Minnesota Department *of* Health
OFFICE OF MEDICAL CANNABIS

Arthritis (osteoarthritis and rheumatoid arthritis)

SEPTEMBER 2016

Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Finally, the federal government-maintained web site of clinical trials, clinicaltrials.gov, was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

Definition

Osteoarthritis (OA) is a degenerative joint condition and it constitutes the most common form of arthritis. It is not a single disease or process; rather it is the outcome of a range of processes leading to pathological structural changes and symptoms in one or more synovial joints. It can develop without any known underlying cause (primary OA), or it can develop

secondary to other processes such as trauma, congenital, mechanical or local factors (for example obesity or hypermobility) or as a sequelae of other inflammatory arthritides (Dunkley 2012). OA is a major source of pain, function limitation, and disability (Felson 1998). The past two decades have brought substantial new insights into what OA is and how it progresses. While the characteristic pathologic feature of OA is hyaline articular cartilage loss, it is increasingly recognized that OA is a disease of the entire joint and that all structures are affected. Bone remodeling and attrition occur relatively early in the disease and fibrocartilage (examples: meniscus; labrum of hip joint) degeneration leads to changes in load distribution. Protrusions of new cartilage develop and ossify, leading to further damage. The synovium can become inflamed and, as it swells, causes a spinal reflex, inhibiting complete activation of muscles that stabilize the joint. This, combined with lack of use, leads to muscle weakness and atrophy. The inflamed synovium triggers changes in the peripheral nervous system, affecting the afferent processing of pain signals from the joint and the surrounding tissues. A major driver of the development of the disease and its progression is aberrant loading of the join. As the joint starts to display damage from the loading by way of cartilage erosion or ligament injury, loading becomes even more aberrant, setting up a cycle of increasing damage and symptoms. Pain and joint instability are the characteristic symptoms of OA. Early in the disease pain comes on with certain activities or actions of the joint, but later pain becomes more constant – probably indicating the development of a central sensitization of the pain. Changes in pain and function appear to have little relation to the trajectory of structural progression. What produces this variety in disease trajectory is not clear (Felson 2009).

Rheumatoid arthritis (RA) is an autoimmune disease characterized by inflammation and swelling of the joint synovia (linings), autoantibody production, cartilage and bone destruction, and systemic features including cardiovascular, pulmonary, psychological, and skeletal disorders (McInness 2011). Its cause is unknown, but there appears to be an inherited risk, as well as increased risk from several environmental and infectious exposures (McInness 2011). RA causes significant disability (Pincus 1984) and impairment of quality of life (Salaffi 2009) and reduces lifespan (Soloman 2003).

Prevalence

Osteoarthritis is the most common form of arthritis. Symptomatic knee OA affects roughly 12% of persons 60 years old or older (Felson 1998). Rheumatoid arthritis affects 0.5-1% of the adult population (Helmick 2008). It can occur at any age, but most often it develops between the ages of 40-50 and its prevalence in women is three times that in men (Dunkley 2012).

Current Therapies

Currently, OA treatment is symptomatic, targeting pain and inflammation and promoting rehabilitation. Acetaminophen (Tylenol) can be effective at relieving pain early in OA, but non-steroidal anti-inflammatory drugs and COX-2 inhibitors are often used for pain and inflammation reduction. Many of these drugs carry risk of cardiovascular and gastrointestinal

disease, however, when used long-term. Physical therapy can help reduce pain and maintain mobility, muscle strength and biomechanical integrity of the joint. Rehabilitative approaches to osteoarthritis include bracing or taping the affected joints, orthotic shoes, and exercise; in general they have modest effect on pain reduction (Felson 2009). In advanced disease with joint failure (disabling joint pain and loss of joint function and deformity) management is surgical with joint replacements (Dunkley 2012). There is hope that future disease-modifying medical therapies targeted at underlying pathological processes will become available, but currently treatment is symptomatic (Dunkley 2012).

The current approach to rheumatoid arthritis treatment is to begin therapy as soon as possible after diagnosis, with zero tolerance for inflammation and the goal of achieving clinical remission. Disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate, hydroxychloroquine, sulpha-salazine, and lefunomide are started early and in combination. If inflammation continues, biologic drugs including anti-tumor necrosis factor drugs, B-cell depletion therapy, and anti-interleukin drugs or inhibitors to co-stimulatory molecules are started within 3-6 months of onset – usually concurrently with at least one of the DMARDs. Drugs used to treat RA have a wide variety of often serious side effects, with the biologic agents putting patients at increased risk of infections. Physical therapy and occupational therapy are important adjuncts to pharmacological treatment (Dunkley 2012). Existing treatments are not optimally effective, sometimes producing no remission or only partial remission. Sustained remission is rarely achieved and requires ongoing therapy (McInness 2011).

