

# Cannabis-based medicinal products in arthritis, a painful conundrum

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## ABSTRACT

**AIMS:** The changing medicolegal climate regarding the medicinal use of cannabinoids in New Zealand will increase the likelihood of patients consulting general practitioners (GPs) about these products. Arthritis is a common medical condition for which cannabis-based products are promoted and used; however, doctors' knowledge about the efficacy and safety of these products in the setting of arthritis may be limited.

**METHODS:** We undertook a rapid review of the medical literature on cannabis-based medicinal products in arthritis.

**RESULTS:** Animal studies have identified endocannabinoid pathways in arthritis that are potentially amenable to interventions. One randomised placebo-controlled trial of Sativex® in adults with rheumatoid arthritis has shown some improvements in pain but not in comparison with a standardised pharmacological treatment regimen. Systematic reviews of cannabis-based products in arthritis have determined that there is currently insufficient evidence to recommend cannabis-based medicines for routine clinical use. There were five ongoing registered clinical trials of cannabis-based products in arthritis, the results of which are yet to be reported.

**CONCLUSIONS:** While animal models have identified possible endocannabinoid pathways in arthritis, there is no clear evidence of benefit in humans or comparative efficacy with current treatments. At this stage, there is little evidence to support GPs prescribing cannabis-based medicinal products for arthritis.

The legal climate regarding the medicinal use of cannabinoids and the public advocacy for access to cannabis-based medicinal products has been changing over the years. With the advent of the Misuse of Drugs (Medicinal Cannabis) Amendment Act,<sup>1</sup> it is increasingly likely that general practitioners (GPs) will encounter patient requests for advice and prescription of cannabis-based medicinal products in daily practice.

Patients often consult the internet ('Dr Google') prior to their GP visit<sup>2,3</sup> and are able to find a wealth of information about medical conditions and treatments.<sup>3</sup> A Google search on the therapeutic potential of cannabis for arthritis using the terms 'cannabis for arthritis' and 'cannabidiol (CBD) for arthritis' generates more than nine million and 24 million results respectively. This may generate high expectations in patients about the clinical utility of

cannabis-based products for management of chronic pain arising from their arthritis and possible cure. However, websites vary enormously in purpose and design, many are commercial companies advertising their wares, and may pay little attention to published and peer-reviewed evidence of efficacy and possible adverse effects of the products they list.

Osteoarthritis (OA) is a common disorder seen in GP practice.<sup>4,5</sup> Chronic pain and the imperfect treatment options such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), opioids and antidepressants with their respective side effect profiles may encourage patients to look for other options to reduce their pain.<sup>6</sup> Musculoskeletal pain is one of the most common reasons cited by users of cannabis in a number of jurisdictions including Canada, where 65% of Health Canada authorised users of medicinal herbal cannabis diagnosed with 'severe arthritis',<sup>7</sup>

and Colorado where 93% of users are registered for 'severe pain'.<sup>8</sup> Arthritis pain has been cited as a reason for cannabis use in over one-third of users in Australia.<sup>9</sup>

In this article we will focus on an imaginary consultation with a 65-year-old patient with a history of moderate to severe OA of the knee. She has been awaiting a knee replacement for two years, and is unhappy with her current pain treatment, which includes paracetamol, NSAIDs and codeine as required. She suffers from frequent breakthrough pain. She now walks with the aid of a walking stick, and feels the pain significantly impacts her quality of life. She visits her GP to seek advice about cannabis-based products for her arthritis, as she read good stories about this 'natural product' for pain on the internet, and believes it has less side effects than the painkillers she is currently taking. She wonders whether it may be of assistance while she is waiting on her knee operation.

While GPs can access helpful resources such as those developed by the Australian Centre for Cannabinoid Clinical and Research Excellence about HOW to prescribe,<sup>10</sup> the rationale as to why cannabis-based products should be effective in this clinical setting is not clear. We assess the current evidence base for cannabis-based products in the management of arthritis pain and joint inflammation that may assist GPs in such a patient consultation, including the molecular rationale for or against the use of cannabis-based medicines in arthritis, the evidence in animal studies and evidence to date of safety and efficacy in established human disease.

