cannabis, begging the question of whether the anxiety was related to the use of an illicit substance. While improvement, or lack thereof, of related symptoms was not the focus of this literature review, they are important factors in evaluating quality-of-life for these patients. Except for the Campbell et al. (2018) study, all the studies that mentioned these quality-of-life indicators reported that they were improved with the use cannabis for adults with chronic pain.

Perhaps even more significant were the adverse effects of taking opioids that many chronic pain patients reported. Negative side effects from the use of prescription opioids (Gill & Young, 2019; Ishida et al., 2019; Lucas et al., 2019; Meng et al., 2016; MDH, n.d.a; Sinha et al., 2019; Zaller et al., 2015) were reported by several studies as reasons patients wished to use cannabis instead of opioids. Several other studies mentioned a desire by patients simply to be "off" opioids, whether from concerns over addiction (Gill & Young, 2019; Sinha et al., 2019; Zaller et al., 2015) or dislike of withdrawal symptoms (Lucas et al., 2019). Knowing that the American Association of Family Physicians (2016) affirmed that "regular opioid use, including use in an appropriate therapeutic context, is associated with both tolerance and dependence,"

every effort should be made to consider cannabis as an alternative for controlling pain for individuals who chronically use opioids, especially for those who express a desire to do so.

Several of the studies evaluated cannabis that was medically ordered, and several of the studies evaluated cannabis that was purchased for 'recreational' purposes, including at adult-use dispensaries (Bachhuber et al., 2019) or illicitly (Campbell et al., 2018). The advantage of purchasing either medical-grade cannabis or legal adult-use cannabis through dispensaries is the ability to purchase specific strains or types, including various THC: CBD ratios, which may be more helpful in controlling pain for this population. The problem with cannabis obtained through illicit means is that the strength and composition are usually unknown. However, regardless of the composition of cannabis or the source, our review suggests that for some people, it improves pain. The prevalence of people substituting non-medically indicated cannabis (Bachhuber et al., 2019; Ishida et al., 2019; Sohler et al., 2018) is a testament that individuals are already exploring this as an option. Additional research is needed to be able to fine-tune the strain and type of cannabis to the type of pain and type of symptom improvement the patient needs.

In examining substitution of cannabis for opioids, most of the studies similarly found that some people with chronic pain reduce their opioid use or stop using opioids altogether to control their pain when also taking cannabis. This held true when patients self-reported opioid use (Bachhuber et al., 2019; Baron et al., 2018; Ishida et al., 2019; Lucas et al., 2019; Sohler et al., 2018; Zaller et al., 2015) and when prescription records for opioids were reviewed for patients either using medical cannabis or in states which allowed medical cannabis (Bradford et al., 2018; Meng et al., 2016; Shah et al., 2019; Vigil et al., 2017; Wen & Hockenberry, 2018). One caveat to consider in respect to the studies reviewing state-level data comparing opioid prescription rates in states with and without medical cannabis legalization is that correlation does not equal

causation. However, this correlation held true when records were reviewed for Medicaid patients at the federal level (Wen & Hockenberry), Medicare Part D patients at the federal level (Bradford et al., 2018) and in a nationwide sample of 10% of commercially insured adults (Shah et al., 2019), suggesting a strong pattern of decreased opioid prescribing when medical cannabis is a legal option for pain control.

The opioid-sparing effect of using cannabis for the treatment of pain may be attributed to a synergistic relationship between cannabis and opioids. CB1 receptors are 10 times denser than mu-opioid receptors in the brain, and are often found in the same areas, including those areas associated with pain pathways (Baron et al., 2018). Cannabis use does not increase opioid levels in the blood (Baron et al., 2018), reducing the concern for increased opioid side effects including respiratory depression. Notably, a pre-clinical study found that the median effective dose (ED50) of morphine given with THC is 3.6 times lower than the ED50 of morphine alone (Baron et al., 2018). Even if the exact physiological mechanism is unknown, the evidence reviewed in this literature affirms that for some people with chronic pain, opioid requirements are decreased when used in conjunction with cannabis.

The paucity of meta-analyses, systematic reviews, and randomized controlled studies available on cannabis and chronic pain is partially hampered by federal restrictions on research involving cannabis due to its Schedule I classification by the FDA. Level I and II evidence such as this would strengthen the findings of the research discussed in this review, the majority of which was Level IV.

Future Implications

Recommendations for Education

Both primary care providers and patients would benefit from education regarding not only the benefits of cannabis as a treatment option for chronic pain, but education as to the processes of certification, registration, and procurement of cannabis. Sickle cell patients with chronic pain felt that their providers were focused on reducing the amounts of opioids prescribed, but neglected to discuss adjunct or alternative therapies, including cannabis, during appointments (Sinha et al., 2019). The benefits of using for cannabis for the treatment of chronic pain are detailed in the previous sections, but the logistics of obtaining medical cannabis merits explanation.

In Minnesota, cannabis is legally available for treatment of 15 medical conditions, including intractable pain and chronic pain (MDH, n.d.b). For a patient to obtain medical cannabis, a physician, PA, or APRN must conduct a physical examination, review of pertinent records, and certify the patient as having a qualifying condition (Institute for Clinical Systems Improvement [ICSI], 2015). The provider only certifies that the patient has a qualifying condition under state law, they do not "prescribe" cannabis. A provider must be registered with the state of Minnesota's Office of Medical Cannabis (OMC) to certify a patient as having a qualifying condition. The patient, once certified, also registers with the OMC. After paying an enrollment fee, they can visit one of the 13 Cannabis Patient Centers located throughout the state to meet with a licensed pharmacist to determine the best dose, type, and frequency based on the patient's condition and symptoms (ICSI, 2015), and the cannabis is dispensed to the patient. Patients wishing to continue using medical cannabis must be re-certified annually by a registered provider. Providing education to all primary care providers regarding this process would help guide discussion with their patients regarding cannabis as an option for pain control. Information for providers and patients is available on the Minnesota Department of Health's

website on this process (ICSI, 2015) but it is unknown how widely this information has been disseminated.

Recommendations for Clinical Practice

In accordance with the 2016 CDC guidelines suggesting opioids not be used as a first-line treatment for patients with chronic pain (Dowell, 2016), primary care providers, including nurse practitioners, should be familiar with the use of cannabis as an alternative to or in conjunction with opioids. They also need to be familiar with the process of registering as a provider and certifying patients with the OMC so that they can effectively address the needs of their patients with chronic pain. Since the MDH does not maintain a list of providers who are registered with the OMC, there is no way for patients to know in advance of their appointment whether their primary care provider can certify them for medical cannabis.

In Minnesota in 2019, there were 24,643 physicians with active state licenses, 3209 actively licensed physician assistants (PAs), and 8,849 actively licensed Advanced Practice Registered Nurses (APRNs) for a total of 36,701 licensed providers (MDH, 2019c; MDH 2019d; MDH, 2019e). However, as of March 11, 2020, only 1,865 of these providers were registered with the OMC and eligible to certify patients for medical cannabis (MDH, 2021). This represents only 5% of all licensed providers in the state of Minnesota. In the first five months that intractable pain was included as a certifiable condition in Minnesota, only 9% of the 265 providers certifying these intractable pain patients were APRNs (MDH, n.d.a). Of the 226 physicians certifying patients for intractable pain during that timeframe 52% listed a specialty in primary care or family medicine (MDH, n.d.a). The impetus is on providers, particular in primary care and nurse practitioners, to register with the OMC within this state so that they can certify patients with chronic or intractable pain that could potentially benefit from medical

cannabis. They should also be knowledgeable about the effects of cannabis, both beneficial and adverse, so they can have evidence-based discussions with their patients about the best approach to manage their pain.

