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Cannabinoid Therapy in Chronic Pain Management

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Cannabinoid Therapy in Chronic Pain Management

by

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Abstract

In 1996, the state of California was the first in the union to allow for the use of medical marijuana. Since then, 28 more states have enacted similar laws (National Conference of State Legislatures, [NCSL], 2017). With the ever-growing opiate problem that has now been classified as an epidemic by the Centers for Disease Control and Prevention, medical marijuana could be a viable alternative to this this problem. As of 2014, the CDC reported opioid deaths were up 369%, which is more than 91 deaths per day from overdose (Centers for Disease Control, [CDC], 2017). The purpose of this study is to compare medical marijuana to opiates in safety and addiction; in addition, the efficacy of using cannabis as an alternative for individuals who deal with chronic pain will be investigated. A literature review was conducted to find systematic reviews, meta-analyses and randomized controlled trials (RCTs) that evaluated medical marijuana and opiates for the treatment of chronic pain. Four databases were surveyed with multiple sources found in CINAHL, Cochrane Database, PubMed and PsycINFO. Current literature shows that cannabinoids may provide potential benefit with short-term use, but not without possible adverse effects. With the current lack of research on long-term treatment of chronic pain with cannabinoids, additional research needs to be conducted to further understand the potential adverse effects associated with cannabinoid use.

Keywords: adverse effects, cannabinoid addiction, cannabinoids, chronic pain, efficacy, medical marijuana, pain management

Cannabinoid Therapy in Chronic Pain Management

Cannabis, cannabinoids and medical marijuana all encompass a topic that is highly controversial, as well as lacking in scientifically based evidence for chronic pain therapy. To date, the Food and Drug Administration (FDA) has approved three different cannabinoid based products that are currently being used for various medical issues, such as Dronabinol (Marinol and Syndros) and Nabilone (Cesamet). Limited amounts of research have been conducted due to the Drug Enforcement Administrations (DEA) schedule of cannabis as a Schedule I drug. The DEA classifies drugs based on four criteria. First, the DEA evaluates the potential for abuse followed by the safety of the drug, the potential for addiction and whether or not it has medical benefits for patients. Based on the scoring of each drug, the DEA classifies drugs into five categories, Schedule I being the most dangerous to Schedule V, which has the lowest potential for causing harm. The schedule associated with cannabis continues to limit research as well as its use, however, many states are reevaluating whether or not it should be illegal. Due to the recent legalization of medical cannabis in multiple states within the United States, it is important to better understand the mechanism of action of medical cannabis (MC), the adverse effects as well as benefits that can be provided through its use. Nugent et al. (2017) note, “Cannabis is increasingly available for treatment of chronic pain, yet its efficacy remains uncertain” (p. 327). Chronic pain is also a highly discussed topic due to the difficult nature of finding proper therapy to improve overall quality of life. Patients who deal with chronic pain are often left with prescription opiates for pain management, all of which have adverse effects. Authors Feingold, Goor-Aryeh, Bril, Delayahu, and Lev-Ran (2017) state, long-term treatment with opioids may be complicated due to tolerance and addiction, which may not be adequately managed and potentially worsen the pain. To better care for the ever-growing population of individuals dealing

with chronic pain, further exploration of cannabinoid therapy would be beneficial. Additional exploration of cannabinoid therapy as a possible alternative to opioid treatment could also prove to be of benefit.

This research project will explore whether cannabinoid therapy is as efficacious and safe as conventional therapy modalities when dealing with chronic pain management. With a better understanding of cannabinoids' adverse effects and beneficial qualities, providers may be more apt to look at alternative therapies for patients who have shown no improvement in quality of life. The lack of data on the efficacy and safety of cannabinoids poses a barrier to physicians' involvement, (Ware, Wang, Shapiro & Collet, 2015). An in-depth evaluation of the adverse reactions, addictive effects as well as clinical and statistical significance will be examined in those who choose to try cannabinoid products for chronic pain therapy. It is important to be involved and to comprehend all aspects of chronic pain and how to thoughtfully manage it in order to improve patient's overall quality of life.

Statement of the Problem

According to Boehnke, Litinas, and Clauw (2016), opiates are one of the most commonly used medications to treat chronic pain. With that notion, opiates are also ineffective for many types of pain as well as associated with addictive and significant morbidity and mortality rates. With the ever-growing opiate epidemic, an alternative treatment modality would be of great benefit. Cannabinoid therapy could be a potential secondary option rather than continued opiate therapy. Cannabinoid use for chronic pain management has been a topic of controversy within the United States for several years and remains so due to the legal restrictions. Regardless of the controversy, there may be benefits for those who deal with chronic pain and for those who seek to eliminate opiates as a treatment option. Because of the growing opioid problem within the

United States, it would be beneficial to begin to consider possible alternative therapies for management if research supports a drugs advocacy and safety.

Research Questions

Is medical cannabis safe to use for chronic pain? What are the documented adverse effects associated with using this medication?

How addictive is medical cannabis compared to other addictive substances? What addictive qualities are associated with starting this medication?

What has been shown to be more effective in the treatment of chronic pain, medical cannabis or opiates?

Methodology

The databases searched for this research topic include CINAHL, Cochrane Database, PubMed and PsycINFO from October 2017 through January 2018. ProQuest RefWorks was utilized for the organization and removal of duplicated articles. From the various search engines, a total of 21,697 articles were found. Keywords were used to narrow the research topic and include: adverse effects, cannabinoids, cannabis, chronic pain, drug therapy, efficacy, marijuana, medical cannabinoids, medical marijuana, meta-analysis, pain, pain management, quality of life, safety, systemic review, and tolerability. These keywords found articles that were added into a search builder. The builder allowed for a more extensive search throughout each database. To further narrow the search, advanced settings and limits of exclusion were used to select articles only relating to clinical trials, comparative study, meta-analysis, randomized controlled trials and systemic reviews. Further exclusion was based upon if the articles were not published in the English language, related to pain other than chronic or non-cancer pain and did not discuss the safety or efficacy of the therapy. Based on these results, 4,021 articles presented, a refined search

to just subject headings were used to further narrow the search. The subject headings used include: “Adverse Effects”[MH], “Cannabinoids”[Mesh], “Cannabinoid Therapy”[Mesh], “Cannabis”[Mesh], “Chronic Pain”[Mesh], “Marijuana Smoking”[Mesh], “Medical Marijuana”[Mesh], “Non-cancer pain”[Mesh], “Quality of life”[Mesh], “Pain” [Mesh], “Cannabis”[MH], “Chronic Pain”[MH], “Drug Therapy”[MH] and “Medical cannabis”[MH]. The subject headings allowed for the research topics to be combined or for topics to be searched alone by using “AND” and “OR” between each subject heading. From the use of the subject headings, the refined searches and exclusion criteria, the articles used within this Literature Review were evaluated and selected for this topic.

Anticipated Results

A review of the available literature reveals that there are limited amounts of research relating to cannabinoid use for chronic non- cancer pain. Due to the limited amount of research, it is anticipated that the information will contain areas of bias and/or have restricted numbers of participants that in turn, will impact the way the research trials were conducted. The difficulty of conducting research on such a tightly monitored drug does not allow for much opportunity for long duration trials. It is anticipated that the research will be focused toward the three current FDA approved cannabinoid drugs: Marinol, Syndros and Casamet, rather than the large spectrum of cannabinoid classes present. With the information provided in the literature review, clinicians will be better informed on cannabinoid products, and how to approach cannabinoid therapy for patients that have chronic pain.

Review of Literature

Cannabinoids for Chronic Pain- Safety and Adverse Events

In theme one, introduction of cannabinoids for chronic pain, seven studies were reviewed for evaluation of the safety and adverse events associated with cannabinoids. Five of the seven studies focused on common adverse events while three found central nervous system (CNS) ties with cannabinoid use. Only one study evaluated cannabinoid use over a long-term trial, the others were confined to shorter trial durations. Due to the short trial durations, each study suggested further research is warranted to better understand the safety outcomes associated with cannabinoid use.