## Methods

We undertook a rapid review of the medical literature that focused particularly on the use of cannabis-based products for arthritis (both osteoarthritis and rheumatoid arthritis (RA)) in animal models as well as observational and interventional trials in humans, and currently registered, not yet reported clinical trials of cannabis-based products for arthritis in humans.

We included all joint arthritis models in animal trials, and used a deliberately wide search that included arthritis, inflammation and pain in humans to ensure we cast as

wide a net as possible over the medical literature.

For pre-clinical trials, all compounds associated with the endocannabinoid system or phytocannabinoids that were used to assess effects on arthritis or any inflammatory condition were considered. For the human studies, trials on OA and RA, the two most common arthritis presentations, were included. Neuropathic pain secondary to spinal OA, the less well-differentiated chronic pains associated with other neuropathies, fibromyalgia and cancers, and neuropathic pain in isolation were not included. Systematic reviews that included identified and synthesised papers on OA and RA, and that drew conclusions based on these trials were included.

The following search strategy was applied in PubMed: ('Cannabinoids' OR 'Delta-9-Tetrahydrocannabinol' OR 'Cannabidiol' OR 'Cannabis') AND ('Arthritis'; 'Inflammation' or 'Pain'); 'Cannabidiol' AND 'Inflammation'. A search of trials was undertaken on the European Clinical Trials Database (EudraCT) and the US National Library of Medicine clinical trial registry (clinicaltrials.gov) using the search terms 'Cannab\*' AND 'arth\*', and then 'Cannab\*' AND 'pain'.

A title and then abstract screening was undertaken by two authors. Where dispute arose with respect to inclusion or otherwise, the remaining authors were asked to review. Where identified trials were included in systematic reviews, these systematic reviews were assessed for their summary findings and relevant meta-analyses. References of included articles were further searched to identify primary literature.

## Results

Is there a molecular rationale for the use of cannabis-based products in arthritis?

Cannabinoid receptors are expressed throughout the nociceptive pathways in animals and in humans, raising the possibility that modulation of this system may result in new forms of analgesia.<sup>11</sup> The most well-known cannabinoid receptors are CB<sub>1</sub> and CB<sub>2</sub>.<sup>12</sup> Phytocannabinoids are naturally occurring cannabinoids found in the cannabis plant, the most well studied

of which are delta<sup>9</sup>-tetrahydrocannabinol (THC) and CBD. THC is known for its psychoactivity and activates both CB<sub>1</sub> and CB<sub>2</sub> receptors.<sup>13</sup> In contrast, CBD is an antioxidant<sup>14</sup> and thought to work synergistically with THC increasing the THC concentrations in serum and the brain,<sup>15,16</sup> but of itself does not act at the endocannabinoid CB receptors at physiologically relevant concentrations.<sup>17</sup>

In humans, endocannabinoid receptors have been found in the synovium of patients with OA and RA.<sup>18</sup> Endocannabinoids have been found in the synovial fluid of arthritic joints, but not in healthy joints,<sup>18</sup> suggesting some 'upregulation' of the endocannabinoid system within the arthritic joint. It is not known whether this upregulation was mirrored systemically or within the central nervous system of these patients. Nor is it clear whether this had a causative role in the arthritis, or whether this was as a result of the pain caused by the arthritis.<sup>18</sup>