Pre-Clinical Research

Numerous studies have been published regarding presence of cannabinoid receptors and endocannabinoids in the joints of humans with OA and RA and studies testing impact of synthetic cannabinoids and endocannabinoid modulators on rodents with research models of OA and RA. Articles described below are representative. Those who want to explore this area in more detail can identify additional articles in the Background and Discussion sections of these articles.

Presence of CB1 and CB2 receptors in OA and RA

Richardson D, Pearson RG, Kurian N, Larif ML, Garle MJ, et al. Characterisation of the cannabinoid receptor system in synovial tissue and fluid in patients with osteoarthritis and rheumatoid arthritis. Arthritis Research & Therapy 2008, 10:R43 (doi:10.1186/ar2401)

Inflamed synovial tissue and synovial fluid were obtained from 13 RA patients and 32 OA patients undergoing total knew arthroplasty and synovial fluid was obtained from 6 normal volunteers. The investigators found evidence that CB1 and CB2 receptors are present in the synovial tissue of RA and OA patients. The endocannabinoids AEA and 2-AG were found in the synovial fluid of RA and OA patients, but not in synovial fluid of healthy volunteers, giving support to the concept of endocannabinoid system involvement within the joints of RA and OA patients.

Osteoarthritis

Schuelert N, Johnson MP, Oskins JL, Jassal K, et al. Local application of the endocannabinoid hydrolysis inhibitor URB597 reduces nociception in spontaneous and chemically induced models of osteoarthritis. *Pain* **2011;152:975-981.**

This study tested the impact of enhancing endogenous cannabinoid levels within the arthritic joint in two rodent models of OA: rats with chemically-induced OA and guinea pigs with naturally-occurring OA. An inhibitor of FAAH, an enzyme that breaks down endocannabinoids, was injected into an artery proximal to an arthritic joint. The injection resulted in decreased firing of pain nerve fibers when the joint was hyper-rotated. Behavioral experiments carried out on the rats showed a beneficial effect of the injection. The amount of weight rats were willing to bear on their hind limbs decreased after induction of OA; subsequent injection of the FAAH inhibitor reduced the amount of hind-limb incapacitance.

Schuelert N, McDougall JJ. Cannabinoid-mediated antinociception is enhanced in rat osteoarthritic knees. *Arthritis & Rheumatism* **2008;58:145-153.**

A rat model of OA was used to test the effect of a synthetic, selective CB1 agonist, ACEA. Injection of ACEA into the arthritic joint reduced firing of pain nerve fibers when the joint was hyper-rotated.

Rheumatoid Arthritis

Cox ML, Haller VL, Welch SP. Synergy between Δ^9-tetrahydrocannabinol and morphine in the arthritic rat. *Eur J Pharm* **2007;567:125-130.**

The effects of morphine and THC, separately and in combination, were tested in a rat model of inflammatory arthritis. The model involves administering a killed mycobacterium preparation (Freund's complete adjuvant) into the skin, which results in a generalized inflammatory arthritis. Drug effect was measured by the paw pressure test. In this test the rat's hind paw is exposed to increasing mechanical pressure. The pressure at which the rat withdraws its limb is defined as the pain pressure threshold. A higher threshold is interpreted as a reduction in pain. In this study THC and morphine were found to have a synergistic interaction in pain reduction in both normal rats and the arthritic-model rats.

Smith FL, Fujimori K, Lowe J, Welch SP. Characterization of Δ9-tetrahydrocannabinol and anandamide antinociception in nonarthritic and arthritic rats. *Pharmacol Biochem Behav* **1998;1:183-191.**

The effect of THC and the endocannabinoid anandamide were tested separately in a rat model of arthritis similar to the model used in Cox 2007. The investigators found that both THC and anandamide reduced pain in normal rats and had a similar pain-reducing effect in arthritic rats. Exploration of impact of a CB1 receptor antagonist showed different results for THC and for anandamide in pain reduction: pain reduction of THC was reduced, but there was no change in

pain reduction for anandamide. And naloxone blocked the pain reducing effect of both THC and anandamide. These findings led the authors to conclude, "This study indicates that anandamide and THC may act at different receptor sites to modulate endogenous opioid levels in mechanical nociception."

