2020

The Effectiveness of Cannabidiol in Rheumatic Disease Pain: A Systematic Review

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N695: Alternate Paper Plan

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May 1, 2020

Abstract

Cannabinoids have long been a part of human culture and medicine, and more recently have been rediscovered for their potential use in the management of rheumatic disease pain. The objective of this review was to evaluate the known clinical effectiveness of cannabidiol treatment for rheumatic disease related pain. The legality and current regulation of these products was also reviewed to establish the current status of federal and state rules regarding their clinical use. Basic definitions of the terms used to differentiate cannabidiol from other cannabinoid products was also outlined. A systematic literature search was then conducted to explore the current pool of evidence pertaining to the defined phenomena of interest and clinical question. Five electronic databases were selected to generate a comprehensive selection of evidence. Twenty-one articles were identified and evaluated for appropriateness of fit within the defined inclusion and exclusion criteria. Articles relating to the use of cannabidiol in any form for the treatment of rheumatic disease pain in adults were included. Research articles pertaining to non-rheumatic diseases, psychiatry, children, adolescents, medical cannabis, or tetrahydrocannabinol alone were excluded. A total of nine studies met inclusion criteria. Findings from those studies concluded that current evidence is lacking in quality, quantity, and in key factors regarding the efficacy, tolerability, and safety of cannabidiol for rheumatic disease relief pain. Furthermore, due to the lack of evidence evaluating cannabidiol use for rheumatic disease pain, additional clinical studies are needed to evaluate their usefulness. Best practice and research recommendations were also proposed based of the systematic review and current body of evidence.

Keywords: cannabidiol, cbd oil, rheumatic disease, treatment, analgesia, safety, effectiveness

Exploring the Effectiveness of Cannabidiol Use in Rheumatic Disease Pain: A Systematic Review

Cannabinoids have been a part of human culture for the past millennia and used for various medicinal purposes (Sarzi-Puttini et al., 2019). Presently, the use of cannabinoids for chronic pain relief is rapidly increasing as the unrestricted availability of these products steadily surges. It is a frequent occurrence to find products containing cannabinoids sold online or at any local convenience or grocery store claiming to aid the management of many conditions including arthritis pain relief. Additionally, the marketing of the cannabidiol or CBD for arthritis pain relief has also exponentially increased, leading to the dissemination of scientifically unsubstantiated claims. Within the scientific community, many uncertainties and controversies remain regarding the role of cannabinoids for the management of rheumatic pain (Perrot & Trouvin, 2019). This is further compounded by the confusion between different forms of cannabis plants and products such as herbal cannabis, medical cannabis, and cannabinoids (Perrot & Trouvin, 2019). Therefore, it is important to differentiate these products and look beyond the anecdotal claims as these ancient drugs are now being rediscovered and reconsidered as potential modern analgesic therapies by patients (Perrot & Trouvin, 2019). This review aims to evaluate the current body of clinical evidence available to support the clinical use of CBD oil for rheumatic disease pain relief in order to suggest clinical practice recommendations.

Background

Cannabinoids have long been used for recreational, medicinal, and even ceremonial purposes (Sarzi-Puttini et al., 2019). Early uses of cannabinoids for medicinal purposes in conditions such as rheumatic pain, constipation, and even malaria, date back to 28th century BC (Sarzi-Puttini et al., 2019). More recently cannabinoid products have been used around the world for its therapeutic properties in chronic pain relief, epilepsy, and opioid addiction. Additionally,

social or recreational use of cannabis products is growing as many states are legalizing their use despite the paucity of evidence regarding their safety and efficacy (Sarzi-Puttini et al., 2019).

Cannabinoids are natural compounds derived from the cannabis plant family. There are more than 100 known cannabinoids; the most common cannabinoids used are tetrahydrocannabinol (THC) and CBD. Derived from the cannabis sativa plant, CBD has been used for centuries in various medicinal preparations for the treatment of chronic pain, a cardinal symptom of many rheumatological diseases (Sarzi-Puttini et al., 2019). Rheumatic diseases, such as osteoarthritis, represent a group of painful conditions where conventional analgesics show poor efficacy and inadequate long-term control of pain relief (Perrot & Trouvin, 2019). Thus, CBD oil has grown to be a popular option as a potential new therapeutic alternative for rheumatic pain (Perrot & Trouvin, 2019). The rationale for its use in arthritis is based not only on its analgesic effects, but also on its anti-inflammatory effects and immunomodulatory activity (Perrot & Trouvin, 2019). Due to its lack of psychoactive properties, CBD oil is a seemingly safe choice for patients who are seeking alternatives for pain relief (Sarzi-Puttini et al., 2019). Nevertheless, centuries old use, the absence of psychotropic properties, and lack of other effective therapies is not sufficient evidence to prove that CBD oil is a useful or safe treatment for rheumatic pain (Sarzi-Puttini et al., 2019).

The legality, safety, and efficacy of CBD is often called into question as many healthcare providers are uncertain of the existing supportive evidence and current regulation of CBD oil. Skepticism of the effectiveness of CBD oil, stemming from the lack of current evidence, has left many health care professionals calling for more validation to be done regarding its usefulness in clinical practice (Sarzi-Puttini et al., 2019). Likewise, validating patient reported treatments that

improve rheumatic disease pain necessitates further clinical studies of CBD oil to determine if it plays any clinical role in the management of these disorders.

Additionally, as the cannabinoid industry explodes into the mainstream consumer market, associated terminology and understanding of specific terms is often misunderstood and misused. Commonly used terms include cannabinoids, cannabidiol, cannabis, hemp, marijuana, hemp seed oil, CBD oil, medical marijuana, THC, and cannabis oil. Often, many of these terms are used interchangeably, leading to confusion for patients and providers alike. Lastly, many products have been found to contain a mixture of cannabinoids with mislabeled concentrations, creating uncertainty surrounding which cannabinoid may be providing relief or found to have harmful side effects.

Definitions

Familiarity with commonly used terminology of CBD products is necessary to understand the clinical phenomenon of interest as their various terms used. Knowledge of the definitions of these terms is important to differentiating CBD from other cannabinoid products.

The Endocannabinoid System

The endocannabinoid system or ECS, is a newly discovered system within the human body. It acts as a homeostatic regulator of functions within the brain, cardiovascular system, digestive track, liver, and even bone (Russo, 2016). This system is comprised of a triad of cannabinoid receptors including CB1, CB2, TRPV1, endogenous cannabinoids such as anandamide, and exogenous cannabinoids such as CBD or THC (Russo, 2016).

Cannabinoids

Cannabinoids are compounds derived from the cannabis plant family. These naturally occurring chemical compounds are the active ingredients found in cannabinoid products (VanDolah et al., 2019). These compounds include THC and CBD.

Tetrahydrocannabinol

THC is the primary psychoactive cannabinoid found in the Cannabis sativa L. plant. THC is a phytocannabinoid or plant-derived cannabinoid that is a CB1 receptor agonist, known for producing intoxicating CNS effects (VanDolah et al., 2019).

