ISSN: 3066-716X
Research Article
Journal of Clinical and Biomedical Advances

The Use of Medical Cannabis for Pain Relief in Osteoarthritis: A Comparative Analysis with Traditional Painkillers

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Submitted: 11 June 2025 **Accepted:** 17 June 2025 **Published:** 22 June 2025

https://doi.org/10.63620/MKJCBA.2025.1042

Citation: *Mohammad, A., & Yousef, A. (2025). The Use of Medical Cannabis for Pain Relief in Osteoarthritis: A Comparative Analysis with Traditional Painkillers. J of Clin Bio Med Adv, 4(3), 01-06.*

Abstract

Objective: *To evaluate the efficacy and safety of medical cannabis as an alternative therapy for osteoarthritis (OA)-related pain compared to traditional painkillers.*

Design: *A comparative analysis of existing clinical and preclinical studies examining the analgesic effects of cannabinoids in OA. The review includes studies on CB1 and CB2 receptor interactions, patient-reported outcomes, and adverse effects.*

Results: *Medical cannabis demonstrates potential for pain relief in OA patients, particularly through modulation of CB1 and CB2 receptors. Some clinical studies report superior pain management and improved quality of life compared to NSAIDs and opioids. However, variability in effectiveness is observed due to differences in dosages, administration methods, and patient comorbidities. Long-term safety concerns, including cognitive side effects and dependency risks, remain unresolved.*

Conclusions: *Medical cannabis presents a promising alternative to conventional analgesics for OA pain, with potential benefits in reducing opioid dependency and side effects. However, large-scale randomized clinical trials are needed to establish standardized dosing, long-term safety, and cost-effectiveness before widespread clinical adoption.*

Keywords: Osteoarthritis, Medical Cannabis, Pain Management, Cannabinoid Receptors, Painkillers

Introduction

Chronic pain lasts over three months due to health issues like injuries or diseases. It includes musculoskeletal, neuropathic, and pain from conditions such as renal or hepatic diseases. Musculoskeletal pain often stems from cartilage damage due to trauma or conditions like osteoarthritis. In osteoarthritis, cartilage breakdown causes joint inflammation. Viscosupplementation helps some, but only about one-third see benefits. Nonsteroidal anti-inflammatory drugs can cause serious gastrointestinal issues. Medical cannabis is gaining popularity for pain management but has side effects. It is essential to evaluate costs and utility-adjusted life years for assessing osteoarthritis pain relief [1]. The use of medical cannabis for pain relief is growing, with 33% of patients using it for chronic pain and 66% for musculoskeletal pain, often caused by osteoarthritis and rheumatoid arthritis. Balancing cost and benefit are vital, but cannabis adop-

tion is outpacing evidence, with uncertain effectiveness and potential harms. While alternative medications also increase costs, the 2018 legislation permitted medical cannabis, necessitating lower costs than traditional treatments before its promotion [2].

Background and Rationale

Pain management is crucial for treating diseases and aiding recovery. Osteoarthritis (OA) affects 250 million people, causing pain, stiffness, and mobility challenges. Non-drug approaches include exercise, physical therapy, dietary changes, focusing on weight control and supplements like omega-3s to cut inflammation. The goal is to enhance life quality while managing economic and safety issues. Analgesics like NSAIDs, paracetamol, and opioids can help, though their effectiveness differs [3]. Analgesia is a critical public health issue, particularly in osteoarthritis (OA), where neuropathic pain and central sensitization frequently occur. Conventional treatments such as NSAIDs and opioids often fall short, with opioids reserved for severe cases. Tramadol combined with paracetamol proves effective primarily in advanced stages or symptomatic radiculopathy linked to lumbar OA. Although transdermal opioids can assist, their success varies with pain duration and individual responses, along with risks of sedation. Due to limited options, there is growing interest in cannabis treatments, but long-term efficacy in OA pain remains unclear. Medical cannabis's role in chronic pain management hinges on its safety profiles and symptom types. Prescribing often occurs alongside comorbidities and polypharmacy. Traditional methods are limited in safety, necessitating combination therapy for patients with multiple joint issues, which raises concerns about tolerance and misuse. Recommendations underscore strategies for progressive joint diseases, advocating for resistant pain management with opioids or anti-epileptic agents, despite uncertainties around the side effects and effectiveness of medical cannabis [4].

