Cannabinoid Therapy in Conjunction with Opioids For Chronic Non-Cancer Pain Management

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Chronic non-cancer pain is a significant and debilitating challenge for patients. It is also a challenge for healthcare providers to develop medication treatment plans that provide effective pain relief. Use of opioids for chronic non-cancer pain has more than quadrupled since 1990 despite limited evidence of effectiveness and rising incidence of adverse events. Increased prescribing of opioids has led to a public health crisis due to diversion of substances, addiction, and overdose (Volkow et al., 2018). Understanding the impact of cannabinoid (CBD) therapy used in conjunction with opioids for management of chronic non-cancer pain can provide insight into alternative pain management strategies that provide better analgesia and fewer side effects compared to opioid therapy alone (NASEM, 2017). This review of the evidence seeks to answer the PICO question "*In adult patients with chronic non-cancer pain does the use of cannabinoids in conjunction with opioids compared to opioids alone decrease patients' perceived or experienced level of pain?"*

The common definition of chronic non-cancer pain is pain that persists three months beyond the expected healing period and is not associated with oncological disease (Cohen et al., 2021). This review includes several types of chronic non-cancer pain within subcategories of neuropathic, chronic disease-based, and other heterogeneous classifications. Cannabinoids are available in a wide variety of forms and dosages. All forms of CBD mentioned in this paper including dronabinol and inhaled cannabis are referred to as CBD. Differentiating effects of individual forms of CBD is beyond the scope of this review.

Opioids have historically been a mainstay of chronic pain treatment but are associated with a high prevalence of adverse effects, including overdose and death (NIH, 2014). Medical CBD use in the United States first occurred following its legalization in California in 1996, and it continues to be used medically with analgesics and antiemetics as adjunctive therapy and as monotherapy (State, 2023). Thirty-seven US States and Washington, D.C. now allow the use of medical CBD, and more than five million Americans are registered medical CBD users (Skillman et al., 2022). According to recent statistics, approximately 21% of American adults (nearly 52 million) experience chronic pain (Rikard et al., 2023). With an increasing number of states legalizing CBD and decreasing stigma surrounding use, understanding the current research about the effectiveness of CBD for chronic non-cancer pain is timely and important.

Search Methods

Studies were obtained by searching electronic databases and scanning reference lists of articles used in this review and articles used for topic research. The search was applied to Google Scholar, PubMed, Cochrane Library, and CINAHL databases. The searches were run from October 4- October 14, 2023. Date filters were applied from publication year 2018 to present. The following free-text search terms were used: cannabinoid*, CBD, Cannabidiol, Dronabinol, cannabis, marijuana; "chronic pain" [tiab:~3], "neuropathic pain", "persistent pain"; and "analgesics, opioid*", opiate*, and narcotic*. PubMed was searched using the following MeSH terms: "chronic pain", cannabinoids, and "analgesics, opioid". This yielded 436 articles to be reviewed. Articles were then individually reviewed and narrowed by the following criteria: studies with adult participants (18+) with chronic pain and inclusion of both cannabinoids and opioids in the study. Articles were excluded from the review for the following reasons: being outside of the specified timeframe, focus on acute pain, focus on cancer-related pain, or if full text was unavailable. Using the designated search parameters and criteria, this search yielded twenty-six articles.

Titles and abstracts of the selected articles were screened for relevance and adherence to the inclusion/exclusion criteria. Based on the articles reviewed the researchers refined the PICO question to be: In adult patients with chronic non-cancer pain (P) does the use of cannabinoids in conjunction with opioids (I) compared to opioids alone (C) decrease patients' perceived or experienced level of pain (O)? The researchers further narrowed the search results to 12 articles by adding the inclusion criteria of requiring studies to have a comparison of opioids alone to opioids with the addition of cannabinoids.

All articles were split between researchers and reviewed using the evidence tables. After author discussion, articles were then narrowed to the required eight articles using the most robust studies, the strongest studies as agreed upon per the Johns Hopkins Evidence Level and Quality Guide (2017), and by the class requirements for the paper (one or two systematic review/meta-analysis, two to three RCT, and clinical practice guidelines).

Literature Review

This review was narrowed to eight studies to answer the PICO question. Most of the reviewed studies assessed several outcomes involving CBD, opioids, and pain. However, this review was limited to patients' perceived or experienced levels of pain and the comparison of CBD with opioids to opioids alone. The selected studies include one combined systematic review and meta-analysis (92 studies), one systematic review of observational studies (7,222 participants), a set of clinical practice guidelines based on 19 systematic reviews, three randomized double-blind placebo-controlled studies (90 total participants), a prospective cohort study on patient perceptions (1,145 participants), and one qualitative study. Regulatory, supply, and funding barriers have limited CBD research, particularly randomized controlled trials (RCT), limiting the availability of studies to review (NASEM, 2017).