Cannabidiol

This is a non-intoxicating cannabinoid extracted from the flowers of the female Cannabis sativa L. plant and is used for its therapeutic properties in pain relief (VanDolah et al., 2019). CBD oil has become especially popular as an over the counter medication because of its low THC levels resulting in medical benefits such as pain relief without the euphoric sensations associated with marijuana (VanDolah et al., 2019). It binds to the TRPV1 receptor and does not have any intoxicating effects.

Hemp

Hemp is a species of the Cannabis sativa L. plant that contains less than 0.3% THC. Often its fibers are used for clothing and its oil is used in cosmetic products. It does not contain enough THC to have psychoactive properties, yet it does contain CBD. As of January 1, 2020, products containing CBD derived from hemp can be legally sold under Minnesota state law (Minnesota Department of Agriculture, 2020).

Hemp Seed Oil

This is created from the seeds of the hemp plant and does not contain any cannabinoids. It is often used as a nutritional supplement or in clothing and fibers. It also contains omega-6 and omega-3 fatty acids and other antioxidants (VanDolah et al., 2019).

Cannabis Oil

Cannabis oil is derived from the marijuana plant which is also of the same plant species Cannabis sativa L. Its THC levels are directly related to genetic differences in cannabis sativa plants and specific growing techniques. Cannabis oil contains high levels of THC and is only legal to produce by medical cannabis manufacturers licensed by the Minnesota Department of Health (Minnesota Department of Agriculture, 2020).

Clinical Phenomenon of Interest

Cannabidiol, or CBD, seems to be available almost everywhere. It is marketed as a product to help with pain, anxiety, and even seizures. There is significant public interest in cannabis derived products despite many unanswered questions regarding the safety, efficacy, and quality of products containing CBD. Additionally, the U.S Food and Drug Administration (FDA) only recognizes the use of CBD products for two rare forms of epilepsy (U. S. Food and Drug Administration, 2019). Thus, an urgent need for analysis of the current body of evidence and its findings is crucial to evaluate the safety, efficacy, and potential for adverse effects of CBD oil.

While some patients may feel that these products are safe, rigorous scientific studies demonstrating their effectiveness and safety are insufficient. Furthermore, providers are often asked by their patients if these products work and if there are any known benefits. Therefore, providers must be astutely aware of scientific evidence regarding the safety and efficacy of CBD oil. Thus, it is imperative that thorough evaluation of existing CBD oil research is conducted and evaluated.

Presently, CBD oil products are being sold as dietary supplements claiming to relieve arthritis pain yet have not been subject to FDA evaluation or been proven to have any therapeutic benefit. There is also limited research regarding the appropriate dosage of CBD oil, any food or drug interactions, or dangerous side effects of CBD oil (FDA, 2019). The FDA has tested the chemical contents of cannabinoid products sold over the counter and again have found they did not contain the levels of CBD as indicated on the label (FDA, 2019). There are also reports of cannabinoid products containing unsafe levels of contaminants such as pesticides, heavy metals, and THC (FDA, 2019). Thus, the potential for patient harm is undeniable given the lack of research needed to identify the proper dosage, the inconsistent labeling of CBD oil sold over the counter, and unproven anecdotal claims associated with these products. The potential to delay seeking appropriate medical care is also greater for patients using alternative therapies for pain relief that are not evidenced to be safe and effective.

Clinical Question

The PICO format was utilized to focus the literature search and refine the topic of clinical interest. In adults experiencing pain due to rheumatic disease (P), how does cannabidiol use (I) compared to no use of cannabidiol (C) influence pain relief?

Clinical Significance for Advanced Practice

Many health care providers are uncertain about the efficacy, legality, and safety of over the counter products containing CBD oil used for pain relief. It is imperative that health care providers have a clear understanding of these aspects and CBD oil's efficacy in treating rheumatic disease pain as patients may seek their counsel on the use of these products. A clear understanding of the clinical research conducted on the chief ingredients found in CBD oil products is the first step to informing primary care providers about the safety and efficacy. It is

well known that there are only a small number of clinical research studies conducted and disseminated regarding CBD oil products, as most research focuses on THC and its primary target, CB1 receptors (VanDolah et al., 2019). Therefore, this lack of evidence significantly impacts the potential for advocacy of the use of these products.

Legal and Regulatory Considerations

The sale of over the counter CBD oil products are currently widespread throughout the United States. With the passage of the 2014 Agricultural Act, the growth of hemp or Cannabis sativa L. with a THC content of no more than 0.3% was legalized for the purposes of research in the United States and was removed from the Controlled Substances Act (VanDolah et al., 2019). It remained illegal, however, to introduce any supplement or food containing CBD into interstate commerce (VanDolah et al., 2019). Thus, most products were therefore imported from Europe, processed, and redistributed within the United States to be sold with little regulation (VanDolah et al., 2019). This led to widespread distribution of unregulated and mislabeled products commonly seen sold in many retail stores.

As of January 1st, 2020, the sale of over-the-counter hemp products containing CBD oil containing less than 0.3% THC can be legally sold under Minnesota law (Minnesota Board of Nursing, 2019). This new regulatory step also aims to reduce mislabeling as labeling conditions are clearly outlined and required for CBD oil products. The new labeling requirements must now include an accurate statement of ingredient amounts, a statement of the amount or percentage of cannabinoids found in each individual dose consumed, and a statement stating that the product does not claim to diagnose, treat, cure, or prevent any disease (Minnesota Board of Nursing, 2019). The label must also state it has not been evaluated or approved by the FDA unless the product has been so approved (Minnesota Board of Nursing, 2019).

Safety and Adverse Effects

Of the few studies conducted examining CBD oil safety, a range of CBD oil doses from 300 milligrams per day for 6 months to 1200 - 1500 milligrams per day for 4 months were used safely (VanDolah et al., 2019). However, studies with larger numbers of participants have found associated side effects with the use of CBD oil including somnolence, decreased appetite, diarrhea, and elevated liver function tests (VanDolah et al., 2019). Furthermore, some drug to drug interactions have been found as a result of the metabolism of CBD oil by the cytochrome P450 enzyme system including warfarin and various epilepsy medications (VanDolah et al., 2019). Lastly, inconsistent branding of the ingredients within these products has included over labeling CBD content and under labeled THC (VanDolah et al., 2019). As a result, severe adverse reactions have led to two hospitalizations due to ingestion of these products (VanDolah et al., 2019).

Methods

A systematic literature search was conducted between the dates of 10/11/19 through 10/25/19 to explore the current evidence pertaining to the defined clinical question. Five electronic databases were selected to generate a comprehensive selection of evidence. Articles were then evaluated for appropriateness of fit within the defined inclusion and exclusion criteria.

Search Strategies

To focus on the outlined clinical question, a broad range of applicable key words were selected and applied when searching all five databases. Boolean operators were also utilized to combine search terms and broaden the results. Key words were matched within all article text. This strategy was used to retrieve all studies examined within this review.