Whiting et al. (2015) designed a meta-analysis and systematic review to determine the benefits and adverse events associated with cannabinoids compared to a placebo or no treatment. A total of 79 randomized controlled trials (6462 participants) from various countries with various placebos met the inclusion criteria. While many of the 79 studies suggested cannabinoids may improve symptoms, many of them did not reach statistical significance. Of the 79, only 28 studies (2454 participants) assessed chronic pain. Within these studies, various types of cannabinoid products were evaluated such as nabiximols, smoked THC, nabilone, THC oromucosal spray, vaporized cannabis and capsules. Of these studies, only two were found to be of low bias risk, while nine were unclear and 17 were high risk. In eight of the 28 studies, patients who reported at least 30% decrease in pain were those who used cannabinoids rather than those who used a placebo (OR = 1.41; 95% CI = 0.99-2.00). Data was also found relating adverse events to cannabinoids in 62 of the 79 studies. Common adverse events noted included dizziness, dry mouth, nausea, fatigue, hallucinations, drowsiness and confusion. Further research

showed that cannabinoids were associated with a greater risk of any kind of adverse event, serious adverse events, as well as, withdrawal (Whiting et al., 2015).

This study demonstrated that cannabinoids are likely to cause adverse events while being used for medical purposes. While participants noted a decrease in pain compared to the placebo in some trials, there was still a lack of statistical evidence for proof. One of the limitations of this study is that various cannabinoids products and dosage types were evaluated at once. It made it difficult to evaluate the results of benefits and adverse events due to the wide variety of products. To better understand the exact effects further analysis on a specific type of cannabinoid as well as dose would be more beneficial. Another thing to note would be this project was funded by the Swiss Federal Office of Public Health. It is unsure if there was any bias in selecting and conducting any of this research but would be beneficial to make note of.

Lynch and Campbell (2011) conducted a systematic review of randomized controlled trials (RCTs) examining cannabinoids in the treatment of chronic non-cancer pain. There was a total of 80 abstracts and only 18 of those (766 participants) met the inclusion criteria for further analysis. Of the 18, only 15 studies indicated there was a significant analgesic effect in cannabinoid users compared to that of the placebo groups. From the studies, no serious adverse effects were noted. Mild to moderate adverse effects were well tolerated overall, however, there were a few cases of participant withdrawal due to these effects. Dizziness, sedation, dry-mouth, nausea and concentration disturbances were among the most common adverse effects. Daily doses of nabilone 2 mg was compared to dihydrocodeine 240 mg and found the mean baseline pain was 69.6 mm on the 100 mm Visual Analogue Scale (VAS) had dropped to 59.93 mm for nabilone and 58.58 for dihydrocodeine. The scores decreased significantly compared to that of the placebo (Lynch & Campbell, 2011).

Limitations to the findings in this study are the small sample sizes, modest effect sizes and short trial durations. It was also documented that cannabis may only decrease pain to a moderate degree and remains to be a substance that is further researched for long duration effects as well as safety and abuse potential. The authors have acknowledged these limitations and voice it is for patients to decide the effectiveness of the therapy as well as the need for further large scale, detailed research trials.

Campbell, Tramer, Carroll, Reynolds, Moore, and McQuay (2001) conducted a qualitative systematic review of randomized controlled trials (RCTs) to evaluate whether or not cannabis is an effective and safe alternative treatment option for pain management. The outcomes of the studies were evaluated based on pain relief scores, pain intensity and adverse effects. A total of 20 RCTs were identified and nine RCTs consisting 222 participants were used within this research. Four different cannabinoids, dosages ranging from 2-10 mg depending on the substance, were used within this trial and the comparators were oral codeine 50-120 mg and oral secobarbital 50 mg. Authors conducted various follow up periods due to the different cannabinoid types and the results were qualitatively summarized. Results showed THC users had a significantly lower breakthrough pain while on morphine compared to the control using just morphine (170 mg vs 410 mg per three weeks). In another group, 5 mg of THC was comparable to 50 mg of Codeine. However, all studies reported adverse effects and two participants withdrew due to the adverse effects. Authors found that 20 mg of THC was sedating in all participants, while 10 mg of THC was better tolerated than 60 mg or 120 mg of codeine, however, it still had a greater frequency of adverse effects such as numbness, dizziness, disconnected thought, slurred speech and muscle twitching. Results also revealed that

cannabinoids were no more effective than codeine and have psychotropic events as well as depressant effects on the central nervous system (CNS) (Campbell et al., 2001).

The authors do not go in depth discussing the limitations of the study which could call into question the validity of the results. One addressed limitation was similar to many of the studies reported prior, a very small study size. They note that only two of the 20 trials had more than 30 participants. Due to the small sample size it is difficult to get an accurate account of the overall findings when only applying the results to such a small population. This study was conducted in 2001 and further research has been conducted on safety and adverse events.

Martín-Sánchez, Furukawa, Taylor and Martin (2009) assessed the efficacy as well as harms of cannabis in the treatment of chronic pain. They designed a systematic review and meta-analysis of double-blind randomized control trials that compared the placebo to any cannabis preparation for chronic pain subjects. The study included eighteen trials in which participants presented with constant or intermittent pain for a minimum of 6 months. The participants were required to have any form of cannabis preparation, which contained at minimum delta-9-tetrahydrocannabinol (THC), other synthetic derivatives of THC were accepted. The control group received a placebo treatment. The trial used, “intensity of pain” numeric analogue scales for participants to rate their pain throughout the study. Harms were analyzed with Odds Ratios (ORs) and number needed to harm (NNH) by examining the number of adverse events experienced by each group participant. Results for the efficacy showed a standard mean deviation in favor of cannabis, a fixed effects model of -0.61 (-0.84 to -0.037) with statistical homogeneity ($I^2 = 0.00\%$; $p = 0.50$). The analysis of harms was divided into perception, motor function and altered cognitive function. Harms related to altered perception (OR = 4.51; 95% CI = 3.05-6.66), $p = .42$, NNH: 7 (6-9); motor function alterations (OR = 3.93; CI = 2.83-5.47), $p =$

.68, NNH: 5 (4-6); and motor function changes (OR = 4.46; 95% CI = 2.37-8.37), $p = .99$, NNH: 8 (6-12). The results of this review found that there was evidence supporting the efficacy of cannabis therapy for those with chronic pain. However, data supported there was a high number of serious adverse events in short-term trials, predominantly linked to central nervous system such as speech disorders, muscle twitching and numbness (Martín-Sánchez et al., 2009).

Due to cannabis' antinociceptive effects, further evaluation and study is warranted to better understand the analgesic effects in patients with chronic pain. The authors remained unbiased and focused on a specific design that allowed for more accurate evaluation of the topic being researched. Due to the small sample size, the statistical significance is lost as well as the short duration period does not allow for comparison to real life and thus results may be less extreme. The study also used different dosage ranges by reference to the same placebo. This resulted in homogenous results decreasing the need for comparison by subgroups. Funding was provided by the Spain National Drug Plan which had no role in the study conduct, analysis or interpretation as noted by the authors.

Ware, Wang, Shapiro, and Collet (2015) conducted a multicenter cohort study over a year's span with a standardized cannabis product, THC (12.5% Tetrahydrocannabinol), to better understand the safety of cannabis use for medical purposes. The study focused on three areas of evaluation: outcomes of serious adverse events and non-serious adverse events of cannabis treatment for chronic pain, to examine whether cannabis effected pulmonary and neurocognitive function and explore the effectiveness of improving pain intensity and quality of life. The study consisted of 431 adult participants from seven clinics within Canada who had chronic non-cancer pain for at least six months. 215 that were recruited to the cannabis group used a mean daily dose of 2.5 g/d of cannabis and 216 controls used no cannabis products. Of the 431 participants, 67

cannabis users and 34 from the control discontinued the study before the year's end due to reasons not otherwise specified within the study. Results showed medical cannabis users were at increased risk of non-serious adverse events, 818, ranging from mild to moderate events such as: headache, nasopharyngitis, nausea, somnolence, and dizziness compared to the 581 events documented in the control (IRR = 1.64, 95% CI = 1.35-1.99). While the medical cannabis group had significantly higher non-serious adverse events, members reported improvements in tension-anxiety, depression-dejection, anger-hostility, and fatigue-inertia compared to the control. Participants in the medical cannabis group had a significantly higher average pain intensity baseline compared to the control, however, more control participants used opioids, antidepressants and anticonvulsants compared to the former. Overall, individuals in the medical cannabis group experienced better pain control than the control (change = .92; 95% CI = .62-1.23) vs (change = .18; 95% CI = -.13) (Ware et al., 2015).