### Preclinical studies

There were 19 pre-clinical trials evaluating the endocannabinoid system and arthritis<sup>19-37</sup> of which seven assessed cannabis plant extracts.<sup>19,20,30-34</sup> The studies often appeared underpowered (insufficient animal numbers for the small effect size and large inter-animal variability). Animal models of OA can be divided into spontaneous (naturally occurring or genetic models) and induced (by surgical manipulation or intra-articular chemical injection). Spontaneous models more closely mimic the progression of human disease but tend to be more costly due to the slow progression and high inter-animal variability.<sup>38</sup> All cannabinoid studies identified utilised chemical injection to induce injury. These use primarily monosodium iodoacetate,<sup>19,29,35,36</sup> di or tri nitrobenzenesulfonic acid,<sup>33,34</sup> collagen<sup>22,23,28,30</sup> and/or Freund adjuvant.<sup>20,22-25,27,28,30-32</sup> These models are primarily used for studying OA pain-related behaviours, but their validity as clinical models for OA has been questioned.<sup>38-40</sup> When utilising these animal models, increased endocannabinoid concentrations have been observed in the spinal cords of arthritic rats, which may modulate the activity of spinal neurons via cannabinoid receptors.<sup>29</sup> Administration of CB<sub>1</sub> and CB<sub>2</sub> receptor blockers directly into the affected joints of rats with experimentally induced arthritis can change nociceptive

activity, although the results are inconsistent.<sup>35,36</sup> CBD may mitigate the progression of induced arthritis in mice, but the exact mechanism for this remains unclear and is unlikely to be associated with CB<sub>1</sub> and CB<sub>2</sub> receptors.<sup>19,30</sup> In many of the preclinical studies, drugs were delivered daily by injection directly into the joint, spinal cord or brain,<sup>19,29,30,32-36</sup> and thus the applicability of these studies to the delivery of cannabis-based products in humans are unclear. Many of the studies utilised synthetic, targeted modulators of endocannabinoid receptors, rather than phytocannabinoids, thus the results may not be generalisable to a medicinal cannabis preparation.

### Clinical studies (Table 1)

In our search of reported human studies, a total of 823 papers were found. There was one randomised controlled trial (RCT) of a fatty acid amid hydrolase (FAAH) inhibitor (designed to increase the concentration of circulating endocannabinoids) in OA,<sup>41</sup> and one RCT of Sativex® (a sublingual spray containing almost equal concentrations of THC and CBD) in RA.<sup>42</sup> There were two systematic reviews of RCTs of cannabis-based medicinal products in a range of arthritides.<sup>6,43</sup> There was one 'overview of systematic reviews in pain management and palliative medicine', which included the two systematic reviews of arthritides along with nine other reviews not specifically related to arthritis.<sup>44</sup> In the clinical studies identified, cannabis-based products included oral, sub-lingual and smoked preparations. Despite a wide range of topical applications available in other jurisdictions, no clinical data relating to these products was identified.

The first RCT was of a fatty acid amide hydrolase (FAAH) inhibitor in 74 patients with late-stage OA of the knee. This RCT was terminated due to futility, as an interim analysis showed that naproxen was efficacious compared to the placebo arm while the FAAH inhibitor was not.<sup>41</sup>

The second RCT was a placebo-controlled trial of Sativex® for pain in 58 patients with rheumatoid arthritis treated over a five-week period.<sup>42</sup> Sativex® treatment resulted in statistically significant improvements in pain on movement, pain at rest, and quality of sleep compared to placebo. There was no effect on morning stiffness.