Scope and Objectives

This review highlights that osteoarthritis (OA) symptoms are primarily pain and stiffness, with pain relief as the main reason for cannabis use. Legal cannabinoid medicines tend to be expensive and low in potency to avert psychotropic effects. Assessing cannabis's efficacy may offer safer alternatives to traditional painkillers, reducing polypharmacy and benefiting National Health Services financially. The work compares studies on the pain-relieving effects of cannabinoids versus traditional analgesics in OA, focusing on effectiveness and sources of variability. The studies investigated neuropathic pain and cannabinoids, focusing on CB2 receptors' role in pain impulse generation, and how cannabis compounds can modulate osteoarthritis pain while emphasizing cannabinoid safety. They aimed to evaluate a new cannabinoid's efficacy in neuropathic pain relief and explore time and dose-dependent responses to various agonists. Research also examined CB2 receptor's analgesic role through fatty acid amide hydrolase inhibition, analyzed receptor expression in central nervous structures, assessed a morphine-cannabinoid preparation's impact on chronic arthritis, and whether increased spinal cord adrenoceptor expression enhances antihyperalgesic effects of a selective CB2 agonist [5].

Pathophysiology of Osteoarthritis

Osteoarthritis is a multifactorial disease with unclear pathogenesis, resulting from joint failure as a functional system. This failure includes disruptions in the synovial membrane, articular cartilage, and subchondral bone, alongside changes in the extracellular matrix and irregular mineral metabolism and innervation. These issues are linked to various physiological and molecular mechanisms that initiate and progress the disease, categorized as primary or secondary types. Recent studies suggest genetic and epigenetic factors are common risk contributors. Trauma, mechanical overload, joint instability, and metabolic disorders also play significant roles, as do chronic joint stress from work-related activities, aging, malformations, or intense exercise. Inflammatory responses involving neutrophils, macrophages, lymphocytes, and inflammatory cytokines, along with unstable antioxidant networks, further contribute to osteoarthritis development [6].

Definition and Prevalence

Osteoarthritis is the primary cause of disability in individuals over 75 in developed nations, with rising prevalence due to aging populations. This chronic joint disease causes cartilage and bone degeneration and is classified into primary (no clear cause) and secondary (associated with specific factors). Symptoms can limit functionality, but effective medications and therapies can alleviate pain and stiffness, particularly night pain linked to inflammation [7].

Mechanisms of Pain in OA

Chronic pain in OA severely limits lifestyles and quality of life for many, with about 40% of adults experiencing regular pain and 20% suffering from chronic pain syndromes. This makes pain a primary reason for doctor visits. While it serves as a biological warning of threats, it also results in personal suffering, affecting families and society. Economic studies reveal the extensive damage caused by pain. The quality of life for OA patients suffers from pain, anxiety, depression, and work inability, leading to inadequate community support. Pain relief methods like NSAIDs and opioids often fail to alleviate suffering and may cause harmful side effects. Long-term use raises risks of addiction and dependence. Pain, crucial for survival, protects the body from harm, with mechanisms active in both peripheral and central nervous systems, though its adaptive advantages can be overlooked today [8].