Systematic Reviews and Meta-analysis

A systematic review and meta-analysis performed by Nielsen et al. (2022) includes 92 studies about the effect of CBD on pain. The focus for this review was a group of five included studies about chronic non- cancer pain. The literature search was performed according to Preferred Reporting Guidelines for Systemic Reviews and Meta-Analyses (PRISMA) with no date limitations, using search terms related to types of opioids and outcomes of interest. Data were extracted by individual reviews performed independently by two authors. The review of these studies revealed conflicting findings. Two studies showed improved analgesic effect when CBD was combined with opioid treatment: pain score reduction from 34.8 (95% CI: 29.4, 40.1) to 24.1 (95% CI: 18.8, 29.4), and mean pain relief score of 31.3 in placebo, 39.7 and 41.7 with CBD (Abrams et al., 2011; Narang et al., 2008). Three studies showed no difference in analgesic effect, having similar mean pain scores with placebo (2.05, [0.21]), (2.917, [2.205]), (2.94, [2.10]) and CBD (2.09 [0.21]), 2.53 [1.702]), (2.05 [2.65]), respectively (Abrams et al., 2020; De Vries et al., 2016; De Vries et al., 2017). While four out of the five studies were randomized, double-blind, and placebo-controlled, they all had small sample sizes and short observational periods thus limiting the overall strength of the studies.

A systematic review was completed by Okusanya et al. (2020). The purpose was to examine the existing literature to assess if medical CBD used in combination with opioids to treat non-cancer pain would reduce opioid dosage. Following a comprehensive literature search of several databases following PRISMA guidelines, a risk of bias assessment, and a quality assessment, nine studies were included in the review. Cochrane's ROBINS-1 tool, and the AXIS tool were used to assess the risk of bias. Articles were excluded that did not match the specific aim of the review including, for example, articles that did not include CBD as an opioid substitute. The studies were grouped and reviewed by CBD use and opioid reduction and CBD use and opioid substitution. The authors reported that the review of studies showed a 64-75% reduction in opioid dosage when used in combination with CBD, and 32-59.3% of patients used CBD for opioid substitution. They reported that the review indicated a likelihood of reducing opioid dosage when combined with CBD. A strength of the review is that the findings, although limited, align with findings from other studies. The limited conclusions were due to the lack of empirical studies available for the review. Studies included were observational and had various biases and limitations including missing data, inadequate outcome measurement, and unclear study objectives. This was a rigorous systematic review that demonstrated a lack of high-level evidence, and the authors reported a likelihood, but not a causal inference, between CBD use and opioid reduction.

Clinical Practice Guidelines

Bell et al. (2023) conducted a systematic review investigating CBD medications for treating chronic pain and co-morbid conditions. Clinical practice guidelines (CPG) were then developed from the available evidence and were aimed to help clinicians and patients understand the risks, benefits, and appropriate therapeutic use of CBD. An electronic search was conducted of peer-reviewed articles to determine study eligibility. Two independent reviewers identified abstracts using PRISMA conventions to include studies that focused on CBD derived from the cannabis plant rather than synthetic or pharmaceutical CBD. A standardized Data Extraction Form was created to analyze the body of evidence from the selected 165 articles. Evidence for CBD in managing chronic pain and co-occurring conditions was measured by indication, dosing, efficacy, tolerability, safety, drug interactions, adverse events, negative effects, and contraindications. Forty-seven studies related to pain management of mixed study design were reviewed, with most reporting at least moderate benefit of CBD to treat chronic pain. Considerations for this recommendation included the assessment of risks from non-serious adverse events (dizziness, dry mouth, nausea, diarrhea) and the benefit of CBD compared to adverse events associated with opioid monotherapy. Identified limitations include the amount of available evidence comparing CBD to opioids or another typical pain treatment, the small number of participants, the short treatment duration, and the risk of bias with subjective measurements of pain. The CPG developed by Bell et al. (2023) guides clinicians treating patients with chronic pain and co-occurring conditions and provides a strong recommendation for CBD to be used as a monotherapy, replacement therapy, or adjunct treatment in people living with chronic central or peripheral neuropathic pain to improve pain outcomes.