The authors of this study note that this may be the only long-term study evaluating the safety of medical cannabis. Compared to the other studies used, this is the only one whose timeframe is longer than one year. The study did have several limitations that need to be addressed. The study had a relatively small sample size as well as a significant dropout rate. The dropout rate could be due to selection bias as noted by the authors or due to a lack of experience with the medication or the adverse events. Individuals within the medical cannabis group were experienced users which hinders results in that more adverse effects were noted with the naïve user compared to that of the experienced user. Lastly, because the study was not randomized or a blinded study, improvements in the efficacy could have been due to being in the study, regression to the mean or natural history of the disease.

Nugent et al. (2017) conducted a systematic review of observational as well as interventional trials to determine if cannabis use in chronic pain adult populations has marked short and long-term physical and mental health effects. New clinical trials as well as cohort studies were searched and a total of 13 systematic reviews and 62 primary studies were evaluated for cannabinoid harm related events. From these results, 30 chronic pain trials were further evaluated for this study. The authors used the numerical rating scale (NRS) from 0 to 10 or participants who had clinically significant improvement of > 30% reduction, or approximately 2 points on the NRS and 20 mm on the visual analogue scale. Results from this study conclude that there is not enough evidence to suggest that cannabis use has potential benefits and harms. The study does highlight that among the general population, there is small, short-term effects in cognition in active users but limited data for adverse mental health effects in the long term. There was also no detection of significant difference between the cannabis group compared to the control group when it came to serious adverse events (IRR = 1.08; 95% CI = 0.57-2.04). This study did evaluate long-term effects associated with cannabis use and found it to be associated with cannabinoid hyperemesis syndrome as well as incident cannabis use disorder (OR = 9.5; 95% CI = 6.4-14.1), both of which the authors believe practitioners and patients should be aware of (Nugent et al., 2017).

The authors acknowledge the limitations within the study and begin mentioning many of the patient populations were selected rather than obtained through randomized control trials. The study also did not evaluate dispensaries and those who get therapy from them. Due to this, many of the studies assessment of cannabinoids is substantially lower than the products that can be obtained from a dispensary. Finally, there is relatively small number of participants from which strict data was obtained. Authors note it was impossible to assess the number per day of cannabis

smoked cigarettes for example. It has been suggested that any methodologically strong research conducted in cannabis research will likely add to the strength of the evidence found thus far. The U.S. Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative all contributed financial support.

Issa, Narang, Jamison, Michna, Edwards, Penetar, and Wasan (2014) conducted a multi-dose, randomized, double-blind, placebo-controlled, crossover trial of 30 chronic non-cancer adult patients using opiate therapy was conducted to identify if oral Dronabinol has psychoactive effects comparable to smoking marijuana. There were two groups evaluated for this study. The first group consisted of 30 individuals using Dronabinol, (10 mg and 20 mg capsules), with prescription opiates; only one of the 30 did not finish the trial due to inability to concentrate. The second group consisted of 20 individuals who were without pain and smoked a low and high dose of marijuana, (1.99% and 3.51% Δ^9 THC). The Addiction Research Center Inventory (ARCI) was used to evaluate and compare dronabinol with smoked marijuana. Findings suggest that oral Dronabinol had similar psychoactive effects to that of smoked marijuana according to the ARCI. The ARCI highlighted that there was not much of a difference between the 10 mg and 20 mg doses of Dronabinol; however, there was a consistent and significant difference when being compared to the placebo. It was noted that although dronabinol takes longer to reach the same peak as smoking marijuana (2 hours compared to 30 minutes), it does not necessarily have the same abuse liability as marijuana (Issa et al., 2014).

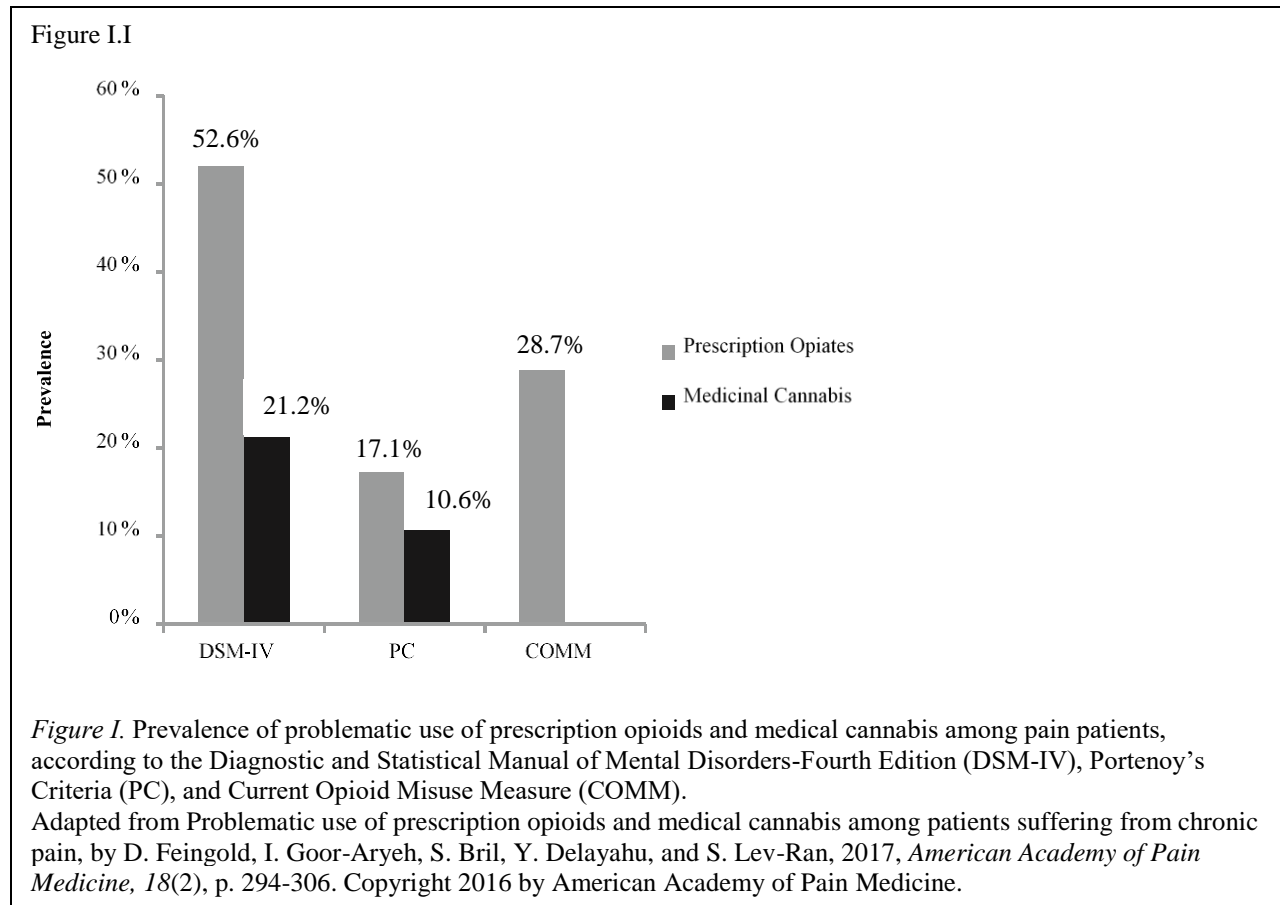
Similar to many of the studies reviewed thus far, the number of subjects was limited and the dronabinol group consisted of a heterogeneous sample on various dosages of opiates. Due to the varied dosages, there is inconsistent comparisons between everyone. Another limitation to the study is that there was no comparison group to the control that used opiates. The authors

acknowledged that opiate therapy can cause similar psychoactive effects to smoking marijuana thus, questioning the validity of the results. The study also only used one primary measure, the ARCI, to compare oral dronabinol to smoked marijuana. With only one means of measurement, there is not sufficient or definitive data to conclude there is abuse potential for a drug. The authors make note that these laboratory findings may or may not translate across to the clinical realm where there could be an increased chance of dronabinol abuse, thus, further study is required on this topic. This study was supported by funding from the Solvay Pharmaceuticals Inc. grant as well as a grant from the national Institute on Drug Abuse.

Comparison of Addictive Substances to Cannabinoids

In theme two, comparison of addictive substances to cannabinoids, three studies were reviewed. Of the three studies, each evaluated a different addictive substance such as opiates, alcohol and nicotine. The substances evaluated were then compared to other common addictive substances to evaluate the extent of addiction between each.

