# Questions and Answers on:

## "Cannabinoids for Medical Use: A Systematic Review and Meta-analysis"

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## What was the background to your review?

Kleijnen Systematic Reviews Ltd (see below) were commissioned by the Swiss Federal Office of Public Health to conduct a systematic review for the effects and adverse events of medical cannabis. Systematic reviews are studies of studies that offer a systematic approach to reviewing and summarising evidence. They follow a defined structure to identify, evaluate and summarise all available evidence addressing a particular research question. We were asked to focus on the following 10 indications which were of particular interest to our commissioners: nausea and vomiting due to chemotherapy, patients with HIV/AIDS, chronic pain, spasticity in patients with multiple sclerosis or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma, and Tourette's syndrome. We only included randomised trials, the most robust design for evaluating the effects of an intervention.

## What are the main findings of your review?

We included almost 80 trials (nearly 6,500 participants). We had most evidence for chronic pain (28 trials), nausea and vomiting due to chemotherapy (28 trials) and spasticity due to MS or paraplegia (14 trials) with less than five studies included for each of the other indications and none for depression. With the exception of the nausea and vomiting due to chemotherapy population, studies generally compared cannabinoids to placebo with only single studies for each indication comparing cannabinoids with an active comparator. In the nausea and vomiting population the majority of studies compared cannabinoids to an active comparator, most commonly prochlorperazine.

Most trials reported greater improvement in symptoms with cannabinoids compared to control groups, however, these did not always reach statistical significance. This may have been due to the small sample sizes of many of the included studies. Cannabinoids were also associated with a greater risk of short term adverse events, including serious adverse events. Common adverse events included dizziness, dry mouth, nausea, fatigue, sleepiness, and euphoria. Overall we found that there was moderate quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity and low-quality evidence to suggest that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep quality, and Tourette syndrome. When determining the quality of the evidence we considered the risk of bias in trials, the consistency of the evidence across the trials, the directness of the evidence (was the trials research question directly applicable to our review question), and the precision of the evidence. This is known as the "GRADE approach" and is used by over 70 organisations and is a standard component of Cochrane systematic reviews (http://www.gradeworkinggroup.org/).

## What are the side effects of taking cannabinoids? Are they worse than you would expect from other prescription drugs?

Overall the proportion of patients who experienced any side effect was 81% of those in the cannabinoid group and 62% of those in the control group, usually placebo (summary OR 3.03 2.42, 3.80). However, there was a lot of variation across studies. Of the 29 studies that reported on the incidence of any adverse event the incidence ranged from 12-97% in the cannabinoid group and 13-80% in the control group. Other than in the nausea and vomiting due to chemotherapy indication, very few of the studies included a comparison with prescription drugs and so it is not possible for us to say whether these side effects were significantly worse than you would expect from prescription drugs for these conditions. Most of the side effects were mild although we did also find an increased risk of serious side effects, the incidence of these in both the cannabinoid and control group was low at around 6% in the intervention group and 4% in the control group.

## Were there any trends in the type of condition researched over time?

We had more older studies than recent studies in our review: a third of the studies included in our review were published before 1990 and the median year of publication was 2004. There were some trends in terms of when studies of particular indications were more likely to be carried out. Most of the studies on nausea and vomiting in patients undergoing chemotherapy were conducted before 1990, although we do have one study for this indication conducted in 2014. The studies conducted in the last five years more commonly evaluated patients with chronic pain and spasticity due to MS, although the earliest study included in our review (published in 1975) was a study in patients with chronic pain.

## What type of cannabinoids did you include in your review and how do these differ from each other?

We included any randomised trial that evaluated a cannabinoid for one of our indications of interest. Cannabinoids are any compound, natural or synthetic, that can mimic the actions of plant-derived cannabinoids. Inhaled marijuana consists of a number of different compounds. In contrast, synthetic cannabinoids usually include just one (THC; nabilone and dronabinol) or two cannabinoids (THC and CBD; nabiximols). We only found two studies that evaluated cannabis.

## What are the implications for clinicians and policy makers?

We have used the same robust evidence based methods to evaluate the effects of medical cannabis (cannabinoids) as we would apply to any other intervention. It is important that all interventions are judged according to the same standards and that the potential benefits and adverse effects of cannabinoids are considered in light of the evidence and are not clouded by the issues around the legal status of cannabis. As systematic reviewers, we have provided a summary of the available evidence which clinicians and policy makers can now use to make recommendations for practice.

## What are the implications for patients?

There is evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. However, this needs to be balanced against an increased risk of side effects such as dizziness, dry mouth, nausea, sleepiness, and euphoria. Although our review did not find any studies on the long term adverse events of medical cannabinoids, other reviews of the long term effects of cannabis have shown an increased risk of psychosis. Individuals considering cannabinoids as a possible treatment for their symptoms should discuss the potential benefits and harms with their doctor.

## What are the implications for future research?

Further large, well conducted, randomised trials are needed to confirm the effects of cannabinoids, especially in areas for which our comprehensive systematic review found no or very little evidence: weight gain in patients with HIV/AIDS, depression, sleep disorders, anxiety disorder, psychosis, glaucoma, and Tourette syndrome. We only found two studies that evaluated cannabis and so further trials evaluating cannabis itself are also required. Two main challenges faced by our review were the poor reporting and lack of standardised outcome measures. Future trials therefore need to adhere to CONSORT reporting standards and report outcome data in a form that can be incorporated into meta-analyses. Poor reporting made it difficult to assess the risk of bias in the included trials and to extract appropriate numerical data for inclusion in meta-analyses (statistical combination of data from primary studies to give an estimate of the effect across all studies). Lack of standardised outcomes meant that included trials reported a wide variety of outcomes measured in different ways making it very difficult to combine data in a meaningful way. Future studies need to assess relevant outcomes (including disease-specific endpoints, quality of life, and adverse events) using standardised outcome measures at similar time points to ensure inclusion in meta-analyses. All ongoing or future trials should be registered, e.g. on clinicaltrials.gov, to make them known to the scientific community, to allow planning of research efforts, and to avoid duplication of work.

## Kleijnen Systematic Reviews Ltd (KSR)

Kleijnen Systematic Reviews Ltd (KSR) is an independent research company that produces and disseminates systematic reviews, cost-effectiveness analyses and health technology assessments of research evidence in health care.

Staff at KSR have many years of experience in preparing systematic reviews and health technology assessments of therapeutic, screening and diagnostic interventions. Such reviews have been used to support policy making, local decision making about commissioning health services, fourth hurdle processes (such as for NICE in the UK, or for IQWiG in Germany), and guideline development. We have extensive experience in all these areas and our names appear as authors on numerous journal publications, technology assessment reports for NICE, systematic reviews for IQWiG, health technology assessment reports, and guidelines.

KSR has also been appointed as a "Centre of Excellence" for Technology Assessment Reviews (TARs) by the National Institute for Health Research (NIHR). In this capacity we are involved in providing TARs for national UK NHS decision-making bodies and policy customers, such as the National Institute for Health and Care Excellence (NICE). Such TARs are most commonly produced to inform NICE Appraisal Committee guidance on the use of new and existing medicines, treatments and procedures within the NHS in England and Wales.

For more information about KSR, please visit our website www.systematic-reviews.com.

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