Randomized Controlled Trials (RCT)

Narang et al. (2008) performed a landmark study about the effect of CBD in addition to existing opioid treatment for chronic non-cancer pain management. The study was a double-blind, placebo-controlled RCT inclusive of 30 patients who reported various types of chronic non-cancer pain and were taking stable doses of opioids for over six months. Patients were randomly assigned to three groups: opioid with placebo, opioid with 10 mg dronabinol, and opioid with 20 mg dronabinol. Total pain relief after eight hours was significantly greater in the intervention groups compared to the opioid with placebo group (20 mg vs placebo at $P < .01$, 10 mg vs placebo at $P < .05$). There was no significant difference between the two intervention groups. While this study has a strong design, its overall strength is limited by the small sample size.

Abrams et al. (2020) conducted a pilot double-blind RCT on the effects of inhaled cannabis in addition to a baseline opioid regimen for sickle cell disease chronic pain. There was a total of 23 adult participants of all ages, both male and female, who had sickle cell disease and were on an opioid regimen. The two groups used either inhaled cannabis or inhaled placebo with their baseline opioid regimen. The intervention regimen was a 1:1 ratio of 9-tetrahydrocannabinol to cannabidiol and was given three times a day over five days. The mean difference between the active and placebo groups were −5.3 (8.1) on day 1 (P = .51), −10.9 (7.0) on day 2 (P = .12), −16.5 (9.2) on day 3 (P = .07), −8.9 (6.7) on day 4 (P = .19), and −8.2 (8.1) on day 5 (P = .32), thus showing there was no statistically significant difference in pain control between the CBD and the placebo. Strengths of the study are the research design and the authors' reported risk of bias. Limitations include a small sample size and short-term pain assessments.

Campbell et al. (2023) designed a within-subject, double-blind, placebo-controlled RCT to evaluate both independent and combined effects of the CBD dronabinol and the opioid hydromorphone on experimentally-induced acute and chronic pain models. The study included 37 participants (24 female, 13 male) diagnosed with knee osteoarthritis who had not used opioids within the previous month. After baseline quantitative sensory testing (QST), self-report measures, and physical and cognitive function testing were completed, participants received one of the following FDA-approved combinations of placebo-placebo, hydromorphone (4 mg)-placebo, dronabinol (10 mg)-placebo and

hydromorphone (4 mg)-dronabinol (10 mg) at the same time. Acute pain was induced by sensory pain measures. Chronic pain was modeled by the application of 10% topical capsaicin cream in combination with thermal stimuli. Self-reported clinical pain severity, drug effects, and abuse potential data were collected using a different visual analog scale for each. Relative to chronic pain outcomes, there was a significant effect of heat pain threshold in the hydromorphone and dronabinol combination, but not placebo or hydromorphone. Hydromorphone and dronabinol were associated with substantial analgesia on QST outcomes. However, the analgesia with the combination was not different from hydromorphone alone. Strengths of the study include the experimental study design and multiple measures to assess pain. Limitations of the study include the small sample size, short-term pain assessment, and limited age group.

Qualitative and Cohort Studies

Lucas et al. (2021) reported their findings from a Canadian multi-site prospective cohort study to assess the impact of medical CBD use on quality of life and prescription drug use, including opioids, among medical CBD users. This was a pretest and post-test repeated measures design that used several tools completed by medical staff with the patient. Data was gathered at baseline, 1 month, 3 months, and 6 months. Findings include that opioid use declined at 6 months with an OR of 0.07 relative to baseline (95% CI, 0.04-0.12; P = <0.001). Strengths of the study include that it was a longitudinal, multi-site, prospective study with a relatively large sample size and that data about prescription drug use was entered by medical staff rather than patient self-reporting. Limitations include that patients were compensated with credits to the dispensary which could affect retention bias; it was a convenience sample; there was self-report of cannabis use so there was a potential for recall bias; and participants could have been using other sources of cannabis in addition to the provided supply.

A qualitative study that examined the perceived effectiveness of CBD was reported by McMahon et al. (2023). The study investigated the short- and longer-term effects of CBD for chronic pain in 51 participants who were initiating CBD use. Once enrolled, the participants completed a baseline survey, 3-4 weeks of Ecological Momentary Assessments (EMA), an open-ended phone interview at the end of the EMA period, and a 3-month follow-up survey. In the phone interview after the EMA survey, participants were asked the question “Overall, how effective do you think the medical cannabis treatment is for your condition?” Participants could share their insight into the effectiveness, observed benefits, and side effects but were not provided with follow-up prompts to address these topics. Two analysts individually coded the interview data using the RaDaR (Rigorous and Accelerated Data Reduction) technique and identified themes. Results reported that more than half of the participants found CBD to be effective for the management of chronic pain, and participants reported improved physical and mental functioning and reduction in the use of pain and psychiatric medications. The strengths of this study are that the findings align with previous studies and researchers used the established RaDaR method. Limitations include the study design, small sample size, short study length, lack of diversity of participants, and lack of controlled follow-up questions.

