Systematic review and meta-analysis of cannabis treatment for chronic pain

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CRD summary
This review concluded that cannabis treatment was moderately efficacious for the treatment of chronic pain, but the risk of potentially serious harms may offset any treatment benefit. The authors' conclusion reflected the evidence presented, but the extent to which it is reliable is potentially compromised by an incompletely reported review process and reliance on trials of less than optimal quality.

Authors' objectives
To evaluate the efficacy and harms of cannabis preparations in the treatment of patients with chronic pain.

Searching
PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched, with no language restriction, to February 2008. Search terms were reported. Further data sources were searched, including several internet websites (listed in the paper), and registers of ongoing trials (Current Controlled Trials Register and ClinicalTrials.gov). References lists of retrieved papers were also scanned. Unpublished data were analysed during the review of included studies.

Study selection
Double-blind, randomised controlled trials (RCTs) of any cannabis preparations (synthetic or otherwise; administered by any route) that minimally contained delta-9-tetrahydrocannabinol, were eligible for inclusion in the review. The control group was required to receive a placebo treatment. Eligible participants were those suffering pathologically- or traumatically-induced constant or intermittent chronic pain, for a minimum of six months.

The outcomes of interest were pain intensity measured by numeric analogue scales, and the number of adverse events.

Over half of the included trials evaluated more than one cannabis intervention arm (various preparations or doses of the same preparation) compared with placebo. One trial was excluded because it assessed smoked cannabis. Trial differences were also noted in terms of type and aetiology of chronic pain. All included patients had chronic pain of a continuous or intermittent nature, and there was comparable baseline pain intensity amongst the intervention groups. Where reported, the mean age of participants ranged from 39 to 63 years; 46 to 95% were female.

The authors did not state how many reviewers selected the studies.

Assessment of study quality
Trial quality was assessed using the Jadad scale, covering randomisation, allocation concealment, withdrawals, and drop-outs. A score of 5 points indicated the highest quality.

Two independent reviewers performed the quality assessment.

Data extraction
For intervention efficacy, data were extracted on initial and final means with standard deviations (SD) to enable the calculation of standardised mean differences (SMDs) for each trial.

For harms, the number of adverse events was extracted to enable the calculation of odds ratios (OR) and 95% confidence intervals (CI). The number needed to harm (NNH) was also reported. Authors were contacted for additional information, where necessary.

The authors did not state how many reviewers carried out the data extraction.
Methods of synthesis
Standardised mean differences (weighted by the inverse of variance method), and odds ratios with 95% confidence intervals were separately pooled in fixed-effect or (in the presence of heterogeneity) random-effects meta analyses. Statistical heterogeneity was assessed using the $I^2$ statistic.

Subgroup analyses were conducted according to trial quality (Jadad score of 3 or less versus 3 or more), study design (parallel versus crossover), pain type (cancer versus non-cancer), and route of drug administration (capsules versus sublingual spray).

Publication bias was explored visually by funnel plot.

Results of the review
Eighteen RCTs (n=809 patients) were included in the review (12 cross-over trials and six parallel trials); sample sizes ranged from 10 to 177 patients. Two trials scored 5, two trials scored 4, six trials scored 2, and eight trials scored 3 points on the Jadad quality scale. Most of the trials did not report on allocation concealment or randomisation method. The adequacy of blinding was not assessed in any trial. Control of attrition bias was addressed in only five trials. There was variability across the trials in the reporting of outcomes. Drop-outs ranged from zero to 20.

Efficacy: A significant reduction in pain intensity was associated with cannabis-based interventions (SMD -0.61, 95% CI -0.84 to -0.37; $I^2$=0%; seven trials). There was no evidence of publication bias.

Harms: A significant increase was reported in risks of central nervous system-related adverse events following cannabis-based interventions; specifically, euphoria (OR 4.11, 95% CI 1.33 to 12.72; $I^2$=0%; NNH 8, 95% CI 5 to 19; four trials), harms related to alterations in perception (OR 4.51, 95% CI 3.05 to 6.66; $I^2$=2.8%; NNH 7; nine trials), events concerning motor function (OR 3.93, 95% CI 2.83 to 5.47; $I^2$ 0%; NNH 5; eight trials), and events relating to cognitive function (OR 4.46, 95% CI 2.37 to 8.37; $I^2$=0%; NNH 8; five trials). There were no significant differences for dysphoria.

An increased risk for gastro-intestinal adverse events was reported, but a statistical synthesis was not conducted due to high heterogeneity.

Subgroup analyses did not materially alter the main results.

Authors' conclusions
Cannabis treatment was moderately efficacious for the treatment of chronic pain, but the risk of potentially serious harms may offset any treatment benefit.

CRD commentary
This review addressed a clear research question and was supported by explicit inclusion criteria. The search strategy included a number of relevant sources, and steps were taken to minimise language and publication biases. The transparency of the study selection and data extraction processes was unclear, so the risk of reviewer errors and/or bias was a possibility.

An appropriate quality assessment tool was used, and the results were used to highlight the reliability of the review findings. Trial details were presented clearly. The chosen methods of synthesis appeared to be appropriate, taking account of statistical heterogeneity. The authors drew attention to several potential methodological flaws arising from the included trials.

Their conclusion reflected the evidence presented, but the extent to which it is reliable is potentially compromised by an incompletely reported review process and reliance on trials of less than optimal quality.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that further well-designed trials are needed to ascertain the balance of benefits and harms associated with cannabis treatment in patients with chronic pain.

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