Recommendations for Policies

The most important policy concern related to using cannabis as a treatment for pain is its FDA classification as a Schedule I controlled substance. To legitimize cannabis as a valid medical treatment, its classification must reflect the existing evidence showing benefit from its use in controlling pain for patients with chronic pain, and therefore be changed. The classification of cannabis as a Schedule I controlled substance currently hampers the ability to research it, even within states that allow for legal medical use of it. Providers are placed in an undesirable position of certifying a patient for a condition for a legal treatment at the state level, knowing it is not FDA approved or even legal at the federal level. The fear of using something deemed illegal at the federal level may also deter patients who would otherwise consider cannabis as an option for controlling pain. Even individuals who use cannabis for medical purposes in states where it is legal are prohibited from owning firearms by the federal government due to cannabis' status as a Schedule I controlled substance (MDH, n.d.c). Because opioids are classified as Schedule II and lower, there are no limitations on firearm possession if an adult is prescribed an opioid. Individuals with chronic pain are more likely to reside in rural areas (Zelaya et al., 2020), a demographic often associated with increased rates of firearm possession, so limitations on their rights to bear arms may be a considerable factor in deciding whether to use medical cannabis for those who may need it the most.

Another policy revision that merits consideration is the legalization of cannabis for adult-use, or recreational use, in addition to medical use. Based on the patterns noted in the research of

the use of recreational marijuana to treat pain (Bachhuber et al., 2018) and self-substitution of cannabis for opioids with non-medical cannabis (Ishida et al., 2019; Sinha et al., 2019; Sohler et al., 2018), it is an idea that may warrant careful appraisal. With only five percent of current providers in Minnesota registered to certify conditions for medical cannabis, and no centralized listing to access the providers who are certified, the barriers to obtaining medical cannabis are self-evident (MDH, 2019c; MDH, 2019d; MDH, 2019e). Medical cannabis is not covered by insurance in the state of Minnesota (MDH, n.d.c), so persons using medical cannabis are paying face value for their cannabis even though it requires at least one visit to a provider for initial certification, a $200 enrollment fee in the Medical Cannabis Program, and annual visits to a provider to be re-certified (MDH, n.d.c). If the cost is the same to the individual regardless of whether it is deemed medical or not, opening cannabis up to recreational use may remove some of these barriers preventing chronic pain patients from exploring this as an option.

Following from this, if medical cannabis is to be considered a legitimate treatment for pain, it should also be covered both by federal and state programs, including Medicare and Medicaid, and private insurance companies as such. Opioids *are* covered under most insurance, so cost and accessibility at the present time may dissuade patients who could benefit from cannabis from considering this as an alternative or adjunct to chronic opioid use. For example, generic oxycodone costs anywhere from a $0-$20 co-pay under Medicare with 99% of Medicare Part D and Medicare Advantage plans covering it (GoodRx, 2020). By contrast, no insurance companies in the state of Minnesota currently cover medical cannabis. If providers are recommending alternatives to opioids for controlling pain in patients with chronic pain, it follows that those alternatives should be covered similarly to the coverage of opioids.

Recommendations for Research

As discussed earlier, further research is indicated in three primary areas for which the literature is lacking. The first is specificity relating to cannabis composition and method of ingestion to best match specific symptoms of pain to the most effective type of cannabis. Baron et al. (2018) began exploring this in their investigation of preferred strains of cannabis for chronic pain patients, and if cannabis is to be considered as a valid treatment for pain, it merits the same kind of research into how best to achieve that as other pharmaceutical options have done in the past. The second area in which further research is indicated is to further differentiate what specific types of pain are improved with cannabis. Meng et al. (2016) detailed this in a case study, but this type of research needs to be extended to large studies investigating sub-types of pain and their response to cannabis. The third area in which a strong indication for additional research is present is the need for randomized clinical trials comparing cannabis directly to opioids to determine what is the most effective means of controlling pain. The evidence reviewed above strongly suggests that cannabis not only helps improve pain in some people, but also allows some people to decrease the amounts of opioids necessary to control their pain. Except for personal experiences recounted during some of the qualitative studies (MDH, n.d.b; Sinha et al., 2019; Zaller et al., 2015), none of the studies examined the efficacy of opioids compared to cannabis. Particularly absent is the availability of data from RCTs which would give additional insight into which treatment is more effective. Legal and ethical limitations prohibit this from being easily accomplished at the present time.

Research is also needed to determine what the potential adverse effects of cannabis are when used as a treatment for chronic pain. Examining this in detail exceeds the scope of this paper, but it is an important consideration in recommending cannabis as a treatment. Even

though no deaths have definitively been linked to an overdose of cannabis or cannabinoids it is known that multiple adverse effects may occur, including impairment of judgement, memory, motor skills and driving ability (Incze et al., 2020). It is also known that, like opioids, cannabis use can be habit-forming over time (Incze et al., 2020) although this is usually examined in context of recreational use. Research on not only the positive, but negative effects of medical cannabis in both the short and long term would help clinicians feel more confident in recommending this as a treatment.

As the data from Minnesota suggests, few providers are registered to certify patients with conditions allowing them to access medical cannabis. Research into what barriers exist to prevent providers from registering with the OMC in Minnesota would be helpful in widening the circle of providers who are able to recommend this as an option for patients with chronic pain.

Conclusion

A review of the most recent literature suggests that in adults with chronic pain, cannabis both improves control of pain and reduces the amounts of opioids necessary to control pain in some individuals. With the 2016 CDC recommendation that opioids should not be a first line treatment for chronic pain (Dowell et al., 2016), cannabis could and should be considered by primary care providers, including nurse practitioners, as a viable alternative to or adjunct to opioids for control of pain in this population. Changing the federal classification of cannabis from a Schedule I controlled substance to one that more accurately reflects its medical value would increase research opportunities and improve access for many adults who may benefit from cannabis as a treatment for chronic pain. Health care providers, particularly nurse practitioners and those working in primary care, should be familiar with the associated provider registration

and patient certification processes related to providing access to medical cannabis for their patients who could benefit from it.

References

American Association of Family Practice Physicians. (2016). *Chronic pain management and opioid misuse: A public health concern (position paper)*. https://www.aafp.org/about/policies/all/chronic-pain-management-opiod-misuse.html

Bachhuber, M., Arnsten, J. H., & Wurm, G. (2019). Use of cannabis to relieve pain and promote sleep by customers at an adult use dispensary. *Journal of Psychoactive Drugs, 51*(5), 400–404. https://doi.org/10.1080/02791072.2019.1626953

Baron EP, Lucas P, Eades J, Hogue O. (2018). Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. *J Headache Pain. 2018 May 24;19*(1):37. https://doi.org/10.1186/s10194-018-0862-2

Benyamin, R., Trescot, A. M., Datta, S., Buenaventura, R., Adlaka, R., Sehgal, N., Glaser, S. E., & Vallejo, R. (2008). Opioid complications and side effects. *Pain Physician*, *11*(2 Suppl), S105–S120.