Synthesis and Critical Analysis

Major findings of this review include that most of the studies demonstrate evidence to support the PICO question either directly or indirectly. Supportive studies showed a reduction in pain, a reduction in opioid use which implies a reduction in pain, or both a reduction in pain and reduction in opioid use, after the addition of CBD. The reviewed studies are good to high quality and include a variety of research designs from five different levels of evidence. Five studies supported the PICO question. Two studies were equivocal. One study refuted the PICO question.

Findings from the studies that support the PICO question describe improved analgesia with the addition of CBD to opioid use. Supportive studies also reported a decrease in opioid dosage when CBD was added. These five supportive studies are of various designs and sizes. Bell et al. (2023) reviewed 19 studies and found sufficient evidence to support the incorporation of CBD use into clinical practice

guidelines for chronic pain as adjuvant therapy to decrease pain and prevent high doses of opioids. The prospective cohort study by Lucas et al. (2021) found a decrease in opioid use when CBD was added. A systematic review of observational studies (Okusanya et al., 2020) concluded that there was a likelihood of reducing opioid dosage when CBD was added. In a qualitative study by McMahon et al. (2023) more than half the participants found CBD to be effective for pain management, and there was a reduction in opioid use. Finally, findings from the RCT by Narang et al. (2008) demonstrated greater pain relief with the addition of CBD to opioids compared to placebo.

Other findings in this review include two studies with equivocal support for the PICO question. Nielsen et al. (2022) systematically reviewed 92 studies, five of which included studies of non-cancer pain. The authors found that the pre-clinical and observational studies showed potential for improved pain control with the addition of CBD. However, the more robust RCT in this review did not support improved analgesia or opioid-sparing with the use of CBD. The other study with equivocal support for the PICO question was an RCT (Campbell et al., 2023) that found a significant analgesic effect when CBD was used with an opioid (hydromorphone) but not significantly different than hydromorphone used alone.

Findings from one study refuted the PICO question. An RCT with a crossover design by Abrams et al. (2020) studied 23 patients on opioids for chronic sickle cell pain. They were admitted to a research center and given either inhaled CBD or placebo over five days. No statistically significant difference was found in the level of pain between CBD and placebo.

Discussion

This review of evidence supports the PICO question "In adult patients with chronic non-cancer pain does the use of cannabinoids in conjunction with opioids compared to opioids alone decrease patients' perceived or experienced level of pain?" Support for this clinical question was found in studies and reviews from five different levels of evidence. Some of the systematic reviews included observational studies and pre-clinical studies, in part (as one study noted) due to the paucity of research. There were small sample sizes and studies with potential bias including convenience sampling, subjective reporting of pain levels, and payment for participation. The RCTs were all small, short-term, and laboratory-based, lacking generalizability to the real world.

The evidence suggests that adding CBD to opioid therapy could be a beneficial management strategy for those with chronic pain. Incorporating this evidence into practice has the potential to improve pain management for the nearly 52 million Americans afflicted with chronic pain disorders. More widespread use could be prompted by additional research about dosing, effects of individual types of CBD, and use in specific subcategories of chronic pain.

Conclusion

This review of available evidence demonstrates that in patients with chronic non-cancer pain, the use of CBD in conjunction with opioids provides an improved benefit of pain relief when compared to opioids alone, an affirmation of the PICO question. Using CBD as monotherapy or adjunctive to other analgesic medications has the potential to improve analgesia and decrease opioid usage. In states where medical CBD is legal, practitioners can use these studies and practice guidelines to consider the introduction of CBD to chronic non-cancer pain management.

Large studies with high-quality evidence for CBD use are lacking, in part due to restrictive federal regulations. Until December 2022, approval for phase-one clinical trials required researchers to show that cannabis has a medical use, and they couldn't show a medical use until clinical research was conducted, an acknowledged dilemma of CBD research (Zarrabi, Frediani, & Levy, 2020). The recent passage of the Medical Marijuana and Cannabidiol Research Expansion Act has made the antiquated processes for CBD research more streamlined (Skillman et al., 2022). However, high-quality research

takes time, and until there is more definitive research, practitioners are left to make treatment decisions about CBD without a sufficient body of evidence.

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