Feingold, Goor-Aryeh, Bril, Delayahu, and Lev-Ran (2017) conducted a cross-sectional study in Israel between two separate clinics and looked at 888 adults receiving treatment for chronic pain and whether or not these patients were more apt to abuse opioids and medical cannabis (MC). Various screening tools used to evaluate patients participating in the study such as the Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition (DSM-IV) Criteria, Portenoy's Criteria (PC) as well as the Current Opioid Misuse Measure (COMM) questionnaire. Further screenings were done for depression, Patient Health Questionnaire (PHQ-9) as well as (GAD-7), generalized anxiety disorder scale to evaluate participants psychiatric comorbidities while using opiates and MC. Of the 888 participants, 471 were treated with prescription opiates, 329 were treated with MC, 77 were treated with both opiates and MC and 5 did not use either



opiates or MC. The results of the study indicated that the participants who were treated with opiates had a greater prevalence of problematic use (52.6%) compared to MC participants (21.2%). The prevalence of problematic use between opiates and MC was documented in *Figure I. I*. Three of the various screening tools were used within the study. Problematic use of opiates for the DSM-V, PC, and COMM are as follows (52.6%, 17.1%, and 28.7%). Problematic use of MC was documented with DSM-V and PC as follows (21.2% and 10.6%). COMM was not used for evaluating problematic use of MC because it solely deals with opiate misuse. Individuals with problematic use of opiates also consumed alcohol (32%), non-prescribed cannabis (19%), LSD (1.1%) and synthetic cannabinoids (0.7%). Likewise, individuals with problematic MC use consumed alcohol (36.9%), Ecstasy (1.1%), LSD (0.05%), Heroin (0.5%). Mental health

screenings also revealed opiate users were more likely to be diagnosed with depression than those using MC (Feingold et al., 2017).

The conclusion of the results reveal there is problematic use in both opiate as well as MC; the combination of the two are associated with patients who have a higher level of pain, alcohol use, depression and anxiety. The authors identified various downfalls in the study. First, the response rate from participants was low, possibly indicating the prevalence of problematic use could be much higher. The data also was obtained by self-report causing the results to be biased due a lack of information. There was also no complete diagnosis for psychiatric evaluation in those individuals who deal with problematic use, only screening instruments were used rather than a face to face follow up.

Darvishi, Farhadi, Haghtalab, and Poorolajal (2015) conducted a meta-analysis on the effects of alcohol use disorder (AUD) on suicidal thought and behavior. A total of 31 studies were included within the research, all of which were published in English. From the selected studies, there was a total of 420,732 participants. The authors used relative risk (RR) and odds ratios (OR) to determine the significance between the studies and participants due to both being used between various studies. “There was a significant association between AUD and suicidal ideation (OR = 1.86; 95% CI = 1.38 to 2.35), suicide attempt (OR = 3.13; 95% CI = 2.45 to 3.81), and completed suicide (OR = 2.59; 95% CI = 1.95 to 3.23 and RR = 1.74; 95% CI = 1.26 to 2.21)” (Darvishi et al, 2015, p. 1). The authors did detect two extreme values within the suicide attempt and completed suicide, these values were excluded from the analysis. Among the studies evaluated for AUD and suicidal ideation and attempt, considerable heterogeneity was documented ($I^2 = 76.8\%$, $p < 0.001$) and ($I^2 = 88.5\%$, $p < 0.001$). Based on the evidence

presented within this study, AUD can be considered a possible indicator of premature death as well as a predictor of suicide (Darvishi et al., 2015).

The study was financially supported by an Islamic Azad University which may or may not have had an impact on the research methods, interpretation and results. The authors did acknowledge that there may be overestimation of the results due to fully adjusted forms of relative risk (RR) and odds ratio (OR) when not all studies did the same. Secondly, 12 studies were excluded due to the fact the full text was not available which may contribute to selection bias. There were also discrepancies across studies that need to be taken into consideration. The OR estimates for suicidal ideation ranged between 0.5 to 3.10, while suicide attempt ranged from 1.5 to 10.50 respectively.

Richter, Pugh, Smith, and Ball (2016) conducted a quantitative, peer reviewed study to assess the extent to which nicotine use occurs with other substances among young adults. Authors also sought to determine other variables such as demographics and implications of research and prevention. Participants were young adults that were gathered from two data sets, the first from the National Survey on Drug Use and Health (NSDUH) followed by Monitoring the Future (MTF). Participants were aged 12 and older ($n = 55,271$) in the NSDUH study and students in the 8th, 10th and 12th grades ($n = 41,551$). Authors examined alcohol, marijuana as well as other illicit drugs and prescription drugs as possible correlates to nicotine product use. The NSDUH data showed that 10.2% of participants used cigarettes only while 4.1% used other nicotine products. Those who used any type of nicotine product were qualified as being dependent upon nicotine. Of the respondents who used any nicotine product, a significant amount of data showed a higher prevalence to other substances such as alcohol, marijuana, poly-substance use as well as substance-use disorders. MFT results had similar findings to that of the

NSDUH study, those who reported nicotine use of any kind had a higher prevalence of alcohol and other drug use. In the 12th graders studied that reported any form of nicotine use, co-occurring use with other substances was documented (79.4% alcohol (OR = 11.5; 95% CI = 8.4-15.7), 59.7% marijuana (OR = 12.7%; 95% CI = 9.5- 16.8), 53.9% poly-substance use (OR = 15.5; 95% CI = 11.4- 21.0), 18.8% prescription drugs (OR = 8.3; 95% CI = 5.4- 12.8), 8.5% other illicit drugs (OR = 19.1; 95% CI = 9.0- 40.6) (Richter et al., 2016).

The results of this study reveal that individuals who become dependent upon any form of nicotine product are of greater likelihood to use other types of substances. Authors acknowledged the two data sets did pose limitations to the study in that they were self-reported estimates which yield less accurate results. The study was also cross-sectional, therefore any association made within the studies was correlated. Lastly, the MTF did not inquire the same questions throughout the study which presents as large amounts of missing data. With these limitations, the results should be noted with slight caution.

Medical Cannabinoids vs Opiate Efficacy

In theme three, medical cannabinoids vs opiate efficacy, five studies were reviewed for statistical and clinical significance. Statistical significance was highlighted in three studies while clinical significance was documented in two of the six. Statistically significant studies documented improvements in pain, quality of life as well as other areas. Clinically significant studies may not have shown statistical support of cannabinoid benefit, but per individual report, improvements were documented. The results reveal both pros and cons to medical cannabinoid use, thus further research is necessary to further understand the effects of this therapy.

Goldenberg, Reid, IsHak, and Danovitch (2017) conducted a systematic review and meta-analysis to better understand three different questions. First, they wanted to determine whether

different forms of cannabis impacted health-related quality of life (HRQoL) conditions differently and if the condition/disease was associated with HRQoL. The authors also wanted to evaluate if the study design impacted the results of cannabis and cannabinoid use and HRQoL. A total of 20 studies were evaluated, 11 were randomized controlled trials (2322 participants) and 9 were of cohort and cross-sectional study designs. Of the 20 studies, only 11 were used for evaluation of the meta-analysis due to measures of variability and means found within each study. The studies were divided into two groups based on cannabis type; six studies evaluated cannabis and 14 studied cannabinoids. Results of cannabis use for increased HRQoL were vague and most effects were non-significant or nearing zero. Some reports showed a mild benefit in some pain conditions while in others there was a decrease in HRQoL. The authors found that cannabis for physical HRQoL did show symptomatic relief but results were unclear if there was statistical significance. The cannabinoid group utilized five variations to assess HRQoL. Each cannabinoid analyzed resulted in different outcomes ranging from being of benefit to no significant documentation. When comparing cannabis and cannabinoids to a control group, no significant effects were documented (CI = -0.34 to 0.44) with physical and mental HRQoL. Although many studies did not report significant effects on HRQoL globally, some improvements were noted such as headaches and sleep disturbances (Goldenberg et al., 2017).

This study demonstrated how HRQoL can be impacted by either cannabinoids or cannabis. However, a major limitation was the HRQoL was often used as a secondary outcome because there was not a uniform quality of life measurement. Trends being evaluated could shift one direction or the other. Another area that is important to note is cannabis and cannabinoid use over different times and different diseases can impact the HRQoL. The study focuses on diseases other than pain in the assessment of the therapy outcome.