Medical Cannabis: Mechanisms and Pharmacology

Research on medical cannabis is booming due to societal interest. Cannabis has over 100 cannabinoids; THC is key for recreational effects, while CBD shows medicinal promise, especially with THC, and has low toxicity in studies. However, mechanisms of CBD's effects are still unclear. CB1 and CB2 primarily bind to Gi/o, inhibiting cAMP production and activating downstream pathways such as protein kinase A (PKA) and mitogen-activated protein kinase (MAPK). GPR55, GPR18, and GPR119 bind to Gi/o, possibly coupling to Gq or Gs. Gq activation stimulates phospholipase C-beta (PLCβ), leading to increased intracellular calcium and activation of protein kinase C (PKC). Cannabinoid effects depend on the released amounts, exposure duration, and specific cells, influencing neuronal responses and body homeostasis [9].

Cannabinoids and their Receptors

The use of medical cannabis for pain relief in osteoarthritis has become a comparative focus against traditional painkillers. Os-

teoarthritis causes considerable pain and disability, often treated with opioids, NSAIDs, and antidepressants, which can lead to addiction and side effects. Medicinal cannabis is emerging as a potential alternative for pain management in OA. Research has revealed that mammalian brains and tissues contain metabolically active lipids called endocannabinoids, which, along with cannabinoids from Cannabis sativa, interact with various receptor proteins in both neural and non-neural tissues. Recent studies aim to explore the therapeutic effects, mechanisms, and side effects of cannabinoids, particularly for chronic pain relief, highlighting their analgesic properties as a new pain management approach [10].

Modes of Administration

The main challenge in using THC and CBD with other cannabinoids like cannabidiodin, anandamide, and N-palmitoylethanolamine is managing the "entourage effect" for effective therapeutic dosages. There is no agreement on dosages in experimental or human settings. Medical marijuana can be ingested through various methods, including inhalation and oral ingestion, with smoking or vaporizing common for beginners, often followed by edible forms [9, 10].

Traditional Painkillers for OA

The pharmacological treatment of OA emphasizes pain relief and improved function, primarily using NSAIDs as the first-line therapy. OA's inflammatory process is tied to prostaglandin activation via the COX-2 enzyme. NSAIDs alleviate pain by reducing cytokines, metalloproteinase enzymes, and GAG in synovial fluid. Selective COX-2 inhibitors target prostaglandin endpoints to minimize side effects, affecting prostaglandin G in kidneys, I2 in vascular endothelium, and E1 in gastric mucosa. NSAIDs are effective for acute pain relief and should be the first choice for OA pain when paracetamol and non-drug treatments fail. However, they pose risks, particularly gastrointestinal issues like dyspepsia, abdominal pain, and bleeding. Yearly NSAID-related complication risks range from 3-4%, with severe bleeding risks between 15-45%, influenced by dosage and duration. Gastroprotective agents like proton pump inhibitors can reduce ulcer complications by about 50% [11].

Commonly Used Medications

Analgesics for OA patients include paracetamol, NSAIDs, and opioids, with complementary options like glucosamine, chondroitin, capsaicin, and Icy Hot. This text discusses medication classes used for OA in the U.S. and their annual costs. Paracetamol is the leading non-opioid analgesic, used by 44% of U.S. adults. NSAID use stands at 8.6% for those aged 20 and older, while opioids are at 6.3%. No universal treatment exists for all OA patients, making tailored medication selection vital for effective OTC regimens [12].

Efficacy and Side Effects

This study seeks to assess the safety and effectiveness of MC products compared to usual care analgesics and enable health economics analyses. The trial will document a patient population that meets clinical criteria. Essential components include clear labeling of outcome measures and robust randomization, allocation concealment, blinding, and patient compliance. To aid healthcare commissioners, normalization processes are needed in outcome measures. An open-label design might improve patient-rated effectiveness scores due to placebo effects. Additionally, functional and coping ability measures can indicate effective pain management. VR usage can add qualitative insights into MC interventions' effectiveness. An increasing number of product-specific withdrawals due to adverse events were noted during the open-label extension study, indicating a potential rising intolerance to chronic cannabinoid use. In short-term RCTs, only 6–8% of patients withdrew due to adverse events, possibly underestimating chronic use risks. The long-term withdrawal rise could imply ineffective cannabinoid exposure. No serious complications were reported after a 12-month follow-up, contrasting with Nabilone, which worsened knee pain over 48 weeks. Many patients experienced adverse events across medications. Before dropout, morphine sulfate showed no significant pain relief for osteoarthritis compared to MC, indicating conservative posology titration. A larger RCT is essential for further exploration, and future studies should compare MC with SC for validation [12].