Data Abstraction Process

Databases searched included CINAHL, CENTRAL, ProQuest, PubMed, and PsycINFO. Detailed database information, general search terms, specific dates, and search restrictions are included in Table 1 of the attached appendix. Studies were found using search terms including "CBD oil," "cannabidiol," "pain," "pain relief," "rheumatic disease," " inflammation," "anti-inflammatory," "treatment efficacy," "arthritis," "analgesic," and "join pain." Search limits applied to database searches consist of only peer reviewed articles authored between 2006-2019, full text available, English language, Adults, Humans, Evidence-based healthcare, literature review, systematic review, abstract available, and scholarly journals. Article titles were then reviewed by the author when database searches concluded 10 hits or less. Titles were eliminated if they contained non-human subjects, children, adolescents, and non-rheumatic diseases. A complete list of unique matches included within this review are indicated in Table 2 in the appendix.

Inclusion/Exclusion Criteria

Articles relating to the use of CBD for the treatment of rheumatic disease pain in adults were included. Relevant studies that reviewed multiple types of cannabinoids individually, including CBD oil, were also incorporated in order to expand the amount of available literature. Research that discussed the history of cannabinoids was also incorporated. A total of 9 articles met inclusion criteria for this analysis. Refer to Table 3 for all reviewed articles with inclusion criteria rationale.

Research articles pertaining to non-rheumatic diseases such as cancer, hepatic disease, epilepsy, children, or adolescents were excluded. Studies pertaining only to the use of medical cannabis or THC were excluded. Topics examining cannabinoid use in psychiatry were also excluded. Refer to Table 3 for all reviewed articles with exclusion criteria rationale.

Literature Review Process

Fifty-three studies were identified using keywords and keyword combinations to search the five databases. Twenty-one studies were further reviewed for a fit with inclusion or exclusion criteria; 32 studies were duplicates. After evaluation of the final search results, nine studies fit the inclusion criteria and were included in this literature review. Those studies included one systematic review of randomized control trials, two randomized control trials, three reviews of mixed trials, one case study, and two articles of expert opinion. Detailed information regarding the purpose, sample size, level of evidence, variables, findings, and implications of all nine included studies are indicated in Table 4 in the appendix.

Literature Review

This literature review aims to identify the current body of evidence pertaining to the therapeutic use of cannabinoids, specifically CBD, for the treatment of rheumatic disease related pain. This research related to the effects of CBD on rheumatic disease pain will be synthesized. After meeting inclusion criteria, the nine studies were evaluated for strength of evidence and substantiation of therapeutic benefit with the use of CBD on rheumatic disease pain.

Study Characteristics

As described in the literature review process section, the highest level of evidence found was one level I systematic review while all other evidence discovered was a mixture of level II, III, VI, and VII. The nine studies included in this review are organized by level of evidence as follows: one systematic review, two randomized control trials (RCTs), three reviews of mixed trials, one case study, and two articles of expert opinion. The level I evidence identified by this systematic review was a systematic review of RCTs, that assessed the outcomes of cannabinoid use in patient with rheumatic disease. Level II studies consisted of two RCTs. Hunter et al.

(2018) evaluated the effects of CBD oil on pain and inflammation in osteoarthritis the knee and Blake et al. (2006) assessed the efficacy of defined dosages of cannabis-based medicine in rheumatoid arthritis pain. Level III studies comprised of three articles that reviewed mixed method studies and non-randomized cohort studies. Ark (2016) conducted a literature review of level II and level III studies examining cannabis or CBD use in rheumatoid arthritis. Bruni (2018) reviewed current clinical trials regarding cannabinoids and their effects on pain and inflammation. While, Kraft (2012) explores the clinical data in cannabinoid use for analgesia. The level VI evidence found consisted of one review of the historical development of research and current evidence on CBD use in numerous diseases including rheumatoid arthritis and other inflammatory diseases (Zuardi, 2008). Finally, level VII evidence included two studies of expert opinion. Miller et al. (2017) provided a historical review of cannabis and expert opinion on current studies assessing the efficacy of cannabinoids in the treatment of joint pain. Booz (2011) aimed to review the utility of non-psychotropic CBD in reducing oxidative stress and inflammation in diseases such as rheumatoid arthritis and neuropathic pain.

Populations Studied

Musculoskeletal pain is one of the most common reasons for primary care visits (Dunphy et al., 2015). Rheumatic diseases contribute to many musculoskeletal pain complaints in primary care as they are associated with chronic pain and inflammation. Rheumatic disease consists of inflammatory and autoimmune conditions that are commonly categorized under the term arthritis (Mayo Clinic, 2020). Osteoarthritis and rheumatoid arthritis are examples of common chronic, articular types of rheumatic disease. Osteoarthritis involves the degeneration of cartilage within joints such as the knee or hip and rheumatoid arthritis affects the synovial membrane within joints causing pain, swelling, and stiffness (Mayo Clinic, 2020). Patients with rheumatic disease related arthritis suffer daily from pain, immobility, stiffness, physical deformity, and limited

range of motion. As many patients with these conditions are seeking relief from the associated pain and stiffness, both these conditions are the primary focus of this review.

Literature Review

Fitzcharles et al. (2016) conducted a systematic review of the effect of cannabinoids on the reduction of pain, sleeping difficulties, fatigue, and quality of life associated with rheumatic diseases. Four randomized control studies met inclusion criteria for the systematic review conducted by Fitzcharles et al. (2016). Two of those studies focused on fibromyalgia syndrome, one study examined chronic spinal pain, and the final study examined rheumatoid arthritis. No randomized control trial involving osteoarthritis was found. Within the single study regarding rheumatoid arthritis an oral combination spray consisting of CBD 2.5 mg and THC 2.7 mg was found to be statistically superior compared to placebo ($p = 0.02$) in reducing morning pain with movement and rest, but not overall pain (Fitzcharles et al., 2016). However, frequent side effects were reported including dizziness, drowsiness, nausea, and dry mouth along with one serious side, a fracture, effect as a result of falling (Fitzcharles et al., 2016). It was unclear, however, if any of these were due to CBD or THC. Ultimately, Fitzcharles et al. (2016) concluded that currently there is insufficient evidence to recommend any cannabinoid preparations for the management of pain associated with rheumatic disease. They also caution that rheumatic disease patients requesting CBD or any cannabis treatment should be made aware of the current absence of evidence for effect and therefore, these therapies should be reserved for those who have exhausted all other pain relief options (Fitzcharles et al., 2016).

Blake et al. (2006) conducted a randomized, double blind control trial of 58 patients with rheumatoid arthritis over the span of five weeks. Using a cannabis-based medicine comprised of THC and CBD, the effectiveness in relieving pain with movement, pain at rest, morning

stiffness, and impact on sleep quality was measured (Blake et al., 2006). This study observed a small but potentially significant analgesic effect with this therapy. Specific to CBD oil, the study detected a modest suppression of inflammation activity, as measured by the Disease Activity Score, suggesting some anti-inflammatory properties related to CBD oil (Blake et al., 2006). These findings suggest some clinical relevance and reinforce the necessity for more detailed studies regarding efficacy, dosage, and formulation of CBD products (Blake et al., 2006).