Borgelt, L. M., Franson, K. L., Nussbaum, A. M., & Wang, G. S. (2013). The pharmacologic and clinical effects of medical cannabis. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 33*(2), 195-209. https://doi.org/10.1002/phar.1187

Bradford, A. C., Bradford, D., Abraham, A., & Adams, G. (2018). Association between US state medical cannabis laws and opioid prescribing in the Medicare Part D population. *JAMA Intern Med, 178*(5), 667-673. http://doi.org/10.1001/jamaintermed.2018.0266

Campbell, G., Hall, W. D., Peacock, A., Lintzeris, N., Bruno, R., Larance, B., Nielsen, S., Cohen, M., Chan, G., Mattick, R. P., Blyth, F., Shanahan, M., Dobbins, T., Farrell, M., & Degenhardt, L. (2018). Effect of cannabis use in people with chronic non-cancer pain

prescribed opioids: Findings from a 4-year prospective cohort study. *Lancet Public Health, 3*(7), e341-e350. https://doi.org/10.1016/S2468-2667(18)30110-5

Centers for Disease Control and Prevention. (2020). *Opioid overdose: Understanding the epidemic*. https://www.cdc.gov/drugoverdose/epidemic/index.html

Dowell, D., Haegerich, T. M., & Chou, R. CDC Guideline for Prescribing Opioids for Chronic Pain. (2016). *MMWR Recomm Rep 2016;65*(RR-1),1–49. https://dx.doi.org/10.15585/mmwr.rr6501e1external icon

Gill, H. K., & Young, S. D. (2019). Exploring cannabis use reasons and experiences among mobile cannabis delivery patients. *Journal of Substance Use, 24*(1), 15–20. https://doi.org/10.1080/14659891.2018.1489012

GoodRx. (2021). *Oxycodone*. https://www.goodrx.com/oxycodone/medicare-coverage

Incze, M. A., Slawek, D., & Cunningham, C. O. (2020). *What should I know about medical cannabis*? JAMA Internal Medicine Patient Page. https://doi.org/10.1001jamainternmed.2020.0018

Institute for Clinical Systems Improvement. (2015). *Health care practitioner guidance for Minnesota's Medical Cannabis Program.* https://www.health.state.mn.us/people/cannabis/docs/practitioners/icsiguide.pdf

Ishida, J. H., Wong, P. O., Cohen, B. E., Vali, M., Steigerwald, S., & Keyhani, S. (2019). Substitution of marijuana for opioids in a national survey of US adults. *PLoS ONE, 14*(10), 1–8. https://doi.org/10.1371/journal.pone.0222577

Lucas P, Baron EP, Jikomes N. (2019). Medical cannabis patterns of use and substitution for opioids & other pharmaceutical drugs, alcohol, tobacco, and illicit substances; results

from a cross-sectional survey of authorized patients. *Harm Reduct J. 2019 Jan 28;16*(1):9. https://doi.org/10.1186/s12954-019-0278-6

Medical Marijuana Project. (2021). *State-by-state language allowing severe pain*. https://www.mpp.org/issues/medical-marijuana/state-state-language-allowing-severe-pain

Melnyk, B. M., & Fineout-Overholt, E. (2015). *Evidence based practice in nursing and healthcare: A guide to best practice* (3rd ed.). Wolters Kluwer.

Meng, H., Hanlon, J., Katznelson, R., Ghanekar, A., McGilvray, I., Clarke, H., & Hanlon, J. G. (2016). The prescription of medical cannabis by a transitional pain service to wean a patient with complex pain from opioid use following liver transplantation: A case report. *Canadian Journal of Anaesthesia*.

Merlin J. S., Long, D., Becker, W. C., Cachay, E. R., Christopolous, K. A., Claborn, K. R., Crane, H. M., Edelman, E. J., Lovejoy, T.I., Mathews, W. C., Morasco, B. J., Napravnik, S., O'Cleirigh, C., Saag, M. S., Starrels, J. L., Gross, R., & Liebschutz, J. M. (2019). Marijuana use is not associated with changes in opioid prescriptions or pain severity among people living with HIV and chronic pain. *J Acquir Immune Defic Syndr, 81*(2), 231-237. https://doi.org/10.1097/QAI.0000000000001998

Minnesota Department of Health. (n.d.a). *Intractable pain patients in the Minnesota Medical Cannabis program: Experience of enrollees during the first five months*. https://www.health.state.mn.us/people/cannabis/docs/about/ipreport.pdf

Minnesota Department of Health. (n.d.b). *Medical cannabis qualifying conditions*. https://www.health.state.mn.us/people/cannabis/patients/conditions.html

Minnesota Department of Health. (n.d.c). *What patients should know before enrolling*:

Frequently asked questions.

https://www.health.state.mn.us/people/cannabis/patients/patientfaq.html

Minnesota Department of Health. (2019a). MDH News Release. *Medical cannabis program to add chronic pain, macular degeneration as qualifying conditions*.

https://www.health.state.mn.us/news/pressrel/2019/cannabis120219.html

Minnesota Department of Health. (2019b). *Benefits reported on patient self-evaluation: Patients with first enrollment July 2015-June 2017.*

https://www.https://www.health.state.mn.us/people/cannabis/docs/about/cohort/c2015_2017_benefitspse.pdf

Minnesota Department of Health. (2019c). *Overview of the physician workforce 2019*.

https://www.health.state.mn.us/data/workforce/phy/docs/cbphys.pdf

Minnesota Department of Health. (2019d). *Minnesota's physician assistant (PA) workforce*.

https://www.health.state.mn.us/data/workforce/phy/docs/cbpa.pdf

Minnesota Department of Health. (2019e*). Minnesota's Advanced Practice Registered Nurse workforce.*

https://www.health.state.mn.us/data/workforce/nurse/docs/2019aprnb.pdf

Minnesota Department of Health. (March 11, 2021). *Medical cannabis weekly updates of registration counts.*

https://www.health.state.mn.us/people/cannabis/about/medicalcannabisstats.html

National Institutes of Health. (2021). *Opioid overdose crisis*.

https://www.drugabuse.gov/drug-topics/opioids/opioid-overdose-crisis

Shah, A., Hayes, C. J., Lakkad, M., & Martin, B. C. (2019). Impact of medical marijuana legalization on opioid use, chronic opioid use, and high-risk opioid use. *JGIM: Journal of General Internal Medicine, 34*(8), 1419–1426. https://doi.org/10.1007/s11606-018-4782-2

Sinha, C. B., Bakshi, N., Ross, D., & Krishnamurti, L. (2019). Management of chronic pain in adults living with sickle cell disease in the era of the opioid epidemic: A qualitative study. *JAMA Netw Open. 2019 May 3;2*(5), e194410. https://doi.org/10.1001/jamanetworkopen.2019.4410