Clinical Studies on Medical Cannabis for OA Pain Relief

The search included meta-analyses, systematic reviews, clinical trials, observational studies, controlled before-after studies, and cross-sectional studies published from January 1, 2000, to March 2, 2021. Factors like obesity, prior joint surgery, lower education, friendships, and participation in sports and cultural activities were associated with medical cannabis use. Obese adults with OA, those less educated, and those with friends using cannabis showed significantly higher usage. The link between obesity and OA, along with the need for effective treatments, highlights the importance of investigating cannabis-based drugs for pain relief and rehabilitation in OA. Limited evidence supports cannabinoid agonists as alternatives for OA-related pain, but their long-term use may be compromised by partial CB1 receptor activation, diminishing analgesic effects and increasing mental health risks. Challenges may arise from selective CB2 receptor targeting and peripheral action. This research suggests OA patients using medical cannabis may experience better pain relief than those on pharmacological treatments.

Methodological Considerations

The review summarizes the methodological characteristics of studies, noting the diverse populations and cannabis types used. Differences in cannabis may explain variations in cannabinoid efficacy, effects, and pain relief doses, influencing the central nervous system's response. Findings underscore the need for further research on various cannabinoids' pharmacokinetic and pharmacodynamic profiles for joint pain to improve treatment algorithms across disease states and ages. Low daily doses of hemp oil significantly improved osteoarthritis pain, enhancing quality of life with fewer major functional impacts compared to traditional anti-inflammatory drugs, which have notable side effects [13].

Key Findings

This section discusses recent literature on the effectiveness of medical cannabis combined with traditional treatments compared to other analgesics. Limited clinical studies on cannabis with standard analgesics hinder meta-analyses in randomized trials, resulting in ambiguous data. Thus, we focus on publications addressing medical cannabis with traditional therapies. Data on medical cannabis are unclear, but published findings indicate fewer adverse reactions and greater pain relief than

non-steroidal anti-inflammatory drugs. This suggests a potential new therapy that could eliminate the safety risks of current treatments while enhancing patient quality of life. Further investigation into medical cannabis for osteoarthritis is necessary. The method of administration (oral, inhalation, etc.) should consider active substance concentration, pharmacokinetics, patient preferences, and potential risks for addiction or adverse effects [14].

Cannabis vs Traditional Painkillers in OA

Osteoarthritis, a complex condition, can lead to severe pain, disfigurement, and limitations. Recent interest has grown in using Cannabis sativa for chronic musculoskeletal pain. We conducted this review to assess the analgesic efficacy and patient satisfaction of medical cannabis compared to traditional painkillers. Amid opioid concerns, some cannabis products have also caused adverse effects. Our findings established statistically and clinically significant differences in NRS and WOMAC scales. Preclinical evidence has focused on balancing the ECS system to enhance OA outcomes and its interaction with CBD in OA models. Future studies will employ randomized controlled trials with valid pain relief measurements using standardized products and fixed dosages. Small-scale pharmaceutical products may help reduce the incidence of NSAID-related issues like heart disease or liver toxicity. Larger studies can deliver more robust clinical evidence. Current OA research suggests it as a viable drug target, while the increasing popularity of cannabis addresses OA symptoms and alleviates traditional painkiller side effects [5].

