Are cannabinoids an effective and safe treatment option in the management of pain: a qualitative systematic review

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Authors' objectives
To establish whether cannabis is an effective and safe treatment option in the management of pain.

Searching
Two authors searched the following sources independently, using different search strategies: MEDLINE from 1966 to 1999; EMBASE from 1974 to 1999; the Oxford Pain Relief Database from 1950 to 1994; and the Cochrane Library (Issue, 3, 1999). The most recent search was conducted in October 1999. The search included different combinations of the following MeSH and free-text terms: 'marijuana', 'marihuana', 'marijuana', 'cannabis', 'cannabinoids', 'THC', 'delta-9-tetrahydrocannabinol', 'nabilone', 'pain', 'analgesia' and 'random*'. Additional reports were identified from the reference lists of retrieved reports and review articles. The search considered publications in any language. Pharmaceutical manufacturers and authors were not contacted. Only full publications in peer-reviewed journals were considered for inclusion in the review. Unpublished data were not sought.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were included in the review.

Specific interventions included in the review
The authors included trials of cannabis given by any route of administration with any analgesic or placebo. No trials evaluated cannabis; all tested substances were cannabinoids. Four different cannabinoids were included in the review: oral delta-9-tetrahydrocannabinol (THC; 5 to 20 mg), an oral synthetic nitrogen analogue of THC (NIB; 4 mg), oral benzopyranoperidine (BPP; 2 to 4 mg), and intramuscular levonantradol (1.5 to 3 mg).

Participants included in the review
The trials had to assess human pain. The trials in the review included participants with cancer pain, chronic non-malignant pain, and post-operative pain.

Outcomes assessed in the review
The outcomes examined in the review were pain intensity scores, pain relief scores, and adverse effects.

How were decisions on the relevance of primary studies made?
Two authors checked all the retrieved reports to see if they met the inclusion and exclusion criteria.

Assessment of study quality
All potentially relevant reports that could be described as a RCT were scored for quality using the validated, 3-item Oxford scale of Jadad et al. (see Other Publications of Related Interest). This scale takes into account proper randomisation, double-blinding, and the reporting of withdrawals and drop-outs Two reviewers independently scored the included papers for quality.

Data extraction
The data were extracted by one author and crosschecked by at least two other reviewers. Data were extracted on the following: the type, dose, and route of administration of the cannabinoids; the controls; the types of pain; the sample size; the study design and duration; outcome measures for pain intensity; pain relief; the use of supplementary analgesia; patients' preferences; and adverse effects.
Methods of synthesis
How were the studies combined?
A narrative synthesis was undertaken.

How were differences between studies investigated?
Details of the individual studies were tabulated and were presented in the text, according to the type of pain being treated.

Results of the review
Nine RCTs were included in the review. The number of participants was unclear.

Cancer pain. In the 5 trials on cancer pain, 128 patients (figure derived from the table) were studied. In one study, 2 to 4 mg oral BPP (a THC congener) was not as effective as codeine sulphate (60 to 120 mg), and was no more effective than placebo in 37 patients. Oral THC (5 to 20 mg) was found to have an analgesic effect when compared with placebo in 10 patients with pain related to advanced cancer. In this study, a dose-response relationship was shown for analgesia but also for adverse effects. In a further study by the same group, oral THC 10 mg was approximately equipotent to codeine 60 mg, and THC 20 mg was approximately equipotent to codeine 120 mg. The higher dose was associated with unacceptable adverse effects. In one trial, NIB given orally was superior to placebo and equivalent to approximately 50 mg of codeine phosphate. In a second study in the same report, this nitrogen analogue was found to be superior to placebo and to 50 mg of secobarbital. However, in both of these trials NIB was felt to be of no clinical use, because of the frequency of the adverse effects.

Chronic non-malignant pain.

Two patients were studied in 2 ‘n of 1 within patient crossover’ trials for 6 weeks and 5 months, respectively. In an experienced cannabis user with familial Mediterranean fever, THC was found to be no better than placebo in terms of visual analogue scores for pain intensity. However, the level of morphine used for breakthrough pain was significantly lower while the patient was taking THC than when taking placebo: 170 mg versus 410 mg per 3 weeks. In a patient with neuropathic pain and spasticity secondary to a spinal cord ependymoma, THC 5 mg and codeine 50 mg were equianalgesic, and both were superior to placebo. Only THC, however, had a beneficial effect on spasticity.

Post-operative pain.

Thirty-six patients (figure derived from the table) were studied in 2 trials (conducted as a two-phase study). Levonantradol was more effective than placebo when given intramuscularly to patients with post-operative pain. Adverse effects with levonantradol were common, although considered mild.

Cannabinoids and adverse effects. Adverse effects were reported in all studies. Two patients withdrew from studies owing to the adverse effects of THC. THC showed a dose-response relationship for adverse effects such as mental clouding, ataxia, dizziness, numbness, disorientation, disconnected thought, slurred speech, muscle twitching, impaired memory, dry mouth, and blurred vision. In addition, at 20 mg, THC was highly sedating in 100% of patients, thus prohibiting its use. THC 10 mg was better tolerated, but the frequency of these adverse effects was still higher than with codeine 60 or 120 mg. Twenty-three reductions in arterial blood-pressure occurred, compared with placebo, but no more than with codeine. Changes in heart rate were not significant. THC 5 mg was well tolerated in neuropathic pain and did not cause an altered state of consciousness. Levonantradol caused adverse effects in most patients, but none withdrew. NIB did not affect heart rate but caused drowsiness in 40% of patients, and was therefore deemed to be of no clinical use. BPP caused a similar degree of sedation to codeine but was ineffective as an analgesic.

Authors’ conclusions
Cannabinoids are no more effective than codeine in controlling pain and have depressant effects on the central nervous system that limit their use. Their widespread introduction into clinical practice for pain management is therefore undesirable. They should not be used in acute post-operative pain. Before cannabinoids can be considered for treating spasticity and neuropathic pain, further valid RCTs are needed.
CRD commentary
The review question was clearly stated, and was well supported by the inclusion and exclusion criteria. The literature search was thorough, covering a number of relevant databases, and the reference lists of retrieved articles were also examined. The search terms and dates were given, and studies published in any language were included. However, there was no attempt to identify unpublished literature, thus raising the possibility of publication bias.

The validity of the included studies was appropriately assessed and study details were presented in the text of the review and in tabular format. The studies were synthesised appropriately in a narrative fashion, according to the type of pain being treated. Some details regarding the review process, such as how many reviewers were involved and whether decisions were made independently, were provided; other details, such as whether the reviewers were blind to source and how disagreements were resolved, were not stated.

The authors' conclusions appear to follow on from the results.

Implications of the review for practice and research
Practice: The authors state that the widespread introduction of cannabinoids into clinical practice for pain management is undesirable. They should not be used in acute post-operative pain.

Research: The authors state that before cannabinoids can be considered for treating spasticity and neuropathic pain, further valid RCTs are needed.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.