Sohler, N. L., Starrels, J. L., Khalid, L., Bachhuber, M. A., Arnsten, J. H., Nahvi, S., Jost, J., & Cunningham, C. O. (2018). Cannabis use is associated with lower odds of prescription opioid analgesic use among HIV-Infected individuals with chronic pain. *Substance Use & Misuse, 53*(10), 1602–1607. https://doi.org/10.1080/10826084.2017.141640

United States Department of Health and Human Services. (2016). *Facing addiction in America: The Surgeon General's spotlight on opioids.* https://addiction.surgeongeneral.gov/sites/default/files/OC_SpotlightOnOpioids.pdf

United States Food and Drug Administration. (2021). *FDA regulation of cannabis and cannabis-derived products, including cannabidiol (CBD).* https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd#approved

Vigil, J. M., Stith, S. S., Adams, I. M., & Reeve, A. P. (2017). Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. *PLoS ONE, 12*(11), 1–13. https://doi.org/10.1371/journal.pone.0187795

Wen, H. & Hockenberry, J. M. (2018). Association of medical and adult-use marijuana laws with opioid prescribing for Medicaid enrollees. *JAMA Intern Med,178*(5), 673-679. https://doi.org/10.1001/jamainternmed.2018.1007

Whiting, P. F., Wolff, R. F., Deshpande, S., Di Nislo, M., Duffy, S., Hernandez, A. V., Keurenties, C., Lang, S., Misso, K., Ryder, S., Schmidlkofer, S., Westwood, M., & Kleijen, J. (2015). Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA, 313*(24), 2456-2473. https://doi.org//10.1001.jama.2015.6358.

Woodbury, A. (2015). Opioids for nonmalignant chronic pain. *AMA J Ethics, 17*(3), 202-208. https://doi.org//10.1001/journalofethics.2015.17.3.ecas1-1503

Zaller, N., Topletz, A., Frater, S., Yates, G., & Lally, M. (2015). Profiles of medicinal cannabis patients attending compassion centers in Rhode Island. *Journal of Psychoactive Drugs, 47*(1), 18–23. https://doi.org/10.1080/02791072.2014.999901

Zelaya, C. E., Dahlhamer, J. M., Lucas J. W., & Connor, E. M. (2020*). Chronic pain and high-impact chronic pain among U.S. adults*. NCHS Data Brief No. 390. https://www.dcc.gov/nchs/products/databriefs/db390.htm

Appendix

Table 1

Database Search Description

Database (or Search Engine)	Restrictions Added to Search	Dates Included in Database	General Subjects Covered by Database
1. PubMed	Free full text, Journal article, Within last 5 years, English Language, Adult (19+ years).	2015-2020	PubMed is a free search engine accessing primarily the MEDLINE database of references and abstracts on life sciences and biomedical topics. The United States National Library of Medicine at the National Institutes of Health maintains the database as part of the Entrez system of information retrieval.
2. EBSCO Host, including Academic Search Premier, CINAHL Plus with Full-Text, Cochrane Central Register of Controlled Trials, Cochrane Database of Systemic Reviews	EBSCO Host (All databases): Find all my search terms, Apply equivalent subjects, Full text, Scholarly (Peer-Reviewed), English Language. Academic Search Premier: Publication type: Periodical, Document Type: Article, Language: English CINAHL Plus with Full-Text: Exclude pre-CINAHL, Research article, English Language	2015-2020	Academic Search Premier provides citations, abstracts, and full text of articles from over 4,600 publications, covering almost every academic subject. CINAHL Plus with Full-Text provides full text access to e-books about nursing and 29 core nursing journals. Cochrane Controlled Trials Register is a bibliography of controlled trials identified by contributors to the Cochrane Collaboration and others, as part of an international effort to hand search the world's journals and create an unbiased source of data for systematic reviews. Cochrane Database of Systematic Reviews contains full text articles, as well as protocols focusing on the effects of healthcare. Data is evidence-based medicine and is often combined statistically (with meta-analysis) to increase the power of the findings of numerous studies, each too small to produce reliable results individually

Database (or Search Engine)	Restrictions Added to Search	Dates Included in Database	General Subjects Covered by Database
	Cochrane Central Register of Controlled Trials: Language: English. Cochrane Database of Systemic Reviews: Language: English, Year of publication-reviews: 2015-2020; Year of publication-protocols: 2015-2020.		

Table 2

Data Abstraction Process

Date of Search	Key Words	Results in PubMed	Results in EBSCO Host
10/15/2020	"opioid" AND "prescription" AND "chronic pain"	226	300
10/15/2020	"opioid" AND "prescription" AND "overdose" AND "practices OR strategies OR approaches"	130	142
10/15/2020	"opioid" AND "prescription" AND "overdose"	300	264
10/23/2020	"opioid" AND "cannabis"	134	244
10/23/20	"opioid" AND "cannabis" AND "chronic" AND pain	17	16
10/25/20	"opioid" AND "cannabis OR marijuana" AND "chronic pain" AND "prescription"	**21**	**8**
11/20/20	Opioid OR opiate OR opioids OR opiates AND medical AND marijuana AND chronic OR persistent OR intractable OR long-term OR long term AND pain	**21**	**19**

Bold numbers include studies to which inclusion/exclusion criteria applied.

Table 3

Characteristics of Literature Included/Excluded

Reference	Inclusion or Exclusion	Rationale
Bachhuber, M., Arnsten, J. H., & Wurm, G. (2019). Use of cannabis to relieve pain and promote sleep by customers at an adult use dispensary. *Journal of Psychoactive Drugs*, *51*(5), 400–404. https://doi.org/10.1080/02791072.2019.1626953	Included	Cross-sectional study of adult cannabis dispensary customers in Colorado examining if cannabis was purchased for pain control and what other pain methods they had tried, including prescription opioids.
Baron, E. P., Lucas, P., Eades, J & Hogue, O. (2018). Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. *J Headache Pain, 2018 May 24, 19*(1). https://doi.org/10.1186/s10194.-018-0862-2	Included	Cohort study of medicinal cannabis users and substitution patterns.
Campbell, G., Hall, W. D., Peacock, A., Lintzeris, N., Bruno, R., Larance, B., Nielsen, S., Cohen, M., Chan. G., & Degenhardt, L. (2018). Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: Findings from a 4-year prospective cohort study. *Lancet Public Health, 3*(7): e341-e350. https://doi.org/10.1016/S2468-2667(18)30110-5	Included	Prospective cohort study of the effect of cannabis usage in chronic non-cancer pain patients who were prescribed opioids.
Carr, D., & Schatman, M. (2019). Cannabis for chronic pain: Not ready for prime time. *American Journal of Public Health, 109*(1), 50–51. https://doi.org/10.2105/AJPH.2018.304593	Excluded	Opinion article regarding author's views on using cannabis for chronic pain.