Narang, Gibson, Wasan, Ross, Michna, Nedeljkovic, and Jamison (2008) investigated the analgesic effects of cannabinoids among adult patients who reported moderate to severe non-cancer pain, at least a 4 on the 0 to 10 numeric rating scale, and who were already using opiate therapy for greater than six months. The research design consisted of two phases. The first began as a randomized, single-dose, double-blinded, placebo-controlled, crossover trial in which participants were randomly given a 10 mg or 20 mg dose of Dronabinol or a placebo. The second phase of evaluation was an extension of the first phase, Dronabinol was used as an adjuvant therapy to their opiate therapy in an open-label titrated trial. One hundred sixty (n =160) individuals were screened and 30 individuals met the final criteria to begin the study. The results of this study concluded that individuals who used Dronabinol in Phase I found significant pain relief after 8 hours per the total pain relief at 8 hours score (TOTPAR), (20 mg vs placebo at $p < .01$, 10 mg vs placebo at $p < .05$). For adjuvant therapy in Phase II, dronabinol proved to have a significant effect in lowering pain from baseline ($p < .001$), decreasing pain bothersomeness as well as increased satisfaction in their therapy ($p < .01$). The use of Dronabinol proved to provide additional analgesia to patients with chronic pain, however, two prominent side effects were documented with the 20 mg dose. Both events related to heightened anxiety that lasted through the treatment day. Similarly, less prominent events were noted such as drowsiness, abnormal thinking, anxiety, eye irritation and anxiety ($p < .05$) (Narang et al., 2008).

These results suggest that cannabinoid therapy is effective for chronic pain management and pain relief. The analysis does suffer due to the small trial size, heterogeneous patient population, no control for Phase II, the length in which the trial for each phase was conducted, as well as a number of patients reported they were not naïve to cannabinoid use. The authors of this

study recognize the limitations as well as drawbacks of the study and recommended further research is warranted to evaluate the efficacy of cannabinoids for adjuvant therapy.

Boehnke, Litinas, and Clauw (2016) conducted a cross-sectional survey in Michigan, evaluating the efficacy of medical cannabis compared to opiates in chronic pain patients. A total of 374 participants who were 18 years of age or older voluntarily joined the survey. Authors used a 2011 Fibromyalgia Survey Criteria (FM score) which ranges from 0 to 31, with 31 representing the most severe pain. The authors used this scale as it correlated with the initial hypothesis that chronic pain is more centralized rather than nociceptive. A 46-question survey was also used to evaluate participants type of pain and reason for medical cannabis use. Of the 374 participants, 244 used cannabis to treat chronic pain (CP) and only 185 completed questionnaires qualifying their data for analysis. Of those with incomplete surveys, the results were not statistically significant. Results of the survey showed individuals with the highest FM score had the least drastic reduction in opiate use (-48%) which was significantly different from the lowest FM score (-79%; $p = .03$). Additionally, respondents reported a significant decrease in the number of medications used before and after cannabis use (2.38 vs. 1.81; $p < 0.001$). Lastly, medication side effects decreased significantly after the use of cannabis (6.51 vs 2.79; $p < 0.001$). The authors combined the results from medication side effects and opiate reduction ($r=.37$, $p = .0002$) and found there are potential health benefits to using cannabis as a replacement therapy for opiates (Boehnke et al., 2016).

The authors of this article make special note towards the limitations of this study and the potential biases that could have caused skewed results. Using the questionnaire could contribute to unreliable recall data in that individuals could indicate whatever they saw fit. Another limitation included participants who had been using cannabis for longer periods of time; creating

a skewed questionnaire because there was no baseline questionnaire completed prior to the long-term management. The authors continue to discuss the lack of representatives for a general population. The participants that were used were recruited from a medical cannabis dispensary providing a narrow population set. The authors offered suggestions for future study to better improve research results such as performing a longitudinal study design that recruits naïve participants to cannabis as well a preliminary baseline pain levels prior to starting therapy.

Aviram and Samuelli-Leichtag (2017) performed a meta-analysis with randomized controlled trials (RCTs) on cannabis-based medicines (CBMs). The goal was to gain knowledge on the efficacy and adverse effects (AEs) of CBMs for chronic pain treatment and postoperative pain treatment. The study compared analgesic effects of CBMs to a placebo. The RCTs consisted of 43 groups initially (2,437 adult patients), while only 24 (1,334 patients) were used for meta-analysis due to eligibility. Pain reduction was noted in limited amounts in chronic non-cancer pain, -0.39 (-0.49 to -0.29 ; $p < 0.0001$). Results of the baseline pain intensity change indicate a fixed-effect model result of -0.35 ($-.43$ to $-.27$; $p < 0.0001$) and a random-effect model showing -0.40 (-0.58 to $-.21$; $p < 0.0001$), both of which are in favor of CBM over the placebo. In some RCTs, there was a clinically significant improvement of a 2 point or more decrease in pain (30% or 50% or more); however, the majority of studies did not show similar effects. The results of the meta-analysis concluded that while pain relief was noted, there was not statistically proven evidence between the studies. Furthermore, over half of the trials that were evaluated reported adverse effects (AEs) experienced by the patients. The most common AEs include central nervous system (CNS) and gastrointestinal system issues (Aviram & Samuelli-Leichtag, 2017).

One of the main limitations acknowledged by the authors was that not all of the studies used within this review met the criteria of the meta-analysis. The fact these studies were used

could have altered the result of the overall study effect. The studies that were evaluated were also almost entirely heterogeneous which could have affected the studies that had short washout periods. The authors discuss that many of the findings did not address the most common method in which cannabis is used, i.e, inhalation as well as whether prior cannabis consumption took place. The study did not address the use of other medications that could also interact with CBMs and the outcomes that were documented.

Deshpande, Mailis-Gagnon, Zoheiry, and Lakha (2015) sought to determine if medical marijuana provides adequate pain relief to patients with chronic non-cancer pain (CNCP) as well as determine the therapeutic doses, adverse effects and specific indications related to medical marijuana use. The authors created a systematic review that was conducted on a group of six randomized control trials involving 226 adults (mean age of 45 to 50 years) in Canada. Of the 6 RCTs, only 5 assessed medical marijuana use and were utilized within the study. Trial duration was short and ranged from 17 days to eight weeks. Authors used the visual analogue scale (VAS) to measure pain in participants. Results reported a statistically significant change in pain reduction with non-serious side effects in the medical cannabis group. The VAS noted a 0.7 average daily difference between that of the placebo (score of 6.1) and medical cannabis group (score of 5.4). Clinically relevant pain reduction was also noted in three studies in which participants were using medical marijuana (46%, 52%, and 61%) compared to the placebo (18%, 24%, and 26%). The participants documented a 2-point decrease in the numerical pain rating scale, which is equivalent to a 30% improvement in pain. While no serious adverse events were documented, medical cannabis was shown to have a greater incidence of adverse events compared to the placebo. One study being evaluated noted a statistically significant ($p < 0.001$)

increase in disorientation, sedation, confusion and dizziness in the cannabis group (Deshpande et al., 2015).

The study concluded while medical marijuana was associated with a reduction in CNCP, there were multiple short-term cognitive adverse effects associated with it. The study was heterogeneous in origin and could not report on the efficacy of cannabis because of this as well as due to the outcome variables. The authors state the cognitive effects documented with medical marijuana are also experienced in opioids and thus the same precautions should be enacted with either drug. Another limitation noted was the amount of medical marijuana participants were exposed to was much lower than what is available on the market. Due to the unknown nature and effects medical marijuana poses to individuals, further research was recommended by the authors of this study as well as incorporating standard measures on quality of life that go beyond pain.

Discussion

The therapeutic properties of cannabinoids are showing promise through low addiction likelihoods and less severe health outcomes compared to other substances used on the market and throughout the world. The National Institutes of Health (NIH) has supported around 281 projects totaling over \$111 million on cannabinoid research. To date, research in the past has been lacking, but due to the potential of cannabinoids for alternative therapy, this area is continuously growing. Within this investment, 49 projects (\$21 million) examined therapeutic properties of cannabinoids, and 15 projects (\$9 million) focused on cannabidiol (CBD). Like other substances, adverse events (AEs) have been documented ranging from mild to severe which should be addressed prior to beginning therapy. Dry mouth, nausea and dizziness are among the mild AEs, while impaired cognition and CNS depression were documented as severe

AEs. Current evidence reveals cannabinoid therapy eliminates and/or decreases pain, improves sleep function as well as decreases the need for further medication.

Is medical cannabis safe to use for chronic pain? What are the documented adverse effects associated with using this medication?

