Cannabinoids for treatment of chronic non-cancer pain: a systematic review of randomized trials
Lynch ME, Campbell F

CRD summary
This generally well-conducted review concluded that cannabinoids were safe and modestly effective for chronic non-cancer (predominately neuropathic) pain, with preliminary evidence in fibromyalgia and rheumatoid arthritis. The authors' conclusions may only be reliable for short-term treatment as included trial treatment periods were relatively short (maximum of six weeks).

Authors' objectives
To evaluate the efficacy and safety of cannabinoids in treating non-cancer chronic pain.

Searching
Twelve databases and trial registers including PubMed, EMBASE, The Cochrane Library and ClinicalTrials.gov were searched up to 7 October 2010 with no restriction on date or language; search terms were reported. Two pharmaceutical company trials sites were also searched. Bibliographies of relevant articles were handsearched. Abstracts, letters, or posters that did not describe the full study were excluded.

Study selection
Randomised controlled trials (RCTs) that compared a cannabinoid with a placebo or active control group where the primary outcome was pain in patients with chronic non-cancer pain were eligible for inclusion. The authors followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) update on the QUORUM (Quality of Reporting of Meta-analysis) statement guidelines for systematic reviews. To be eligible any pain measuring scale could be utilised: the numeric rating scale for pain (NRS); visual analogue scale for pain (VAS); the Neuropathy Pain Scale; or the McGill Pain Scale. Trials with fewer than 10 patients were excluded. Secondary outcomes included adverse events (serious adverse events as defined in the review; drug related withdrawal; and most frequently reported side effects), level of function, sleep and quality of life.

The cannabinoids used in included trials were: oromucosal extracts of cannabis-based medicine (39% studies) delivered by spray; smoked cannabis (concentration range 0% to 9.4% in 22% studies); nabilone (range 0.25 to 2mg/day in 22% studies); dronabinol (10 or 20mg/day in 11% studies); and a synthetic analogue of THC-11-oic acid (one trial). Regimens varied widely. The mean treatment duration was 2.8 weeks (range six hours to six weeks). The comparison group was placebo in all except one trial, which used dihydrocodeine. The clinical conditions treated were mostly neuropathic pain (72% trials, including HIV neuropathy in two trials) and multiple sclerosis (three trials). Single trials studied spasticity-related pain, arthritis, and chronic spinal pain. Other types of pain treated in the remaining trials included rheumatoid arthritis, fibromyalgia, adjunct to opioids for mixed-chronic pain, and mixed-chronic pain.

One reviewer performed an initial study selection excluding articles that were clearly not relevant; two independent reviewers performed a second selection which included checking that studies were randomised.

Assessment of study quality
A modification of the Oxford scale was used to assess trial quality, giving a score for seven criteria including randomisation, allocation concealment, double blinding, and patient flow. Trials were excluded if they did not score 1 for randomisation.

Two reviewers independently performed the quality assessment, with discrepancies resolved by discussion.

Data extraction
Individual trial results were extracted with their significance, along with data on adverse events. Authors were contacted for additional information.
The authors did not report how many reviewers performed the data extraction.

**Methods of synthesis**
A narrative synthesis was performed due to trial heterogeneity for cannabinoids used, regimens, clinical conditions, follow-up periods and outcome measures. The results were summarised for each treatment type.

**Results of the review**
Eighteen RCTs were identified (925 patients, range 13 to 160, from Table 1); 766 completed participants met the inclusion criteria. The trials had a mean Oxford Score of 6.1. There were 13 cross-over trials and the rest had parallel groups.

**Overall efficacy**: Fifteen of 18 trials showed a significant analgesic effect. Four of six trials reported significantly improved sleep; the effects were modest. Adverse events were described as transient or mild to moderate, and well tolerated, not leading to withdrawal from the trial. There were no serious adverse events according to the review definition. Withdrawals due to side effects ranged from 0% to 18%. Results for the level of function were presented (five trials).

**Cannabis** (four RCTs): All trials showed a significant improvement in neuropathic pain for smoked cannabis versus placebo with no serious adverse events.

**Oromucosal extracts of cannabis based medicine** (seven RCTs): Six trials showed a significant improvement in chronic pain versus placebo. Five of seven trials reported no serious adverse events. One trial of rheumatoid arthritis found a significant decrease in disease activity.

**Nabilone** (four RCTs): Three trials found a significant analgesic effect compared with placebo; the fourth trial found that both nabilone and dihydrocodeine reduced pain to a similar extent. One of four trials reported no serious adverse events.

**Dronabinol** (two RCTs): Both trials found a significant reduction in pain compared with placebo.

**THC-11-oic acid analogue** (CT-3 or ajulemic acid; one RCT): There was a significant improvement in pain intensity after three hours, but not after eight hours compared with placebo, with no serious adverse events.

**Authors' conclusions**
There was evidence that cannabinoids were safe and modestly effective for chronic non-cancer (predominately neuropathic) pain with preliminary evidence in fibromyalgia and rheumatoid arthritis.

**CRD commentary**
The review addressed a well-defined question for participants, interventions, study design and relevant outcomes. Relevant databases were searched with no restrictions on language; the search included unpublished studies. Efforts were made to reduce error and bias for some review processes, but they were not reported for data extraction.

Trial quality was assessed using suitable criteria; the quality was considered excellent. Quality summary scores could be considered not helpful, but the trial quality was high. Relevant trial details were reported, but details of participant age and gender were not provided. A narrative synthesis was performed due to general trial variability. The results were separated by intervention type. Most of the included trials were small (only two had more than 100 patients) and treatment periods were relatively short (maximum six weeks).

The review was generally well conducted. The authors' conclusions may only be reliable for short-term treatment, but may not be for longer term treatment.

**Implications of the review for practice and research**
**Practice**: The authors stated that it was reasonable to consider cannabinoids as a treatment option in the management of chronic neuropathic pain and also for other types of chronic pain such as fibromyalgia and rheumatoid arthritis.

**Research**: Further large trials of longer duration that examine efficacy and safety of specific cannabinoids in
homogeneous populations were required, including effects on pain and function, and the potential for abuse.

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