Reference	Inclusion or Exclusion	Rationale
Char, D. (2016). Supervised controlled substance use. *American Journal of Bioethics, 16*(4), 56–58. https://doi.org/10.1080/15265161.2016.114529	Excluded	Opinion article regarding author's views on legalization of illicit substances.
Darnall, B. D., & Humphreys, K. N. (2018). An experimental method for assessing whether marijuana use reduces opioid use in patients with chronic pain. *Addiction, 113*(8), 1552–1553. https://doi.org/10.1111/add.14239	Excluded	Study protocol. Study not completed.
Desai, R. J., Jin, Y., Franklin, P. D., Lee, Y. C., Bateman, B. T., Lii, J., Solomon, D.H., Katz, J.N. & Kim, S.C. (2019). Care providers with long-term prescription opioid use in Medicare patients with severe osteoarthritis: A cohort study. *Arthritis Rheumatology,* 71(5), 712-721. https://doi.org/10.1002/art.40834	Excluded	Examines relationship between geography and access to health care providers.
Gill, H. K., & Young, S. D. (2019). Exploring cannabis use reasons and experiences among mobile cannabis delivery patients. *Journal of Substance Use, 24*(1), 15–20. https://doi.org/10.1080/14659891.2018.1489012	Included	Cross-sectional study of patients using a medical cannabis delivery system examining why they use cannabis.
Hudgins, J. D., Porter, J. J., Monuteaux, M. C., & Bourgeois, F. T. (2019). Prescription opioid use and misuse among adolescents and young adults in the United States: A national survey study. *PLoS Medicine, 15*(11), 1–15. https://doi.org/10.1371/journal.pmed.1002922	Excluded	Included adolescents in study regarding prescription opioid use.
Ishida, J. H., Wong, P. O., Cohen, B. E., Vali, M., Steigerwald, S., & Keyhani, S. (2019). Substitution of marijuana for opioids in a national survey of US adults. *PLoS ONE, 14*(10), 1–8. https://doi.org/10.1371/journal.pone.0222577	Included	Cross-sectional study of adults in the United States who reported using prescription opioids for pain to examine rates of cannabis substitution.

Reference	Inclusion or Exclusion	Rationale
Lawental, M., Surratt, H. L., Buttram, M. E., & Kurtz, S. P. (2018). Serious mental illness among young adult women who use drugs in the club scene: co-occurring biopsychosocial factors. *Psychology, Health & Medicine, 23*(1), 82–88. https://doi.org/10.1080/13548506.2017.1330545	Excluded	Cross-sectional study of recreational drug use by young women.
Lucas, P., Baron, E. P. & Jikomes, N. (2019). Medical cannabis patterns of use and substitution for opioids & other pharmaceutical drugs, alcohol, tobacco, and illicit substances; results from a cross-sectional survey of authorized patients. *Harm Reduct J, 16*(1). https://doi.org/10.1186/s12954-019-0278-6	Included	Cross-sectional study of medical cannabis patients in Canada and substitution for opioids.
Meng, H., Hanlon, J., Katznelson, R., Ghanekar, A., McGilvray, I., Clarke, H., & Hanlon, J. G. (2016). The prescription of medical cannabis by a transitional pain service to wean a patient with complex pain from opioid use following liver transplantation: A case report. *Canadian Journal of Anaesthesia.*	Included	Case study of weaning post-operative patient with acute-on-chronic pain from long-term opioids by supplementing pain control with cannabis.
Merlin, J. S., Long, D., Becker, W. C., Cachay, E. R, Christopolous, K.A., Claborn, K. R., Crane, H. M., Edelman, E. J., Lovejoy, T. I., Mathews, W.C., Morasco, B. J., Napravnik, S., O'Cleirigh, C., Saag, M. S., Starrels, J. L., Gross, R. & Liebschutz, J.M. (2019). Marijuana use Is not associated with changes in opioid prescriptions or pain severity among people living with HIV and chronic pain. *J Acquir Immune Defic Syndr, 81*(2),231-237. https://doi.org/10.1097/QAI.0000000000001998	Included	Cross-sectional study of cannabis usage in patients with HIV and chronic pain.

Reference	Inclusion or Exclusion	Rationale
Monti, L., Stefanucci, A., Pieretti, S., Marzoli, F., Fidanza, L., Mollica, A., Mirzaie, S., Carradori, S., De Petrocellis, L., Schiano Moriello, A., Benyhe, S., Zádor, F., Szűcs, E., Ötvös, F., Erdei, A. I., Samavati, R., Dvorácskó, S., Tömböly, C., & Novellino, E. (2016). Evaluation of the analgesic effect of 4-anilidopiperidine scaffold containing ureas and carbamates. *Journal of Enzyme Inhibition & Medicinal Chemistry, 31*(6), 1638–1647. https://doi.org/10.3109/14756366.2016.1160902	Excluded	Research paper on fentanyl analogs and their analgesic effects.
News and Notes. (2016). *Addiction, 111*(6), 1123–1127. https://doi.org/10.1111/add.13424	Excluded	Updates on prescription monitoring services.
Novak, S. P., Peiper, N.C & Zarkin, G. A. (2016). Nonmedical prescription pain reliever and alcohol consumption among cannabis users. (2016). *Drug Alcohol Depend. 1(*159), 101-8. https://doi.org/10.1016/.j.drugalcdep.2015.11.039	Excluded	Examines non-medical opiate use.
Olmstead, T. A., Yonkers, K. A., Ondersma, S. J., Forray, A., Gilstad, H. K., & Martino, S. (2019). Cost-effectiveness of electronic- and clinician-delivered screening, brief intervention and referral to treatment for women in reproductive health centers. *Addiction, 114*(9), 1659–1669. https://doi.org/10.1111/add.14668	Excluded	Cross-sectional study of illicit drug use by women seeking care at reproductive health centers.
Orhurhu, V., Olusunmade, M., Urits, I., Viswanath, O., Peck, J., Orhurhu, M. S., Adekoya, P., Hirji, S., Sampson, J., Simopoulos, T., & Jatinder, G. (2019). Trends of opioid use disorder among hospitalized patients with chronic pain. *Pain Practice, 19*(6), 656–663. https://doi.org/10.1111/papr.12789	Excluded	Secondary analysis of patients hospitalized for chronic pain to assess prevalence of opioid use disorder. Does not specify whether opioid use disorder is from prescription or illicit opioids.

Reference	Inclusion or Exclusion	Rationale
Park, J. N., RouhaniI, S., Beletsky, L., Vincent, L., Saloner, B., & Sherman, S. G. (2020). Situating the continuum of overdose risk in the social determinants of health: A new conceptual framework. *Milbank Quarterly, 98*(3), 700–746. https://doi.org/10.1111/1468-0009.12470	Excluded	Policy proposal regarding solutions to the (non-prescription) opioid epidemic.
Rogers, A. H., Shepherd, J. M., Paulus, D. J., Orr, M. F., Ditre, J. W., Bakhshaie, J., & Zvolensky, M. J. (2019). The interaction of alcohol use and cannabis use problems in relation to opioid misuse among adults with chronic pain. *International Journal of Behavioral Medicine, 26*(5), 569–575. https://doi.org/10.1007/s12529-019-09813-3	Excluded	Focused on misuse of cannabis and opioids.
Sanger, N., Bhatt, M., Shams, I., Shahid, H., Luo, C., Tam, S. L., Samaan, M. C., de Souza, R., Thabane, L. & Samaan, Z. (2018). Association between socio-demographic and health functioning variables among patients with opioid use disorder introduced by prescription: A prospective cohort study. *Pain Physician, 21*(6), E623-E632.	Excluded	Subject is opioid use disorder.
Shah, A., Hayes, C. J., Lakkad, M., & Martin, B. C. (2019). Impact of medical marijuana legalization on opioid use, chronic opioid use, and high-risk opioid use. *JGIM: Journal of General Internal Medicine, 34*(8), 1419–1426. https://doi.org/10.1007/s11606-018-4782-2	Included	Retrospective analysis of correlation between medical marijuana usage and prescription opioid use.