Cannabinoids have been around for many centuries and to date, it has begun to take a different face. Medical cannabis and cannabinoids are becoming more popular for various medical conditions, most notably, chronic pain. In the United States, medical cannabis can either be man-made or synthesized from the marijuana plant. Dronabinol currently is the only medical prescription (Rx) used within retail pharmacy; further cannabinoid substances are obtained at dispensaries. Due to the ever-changing role of cannabinoids, there is concern on whether it is safe for patient use.

A study conducted by Narang et al. (2008) mentions patients who used dronabinol reported significant pain relief, reduced pain bothersomeness and increased satisfaction compared with the baseline. The results of this study further concluded that when dronabinol was used in conjunction with opiates, additional analgesic relief was noted.

Further assessment of cannabinoid safety was conducted by Ware et al. (2015). The study assessed the safety of medical cannabis and found there was no change in overall organ system function. Neurocognitive testing revealed there was no difference in function after one year of medical cannabinoid use. There was no significant change in pulmonary function tests, however, residual volume was slightly decreased. The decrease in residual volume was most likely due to the smoked cannabinoids or other predisposing conditions prior to cannabinoid use. Blood testing also showed no change in liver, renal or endocrine function compared to the baseline one year prior. The results of long term cannabinoid effects as well as trials evaluating the effects on

the body are in the minority. Furthermore, additional studies are warranted in order further document whether other medical cannabis is safe for long term treatment of chronic pain.

Medical cannabis and cannabinoids have been associated with many adverse events (AEs) similar to those of common medications. Some of the most common AEs associated with medical cannabis and cannabinoid products include dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, drowsiness, confusion and hallucination (Whiting et al. 2015). Whiting et al. noted the data relating to the various AEs did not show any evidence relating to the type of cannabinoid used, rather the amount of cannabinoid was associated with greater likelihood of AEs. Dose of cannabinoids leads to a greater likelihood of experiencing AEs. In contrast to the previous study, Ware et al. (2015) found that increasing the daily dose of cannabinoid did not lead to increased serious adverse events or adverse events (IRR = 1.08, 95% CI = .57-2.04). While at the other end of the spectrum, a study conducted by Martín-Sánchez et al., (2009) concluded cannabinoid compounds pose more risk than benefit, and can possibly cause secondary problems for the patient.

Lynch and Campbell (2011) found the following relating to sedation, dizziness, dry mouth, nausea and concentration disturbances:

Adverse effects were generally described as well tolerated, transient or mild to moderate and not leading to withdrawal from the study. This is a significant difference from the withdrawal rates seen in studies of other analgesics such as opiates where the rates of abandoning treatment are in the range of 33%. (p. 741)

The percentages of patients who withdrew from the studies stated it was due to inadequate pain relief and/or the adverse side effects. Similarly, Narang et al. (2008) documents that despite the side effects of dronabinol in 10 mg or 20 mg doses, there was a significant difference in patient

satisfaction compared to the placebo ($p < 0.01$). There was no difference between the 10 mg and 20 mg doses in terms of pain relief. Campbell et al. (2001) analyzed whether single doses of cannabinoids, specifically delta-9-tetrahydrocannabinol (THC) 5-20 mg, would be useful for breakthrough pain in acute or chronic settings. Results revealed it was no more effective than Codeine 50-120 mg when controlling pain. The results from this study documented the 10 mg of THC being more depressive on the CNS than 60-120 mg of codeine. Of note, common dosages of codeine range between 30-60 mg for pain management.

Mental health changes have been of great concern with the use of medical cannabis, most commonly CNS depressive effects. Like many other types of medications, medical cannabis has been documented to have serious AEs. Nugent et al. (2017) state cannabis has potentially serious adverse effects on mental health as well as cognition, but there is limited data to suggest the magnitude of risk or who is at greater risk. A study conducted by Issa et al. (2014), found dronabinol had significantly greater addiction research center inventory (ARCI) subscales compared to the placebo. This means dronabinol had similar psychoactive effects when compared to smoking marijuana. The psychoactive effects took longer to take effect with dronabinol compared to recreational marijuana (2 hours with oral dronabinol compared to 30 minutes with smoked marijuana). The authors of this study stated that dronabinol does not necessarily have the same abuse liability as marijuana, but it should be taken into consideration as a potential risk for those using it for pain relief.

Little evidence has been found on long term use of medical cannabis, but according to Nugent et al. (2017), long term cannabis use was associated with cannabinoid hyperemesis syndrome (CHS). Patients experience severe cyclic vomiting, which can be alleviated by stopping cannabis products or taking hot showers. Little is known about CHS to date and further

research is warranted. If the cyclic vomiting continues, individuals are at risk for dehydration, electrolyte imbalances and other potentially severe conditions.

How addictive is medical cannabis compared to other addictive substances? What addictive qualities are associated with starting this medication?

According to the CDC (2017), 1 in 10 marijuana users will become addicted compared to as many as 1 in 4 patients using opiates becoming addicted. Over 1 million individuals a year will become addicted to nicotine. Some of the most commonly abused drugs today include alcohol, cocaine, heroin, LSD, marijuana, prescription opioids, prescription sedatives, tranquilizers, prescription stimulants, and tobacco (National Institutes of Health [NIH], 2017). These substances also can have severe withdrawal symptoms associated with them. Opiates, prescription sedatives and tranquilizers, as well as steroids, were at the top of the list for the most withdrawal symptoms, and it was suggested medical attention be sought if withdrawal symptoms begin to occur. Lüscher (2018) wrote, withdrawal symptoms of cannabinoids are mild and short lived. In relation to other substances, it appears that withdrawal symptoms may be more tolerable with cannabinoids than other substances. When comparing medical cannabis to other addictive substances used around the world, cannabinoids rank relatively low in addiction rates compared to other commonly used substances. Lüscher highlights many of these differences in *Table 1*. An important aspect of the table that needs addressing is that the authors did not fully document the relative risk ratio on the far-right column. The ratio is more accurate when decimals are used, but in this graph the RR does not use decimals to document the result. Opioids, nicotine and alcohol all rank higher than cannabinoids in terms of the relative risk (RR) of addiction. The greater the number associated with relative risk, the greater the chance of addiction. Likewise, morphine,

heroin, codeine and oxycodone all induce strong tolerance and dependence which can lead to addiction.

Table 1
The mechanistic classification of drugs of abuse

Name	Main Molecular Target	Pharmacology	Effect on Dopamine (DA) Neurons	RR ²
Drugs That Activate G Protein-Coupled Receptors				
Opioids	μ -OR (G_{i0})	Agonist	Disinhibition	4
Cannabinoids	CB ₁ R(G_{i0})	Agonist	Disinhibition	2
γ - Hydroxybutyric acid (GHB)	GABA _B R(G_{i0})	Weak Agonist	Disinhibition	?
LSD, mescaline, psilocybin	5-HT _{2A} R(G_q)	Partial Agonist	—	1
Drugs That Bind to Ionotropic Receptors and Ion Channels				
Nicotine	nAChR($\alpha 4\beta 2$)	Agonist	Excitation	4
Alcohol	GABA _A R, 5-HT ₃ R, nAChR, NMDAR, Kir3 channels		Excitation, disinhibition (?)	3
Benzodiazepines	GABA _A R	Positive Modulator	Disinhibition	3
Phencyclidine, ketamine	NMDAR	Antagonist	—	1
Drugs That Bind to Transporters of Biogenic Amines				
Cocaine	DAT, SERT, NET	Inhibitor	Blocks DA uptake	5
Amphetamine	DAT, NET, SERT, VMAT	Reverses transport	Blocks DA uptake, synaptic depletion	5
Ecstasy	SERT > DAT, NET	Reverses transport	Blocks DA uptake, synaptic depletion	?

Note. From Basic and Clinical Pharmacology, 14e, by B.G. Katzung (Ed.), 2014, New York, NY: McGraw-Hill. Copyright 2015 by McGraw-Hill Education.

^a5-HT₃R, serotonin receptor; CB₁Rm cannabinoid-1 receptor; DAT, dopamine transporter; GABA, γ -aminobutyric acid; Kir3 channels, G protein-coupled inwardly rectifying potassium channels; LAD, lysergic acid diethylamide; μ -OR, μ -opioid receptor; nAChR, nicotine acetylcholine receptor; NET, norepinephrine transporter NMDAR, *N*-methyl-D-aspartate receptor; R, receptor; SERT, serotonin transporter; VMAT, vesicular monoamine transporter; ?, indicates data not available.