Inclusion Criteria and Search Strategy

This study adhered strictly to systematic review protocols. A search for studies was conducted in electronic databases and reference lists of eligible articles were reviewed. The search strategy involved: 1) a comprehensive search using keywords for cannabinoid use and OA-related pain, along with synonyms; 2) OA keywords were developed in consultation with a joint specialist. These guidelines align with established reporting standards for systematic reviews. The article selection for validation involved three experienced reviewers in three stages, with a fourth arbitrator to resolve disagreements. Initially, two decision-makers independently reviewed articles from electronic database searches, eliminating duplicates. They screened titles and abstracts against specific criteria, excluding review studies, animal studies, case reports, and observational studies. However, all studies related to using cannabinoids for OA-related pain treatment were included. After initial selection, the reviewers confirmed that articles in the secondary phase met evaluation standards before proceeding with data collection and extraction [15].

Statistical Methods and Data Synthesis

Statistical analysis was conducted on studies meeting specific inclusion and exclusion criteria. Data collection involved gathering details like study design, country, year, number of participants, intervention type, disease specifics, data type, impacted human joint, intervention duration, daily active compound dose, and study objectives. We analyzed full texts of qualifying studies and could only conduct on suitable studies for comparative analysis and heterogeneity resistance. Odds ratios were calculated with 95% confidence intervals and findings evaluated with a funnel plot. Owing to the limited eligible studies for osteoarthritis treatment in this meta-analysis, a qualitative review was performed, expressing results through narrative synthesis techniques in discussions [16].

Results and Discussion

Etolodac showed higher consumption at elevated doses, which links to an increased risk of arterial thrombotic events for users. The substantial doses of paracetamol/caffeine and etolodac indicate a potential risk of toxicity, particularly gastrointestinal and cardiovascular, alongside elevated costs from greater tablet usage. Furthermore, the increased consumption of dexketoprofen/tramadol over other medications did not correlate with enhanced pain relief, necessitating more pharmacy visits for additional packets. Although effective pain management in OA can reduce, hospital stays and costs, our study targets outpatient experiences. Hyaluronic acid's mean usage was significantly lower than another survey, despite being reimbursed by the National Health System, and the evaluated drugs are becoming more prevalent in prescriptions.

Another point of interest is opioid consumption. Tramadol use did not provide better pain relief than medical cannabis. Patients treated with medical cannabis consumed half the amount of tramadol compared to those on dexketoprofen/tramadol. The three average variables showed better results for medical cannabis, which positively affects patients. Opioid use in PTOA is concerning due to its relation to motor vehicle accidents. Medical cannabis enhances patients' quality of life, providing consistent relief from chronic pain when used properly. While the cost of medical cannabis is higher than tramadol, the added benefits of lower disability, reduced constipation, and fewer alternative painkillers can justify the cost-effectiveness despite higher treatment expenses. Concerns about cost, access to administration, appointment difficulties, potential side effects, and drug interactions hinder adoption; one patient expressed reluctance due to these issues, particularly regarding apixaban and previous warfarin treatment. Resolving drug costs through National Health System inclusion and carefully analyzing benefit-risk balances based on patient conditions could improve acceptance, but interaction concerns remain unresolved, highlighting the need for further interaction analysis [10].

Safety and Adverse Effects

Adverse events were more common in active treatment groups during follow-up. In one experimental study, 15% of participants in the THC/CBD group, 3% in the THC group, and 10% in the placebo group withdrew due to adverse events likely related to the medication. The most frequent adverse event in the THC/CBD group was dizziness or feeling "high," affecting 7% of participants, compared to 4% in the THC group, 1% in the placebo group, and 0.9% in the nabumetone group. During the double-blind phase, adverse events related to the medication occurred in 25% of THC/CBD participants, 4% in the THC group, and 12% in the placebo group. Adverse events were similarly reported in the THC/CBD and placebo groups during the open-label phase, although they became less frequent over time. In another RCT, three participants withdrew due to anti-inflammatory medication-related adverse events, and minor gastrointestinal effects were more prevalent compared to the control group. Prior to crossover, no significant adverse effects were noted with paracetamol use in knee osteoarthritis patients. Gastrointestinal intolerance was the most common adverse effect in the RCT.