Krustev E, Reid A, McDougall JJ. Tapping into the endocannabinoid system to ameliorate acute inflammatory flares and associated pain in mouse knee joints. *Arthritis Research & Therapy* **2014, 16:437**

The effect of a synthetic inhibitor (URB597) of an enzyme (FAAH) that degrades the endocannabinoid anandamide was tested using a mouse model of inflammatory arthritis. Inhibition of the enzyme results in higher levels of anandamide. Anandamide has anti-inflammatory and analgesic qualities, and it was hypothesized that local administration of URB597 would result in evidence of decreased joint inflammation and pain. The mouse model of inflammatory arthritis was created by injecting an irritating substance (kaolin and carrageenan) into the mouse's right knee join. White blood cell adherence and blood flow within the joint were measures of inflammation. Hind limb weight bearing and sensitivity to hair filament testing were measures of pain. Hallmarks of decreased inflammation, decreased white blood cell rolling and decreased hyperemia were seen with low doses of URB597, but not with high doses. And injection of URB597 improved both hind limb weight bearing and the hair withdrawal thresholds. This led the authors to conclude, "These results suggest that the endocannabinoid system of the joint can be harnessed to decrease acute inflammatory reactions and the concomitant pain associated with these episodes."

Fukuda S, Kohsaka H, Takayasu A, Yokoyama W, et al. Cannabinoid receptor 2 as a potential therapeutic target in rheumatoid arthritis. *BMC Musculoskeletal Disorders* **2014, 15:275.**

This article describes both studies done on mice and studies done on human tissues.

1. A selective CB2 receptor agonist (JWH133) was tested on mice with murine-model rheumatoid arthritis. Use of JWH133, injected intraperitoneally, resulted in less synovial inflammation and bone destruction than in control mice.
2. CB2 receptor density was found to be higher in humans with RA than in humans with OA.
3. Fibroblast-like synovial cells from human RA synovium were cultured and then stimulated with a chemical that stimulates production of inflammatory mediators. Co-administration of JWH133 was found to dose-dependently suppress production of the inflammatory mediators.

Clinical Trials

Two clinical trials of a cannabinoid for treatment of arthritis patients were found and are summarized below. In addition, ClinicalTrials.gov lists one trial (NCT02324777), a

randomized double-blind placebo-controlled, proof-of-concept crossover trial of vaporized cannabis in adults with painful osteoarthritis of the knee. 40 adults age ≥50 with primary OA will be recruited at two Canadian centers. Participant response will be assessed at a variety of time points (0 to 180 minutes) after inhaling vaporized cannabis of different THC/CBD ratios. Primary outcome measure is pain reduction. Secondary measures include functional outcomes; pharmacokinetic measures of plasma cannabinoid metabolites; changes in blood pressure, heart rate, hematocrit, renal function, liver enzymes; psychoactive adverse events, and global rating of preference for each cannabis preparation. Estimated date of completion is May, 2016.

Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology* **2006;45(1):50-52.**

This was a double-blind, randomized, placebo-controlled study carried out for five weeks in patients diagnosed with rheumatoid arthritis (RA) on a stable regimen of traditional therapy but who did not gain adequate pain relief from standard treatments. A total of 58 participants (12 male/46 female; average age 62.8 years) met the inclusion criteria and 31 were randomized to treatment, while 27 received placebo. The patients were instructed to limit use to evening dosing to prevent daytime intoxication from the Sativex oral spray (2.7 mg THC/2.5 mg CBD per 100 μl actuation[spray]) that was used throughout the trial. The titration schedule was one actuation before bed and increase by one actuation every two days, based on patient response, up to a maximum of six actuations per night.

The primary endpoint tested was based on a 0-10 pain scale assessing pain upon movement each morning and comparing the baseline rating to the average of the last 14 days of the trial. Secondary outcomes were pain at rest, sleep quality, morning stiffness, the Short Form McGill Pain Questionnaire (SF-MPQ), and the 28-Joint Disease Activity score (DAS28). All outcomes except morning stiffness and SF-MPQ intensity showed a statistically significant improvement when compared to placebo, including the SF-MPQ "pain at present" rating. Side effects were approximately twice as common in the active treatment group than in the placebo group. All but two of the side effects in the active treatment group were mild or moderate; two patients rated side effects as severe (constipation, malaise). The side effects more common in the active treatment group than in the placebo group were mild dizziness, dry mouth, light-headedness and fall. Three patients withdrew from the study because of side effects – all 3 from the placebo group. There were no serious s adverse events in the active treatment group and two in the placebo group.

A recent Cochrane Review of neuromodulators for pain management in rheumatoid arthritis (Richards 2012) includes the Blake 2006 study and provides detailed discussion of its strengths and weaknesses. The authors conclude there is weak evidence that oromucosal cannabis is superior to placebo in reducing pain in patients with RA, but that the potential harms from side effects outweigh any modest benefits achieved.