^bDrugs fall into one of three categories, targeting either G protein-coupled receptors, ionotropic receptors or ion channels, or biogenic amine transporters.

^cRR, relative risk of addiction; 1 = nonaddictive; 5 = highly addictive.

Another very common and easily accessible substance is alcohol. Addiction to alcohol is not very common, but for those who do become addicted it becomes a serious health issue. Alcohol dependence and abuse has been linked with many health-related problems and diseases, one of which is the most well-known, liver damage. Individuals who become addicted to alcohol can experience very severe withdrawal symptoms rivaling opiates. Withdrawal symptoms such as tremor, agitation and anxiety become apparent 6-12 hours after cessation and symptoms can be severe (Lüscher, 2018). Alcohol is also associated with higher rates of suicide. This correlation can also be seen with the opiate epidemic due to overdosing on the medications. Darvishi et al. (2015) found significant association between alcohol and suicidal ideation (OR = 1.86; 95% CI = 1.38, 2.35), suicide attempt (OR = 3.13; 95% CI = 2.45, 3.81); and completed suicide (OR = 2.59; 95% CI = 1.95, 3.23 and 95% CI = 1.26, 2.21) within their study. Unlike other forms of addictive substances, alcohol works on many different receptors in the brain as well as the cellular function. Opiates, cannabinoids and tobacco chiefly rely on specific receptors in the brain rather than many, like alcohol. Due to the various receptors in which alcohol works upon, it may explain why alcohol is ranked so highly among these other addictive substances.

Feingold et al. (2017) concluded that problematic use of opiates was more prevalent than problematic use of medical cannabis. After prolonged abstinence of opiate use, recovery in cognition is possible, however, it may take some time. Individuals who deal with chronic opiate abuse are less likely to have full recovery in cognition. Various neuroimaging techniques have been developed to evaluate opiate use on brain function. Significant differences in cognitive and motor impulsivity have been documented with chronic opiate use.

One of the most commonly known and used substances around the world is tobacco and nicotine. These elements surpass all other forms of known addictive substances and it has been

documented that more than 50 % of the adult population in some countries around the world are affected (Lüscher, 2018). The use of these products causes many associated diseases, many of which are reversible and preventable. Premature deaths are a leading factor associated with tobacco use. The CDC reports that around 400,000 adults die from nicotine related diseases each year. The number of deaths due to opiates continues to rise, and is becoming a potential rival to the documented nicotine related deaths (CDC, 2017). Due to so many health-related risks, many areas have banned smoking in public to prevent second hand smoke exposure, as well as a triggered relapse in those who have quit. Hatsukami, Stead, and Gupta (2008) state, “The portion who can achieve abstinence for at least 1 week is 25-51% and at least 3 months is 10-20%. By 6 months, only 3-5% have achieved longstanding abstinence” (p. 2035). Richter et al. (2016) have shown that early use of nicotine products leads to a higher likelihood of starting other abusive substances such as opiates, marijuana and alcohol to name a few. Although tobacco and nicotine withdrawal is mild compared to opiates, and may resemble cannabinoids, those who succeed with cessation have a very high likelihood of relapse.

What has been shown to be more effective in the treatment of chronic pain, medical cannabis or opiates?

In a study conducted by Ware et al. (2015), a visual analogue scale (VAS) was used to assess the perception of pain in patients. There was a reported difference in the VAS score between the placebo and the cannabinoid group. The results of the placebo score were 6.1 while the cannabinoid group was 5.4 respectively. Goldenberg et al. (2017) summarize findings pertaining to cannabinoids and cannabis in relation to health-related quality of life (HRQoL) and pain. The goal of measuring HRQoL is to assess physical, mental, emotional and social functioning of patient health. The findings suggest that the correlation between cannabinoids and

HRQoL are weakly positive in the seven diseases being researched (pain, multiple sclerosis, amyotrophic lateral sclerosis, traumatic brain injury, cancer related anorexia-cachexia syndrome, inflammatory bowel disease and human immunodeficiency virus). Some of the patients using cannabinoids for more common conditions, such as chronic pain, multiple sclerosis and inflammatory bowel disorder reported slight improvement in HRQoL, but not a statistically significant value. The conclusion of the findings revealed there is no significant effect on HRQoL, but for pain related diseases, this could be separate from the trend found in this study. The difficulty in determining whether the overall HRQoL was impacted in a positive way depends on each study design as well as duration.

There is an idea, that medical cannabis and cannabinoid products could aid in the current opiate epidemic as well as decrease the pain individuals endure. Boehnke et al. (2016) found that those who used cannabis for pain found not only improvement in pain symptoms, but a reduction in their current medications. According to Boehnke et al., *Table 2* demonstrates many individuals reported a decrease in their mean number of medications (2.38 vs 1.81, respectively, $p < .001$), most notably opiates, nonsteroidal anti-inflammatory and antidepressants. Not only was there documented reduction in opiate use, but a decrease in medication side effects ($r = .37$, $p = .0002$), indicating there is potential health benefits to replacing opiates with cannabis. The results of this study are focused on areas in which dispensaries are accessible to patients, thus there are areas that were not surveyed that could have further impacted the results.

When surveying patient populations with chronic pain, Feingold et al. (2017) documented there was a greater prevalence of problematic use in opiate users compared to medical cannabis users. The study measured three different variables to aid in determining the overall prevalence of problematic prescription use. The first variable of study was the Diagnostic

Table 2

Medication classes used before and after initiation of cannabis among the study population

MEDICATION TYPE	USE BEFORE INITIATION OF CANNABIS, N/N (%)	USE AFTER INITIATION OF CANNABIS, N/N (%)
Opioids	119/184 (65)	33/184 (18)
Nonsteroidal anti-inflammatory drugs	115/184 (62)	38/184 (21)
Disease-modifying antirheumatic drugs	15/184 (8)	3/184 (2)
Antidepressants	72/184 (39)	25/184 (14)
Serotonin–norepinephrine reuptake inhibitors	13/184 (7)	3/184 (2)
Selective serotonin reuptake inhibitors	34/184 (18)	8/184 (4)
Other	69/184 (38)	40/184 (22)

Note. From Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain, by K. Boehnke, E. Litinas, D. Clauw, 2016, *The Journal of Pain*, 17(6), p. 739-744. Copyright 2016 by the American Pain Society. *“Study participants reported using fewer medication classes of all categories after inhalation of cannabis use.*

and Statistical Manual of mental Disorders- Fourth Edition (DSM-IV). The DSM-IV is a manual used to help diagnose mental health disorders. Portenoy’s Criteria (PC) was the second variable and is a 10-item self-reported questionnaire that focuses on two main areas; first, having an intense desire for a drug and second, having a strong concern over the drugs availability. Patients also need to have one more positive finding, such as unsanctioned dose escalation for there to be documented problematic use. Current Opioid Misuse Measure (COMM) was the final test. It is a 17-item self-reported questionnaire where all items are rated from “0 = never to 4 = very often.” According to Feingold et al., *Figure 1* located on p. 20, demonstrated there is a significant difference in problematic use between opiate use and medical cannabis. The results are as

follows, 52.6 %, 17.1%, and 28.7% for the DSM-IV, PC, and COMM in patients with opiate treatment (with or without medical cannabis use) and 21.2%, 10.6% for DSM-IV and PC for medical cannabis treatment (with or without opiate use). The conclusion of this study showed that individuals with problematic opiate use reported a higher average ($p < 0.01$) and maximum ($p < 0.05$) level of pain than those without. Individuals associated with problematic use were those who had used medical cannabis for greater than five years or more ($p < 0.05$). Individuals who used opiates compared to those who used cannabinoids were all documented of having a greater association with depression and anxiety, 88% with opiates by comparison 46.5% with medical cannabis.

Ware et al. (2015) found that patient's physical function was greatly improved at their six and 12 month follow up appointments. "Average," "low," "current" and "highest" pain intensity was documented and the results revealed cannabis decreased the intensity in all trials compared to the placebo. Patients also reported a higher HRQoL score in other studies which relates to having a lower pain intensity score because there is less debilitation from their condition.

Deshpande, Mailis-Gagnon, Zoheiry, and Lakha (2015) state there was clinically meaningful pain reduction in cannabis users compared to the placebo. For there to be clinical significance, a decrease in pain of two points on a numerical pain rating scale from 0 to 10 or a 30% improvement in the intensity of pain would qualify.