Using transdermal synthetic CBD oil gel, Hunter et al. (2018) evaluated the safety and efficacy of this therapy for the treatment of knee pain due to osteoarthritis in humans. A randomized, double-blind placebo controlled multiple dose study of 321 patients was conducted over 12 weeks on adults with knee pain due to osteoarthritis (Hunter et al., 2018). Topically, a dosage of 250mg twice per day was given versus a placebo (Hunter et al., 2018). Following a one-week washout period, implemented to allow cessation of any current analgesics and systemic elimination, a one-week baseline period was conducted to capture daily worst pain ratings using a 0 to 10 numeric rating scale (Hunter et al., 2018). Weekly thereafter, pain scores were then captured using the same pain rating scale and evaluated for changes from baseline ratings during the trial period (Hunter et al., 2018). Adverse effects noted during this trial included application site dryness and headache (Hunter et al., 2018). After 12 weeks of blinded treatment, Hunter et al. (2018) found there were no statistically significant differences between the placebo group and CBD gel treatment group on osteoarthritis related pain relief.

Examining randomized and non-randomized control trials, Ark (2016) evaluated literature regarding chronic pain due to rheumatoid disease and the utilization of cannabis or CBD. Three human RCTs were reviewed and limited evidence to support CBD for treatment of pain caused by inflammatory pathways, autoimmune processes, or neurodegeneration was

summarized (Ark, 2016). Conclusions drawn from this mixed review indicated that more human studies are needed to determine the efficacy of CBD oil for the treatment of rheumatic disease (Ark, 2016).

An abundant amount of patient testimonies exists regarding the anecdotal therapeutic effects of CBD for pain despite the insufficient amounts of rigorous clinical studies conducted (Bruni et al., 2018). Thus, Bruni et al. (2018) surveyed current clinical trials regarding cannabinoids and their effects on pain and inflammation. Additionally, they analyzed various CBD oil administration and delivery forms, such as transdermal and oral-mucosal routes for therapeutic benefit (Bruni et al., 2018). Conclusions drawn from this review regarding CBD-based products for therapeutic pain reduction purposes in forms such as oils, tinctures, and vapors, recommend careful consideration when using these products as any potential health risks or benefits have not been fully established (Bruni et al., 2018). They caution that while CBD use by patients is increasing, additional scientific evaluation of CBD is essential in order to determine quality, safety, and efficacy data (Bruni et al., 2018).

Kraft (2012) acknowledged that there has been a recent resurgence in the medical use of the cannabis sativa plant for the purpose of analgesia. Thus, Kraft (2012) analyzed clinical data from human trials of multiple forms of cannabinoids, including CBD oil. They concluded that due to small sample sizes and short trial durations, findings from these studies were unclear regarding the analgesic effects of cannabinoids on rheumatic pain (Kraft, 2012). Some supportive evidence found marginal analgesic effects when used as adjuvant therapies but recommend that additional well-designed human control studies must be done to confirm these findings (Kraft, 2012).

Zuardi (2008) acknowledge that CBD oil has a wide range of potential pharmacological effects for many conditions including rheumatoid arthritis. The researchers speculate that the suppressive effects of CBD oil on immune response and along with the production of pro-inflammatory mediators suggest some usefulness in rheumatic disease pain (Zuardi, 2008). However, a notable finding from this review indicated that the effects of CBD oil were likely dose dependent, emphasizing that the lowest most effective dose must be a central factor in future CBD research (Zuardi, 2008). Additionally, due to the multiple potential mechanisms of action identified, further research is needed to clarify and underline any potential beneficial effects of CBD oil (Zuardi, 2008).

Reducing oxidative stress is often a key target for therapeutic uses of CBD oil. Booz (2011) discussed the recent studies suggesting that CBD may have some utility in reducing oxidative stress and inflammation within rheumatoid arthritis. They suggest the therapeutic action of CBD oil is triggered by the suppression of immune response, specifically by inducing apoptosis of lymphocytes (Booz, 2011). However, the mechanism of action surrounding the anti-inflammatory activities of CBD oil remains to be well-defined (Booz, 2011). Early conjecture suggests this may be the result of interruption within intercellular signaling (Booz, 2011). Ultimately, given the potentially positive properties such as suspected anti-inflammatory activity, immunosuppressive actions, and lack of psychotropic effects of CBD oil, further therapeutic studies regarding the utility of this drug are recommended (Booz, 2011).

Finally, the expert opinion of Miller and Miller (2017) acknowledges that the effects of herbal cannabinoids in humans with joint pain needs to be more accurately assessed because many patients are choosing to self-medicate with these products. They also recognize that patients are reporting benefit from the use of cannabinoids, including CBD, and call for more

rigorous clinical evidence to support these claims (Miller & Miller, 2017). Furthermore, they point out that it is unclear if CBD alone is helpful in producing analgesic effects as limited examination of the effects of individual cannabinoids in patients with rheumatic diseases has been conducted (Miller & Miller, 2017). Their findings suggest that due to the lack of rigorous clinical studies, there is not enough data to support CBD oil for the treatment of joint pain despite the many anecdotal patient statements (Miller & Miller, 2017).

Quality Indicators

Multiple researchers acknowledged the importance of seeking new rheumatic disease pain analgesics as traditional analgesics show poor efficacy and leave many patients with uncontrolled rheumatic disease pain. The articles reviewed included contribution from many key stakeholders including physicians, nurse practitioners, and pharmacists. The hierarchy of evidence resulting from this review, however, varied in strength and appropriateness to answer the defined clinical question. The use of true experimental research designs to provide the highest levels of confidence to answer the clinical question was limited in the current body of low-quality evidence. Lower level of confidence studies utilizing non-experimental designs were found to be more prevalent within the literature. Additionally, the two experimental studies available evaluating the defined clinical question varied largely in sample size and in their measurement of treatment effects. At present, there are also many confounding variables identified within the research including mixed patient populations, different cannabinoid preparations, various formulations, and wide dosing ranges (Bruni et al., 2018). On the other hand, despite the multiple research designs used, recommendations regarding the use of CBD for rheumatic disease pain were all together consistent.

Gaps in Literature

Major gaps in literature stem from the absolute lack of research regarding CBD in general. At present, very few human studies provide tangible evidence concerning the appropriate dose, route, frequency, safety, and efficacy of CBD. Furthermore, available human research studies related solely to CBD oil use for rheumatic disease pain are even more meagre, as most research has been conducted for its use in conditions such as cancer related pain and epilepsy. Thus, rigorous human clinical control trials aimed to determine both long and short-term effects, lowest efficacious dose, most effective route, safety, and risk of adverse effects must be conducted in order to strengthen the evidence regarding the use of CBD oil for rheumatic disease pain.

As many studies within this review contained various modes of administration, the most effective route remains unknown. Additionally, this gap significantly weakens the pool of current research as parallels are unable to be made amongst data. In addition, this variance further impedes any supportive evidence validating the lowest efficacious dose with the fewest side effects. Thus, it remains that additional rigorous evidence is needed to determine the most efficacious, safe, and efficient mode of administering CBD.