**Table 1:** Published randomised controlled clinical trials of cannabis-based products in arthritis.

<b>Author: Journal: Title</b>	Blake DR et al, Rheumatology, 2006.	Huggins et al, Pain, 2012.
<b>Study type</b>	Randomised, double-blind, parallel group study	Randomised, double-blind, double dummy, placebo- and active-controlled crossover design
<b>Disease</b>	Rheumatoid Arthritis (meeting American College of Rheumatology criteria, not adequately controlled by standard medications)	Osteoarthritis
<b>Patients</b>	N=58 (31 Sativex®, 27 placebo)	74 (37/36)
<b>Other medications</b>	Continued concurrent medications  NSAIDs and prednisolone had to be stabilised for 1 month and DMARDs for 3 months prior to enrolment	Discontinued all current analgesic therapy
<b>Intervention</b>	Sativex: oromucosal spray  1 spray: 2.7mg THC: 2.5mg Sativex®	Oral dose: 37: PF-04457845 (FAAH inhibitor) followed by placebo (or vice versa), 36: naproxen followed by placebo (or vice versa)
<b>Dose</b>	Started on 1 spray nocte, which was increased by 1 spray every 2/7 to a max of 6  Mean daily dose in final week(sprays)  5.4 CBM 5.3 placebo	Naproxen 500mg BD PF-04457845 (FAAH Inhibitor) 4mg QID
<b>Duration</b>	5 weeks	2 weeks double-blind treatment followed by 2 weeks washout period. Crossover
<b>Outcome measurements</b>	Primary: morning pain on movement Numerical Rating Score (NRS) Secondary: NRS measures of pain at rest, sleep quality and morning stiffness. SF-MPQ, 28-joint disease activity score (DAS28)	Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscore (0–20), WOMAC stiffness domain score, WOMAC Physical Function domain score, WOMAC Total score. 11-point NRS, use of rescue medication. Hospital and Anxiety Depression Scale (HADS [58])
<b>Results</b>	Statistically significant improvement in pain on movement, pain at rest (3.1 THC/CBD, 4.1 placebo), quality of sleep (3.4 THC/CBD, 4.6 placebo), DAS28 (5.0 THC/CBD, 5.9 placebo) and the SF-MPQ.  No significant change in intensity of pain.	Mean differences (80% confidence intervals) from placebo in WOMAC pain score were 0.04 (0.63 to 0.71) for PF-04457845 and 1.13 (1.79 to 0.47) for naproxen, indicating that whilst naproxen seemed efficacious, PF04457845 was not differentiated from placebo. The study was stopped at the interim analysis due to futility in the FAAH arm.
<b>Adverse events</b>	Withdrawals 0 in the Sativex® group, 3 (11%) for placebo. SAE: 0 serious AE in Sativex® group, 2(7%) in placebo group. AE: in Sativex® group mild or moderate intensity except for 2 (6%) rated severe) vs 6 (22%) in the placebo group. THC/CBD:placebo AEs (%): Dizziness (26:4), lightheadedness (10:4), dry mouth (13:0), nausea (6:4), falls (6:0), vomiting (0:7), Palpitation (0:7), Drowsiness (3:4), Constipation (3:4)	No evidence of cannabinoid-type adverse events

The large majority of adverse events were mild or moderate, and there were no adverse event-related withdrawals or serious adverse events in the active treatment group.<sup>42</sup>

Both of these RCTs were included in a systematic review of RCTs of cannabinoids in rheumatic diseases,<sup>45</sup> which also included two RCTs of cannabinoids in fibromyalgia.<sup>46,47</sup> When the data for all four RCTs were combined the authors concluded that “Extremely small sample sizes, short study duration, heterogeneity of rheumatic conditions and products, and absence of studies of herbal cannabis allow for only limited conclusions for the effects of cannabinoids in rheumatic conditions. Pain relief and effect on sleep may have some potential therapeutic benefit, but with considerable mild to moderate adverse events. There is currently insufficient evidence to recommend cannabinoid treatments for management of rheumatic diseases pending further study.”<sup>45</sup>

The second systematic review of cannabinoids in chronic pain associated with rheumatic diseases<sup>43</sup> contained the Sativex® rheumatoid arthritis trial,<sup>42</sup> the two fibromyalgia trials<sup>46,47</sup> and a cross-over study of nabilone versus placebo in 30 patients with chronic pain associated with a ‘pathologic status of the skeletal and locomotor system’.<sup>48</sup> The nabilone study reported significant benefits with respect to pain reduction and quality of life, and patient preference for nabilone as a treatment in the follow-up period. The treatment periods were of four weeks’ duration, the risk of bias could not be assessed and the reported statistics did not lend themselves to meta-analysis.<sup>48</sup> When the results of all four RCTs were combined, the authors concluded that “The low quantity and quality of data available on the efficacy, tolerability and safety of cannabinoids in chronic pain refractory to conventional treatment associated with rheumatic diseases do not allow for any current recommendation for routine clinical use.”<sup>43</sup>