Reference	Inclusion or Exclusion	Rationale
Sinha, C. B., Bakshi, N., Ross, D. & Krishnamurti, L. (2019). Management of chronic pain in adults living with sickle cell disease in the era of the opioid epidemic: A qualitative study. *JAMA Netw Open, 2*(5). https://doi.org/10.1001/jamanetworkopen.2019.4410	Included	Qualitative study of adults with sickle cell disease and chronic pain who were prescribed opioids.
Sohler, N. L., Starrels, J. L., Khalid, L., Bachhuber, M. A., Arnsten, J. H., Nahvi, S., Jost, J., & Cunningham, C. O. (2018). Cannabis use is associated with lower odds of prescription opioid analgesic use among HIV-Infected individuals with chronic pain. *Substance Use & Misuse, 53*(10), 1602–1607. https://doi.org/10.1080/10826084.2017.1416408	Included	Secondary data analysis of rate of prescription opioid use by people with HIV and chronic pain and concomitant use of illicit drugs, including cannabis.
Vigil, J. M., Stith, S. S., Adams, I. M., & Reeve, A. P. (2017). Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. *PLoS ONE, 12*(11), 1–13. https://doi.org/10.1371/journal.pone.0187795	Included	Cohort study of individuals enrolled in medical cannabis program in New Mexico and prescription opiate use.
Wall, M. M., Liu, J., Hasin, D. S., Blanco, C. & Olfson, M. (2018). Use of marijuana exclusively for medical purposes. *Drug Alcohol Depend, (*195),13-15. https://doi.org/10.1016/j.drugalcdep.2018.11.009	Excluded	Examines non-prescription opiate use disorder.
Wen, H. & Hockenberry, J. M. (2018). Association of medical and adult-use marijuana laws with opioid prescribing for Medicaid enrollees. *JAMA Intern Med, 78*(5), 673-679. https://doi.org/10.1001/jamainternmed.2018.1007	Included	Cross-sectional study of Medicaid enrollees who were prescribed opioids during implementation of state medical cannabis laws
Zaller, N., Topletz, A., Frater, S., Yates, G., & Lally, M. (2015). Profiles of medicinal cannabis patients attending Compassion Centers in Rhode Island. *Journal of Psychoactive Drugs, 47*(1), 18–23. https://doi.org/10.1080/02791072.2014.999901	Included	Cross-sectional study of medicinal cannabis patients as to why they were prescribed cannabis.

Table 4

Literature Review Table of All Studies Included

Citation	Purpose of the Study	Population (p)/ Number (n)/ Setting (s)	Study Type and Level of Evidence	Instruments and Variables	Findings	Implications
Bachhuber, M., Arnsten, J. H., & Wurm, G. (2019). Use of cannabis to relieve pain and promote sleep by customers at an adult use dispensary. *Journal of Psychoactive Drugs, 51*(5), 400–404. https://doi.org/10.1080/02791072.2019.1626953	Determine why adult recreational cannabis users were purchasing cannabis.	p= Adults purchasing recreational cannabis who did not have medical certification/ n=1000/ s=2 cannabis dispensaries in Colorado	Cross-sectional study Level VI	I: Electronic survey. V: N/A	65% of respondents purchased cannabis to relieve pain. Of those taking opioid analgesics, 88% reduced their dose of or stopped taking opioids.	Many adults purchasing non-medical cannabis through dispensaries are using it to control pain. Opioid use in these adults has decreased.
Baron, E. P., Lucas, P., Eades, J. & Hogue O. (2018). Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis	To identify patterns of cannabis treatment in migraine and headache, as compared to arthritis and chronic pain, and to	p= Canadian medical cannabis users registered through Tilray, a federally authorized	Cross-sectional cohort study Level IV	I: Electronic survey. Migraine patients were additionally administered the ID Migraine questionnaire. V: NA	Chronic pain was the most common reason for cannabis use. Of the chronic pain users of cannabis, 72% of opiate users reported substituting opiate use with cannabis use.	More people with chronic pain than any other condition reported using medical cannabis for symptom control, of these users, the

Citation	Purpose of the Study	Population (p)/ Number (n)/ Setting (s)	Study Type and Level of Evidence	Instruments and Variables	Findings	Implications
cohort. *J Headache Pain, 19*(1),37. https://doi.org/ 10.1186/s10194-018-0862-2	analyze preferred strains, biochemical profiles, and substitution of prescribed medications with cannabis.	cannabis production, distribution and research company in Canada. n=2032.				majority who also were using opioids were able to substitute these with cannabis.
Campbell, G., Hall, W.D., Peacock, A., Lintzeris, N., Bruno, R., Larance, B., Nielsen, S., Cohen, M., Chan, G., Mattick, R.P., Blyth, F., Shanahan, M., Dobbins, T., Farrell, M. & Degenhardt, L. (2018). Effect of cannabis use, in people with chronic non-cancer pain prescribed opioids: Findings from a 4-year prospective cohort study. *Lancet Public Health, 3*(7),e341-e350. https://doi.org 10.1016/S2468-2667(18)30110-5	Investigate cannabis use in people living with chronic non-cancer pain who had been prescribed opioids, including their reasons for use and perceived efficacy of cannabis; associations between amount of cannabis use and pain,	p=Australians with chronic pain and prescriptions for opioids. n=1514 s= patients were recruited through community pharmacies	Cross-sectional cohort study Level IV	I: Baseline interviews with phone or self-administered questionnaire follow-up annually for 4 years. V: Outcome: pain severity score, pain self-efficacy score, generalized anxiety severity score, decrease in prescribed opioid dose and discontinuation of opioids.	At 4-year follow-up, compared with people with no cannabis use, participants who used cannabis had a greater pain severity score, greater pain interference score, lower pain self-efficacy scores and greater generalized anxiety disorder severity scores. No evidence was shown to support a temporal relationship between cannabis use and pain severity or pain interference, and no evidence supported that cannabis use reduced prescribed opioid use or increased rates of opioid discontinuation.	Cannabis use was common in people with chronic non-cancer pain who had been prescribed opioids, but there was no evidence that cannabis use improved patient outcomes.