During the trial, a gastroprotective medication was provided, and adjusted doses of celecoxib and naproxen were used to alleviate gastrointestinal issues. No upper GI disorders were noted from paracetamol treatment, aligning with other studies. Adverse events are more frequent in clinical practice with cannabis-based medicine, possibly because RCT participants are more aware of their treatment in structured environments. There may also be dosage restrictions on cannabis-based medicines for chronic pain in studies, potentially reducing analgesic effects. Most adverse events are linked to medicinal cannabis, with reactions ranging from mild to severe, including reversible cognitive disorders, dizziness, and mental illness [17].

Short-Term and Long-Term Risks

The use of medical cannabis for osteoarthritic pain relief carries risks such as cardiovascular events, mortality, pancreatitis, suicidal behavior, and gynecomastia. Combining opioids with cannabis heightens the risk of self-harm, including traffic fatalities. The advantages of using cannabis for pain relief are limited and considered inferior alongside opioids. Replacing opioids with cannabis has not proven effective for chronic arthritic patients reliant on opioids. Although short-term cannabis use likely poses minimal hepatotoxicity risk, the long-term effects are uncertain. Most available data come from case reports rather than clinical trials. Long-term, high-dose cannabis use increases dependence risk, potentially leading to negative psychiatric and health consequences, which could outweigh benefits. Osteoarthritis patients often have comorbidities, raising their health risks when using cannabis. Currently, there is insufficient evidence to recommend cannabis for initial pain relief, particularly for moderate to severe chronic pain, as opioids typically offer superior relief. However, opioids pose addiction and abuse risks, other pain relievers carry potential for fatal adverse events at high doses [13].

Conclusion and Future Directions

Osteoarthritis (OA) is a complex issue not effectively addressed by traditional painkillers, which only improve quality of life and exacerbate comorbid disorders. Medical cannabis, with its analgesic effects, alleviates anxiety and depression linked to pain, though its precise mechanism remains unclear. Both humans and rats show benefits from its pharmacological effects on OA, making it a promising alternative to traditional pain relief methods that only address symptoms rather than root causes. Our comparative analysis supports medical cannabis as a potential first-line treatment for severe OA pain, highlighting cannabinoid receptor agonists and antagonists as effective alternatives to opioids. The knowledge gathered from clinical and experimental studies enhances our understanding of OA-related pain, paving the way for better therapies. Future research is essential to build scientific evidence for medical cannabis in treating age-related ailments and to investigate its bioavailability and toxicological properties [5].

Summary of Key Findings

This study demonstrated that medical cannabis more effectively relieved symptoms and improved sleep for knee osteoarthritis than traditional painkillers like nimesulide and pregabalin. Pregabalin negatively affected sleep, and nimesulide affected attention and memory. Overall, nimesulide was less effective than medical cannabis, highlighting its significant benefits and safety. Despite limited sample sizes and few adverse events, definitive safety conclusions remain elusive. The study focused on optimal pain management for breakthrough pain episodes.

Implications for Clinical Practice

Osteoarthritis is the most prevalent arthritis in the world. Despite available pharmaceuticals for pain relief, many patients find them ineffective and turn to high doses of traditional painkillers, which carry side effects and long-term risks. This study highlights the limitations of traditional painkillers and suggests considering alternatives for osteoarthritis pain management. Despite the limited use of alternatives for osteoarthritis pain, there is a need for accessible treatments. Current painkillers are often ineffective, highlighting the importance of exploring options such as pharmacological treatments, alternative medicines, and physical therapies. Emerging treatments show promise, but many questions and lack of clinical guidelines persist. Traditional pharmacological methods continue to dominate pain management in osteoarthritis [18].

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