The overview of systematic reviews in pain management and palliative medicine included both the systematic reviews previously reported.<sup>44</sup> The authors reported that there was inadequate evidence for benefit of any cannabis-based products for any of

the conditions they assessed and noted the psychiatric and central nervous system side effects. They also commented that “The public perception of the efficacy, tolerability, and safety of cannabis-based medicines in pain management and palliative medicine conflicts with the findings of systematic reviews and prospective observational studies conducted according to the standards of evidence-based medicine.”<sup>44</sup>

The use of cannabis-based medicines that include THC was accompanied by mild to moderate adverse effects, most of which were related to dizziness, somnolence and the perception of feeling ‘high’.<sup>42–45</sup> Both clinical trials reported were of short duration. No prospective studies investigating the long-term adverse effects of cannabis-based medicinal products were found. There were no cohort studies or cross-sectional studies specific to cannabis-based medicinal products in arthritis found. There was one observational study that found an association between high levels of smoked cannabis and high levels of bone turnover and osteoporosis.<sup>49</sup>

### Registered clinical trials in progress

There were five clinical trials of cannabis-based medicinal products in the treatment of arthritis found in US and European trial registries.<sup>50–54</sup> All studies are listed as incomplete and have no results available yet.

Due to the paucity of clinical trials and the heterogeneity of products used and outcomes assessed, a meta-analysis of available data could not be undertaken.

## Discussion

This rapid review shows that the endocannabinoid system might play a role in acute nociception and inflammation in both animals and humans, however the full extent of its role in arthritis is unclear. The methodology used in most animal trials apply mainly to experimentally induced arthritis and the modes of administration of the cannabis-based medicinal products are not widely generalisable to humans. In human trials, Sativex® claims some efficacy in reducing pain and improving sleep in 58 patients with RA over a five-week period, while FAAH inhibitors that increase circulating endocannabinoids had no efficacy

in OA. Beyond this, evidence is limited.<sup>42</sup> There are a number of trials in humans in progress, and we look forward to publication of the results.

The limited amount of evidence-based peer-reviewed medical literature concerning cannabis-based medicinal products contrasts starkly with the wealth of information that can be found on the internet, highlighting the need for the GP to be prepared, well-informed and able to provide accurate information to their patients. While we were able to generate 823 papers from our search, there were only two published RCTs specific to arthritis; one in RA,<sup>42</sup> and one of a FAAH inhibitor that showed promise in animal models<sup>55</sup> but was abandoned due to futility in human trials as it was not better than placebo,<sup>41</sup> highlighting the difficulty of translating the results of pre-clinical studies directly to humans.<sup>56</sup> The mechanism for pain and inflammation may differ between the two species, many pre-clinical trials have been undertaken on animal models of artificially initiated acute arthritis and the modes of drug administration used in animal studies (intrathecal, intra-articular or intraperitoneal for example) is often not desirable or practical in humans. Further, the comparison with a placebo arm does not reflect the current gold-standard for treatment for arthritis or chronic pain. One might expect that the magnitude of any benefits seen in cannabis-based products versus placebo would be reduced in RCTs where the comparator arm included gold standard analgesic agents and the intervention arm may have a cannabis-based product as an adjunctive therapy.

The Sativex® trial in patients with RA claims some efficacy.<sup>42</sup> Whether the reduction in pain is due to the psychoactive effects of the THC or some other disease-modifying mechanism is unclear. As well as reduced subjective pain with movement and at rest, the authors report a statistically significant difference in the Disease Activity Score 28 (DAS28) between the two groups and describe this as a significant depression of disease activity. The DAS28 is a composite score that includes a count of painful joints, a count of swollen joints, a measure of serum inflammatory

markers, and a visual analogue score of a 'global assessment of health'.<sup>57</sup> Changes in the DAS28 subgroups were not reported, so it is unclear how much of the change has been driven by patient-reported global assessment of health or pain reduction compared to the more objective measures of swollen joints and inflammatory markers. The mean DAS28 in the Sativex® group was 5.9 at baseline, consistent with a high level of disease activity, and the mean score at the end of the trial was 5.0, consistent with a moderate level of activity.<sup>57</sup> However, a clinically meaningful reduction in the DAS28 is considered to be >1.2 when disease activity is high, greater than that reported in the RCT.<sup>57</sup> The proportions of patients in each group achieving a clinically meaningful reduction in disease activity according to the DAS28 is not reported, nor is the proportion of participants in each group achieving remission.