Citation	Purpose of the Study	Population (p)/ Number (n)/ Setting (s)	Study Type and Level of Evidence	Instruments and Variables	Findings	Implications
	mental health, and opioid use; the effect of cannabis use on pain severity and interference over time; and potential opioid-sparing effects of cannabis.			Exposure: Cannabis use.		
Ishida, J. H., Wong, P. O., Cohen, B. E., Vali, M., Steigerwald, S., & Keyhani, S. (2019). Substitution of marijuana for opioids in a national survey of US adults. *PLoS ONE, 14*(10), 1–8. https://doi.org/10.1371/journal.pone.0222577	To examine the prevalence of cannabis substitution for opioids in US adults taking opioids for pain.	P= 16,280 randomly selected US adults sent a survey regarding marijuana and prescription opioid use. n=9003 respondents. Of those, 486	Cross-sectional, cohort study Level IV	I: Electronic survey. Prior to administration, survey was tested on a convenience sample of 40 adults to ensure question reliability and validity. V: Outcome: Amount of opiate use Exposure: cannabis use.	Forty-one percent reported a decrease or cessation of opioid use due to marijuana use; 46% reported no change in opioid use; and 8% reported an increase in opioid use. The most commonly reported reasons for substitution were better pain management (36%) and fewer side effects (32%) and withdrawal symptoms (26%).	In a nationally representative survey of US adults, substitution of marijuana for opioids, which included a substantial degree of opioid discontinuation (~20%), was common. Better self-reported pain management

Citation	Purpose of the Study	Population (p)/ Number (n)/ Setting (s)	Study Type and Level of Evidence	Instruments and Variables	Findings	Implications
		reported using both marijuana and opioids in the past year.				and fewer side effects and withdrawal symptoms were the most common reasons for substitution.
Lucas, P., Baron, E. P. & Jikomes, N. (2019). Medical cannabis patterns of use and substitution for opioids & other pharmaceutical drugs, alcohol, tobacco, and illicit substances; results from a cross-sectional survey of authorized patients. *Harm Reduct J, 16*(1), 9. https://doi.org/10.1186/s12954-019-0278-6	1. Describe the demographics of medical cannabis user and their use of prescription drugs, alcohol, tobacco, and illicit substances. 2. Assess the pattern of substitution of cannabis for other substances and drugs. 3. Assess factors influencing	p= Canadian medical cannabis users registered through Tilray, a federally authorized cannabis production, distribution and research company in Canada. n=2032.	Cross-sectional cohort study Level IV	I: 239 question survey. V: Outcome: Change in use of prescribed opioids Exposure: Medical cannabis.	The most commonly cited substitution was for prescription drugs (69.1%, n = 953), followed by alcohol (44.5%, n = 515), tobacco (31.1%, n = 406), and illicit substances (26.6%, n = 136). Opioid medications accounted for 35.3% of all prescription drug substitution (n = 610). Of the 610 mentions of specific opioid medications, patients report total cessation of use of 59.3% (n = 362).	The findings provide insight into patient patterns of medical cannabis use, and the subsequent self-reported impacts on the use of opioids, suggesting that increased regulated access to medical and recreational cannabis can result in a reduction in the use of and subsequent harms

Citation	Purpose of the Study	Population (p)/ Number (n)/ Setting (s)	Study Type and Level of Evidence	Instruments and Variables	Findings	Implications
	cannabis substitution.					associated with opioids.
Meng, H., Hanlon, J., Katznelson, R., Ghanekar, A., McGilvray, I., Clarke, H., & Hanlon, J. G. (2016). The prescription of medical cannabis by a transitional pain service to wean a patient with complex pain from opioid use following liver transplantation: A case report. *Canadian Journal of Anaesthesia*.	Case study of weaning post-operative patient with acute on chronic pain from long-term opioids by supplementing pain control with cannabis.	n=1 s=liver transplant patient who was on opiates prior to surgery for chronic pain and who was attempting to wean down his opiate use after discharge.	Case report Level VI	NA	Reductions in opioid consumption were achieved with the administration of medical cannabis in a patient with acute postoperative pain superimposed on a chronic pain syndrome and receiving high doses of opioids. Cannabis started at 6 weeks post-op and at 5 months post-op was down to 6 mg/day from 30 mg/day of hydromorphone and functional status was excellent.	Highlights potential of adjuvant cannabis therapy to help in weaning patients from prescribed opioids.
Merlin, J. S., Long, D., Becker, W. C., Cachay, E. R., Christopolous, K. A., Claborn, K. R., Crane, H. M., Edelman, E. J., Lovejoy, T. I., Mathews, W. C., Morasco, B. J., Napravnik, S., O'Cleirigh, C., Saag, M. S., Starrels, J. L., Gross,	To investigate whether marijuana use among PLWH (people living with HIV) who have chronic	p=433 PLWH and chronic pain. n=120 of this subset of PLWH and chronic pain who also used	Data analysis from a large, ongoing national prospective cohort study of chronic	I: Self-reported measures of chronic pain and marijuana use at an index visit and follow up for 1 year in the Center for AIDS Research	Neither increases nor decreases in marijuana use were associated with changes in pain severity, and marijuana use was not associated with either lower odds of opioid initiation or higher odds of opioid discontinuation.	The researchers did not find evidence that marijuana use in PLWH and chronic pain is associated with improved pain outcomes or

Citation	Purpose of the Study	Population (p)/ Number (n)/ Setting (s)	Study Type and Level of Evidence	Instruments and Variables	Findings	Implications
R. & Liebschutz, J. M. (2019). Marijuana use is not associated with changes in opioid prescriptions or pain severity among people living with HIV and chronic pain. *J Acquir Immune Defic Syndr, 81*(2), 231-237. https://doi.org/10.1097/QAI.0000000000001998	pain is associated with changes in pain severity and prescribed opioid use (prescribed opioid initiation and discontinuation).	marijuana in the past three months. s=established patients in the CNICS system.	pain and HIV outcomes embedded within the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS). Level IV	Network of Integrated Clinical Systems (CNICS). V: Exposure: Self-reported marijuana use. Outcome: Changes in pain and initiation or discontinuation of opioids during the study period.		reduced opioid prescribing.
Shah, A., Hayes, C. J., Lakkad, M., & Martin, B. C. (2019). Impact of medical marijuana legalization on opioid use, chronic opioid use, and high-risk opioid use. *JGIM: Journal of General Internal Medicine, 34*(8), 1419–1426. https://doi.org/10.1007/s11606-018-4782-2	To investigate the correlation between medical marijuana usage and prescription opioid use.	p= A 10% sample of a nationally representative database of commercially insured population was used to gather information on opioid	Secondary data analysis of cohort study Level IV	I: NA V: Exposure variable: whether medical marijuana laws were in effect during the year. Outcome variables: prescription opioid use, chronic opioid	In the fully adjusted analyses, MML was associated with a lower probability of opioid use, chronic opioid use and high-risk opioid use.	Medical marijuana legalization was associated with lower odds of opioid use, chronic opioid use, and high-risk opioid use when controlling for many state-level and patient-level

Citation	Purpose of the Study	Population (p)/ Number (n)/ Setting (s)	Study Type and Level of Evidence	Instruments and Variables	Findings	Implications
		use, chronic opioid use, and high-risk opioid use for the years 2006–2014. A sub-group analysis was performed on chronic non-cancer pain patients. n =4,840,562 subgroup: Approximately 35% had a diagnosis of chronic pain.		use, high-risk opioid use.		factors in both the general population and the subgroup of adults with chronic non-cancer pain.