Best practices and recommendations found within this review were not promising regarding CBD oil use for rheumatic disease pain. Most literature findings resulted in the call for more rigorous studies to be conducted before any further practice related guidance could be drawn. In fact, while many studies emphasized the importance of seeking new rheumatic pain management strategies, none could conclude that CBD oil use for the treatment of rheumatic disease pain was better than current pain management strategies. Ultimately, the level of evidence supporting the use of CBD oil in rheumatic disease pain is minimal and therefore, clinical practice recommendations suggest limited routine use.

Discussion

Cannabinoids have long been used for recreational and medicinal purposes. More recently cannabinoid products have been used across the world for their therapeutic properties in chronic pain relief, epilepsy, and even addiction. Due to its low THC concentration, the cannabinoid CBD oil has become popular as an over the counter medication for rheumatic disease pain relief. Notably, regulation of these products is limited, allowing for inconsistent labeling of CBD oil sold over the counter. However, with the passage of the 2014 Agricultural Act, the growth of hemp or Cannabis sativa L. with a THC content of no more than 0.3% was legalized for the purposes of research in the United States and CBD was removed from the controlled substances act (VanDolah et al., 2019). This has led to state law changes regarding its sale and new labeling requirements.

Many uncertainties remain regarding the roll of cannabinoids for the management of rheumatic pain. Despite the paucity of evidence regarding their safety and efficacy, patients frequently use these products for pain relief for their rheumatic disease. In summary of the evidence identified for this review, a modest suppression of inflammation activity suggests anti-inflammatory and immunomodulating properties of CBD oil and potentially indicates some clinical relevance (Blake et al., 2006). However, direct correlation to exact mechanisms are not able to be concluded and therefore only reinforce the need for more detailed studies regarding efficacy, lowest effective dose, and most appropriate formulation of CBD products (Blake et al., 2006). Other supportive evidence found indicated marginal analgesic effects when used as adjuvant therapy and recommended that additional well-designed human control studies must be done to confirm these findings (Kraft, 2012). On the other hand, some studies found side effects including dizziness, drowsiness, nausea, and dry mouth, yet it was unclear whether these were

due to CBD or another ingredient within the product. Additionally, multiple authors pointed out that any potential health risks or benefits have not been fully established and further research is needed to explore these areas. A common theme found within all nine articles reviewed indicated that given the potentially positive properties including anti-inflammatory activity, immunosuppressive actions, and lack of psychotropic effects, further therapeutic studies regarding the utility of CBD oil are warranted. While many studies emphasized the importance of seeking new rheumatic pain management strategies, none could conclude that CBD oil use for the treatment of rheumatic disease pain was better than current pain management therapies.

To date, the available evidence related to the clinical question is minimal. There are very few rigorous studies conducted that solely assess the clinical effectiveness of CBD oil for rheumatic disease related pain. Far more literature containing anecdotal evidence or expert opinion is available at this time. As safer and more effective alternative therapies for the relief of rheumatic disease is sought, it is imperative we do our due diligence and scientifically study the potential CBD oil may provide in pain relief before we advise its routine use. Anecdotal statements cannot be allowed to supersede evidenced based, high-quality research regarding CBD nor risk patient harm by recommending its use without scientific proof of its safety. Many studies within this review brought forward concerns for unknown harms or side effects if careful examination of CBD oil use for rheumatic disease pain if left undone. Therefore, it is important to take the time to formulate multiple thorough experimental studies that assess the safety and efficacy of CBD oil in rheumatic disease pain. Imperatively, these studies must align and analyze appropriate route, strength, short and long-term effects, side effects, risk for addiction, efficacy and safety before any recommendations for use can be made.

Finally, it is imperative that health care providers have a clear understanding of the efficacy of CBD oil in relieving rheumatic disease pain as patients may seek their counsel on the use of these products. Many studies within this review acknowledged that due to various modes of administration, the most effective route and lowest effective dose of CBD remains unknown. As a result, the research found to date is inconclusive regarding the efficacy of CBD oil for rheumatic disease pain relief. Thus, it remains that additional rigorous evidence is needed to determine the most efficacious, safe, and efficient mode of administering CBD. Due to the lack of congruent evidence found in this review, it is surmised that health care providers should not advocate for routine use of CBD oil until further rigorous studies are conducted.

Implications for Future

At present, due to the lack of available evidence-based literature needed to answer the identified clinical question, few proposals for CBD as a future therapy in rheumatic disease pain are suggested. The following areas have been identified for discussion of necessary future recommendations and include clinical practice management, patient and provider education, key research needs, and requests for healthcare policy.

Clinical Practice Recommendations

Maintaining clinical curiosity and a healthy respect for skepticism is key to the exploration of new pain management options within rheumatic disease. At present, current traditional analgesic management is inadequate, leaving many patients seeking new therapies for pain relief. Yet, due to the low quantity and quality of available evidence on the efficacy, tolerability, and safety of CBD in rheumatic disease pain relief, recommending CBD oil for routine clinical is not advised (Fitzcharles, 2016). Therefore, CBD oil should only be cautiously considered as an adjunctive, complementary therapy in the management of rheumatic disease

pain (Sarzi-Puttini et al., 2019). Until known safety, efficacy, side effects, and confidence in accurate over the counter drug labeling is observed, providers should prudently address patient questions regarding routine CBD use for rheumatic disease pain.

Recommendations for Research

CBD is a non-intoxicating and potentially useful substance with increasing patient interest (VanDolah, 2019). Despite non-FDA approval for therapeutic use, patients continue to use CBD oil regardless of potential safety concerns, side effects, or lack of evidence supporting its therapeutic benefit (VanDolah, 2019). This considerably risky choice, especially in patients with rheumatic disease, stems from the poor pain management therapies currently available and a desperate need for potentially better pain relief alternatives such as CBD oil. Therefore, more research is obligatory to better understand its potential for efficacy, safety, and to define its role in the management of rheumatic disease pain (Fitzcharles, 2016). It is also essential that future research studies must astutely examine dosages and concentration as some research suggests these are pivotal factors needed to determine efficacy and safety (Zuardi, 2008). Without a doubt, future rigorous double-blind randomized placebo control trials aimed at determining the short- and long-term efficacy and safety of CBD oil are desperately needed as patients are using CBD products despite the lack of evidence.

Education Recommendations

There are more than one hundred known cannabinoids derived from the cannabis plant but the most commonly known are THC and CBD. Due to popularity, the sale and use of these products has grown significantly in recent years. Concerningly, this rapid increase has left many patients and providers unclear about the ingredients in the numerous different cannabinoid products available both over the counter and by prescription. As cannabinoid compounds vary in their active ingredients and systemic effects, clear understanding of the commonly used

cannabinoids is crucial for patients and providers. Therefore, education must be intended to inform patients and providers about the different cannabinoid compounds sold, their effects, and their respective the terminology. Furthermore, this education is essential for healthcare providers in order to have a strong familiarity with each product and accurately provide patients with information about cannabinoids when approached.

The regulation of cannabinoid products varies significantly at the federal and state level, leading to ongoing confusion related to CBD oil legality. Furthermore, recent changes regarding the growth of hemp plants for commercial cultivation leaves many unclear on whether CBD oil from hemp is legal to be sold and consumed. Thus, dissemination of the current regulations of these products should be done in order to provide patients and providers with clarity regarding the legality of CBD oil in their state.