Huggins JP, Smart TS, Langman S, Taylor L, Young T. An efficient randomized, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-

04457845, which modulates endocannabinoids but fails to induce effective analgesia in patients with pain due to osteoarthritis of the knee. *Pain* **2012;153:1837-1846.**

This randomized, double-blind, cross-over study assessed the effect of an FAAH inhibitor on pain in a human population with osteoarthritis. FAAH is an enzyme that metabolizes the endocannabinoid anandamide. Inhibition of FAAH was hypothesized to lead to increased levels of anandamide and related compounds and result in pain reduction, as has been observed in animal models of OA. 74 patients with OA were recruited and randomized into either the arm receiving PF-04457845 or the arm receiving Naproxen, the standard of care for treating OA symptoms. The trial involved 2 two-week treatment periods separated by a 2-week washout interval. In double-blind fashion, patients received active treatment in one of the treatment periods and placebo in the other. The Naproxen arm was carried out to test the validity of the washout period. Despite evidence of potent inhibition of FAAH and increase in endocannabinoid precursers, patients in the PF-04457845 group showed no difference in pain reduction with active treatment, compared to placebo, and the study was stopped at the interim analysis for futility.

Observational Studies

No published observational studies were found related to use of cannabis or cannabinoids as therapy for pain or other symptoms in patients with osteoarthritis or rheumatoid arthritis. There are however, many testimonials and accounts of benefits from use of cannabis in RA and OA patients on web sites maintained by individuals and by organizations.

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the treatment of osteoarthritis or rheumatoid arthritis were found.

References

Cox ML, Haller VL, Welch SP. Synergy between Δ^9-tetrahydrocannabinol and morphine in the arthritic rat. *Eur J Pharm* 2007;567:125-130.

Dunkley L, Tattersall R. Osteoarthritis and the inflammatory arthritides. *Surgery* 2012;30:67-71.

Felson DT. Developments in the clinical understanding of osteoarthritis [Review]. *Arthritis Res Ther* 2009;(1):203. Doi: 10.1186/ar2531.

Felson DT, Zhang &. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. *Arthritis Rheum* 1998;41:1343-1355.

Fukuda S, Kohsaka H, Takayasu A, Yokoyama W, et al. Cannabinoid receptor 2 as a potential therapeutic target in rheumatoid arthritis. *BMC Musculoskeletal Disorders* 2014, 15:275.

Helmick CG, Felson DT, Lawrence RC, et al for the National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. *Arthritis & Rheumatism* 2008;58:15-25.

Huggins JP, Smart TS, Langman S, Taylor L, Young T. An efficient randomized, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-04457845, which modulates endocannabinoids but fails to induce effective analgesia in patients with pain due to osteoarthritis of the knee. *Pain* 2012;153:1837-1846.

Krustev E, Reid A, McDougall JJ. Tapping into the endocannabinoid system to ameliorate acute inflammatory flares and associated pain in mouse knee joints. *Arthritis Research & Therapy* 2014, 16:437

McInness IB. The pathogenesis of rheumatoid arthritis. *NEJM* 2011;365:2205-2219.

Pincus T, Callahan LF, Sale WG et al. Severe functional declines, work disability, and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. *Arthritis Rheum* 1984;27:864-872.

Richards R. Whittle SL, Buchbinder R. Neuromodulators for pain management in rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2012, Issue 1. Art. No.:CD008921.

Richardson D, Pearson RG, Kurian N, Larif ML, Garle MJ, et al. Characterisation of the cannabinoid receptor system in synovial tissue and fluid in patients with osteoarthritis and rheumatoid arthritis. Arthritis Research & Therapy 2008, 10:R43 (doi:10.1186/ar2401)

Salaffi F, Sarzi-Puttini {, Girolimetti R, et al. Health-related quality of life in fibromyalgia patients: a comparison with rheumatoid arthritis patients and the general population using the SF-36 health survey. *Clin Exp Rheumatol* 2009;27(5 Suppl 56):S67-74.

Schuelert N, Johnson MP, Oskins JL, Jassal K, et al. Local application of the endocannabinoid hydrolysis inhibitor URB597 reduces nociception in spontaneous and chemically induced models of osteoarthritis. *Pain* 2011;152:975-981.

Schuelert N, McDougall JJ. Cannabinoid-mediated antinociception is enhanced in rat osteoarthritic knees. *Arthritis & Rheumatism* 2008;58:145-153.

Smith FL, Fujimori K, Lowe J, Welch SP. Characterization of Δ9-tetrahydrocannabinol and anandamide antinociception in nonarthritic and arthritic rats. *Pharmacol Biochem Behav* 1998;1:183-191.

Solomon DH, Karlson EW, Rimm EB, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 2003;107:1303-1307.

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