Of potential concern, an association between high levels of cannabis smoking and osteoporosis has been described,<sup>49</sup> suggesting that future clinical trials should consider incorporating the assessment of circulating biomarkers of bone health and disease into their clinical trial programmes, particularly when investigating chronic conditions that may require long-term treatments, and in trials associated with bone and joint health.

There were no human studies found that assessed CBD only preparations in OA or RA. CBD is considered an antioxidant,<sup>14</sup> with some anti-inflammatory properties.<sup>14,58</sup> These properties are commonly referred to on websites,<sup>59,60</sup> as well as reference to its 'non-psychoactive' (and by inference safe) properties.<sup>59,60</sup> While CBD may not make patients 'high' as THC does, CBD is an agonist at serotonin receptors,<sup>61</sup> and may have some psychoactive properties such as anxiolysis, possible improved mood and sedation. This is an important consideration if prescribing with other medications. Notably, in New Zealand, while CBD is no longer a controlled drug, products still require a prescription, must have less than 2% THC, and none are approved by Medsafe or funded by Pharmac, therefore any costs associated with obtaining these products are borne by the patient.

There are some limitations that should be considered in the context of this rapid review. The topic was difficult to limit to OA and/or RA, due to the heterogeneous nature of the medical literature. The two discrete trials that we identified were included in three systematic reviews, two of which covered rheumatic arthritides, and one of which covered chronic pain management and palliative care, perhaps highlighting the difficulty of clearly differentiating disease states and pain management. Neuropathic pain was excluded from this review; however, there is some evidence that there is a subgroup of patients with chronic osteoarthritis that develop central sensitisation over time.<sup>62</sup> There are a number of systematic reviews of cannabis-based products in chronic neuropathic pain with mixed findings, including potential short-term benefits of inhaled cannabis,<sup>63</sup> marginal efficacy of short- to intermediate-term adjunctive cannabis-based products but with reduced tolerability compared to placebo,<sup>64</sup> and that potential benefits may be outweighed by the risk of harm.<sup>65</sup> We did not include studies of chronic pain, as arthritis patients were not separately reported in these studies.

## Conclusion

How might a GP respond to Mary's questions about cannabis-based medicinal products for her osteoarthritis? At the molecular level, endocannabinoid receptors are expressed throughout nociceptive pathways in humans and have been found in the synovium of joints affected by OA and RA. Animal models have provided some evidence of a relationship between the endocannabinoid system, pain and arthritis, the mechanism of which is unclear. There is no current published medical evidence for cannabis-based products in the treatment of OA in humans, although there may be some efficacy of Sativex® for some symptoms of RA. In all trials the duration of treatment has been short and the long-term effects, beneficial or otherwise, of cannabis-based products are not established. While acknowledging the limitations of the treatment regimen currently in place, and the negative impact of OA on Mary's quality of life, the potential adverse effects of cannabis-based products, the lack of definitive evidence of benefit in OA and the lack of information about the long-term effects of cannabis-based medicinal products do not support a prescription at this time.

**Competing interests:**

Prof Michelle Glass and Drs Karen Oldfield, Alex Semprini and Irene Braithwaite are members of the Medical Cannabis Research Collaborative, an impartial collaboration of academics and regulatory experts in the field of cannabis-based medicine development. The Medical Research Institute of New Zealand has undertaken research activity Heliuss Therapeutics, Hikurangi Enterprises and Whakaora Pharma, all of which are New Zealand-based medicinal cannabis companies. There are no other conflicts of interest to declare. The Medical Research Institute receives Independent Research Organisation funding from the Health Research Council of New Zealand.

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