Oftentimes providers are questioned by patients about CBD oil use for pain relief. However, because little evidence is known about the therapeutic benefit of CBD, doubt in its effectiveness is presented. This cannabinoid skepticism, while fitting given the lack of evidence, must be confronted in order to develop a greater understanding of the therapeutic role of CBD oil (Sarzi-Puttini et al., 2019). It is important that providers to maintain mental flexibility and openness to seeking safer and more effective alternatives for rheumatic disease pain as conventional therapies are failing to provide adequate relief (Sarzi-Puttini et al., 2019). To support this, providers must be educated on the current body of evidence, its recommendations, and advocate for further rigorous research studies to be conducted in order to better guide patients.

Ultimately, despite the lack of high-quality evidence, patients continue to use CBD oil for rheumatic disease pain relief. With an open-minded approach, providers must use caution when

recommending CBD oil to patients until additional studies have been conducted. To best guide patients understanding, informed providers should share the findings from the current body of evidence regarding the efficacy and safety of these products with patients. In addition, a collaborative approach should be maintained if patients choose to use CBD oil in order to maintain patient trust and safeguard quality of life.

Recommendations for Policy

Presently, no guidelines have been endorsed by a national guideline clearinghouse or rheumatology association recommending CBD oil for the management of rheumatic disease pain (Sarzi-Puttini et al., 2019). Furthermore, because of the lack of evidence some rheumatology associations recommend against using cannabinoids for the treatment of pain associated with rheumatological conditions including osteoarthritis (Sarzi-Puttini et al., 2019). At present time, recommendations for policy changes cannot be made due to the lack of high-quality evidence supporting CBD oil's efficacy and safety for the treatment of rheumatic disease pain. Any recommendations for future policy changes must be made based on rigorous evidence-based studies as anecdotal testimony and expert advice is not enough to protect patients from any unknown harmful effects.

Conclusion

The paucity of supporting evidence that exists leaves many questions unanswered regarding CBD oil's place in the clinical management of rheumatic disease pain. It is not a secret that the current analgesic drugs are suboptimal at best for the management of rheumatic disease pain (Sarzi-Puttini et al., 2019). Furthermore, some have even led to catastrophic health related effects such as addiction and even death and have done little to improve the quality of life for patients with rheumatic disease (Sarzi-Puttini et al., 2019). Taking this into consideration, safer

alternative therapies for pain management are desperately needed as rheumatic diseases are lifelong and require clinically proven safe analgesic drugs to safeguard quality of life (Sarzi-Puttini et al., 2019). Thus, it is imperative to maintain openness to potentially safer alternatives to rheumatic disease pain such as CBD oil. Now more than ever patients are seeking alternative therapies for rheumatic disease pain, the necessity for rigorous clinical studies designed to determine whether CBD oil is an effective and safe alternative has never been more imperative. In conclusion, providers alike should take a careful approach regarding the use of CBD oil for patients with rheumatic disease pain by limiting advocacy to those who have exhausted all other pain relief options until additional high-quality evidence is readily available.

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Appendix

Table 1

Database Search Description

Database	Restrictions Added to Search	Dates Included in Database	General Subjects Covered by Database
CINAHL Plus with Full Text	Full Text; English Language; Peer Reviewed; Abstract Available; Adult; Human	2010-2019	Provides full text access to 29 core nursing journals and 17 allied health disciplines. It covers topics including nursing, biomedicine, health sciences librarianship, alternative/complementary medicine, consumer health.
PubMed	Full Text; English Language; Abstract Available; Humans	2009-2019	PubMed includes the fields of biomedicine and health, life sciences, behavioral sciences, chemical sciences, and bioengineering. MEDLINE is the primary component of PubMed.
CENTRAL	Full Text; English Language; Peer Reviewed; Research Article; Abstract available; Humans	2006-2019	This database contains full text articles and protocols focusing on the effects of healthcare. It contains evidence-based reports of randomized controlled trials.
PsycINFO	Full Text; English Language; Peer Reviewed; Systematic review; Literature review; Humans	2008-2019	Provides access to international literature in psychology and related disciplines. It provides high quality literature regarding psychiatry, education, business, medicine, nursing, pharmacology, law, linguistics, and social work.
ProQuest Central	Full Text; English Language; Peer Reviewed; Evidence-based Healthcare; Scholarly Journals	2010-2019	Provides access to full text articles from scholarly journals in areas such as health and medical, nursing and allied health, science and technology or social sciences.

Table 2

Data Abstraction Process: Hits per Database

Date of Search	Key Words	CINAHL Plus with Full Text	PubMed	CENTRAL	PsycINFO	ProQuest Central
10/11/19	"Cannabidiol"	153	825	502	235	860
10/11/19	"CBD oil"	0	21	41	**1**	11
10/17/19	"Cannabidiol" AND "joint Pain"	0	**3**	**1**	25	81
10/17/19	"Cannabidiol" AND "Joint pain" AND "Anti-inflammatory"	0	**2**	0	**1**	**3**
10/18/19	"Cannabidiol" AND "Arthritis"	**2**	**3**	**4**	**1**	73
10/18/19	"Cannabidiol" AND "Rheumatic disease"	0	**3**	**2**	0	66
10/22/19	"Cannabidiol" AND "Rheumatic disease" AND "Anti-inflammatory"	0	**2**	**1**	0	23
10/24/19	"Cannabidiol" AND "Rheumatic disease" AND "Inflammation"	0	**1**	0	0	48
10/24/19	"Cannabidiol" AND "Rheumatic disease" AND "Pain"	0	**4**	**2**	0	54
10/24/19	"Cannabidiol" AND "Rheumatic disease" AND "Pain Relief"	0	**1**	0	0	27
10/24/19	"Cannabidiol" AND "Rheumatic disease" AND "Analgesic"	0	**2**	**1**	0	11
10/24/19	"Cannabidiol" OR "CBD Oil" AND "Rheumatic disease" AND	64	**1**	15	**1**	14

	"Anti-inflammatory"					
10/25/19	"Cannabidiol" OR "CBD Oil" AND "Rheumatic disease" AND "Inflammation"	0	**2**	14	0	14
10/25/19	"Cannabidiol" OR "CBD Oil" AND "Rheumatic disease" AND "Pain"	17	**3**	16	**1**	76
10/25/19	"Cannabidiol" OR "CBD Oil" AND "Rheumatic disease" AND "Pain relief"	14	**1**	14	0	75
10/25/19	"Cannabidiol" OR "CBD Oil" AND "Rheumatic disease" AND "Analgesic"	14	**2**	15	0	760
10/25/19	"Cannabidiol" OR "CBD Oil" AND "Rheumatic disease" AND "Treatment efficacy"	0	**1**	16	**1**	44

