Adverse effects of medical cannabinoids: a systematic review

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CRD summary
This systematic review aimed to assess the safety of medical cannabinoids. The authors concluded that short-term use of medical cannabinoids appears to increase the risk of non-serious adverse events, but that risks associated with long-term use were poorly reported. Overall this was a well conducted systematic review and the authors' conclusions are likely to be reliable.

Authors' objectives
To assess the safety of medical cannabinoids.

Searching
MEDLINE, EMBASE and PsycINFO were searched from inception to October 2007. Search terms were reported. Reference lists from selected articles and reviews were also searched for other potentially relevant studies. Studies published in English, French, Spanish or German were eligible for inclusion.

Study selection
Randomised controlled trials (RCTs) assessing the safety and efficacy of medical cannabinoids, where adverse events were quantified, were eligible for inclusion. Observational studies in which medical cannabinoids were the main exposure and adverse events were the primary outcome were also eligible for inclusion. Case reports describing adverse events in people exposed to medical cannabinoids were also eligible for inclusion. Studies of synthetic cannabinoids, combination treatments that included cannabinoids or the recreational use of cannabis were excluded from the review. Studies on treatments for cannabis dependence or cannabis cessation and studies on the effects of cannabis on school achievement, marriage, criminal behaviour or hormone levels were also excluded.

In the majority of the included studies patients suffered from cancer or multiple sclerosis and the cannabinoid was administered to address symptoms such as pain or nausea and vomiting induced by chemotherapy. The cannabinoid preparations investigated were oral Δ-9-tetrahydrocannabinol, oral Δ-9-tetrahydrocannabinol-cannabidiol or oromucosal Δ-9-tetrahydrocannabinol-cannabidiol. The median duration of cannabinoid exposure was two weeks (range eight hours to 12 months). In the majority of studies the control group received placebo, in some studies control groups received standard care.

Two reviewers independently assessed the titles and abstracts of studies for inclusion in the review. Disagreements were resolved through discussion.

Assessment of study quality
Two reviewers independently assessed the quality of the included RCTs using the Jadad scale, and the included observational studies using the Downs and Black checklist. Disagreements were resolved through discussion.

Data extraction
Data were extracted on serious adverse events and non-serious adverse events (according to definitions recommended by the International Conference on Harmonisation) by one reviewer, which was checked by a second reviewer. The incidence rate of adverse events in RCTs was calculated by dividing the number of events by the corresponding cumulative person-years (which was calculated by combining the person-years for all participants in the study exposed to cannabis). The cumulative person-years for patients exposed to the control was calculated in the same way. Rate ratios (RR) with 95% confidence intervals (CIs) were calculated for each trial. In the case of zero events, 0.5 was added to each count.

Methods of synthesis
Incidence rates of serious and non-serious adverse events for patients assigned to cannabis groups and control groups
were each combined. RRs were pooled using a random effects model. Statistical heterogeneity was assessed using the $\chi^2$ test and the $I^2$ statistic. Subgroup analyses were performed according to the type of cannabis preparation, duration of exposure, study design and study population. For non-serious adverse events RRs were also pooled for each system organ class.

**Results of the review**

Thirty-one studies were included in the review, including 23 RCTs (n=3,141, range six to 630) and eight uncontrolled observational studies (number of participants unclear). For the RCTs there was a total of 445 person-years of cannabinoid exposure and a total of 239 person-years of control exposure. The median Jadad score for the RCTs was 4 out of a possible 5 (range 2 to 5).

**Results from RCTs**

**Serious adverse events:** There was no statistically significant difference in the incidence of serious adverse events following medical cannabinoid exposure compared to control (RR 1.04; 95% CI: 0.78, 1.39). There were a total of 164 serious adverse events amongst the 1,932 participants assigned to cannabinoid therapy and 60 serious adverse events amongst the 1,209 participants assigned to control groups. There was no statistically significant difference in the incidence of death following medical cannabinoid exposure compared to control (RR 2.66, 95% CI: 0.77, 9.28).

**Non-serious adverse events:** There was a statistically significantly higher incidence of non-serious adverse events following medical cannabinoid exposure compared to control (RR 1.86, 95% CI: 1.57, 2.21), although there was significant heterogeneity between studies. There were a total of 4,615 non-serious adverse events amongst the 1,932 participants assigned to cannabinoid therapy and 1,641 non-serious adverse events amongst the 1,209 participants assigned to control groups.

**Cannabinoid preparation subgroups:** In subgroup analyses of different cannabinoid preparations, a statistically significantly higher incidence of non-serious adverse events remained for oromucosal $\Delta$-9-tetrahydrocannabinol-cannabidiol (RR 1.88, 95% CI: 1.48, 2.39) and oral $\Delta$-9-tetrahydrocannabinol (RR 2.18, 95% CI: 1.59, 2.99). There was no significant difference between oral $\Delta$-9-tetrahydrocannabinol-cannabidiol and control (RR 1.31, 95% CI: 0.88, 1.96). Subgroup analyses of study design and study population did not significantly alter the pooled RR for non-serious adverse events.

**Results from observational studies**

There were 39 serious adverse events and 3,553 non-serious adverse events reported.

**Authors’ conclusions**

Short-term use of medical cannabinoids appears to increase the risk of non-serious adverse events. Risks associated with long-term use were poorly characterised in the existing studies. Further high quality trials are required.

**CRD commentary**

This review addressed a clear question and was supported by appropriate inclusion criteria. The authors searched electronic databases and reference lists to identify relevant studies but no sources of unpublished data were searched. This increased the potential for publication bias. Validity of the included RCTs was assessed using a published checklist but results were not reported for individual trials, although the median quality score was high. The authors acknowledged that the Jadad score achieved by studies does not adequately reflect the quality of reporting of safety data. Adequate measures were taken to reduce the potential for reviewer bias and error in screening titles and abstracts of identified studies, assessing the quality of the included studies and data extraction procedures. Adequate details of the included studies were presented for RCTs. Appropriate methods were used to pool the results of the included RCTs and to assess statistical heterogeneity. Overall this was a well-conducted systematic review and the authors’ conclusions are likely to be reliable.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.
Research: The authors stated that the safety of the synthetic cannabinoid nabilone needs to be studied separately, and that safety and efficacy data on smoked medicinal cannabis are urgently needed. The safety of medical cannabinoids should be assessed separately from the safety of recreational cannabis use, owing to differences in amounts used, existence of co-morbidities and the methods of drug delivery. More studies with a longer duration of exposure are required to further assess the safety of medical cannabinoids, in order to detect rare adverse events and address concerns regarding tolerance and the development of cognitive and behavioural effects.

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Record Status
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.