Citation	Purpose of the Study	Population (p)/ Number (n)/ Setting (s)	Study Type and Level of Evidence	Instruments and Variables	Findings	Implications
Sinha, C. B., Bakshi, N., Ross, D. & Krishnamurti, L. (2019). Management of chronic pain in adults living with sickle cell disease in the era of the opioid epidemic: A qualitative Study. *JAMA Netw Open,* 2(5), e194410. https://doi.org/10.1001/jamanetworkopen.2019.4410	To evaluate participants perceptions of any changes to their pain management associated with the 2016 guidelines from the Centers for Disease Control and Prevention.	p= Adults with sickle cell disease. N=15. s=patients recruited from national sickle cell conference and two sickle cell clinics.	Qualitative study. Level VI	I: Semi-structured phone interviews. V: NA	Participants reported that recently their opioid prescriptions had become more restrictive, were more closely monitored, and were increasingly difficult to fill in pharmacies. Participants also described increased stigmatization about opioid use and that their medical care was being affected by the physician's exclusive focus on reducing pain medication use. There was an emerging interest among adult patients in the consideration of the use of alternative therapies, including marijuana, to manage pain.	The opioid epidemic may have negatively affected patients' care by increasing barriers to opioids. Patients felt that they lacked access to non-opioid options, including medical cannabis.
Sohler, N. L., Starrels, J. L., Khalid, L., Bachhuber, M. A., Arnsten, J. H., Nahvi, S., Jost, J., & Cunningham, C. O. (2018). Cannabis use is associated with lower odds of prescription opioid analgesic use among HIV-Infected individuals with chronic pain.	To explore patterns of use of cigarette, alcohol, and illicit drugs in HIV-infected people with chronic pain who were	p= 459 adults infected with HIV who reported chronic pain. n= 371 who reported	Secondary data analysis of cohort study Level IV	I: Interview questionnaire consisting of 31 questions. Interviews conducted in private setting in office or over phone. V: Outcome: Current use of a	Analysis of cigarette, alcohol, and illicit drug use patterns found that only cannabis use was independently associated with prescribed opioid analgesic use after adjusting for potential confounders and other substance use. Compared with nonusers, those who reported cannabis use were significantly less likely to report prescribed opioid	Findings provide evidence of an association between cannabis use and reduced opioid analgesic use.

Citation	Purpose of the Study	Population (p)/ Number (n)/ Setting (s)	Study Type and Level of Evidence	Instruments and Variables	Findings	Implications
Substance Use & Misuse, 53(10), 1602–1607. https://doi.org/10.1080/10826084.2017.1416408	prescribed opioid analgesics.	prescribed opiate use. s= screening interviews conducted as part of Project FIRST, a randomized trial of abstinence-reinforcing financial incentives to improve HIV outcomes among HIV-infected drug users that was conducted in the Bronx, New York		prescribed opioid analgesic. Exposure: self-reported current use of cigarettes, alcohol, or illicit drugs, including nonprescribed opioid analgesics, cannabis, heroin, and cocaine (within the past 30 days).	analgesic use.	
Vigil, J. M., Stith, S. S., Adams, I. M., & Reeve, A. P. (2017).	To examine the relation between	p=people with chronic	Historical cohort	I: Prescription Monitoring Program opioid	Clinically and statistically significant evidence of an association between MCP	Evidence regarding decreased opioid

Citation	Purpose of the Study	Population (p)/ Number (n)/ Setting (s)	Study Type and Level of Evidence	Instruments and Variables	Findings	Implications
Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. *PLoS ONE, 12*(11), 1–13. https://doi.org/10.1371/journal.pone.0187795	enrollment in the New Mexico Medical Cannabis (MMC) program and opioid prescription use.	pain who were prescribed opioids. n=37 enrolled in MMC program, n=29 non-enrolled in MMC	study. Level 4.	records reviewed over a 21-month period to measure cessation and reduction. MCP patient-reported benefits and side-effects of using cannabis one year after enrollment were also recorded. V: Outcome: cessation or decrease in amt of opioid prescribed. Exploratory: Registration or non-registration in MMC.	enrollment and opioid prescription cessation and reduction. Survey responses indicated improvements in pain reduction, quality of life, social life, activity levels, and concentration, and few side effects from using cannabis one year after enrolling in the MCP.	use and improved quality of life suggests medical cannabis should be considered for adults with chronic pain.
Wen, H. & Hockenberry, J. M. (2018). Association of medical and adult-use marijuana laws with opioid prescribing for Medicaid enrollees. *JAMA Intern Med,*	To examine the association of state implementation of medical and adult-use	p= all Medicaid fee-for-service and managed care enrollees,	Quasi-experimental difference-within-differences design	I: NA V: outcome Opioid prescribing rate, measured as the number of opioid	State implementation of medical marijuana laws was associated with a 5.88% lower rate of opioid prescribing. The implementation of adult-use marijuana laws, which all occurred in states with existing	The opioid prescribing rate was lower in states that allowed both medical and adult

Citation	Purpose of the Study	Population (p)/ Number (n)/ Setting (s)	Study Type and Level of Evidence	Instruments and Variables	Findings	Implications
178(5), 673-679. https://doi.org/10.1001/jamainternmed.2018.1007	marijuana laws with opioid prescribing rates and spending among Medicaid enrollees	who are a high-risk population for chronic pain, opioid use disorder, and opioid overdose. n=1059 state-quarter reports of State Drug Utilization Data from the Centers for Medicare and Medicaid Services (CMS)	(adjusted pre-post trend difference analysis) Level IV	prescriptions covered by Medicaid on a quarterly, per-1000-Medicaid-enrollee basis. Exposure: State implementation of medical and adult-use marijuana laws.	medical marijuana laws, was associated with a 6.38% lower rate of opioid prescribing.	recreational marijuana.
Zaller, N., Topletz, A., Frater, S., Yates, G., & Lally, M. (2015). Profiles of medicinal cannabis patients attending compassion centers in	To investigate socio-demographics and reasons for medicinal	p=medical cannabis dispensary patients in Rhode Island who	Cross-sectional qualitative study. Level 6.	I: survey which included assessment of pain interference using the Brief	69% of participants reported experiencing chronic pain and described feeling “much better” with the use of medicinal marijuana (85%). 92%	The majority of study participants sought to obtain relief from chronic pain and

Citation	Purpose of the Study	Population (p)/ Number (n)/ Setting (s)	Study Type and Level of Evidence	Instruments and Variables	Findings	Implications
Rhode Island. *Journal of Psychoactive Drugs, 47*(1), 18–23. https://doi.org/10.1080/02791072.2014.999901	marijuana use among medical cannabis dispensary patients in Rhode Island.	were recruited from one of two Compassion Centers (medical dispensaries) n=200		Pain Inventory (BPI). V: NA	considered medicinal marijuana to have fewer unwanted side-effects than conventionally prescribed pain management medications. >50% of participants reported using cannabis in place of prescription drugs or were making serious attempts to wean off high doses of prescription drugs, such as opioids prescribed for chronic pain.	other debilitating chronic medical illnesses through use of medicinal cannabis. Most patients interviewed report that medicinal cannabis improves their pain symptomology, and are interested in alternative treatment options to opioid-based treatment regimens.