***BOLD** = articles reviewed for match with systematic review inclusion criteria

Table 3

Characteristics of Literature Included and Excluded

Reference	Included / Excluded	Rationale
Amin, M. R., & Ali, D. W. (2019). Pharmacology of medical cannabis. *Advances in Experimental Medicine and Biology, 1162*, 151-165. https://doi.org/10.1007/978-3-030-21737-28	Excluded	Reviews the use of medical cannabis as a medicinal agent in the treatment of pain and inflammation in epilepsy and neurodegenerative diseases.
Ark, E. J. (2016). Cannabis Therapy in Patients with Rheumatoid Disease. *International Student Journal of Nurse Anesthesia, 15*(2), 92–101.	Included	Literature review of Level II and Level III studies examining cannabis or cannabidiol use in rheumatoid arthritis.
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. *Journal of Headache & Pain, 19*(1), 1. https://doi-org/10.1186/s10194-018-0862-2	Excluded	Studies the use of medical cannabis for patients with headache, arthritis, and chronic pain.
Blake, D. R., Robson, P., Ho, M., Jubb, R.W., & McCabe, C.S. (2006). Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology, 45*(1), 50–52. https://doi.org/10.1093/rheumatology/kei183	Included	Randomized control trial assessing the efficacy of cannabis-based medicine for the treatment of pain due to rheumatoid arthritis.
Booz, G. (2011). Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress. *Free Radical Biology and Medicine, 51*(5), 1054–1061. https://doi.org/10.1016/j.freeradbiomed.2011.01.007	Included	Literature review of the utility of non-psychotropic cannabidiol in reducing oxidative stress and inflammation in diseases such as rheumatoid arthritis and neuropathic pain.

Reference	Included / Excluded	Rationale
Bruni, N., Della-Pepa, C., Oliaro-Bosso, S., Pessione, E., Gastaldi, D., & Dosio, F. (2018). Cannabinoid delivery systems for pain and inflammation treatment. *Molecules: A Journal of Synthetic Chemistry and Natural Product Chemistry, 23*(10). https://doi.org/10.3390/molecules23102478	Included	Explores the most current clinical trials in the cannabinoid delivery field, focusing on pain and inflammation treatment.
Brunt, T. M., Van Genugten, M., Höner-Snoeken, K., Van, D. V., & Niesink, R. J. M. (2014). Therapeutic satisfaction and subjective effects of different strains of pharmaceutical-grade cannabis. *Journal of Clinical Psychopharmacology, 34*(3), 344-349. https://doi.org/10.1097/JCP.0000000000000129	Excluded	Measures the therapeutic effects of pharmaceutical-grade cannabis.
Crippa, J. A. S., Zuardi, A. W., & Hallak, J. E. C. (2010). Therapeutical use of the cannabinoids in psychiatry. *Brazilian Journal of Psychiatry 32*, S56-S65.	Excluded	Reviews cannabinoids use in psychiatry.
Farooqui, M. T., Khan, M. A., Cholankeril, G., Khan, Z., Abdul, M. K. M., Li, A. A., Shah, N., Wu, L., Haq, K., Solanki, S., Kim, D., & Ahmed, A. (2019). Marijuana is not associated with progression of hepatic fibrosis in liver disease: a systematic review and meta-analysis. *European Journal of Gastroenterology & Hepatology, 31*(2), 149–156. https://doi.org/10.1097/MEG.0000000000001263	Excluded	Study examines Marijuana and hepatic disease.
Fitzcharles, M., Baerwald, C., Ablin, J., & Häuser, W. (2016). Efficacy, tolerability and safety of cannabinoids in chronic pain associated with rheumatic diseases (fibromyalgia syndrome, back pain, osteoarthritis, rheumatoid arthritis). *The Pain, 30*(1), 47–61. https://doi.org/10.1007/s00482-015-0084-3	Included	A systematic review of RCTs focused on the treatment of FMS, OA, and RA with herbal cannabis or pharmaceutical cannabinoid products.

Reference	Included / Excluded	Rationale
Hendricks, O., Andersen, T.E., Christiansen, A.A., Primdahl, J., Hauge, E.M., Ellingsen T, Horsted, T. I., Bachmann, A. G., Loft, A.G., Bojesen, A. B., Ostergaard, M., Hetland, M. L., Krogh, N. S., Roessler, K. K., & Petersen K. H. (2019). Efficacy and safety of cannabidiol followed by an open label add-on of tetrahydrocannabinol for the treatment of chronic pain in patients with rheumatoid arthritis or ankylosing spondylitis: protocol for a multicentre, randomised, placebo-controlled study. *British Medical Journal Open, 9*(6). https://doi-org/10.1136/bmjopen-2018-028197	Excluded	Evaluates the efficacy and safety of medical cannabis in the treatment of pain in patients with RA and AS with low disease activity.
Hunter, D., Oldfield, G., Tich, N., & Messenheimer, J. (2018). Synthetic transdermal cannabidiol for the treatment of knee pain due to osteoarthritis. *Osteoarthritis and Cartilage, 26*, S26. https://doi.org/10.1016/j.joca.2018.02.067	Included	Evaluates the reduction of pain and inflammation in osteoarthritis knee pain with CBD oil use.
Jehad, A. B., Korang, S. K., Feinberg, J., Maagard, M., Gluud, C., Mathiesen, O., & Jakobsen, J. C. (2019). Cannabinoids versus placebo or no intervention for pain: Protocol for a systematic review with meta-analysis and trial sequential analysis. *British Medical Journal Open, 9(*10), e031574. http://dx.doi.org/10.1136/bmjopen-2019-031574	Excluded	Proposes a protocol for systematic review of cannabinoid studies.
Katz-Talmor, D., Katz, I., Porat-Katz, B., & Shoenfeld, Y. (2018). Cannabinoids for the treatment of rheumatic diseases — where do we stand? Nature Reviews. *Rheumatology, 14*(8), 488-498. https://doi.org/10.1038/s41584-018-0025-5	Excluded	Review Medial Cannabis treatment for Rheumatic disease.

Reference	Included / Excluded	Rationale
Kraft, B. (2012). Is there any clinically relevant cannabinoid-induced analgesia? *Pharmacology, 89*(5-6), 237-46. https://doi.org/10.1159/000337376	Included	Review of the analgesic properties of cannabinoids on pain.
McPartland, J. M., Guy, G. W., & Marzo, V. D. (2014). Care and feeding of the endocannabinoid system: A systematic review of potential clinical interventions that upregulate the endocannabinoid system. *Public Library of Science One, 9*(3). http://dx.doi.org/10.1371/journal.pone.008956	Excluded	A systematic review of clinical interventions that increase the endocannabinoid system.
Miller, R. J., & Miller, R. E. (2017). Is cannabis an effective treatment for joint pain? *Clinical and Experimental Rheumatology, 107*(5), 59-67.	Included	Expert opinion on preclinical and human data regarding the efficacy of cannabis in the treatment of joint pain.
Naftali, T., Mechoulam, R., Gabay, G., Stein, A., Bronshtein, M., Mari, A., & Konikoff, F.M. (2013). Cannabidiol treatment does not affect active Crohn's disease. *Gastroenterology, 144*(5), S180.	Excluded	Examines CBD use in Crohn's disease.
Pruskowski, J. (2019). Analgesic Effects of Pharmaceutical-Grade Cannabis in Chronic Pain Patients with Fibromyalgia. *Journal of Pain and Symptom Management, 58*(3), 555–556. https://doi.org/10.1016/j.jpainsymman.2019.07.001	Excluded	Reviews effects of pharmaceutical grade cannabis.
Reznik, S., Gardner, E., & Ashby, C. (2016). Cannabidiol: A potential treatment for post Ebola syndrome? *International Journal of Infectious Diseases, 52*, 74–76. https://doi.org/10.1016/j.ijid.2016.09.020	Excluded	Examines CBD use in post Ebola treatment.
Zuardi, A. W. (2008). Cannabidiol: From an inactive cannabinoid to a drug with wide spectrum of action. *Brazilian Journal of Psychiatry, 30*(3), 271-280.	Included	Describes the historical development of research and current evidence on cannabidiol.