Nugent et al. (2017) conducted research relating to cannabis in treating chronic pain in 22 randomized controlled trials (RCTs), two systemic reviews as well as eight further studies. The goal was to determine whether patients had a decrease in chronic pain following cannabis treatment. A numerical rating scale (NRS) as well as the visual analogue scale was used. Results showed a significant improvement in pain, a decrease of greater than 30% or two points on the

NRS scale as mentioned above. Nugent et al. also discussed findings found from National Academies of Sciences, Engineering, and Medicine. Findings were indicative of substantial benefit in chronic pain reduction in those who used cannabis. In those who used cannabinoid products, the AEs were of mild to moderate nature, contrary to some of the results found in other studies.

While there are numerous studies included within this research, one cannot make conclusions solely on the findings. This project was designed to present the research in a meaningful way and make inferences based on the studies. Furthermore, the research did not include in depth statistical analysis of each study's statistics which would have provided further explanation of the results. Lastly, further research on this topic is needed in order to needs to further understand the benefits, safety and interactions that are associated with medical cannabis and cannabinoid products.

Applicability to Clinical Practice/Policy

Due to the ever-changing field of medicine, as well as the different therapy modalities used for treatment of chronic pain, it is important to understand the different options available for use. Currently, there is a growing problem of overprescribing opiates as well as associated addiction and overdose due to these medications. With the legalization of cannabinoids, as well as the possible potential of its benefit for chronic pain therapy, this may be an option to help alleviate the current opiate epidemic.

Current research is showing there is benefit to medical cannabis as well as cannabinoids for certain chronic diseases and pain conditions such as fibromyalgia, neuropathy, multiple sclerosis, cystic fibrosis, migraines and gastrointestinal conditions to name a few. In some cases, there have been documented serious adverse events associated with the medication, however,

those situations are in the minority. Adverse events such as central nervous system depression, altered mental status and depressant effects were noted with cannabinoid use; of note, these events are also documented with the use of opiate medications.

This therapy, while still controversial, is a possible positive alternative for pain management and like every other medication, clinicians should discuss the possible adverse events as well as the potential benefits associated with its use. Further research is needed to confirm if cannabinoid therapy is of greater benefit to opiate therapy, however, every individual is unique with different complaints and conditions, thus not every therapy will work for everyone. It does seem that there may be more benefit to using cannabinoids over opiate therapy due to the lower chances of addiction, similar or lessened side effects and possible decreased need for other pain medications. Opiate therapy on the other hand, tends to cause addiction and tolerance which leads to increasing the medication dosage, both of which are what cannabinoid therapy would help resolve.

While it appears, current research is in favor for medical cannabinoid treatment or as an adjunct therapy, results are not conclusive throughout the studies as well as there is not enough research to fully support its use at this time. Following more trials and studies, this form of therapy will be better understood, as well as if it will further aid in decreasing the current opiate need for chronic pain management. It is important for providers to begin to understand and take action against this growing opiate problem as well as consider possible alternatives to alleviate patient pain. Further research, as well as focused projects pertaining to specific chronic pain conditions, will be of benefit to better understand medical cannabis and cannabinoid products.

References

- Aviram, J. & Samuelly-Leichtag, G. (2017). Efficacy of cannabis-based medicines for pain management: a systematic review and meta-analysis of randomized controlled trials. *Pain Physician Journal*, 20(6), E755-E596. Retrieved from <http://www.painphysicianjournal.com>
- Boehnke, K., Litinas, E., & Clauw, D. (2016). Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. *The Journal of Pain*, 17(6), 739-744. <http://doi.org/10.1016/j.jpain.2016.03.002>
- Campbell, F., Tramer, M., Carroll, D., Reynolds, D., Moore, R., & McQuay, H. (2001). Are cannabinoids as effective and safe treatment option in the management of pain? A qualitative systematic review. *British Medical Journal*, 323(7303), 13-16. <http://doi.org/10.1136/bmj.323.7303.13>
- Centers for Disease Control and Prevention (2017). Opioid overdose; understanding the epidemic. Retrieved from <https://www.cdc.gov>
- Darvishi, N., Farhadi, M., Haghtalab, & Poorolajal., J. (2015). Alcohol-related risk of suicidal ideation, suicide attempt, and complicated suicide: A meta-analysis. *PLoS ONE*, 10(5): 1-14. <http://doi.org/10.1371/journal.pone.0126870>
- Deshpande, A., Mailis-Gagnon, A., Zoheiry, N., & Lakha, S. (2015). Efficacy and adverse effects of medical marijuana for chronic noncancer pain. Systematic review of randomized controlled trials. *Canadian Family Physician*, 61(8), E372-E381. Retrieved from <http://www.cfp.ca/content/61/8/e372>
- Feingold, D., Goor-Aryeh, I., Bril, S., Delayahu, Y., & Lev-Ran, S. (2017). Problematic use of prescription opioids and medical cannabis among patients suffering from chronic pain.

- American Academy of Pain Medicine*, 18(2), 294-306. <http://doi.org/10.1093/pm/pnw134>
- Goldenberg, M., Reid, M., IsHak, W., & Danovitch, I., (2017). The impact of cannabis and cannabinoids for medical conditions on health-related quality of life: A systematic review and meta-analysis. *Drug and Alcohol Dependence*, 174, 80-90. <http://doi.org/10.1016/j.drugalcdep.2016.12.030>
- Hatsukami, D., Stead, L., & Gupta, P. (2008). Tobacco addiction. *Lancet*, 371: 2027-2038. [http://doi.org/10.1016/S0140-6736\(08\)60871-5](http://doi.org/10.1016/S0140-6736(08)60871-5)
- Issa, M., Narang, S., Jamison, R., Michna, E., Edwards, R., Penetar, D., & Wasan, A. (2014). The subjective psychoactive effects of oral dronabinol studies in a randomized, controlled crossover clinical trial for pain. *Clinical Journal of Pain*, 30(6), 472-478. <http://doi.org/10.1097/AJP.0000000000000022>
- Lüscher, C. (2018). Drugs of abuse. In B.G. Katzung (Ed.), *Basic & clinical pharmacology*, 14e (Chapter 32). New York, NY: McGraw-Hill. Available from AccessMedicine
- Lynch, M., & Campbell, F. (2011). Cannabinoids for treatment of chronic non-cancer pain; A systematic review of randomized trials. *British Journal of Clinical Pharmacology*, 72(5), 735-744. <http://doi.org/10.1111/j.1365-2125.2011.03970.x>
- Martín-Sánchez, E., Furukawa, T., Taylor, J., & Martin, L. (2009). Systematic review and meta-analysis of cannabis treatment for chronic pain. *American Academy of Pain Medicine*, 10(8), 1353-1368. <http://doi.org/10.1111/j.1526-4637.2009.00703.x>
- National Conference of State Legislatures (2017). State medical marijuana laws. Retrieved from <https://www.ncsl.org>
- National Institutes of Health (2017). Commonly abused drugs. *National institute on drug abuse*. Retrieved from <http://www.drugabuse.org>

- Narang, S., Gibson, D., Wasan, A., Ross, E., Michna, E., Nedeljkovic, S., & Jamison R. (2008). Efficacy of Dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *The Journal of Pain*, 9(3), 254-264. <http://doi.org/10.1016/j.jpain.2007.10.018>
- Nugent, S., Morasco, B., O'Neil, M., Freeman, M., Low, A., Kondo, K., . . . Kansagara, D. (2017). The effects of cannabis among adults with chronic pain and an overview of general harms. *Annals of Internal Medicine*, 167(5), 319-332. <http://doi.org/10.7326/M17-0155>
- Richter, L., Pugh, B., Smith, P., & Ball, S. (2016). The co-occurrence of nicotine and other substance use and addiction among youth and adults in the United States: Implication for research, practice, and policy. *The American Journal of Drug and Alcohol Abuse*, 43(2), 132-145. <http://doi.org/10.1080/00952990.2016.1193511>
- Ware, M., Wang, T., Shapiro, S., & Collet, J. (2015). Cannabis for the management of pain: Assessment of safety study. *The Journal of Pain*, 16(12), 1233-1242. <http://doi.org/10.1016/j.jpain.2015.07.014>
- Whiting, P., Wolff, R., Deshpande, S., Di Niso, M., Duffy, S., Hernandez, A., . . . Kleijnen, 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>