Reference	Included / Excluded	Rationale
http://dx.doi.org/10.1590/S1516-44462008000300015		

Table 4

Literature Review Table of All Studies Included

Citation	Study Purpose	Pop (N) / Sample Size (n) / Setting(s)	Design/Level of Evidence (Melnyk & Fineout-Overholt, 2015)	Variables / Instruments	Findings	Implications
Ark, 2016	Literature review of Level II and Level III studies examining cannabis or cannabidiol use in rheumatoid arthritis.	N/A	Level III, Review of RCT and Non-RCT studies.	N/A	-Limited evidence supports cannabidiol for treatment of pain caused by inflammatory pathways, autoimmune processes, or neurodegeneration.	More human studies are needed to determine efficacy in the treatment of rheumatoid disease, neuropathic and autoimmune pain.
Blake et al., 2006	Assesses the efficacy of defined dosages of cannabis-based medicine in rheumatoid arthritis pain.	n=58	Level II, RCT	Primary efficacy variable was pain with movement measured by a 0–10 numerical rating scale (NRS) each morning. Secondary	-Cannabis-based medicine produced significant improvements in NRS pain scores, sleep quality and DAS28 scores.	Larger scale research is indicated.

Citation	Study Purpose	Pop (N) / Sample Size (n) / Setting(s)	Design/Level of Evidence (Melnyk & Fineout-Overholt, 2015)	Variables / Instruments	Findings	Implications
				outcomes included NRS measures of pain at rest, sleep quality and morning stiffness. The Short-Form McGill Pain Questionnaire (SF-MPQ) and the 28-joint disease activity score (DAS28) were also used.		
Booz, 2011	Reviews the utility of non-psychotropic cannabidiol in reducing oxidative stress and inflammation in diseases such as rheumatoid arthritis and neuropathic pain.	N/A	Level VII, Expert opinion with supportive qualitative evidence	N/A	-CBD attenuates inflammation through intracellular signaling events. -CBD also has modest antioxidant properties.	The therapeutic utility of CBD is a relatively new area of investigation. Additional studies regarding the effects of CBD on inflammation and oxidative stress are needed.
Bruni et al., 2018	Review of current clinical trials regarding	N/A	Level III,	N/A	-Insufficient amounts of rigorous clinical studies have been	Additional evaluation of Cannabidiol is

Citation	Study Purpose	Pop (N) / Sample Size (n) / Setting(s)	Design/Level of Evidence (Melnyk & Fineout-Overholt, 2015)	Variables / Instruments	Findings	Implications
	cannabinoids and their effects on pain and inflammation.		Review of RCTs and Non-RCTs		conducted regarding cannabidiol and pain. -Cannabinoids have been associated with an increased risk of short-term side effects -Clinical evidence to date is confounded by several factors, including mixed patient populations, different cannabinoid preparations, various formulations, and wide dosing ranges.	required to determine quality, safety and efficacy data.
Fitzcharles et al., 2016	A systematic review of four RCTs regarding treatment of FMS, OA, and RA with herbal cannabis or pharmaceutical cannabinoid products.	4 RCTs	Level I, Systematic Review of RCTs	N/A	-There is insufficient evidence to recommend any cannabinoid preparations for symptom management of chronic pain associated with rheumatic diseases.	Additional control studies are need.
Hunter et al., 2018	Evaluates the effects of CBD oil on pain and	n=321	Level II, RCT	The primary efficacy variable was a change from baseline	-After 12 weeks of blinded treatment, baseline pain NRS was	Cannabidiol has shown some effect in

Citation	Study Purpose	Pop (N) / Sample Size (n) / Setting(s)	Design/Level of Evidence (Melnyk & Fineout-Overholt, 2015)	Variables / Instruments	Findings	Implications
	inflammation in osteoarthritis the knee.			in the pain numeric rating. A key secondary endpoint an average weekly improvement in worst pain score of > 30% (responder analysis) and decrease in WOMAC physical function at least 20% at last observation.	not statistically different than placebo. -Notably, men had significantly decreased worst pain score at 250mg /day than those who received placebo.	reducing pain and inflammation but additional well controlled studies evaluating CBD for osteoarthritis (OA) in humans are needed.
Kraft, 2012	Explores the clinical data in cannabinoid use for analgesia.	N/A	Level III, Review of RCT and Non-RCTs	N/A	-Clinical data from human trials is unclear regarding the analgesic effects of cannabinoids on pain. -Small sample sizes and short trial duration were a few variables discovered that impacted study findings.	Additional well-designed human control studies are needed to confirm the analgesic effects of cannabinoids on pain.

Citation	Study Purpose	Pop (N) / Sample Size (n) / Setting(s)	Design/Level of Evidence (Melnyk & Fineout-Overholt, 2015)	Variables / Instruments	Findings	Implications
					-Cannabinoids analgesia properties are moderate to mild and insufficient for the treatment of severe pain but may be useful as adjuvant therapies.	
Miller & Miller, 2017	Historical review of cannabis and expert opinion on current studies assessing the efficacy of cannabinoids in the treatment of joint pain.	N/A	Level VII, Expert opinion	N/A	-Rigorous clinical evidence is not available to support its use in treating joint pain. -Numerous surveys and qualitative suggests patients indicate benefit from cannabinoid use. -It is unclear if active cannabinoids such as THC are essential for producing analgesic effects or if non-psychotropic substances such as CBD are also helpful.	The effects of herbal cannabinoids in humans with joint pain needs to be accurately assessed.

Citation	Study Purpose	Pop (N) / Sample Size (n) / Setting(s)	Design/Level of Evidence (Melnyk & Fineout-Overholt, 2015)	Variables / Instruments	Findings	Implications
Zuardi, 2008	Reviews the historical development of research and current evidence on cannabidiol use in numerous diseases including rheumatoid arthritis, other inflammatory diseases.	N/A	Level VI, Review of case studies, RCTs, and Non-RCTs	N/A	-CBD has a wide range of pharmacological effects for many conditions including rheumatoid arthritis. -Study results of CBD efficacy indicate the dose is a pivotal factor in future research.	Additional randomized clinical trials are needed to confirm therapeutic effects of CBD oil and its dosage.