# Strengthening the evidence for medicinal cannabis and cannabinoids

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## Introduction

Draft recommendations by NICE[1] did not recommend prescription of unlicensed cannabis-based products to patients on the NHS. The potential benefits for chronic pain were considered too small in relation to costs, and the quality of evidence was rated too low to make recommendations for severe treatment-resistant epilepsy.[1] At present, the only access to cannabis is through prescriptions at private clinics[2] (which are prohibitively expensive) or via the illicit market (which carries risk of prosecution). Given the strong demands for access to these products by patients and their carers[3] there is an urgent need to strengthen the evidence and to make these products available in cases where they are known to be efficacious and safe.

Cannabis-based medicines vary in their content of delta-9-tetrahydrocannbinol (THC) and cannabidiol (CBD) which have contrasting mechanisms of action, efficacy and safety.[4] Some cannabis-based medicines include a combination of THC and CBD which can interact with each other when co-administered.[5] Although Randomised Controlled Trial (RCT) evidence is stronger for certain formulations (such as CBD for severe treatment-resistant epilepsy[4]) patients have expressed a preference for other treatments such as THC combined with CBD.[3] Gathering evidence for such treatments is a key priority that can be addressed using novel RCT designs and patient registries.

In order to compare varied cannabis-based products efficiently, RCTs can follow adaptive designs.[6] For example, patients can be initially randomised to one of several treatment arms such as THC, CBD, or THC combined with CBD. Interim analysis can eliminate treatment arms with poor efficacy or safety at an early stage, while randomisation continues to potentially efficacious doses to strengthen the certainty of evidence.

Cannabis-based products have been investigated for a wide range of possible medical indications, some of which may share common pathologies of the endocannabinoid system.[7] Where multiple disorders are characterised by the same underlying mechanism, basket trials[8] can investigate a single targeted intervention across multiple diagnostic categories. Alternatively where different mechanisms are known to give rise to a common medical diagnosis, umbrella trials[8] can stratify patients into different treatment arms based on underlying disease mechanism and allocate targeted interventions to each group.

Stratification can also occur at the level of the individual patient. N-of-1 trials[9] use within-patient, randomized, double-blind, crossover comparisons to compare active and control treatments in a cyclical manner. N-of-1 trials can establish cause-effect relationships within an individual to identify efficacy and safety, and the results from multiple patients can be meta-analysed. N-of-1 trials have been successfully applied to cannabis-based products (THC, CBD, or THC combined with CBD) for chronic pain[10] and could be used for severe treatment-resistant epilepsy. They are ideally suited to specific situations such as treatment for compassionate reasons, unlicensed use, and for patients who fail to respond to conventional treatments[11] making them especially suitable for investigating cannabis-based medicines in some patients. Classification of a patient as a "responder"[9] on a case-by-case basis could offer strong evidence for continued prescription.

RCTs are not the only source of evidence. There are many examples of pharmacological treatments for medical indications approved by the EMA and FDA without RCTs.[12] Non-RCT sources of evidence used to support drug approvals include randomised trials without a control group (e.g. different doses of active drug with no placebo), historical control studies, and observational studies.[12] In cases where cannabis-based medicines are provided on private prescription,[2] patient registries can be used to generate observational data. Such data can be

rapidly generated at minimal cost, and may be compiled with registries outside of the UK such as Canada and Israel to generate large samples of data providing real-world clinical evidence.

Initial public funding to support research on cannabis-based products has been offered through dedicated calls from the National Institute of Health Research. However, the House of Commons Health and Social Care Committee[13] raised concerns about the unwillingness of industry to provide cannabis-based products for research or to support or conduct clinical trials on their products. Further involvement from industry could increase access to cannabis-based products in a research context without the excessive costs of private prescriptions to patients.[2] Providing access to cannabis-based products in a research context could offer patients balanced information on their likelihood of benefiting from them according to the evidence at present.

The current low certainty of evidence for cannabis-based products alongside clear patient demand requires novel solutions. Further RCTs for cannabis-based medicines are urgently needed, and novel RCT designs such as N-of-1 trials can provide results that are immediately beneficial for both the patient and clinician.[9] Like all methodologies, RCTs have their own limitations and relying on these alone may result in biased estimates of effect. Data should be sought from alternative methods such as observational patient registries and triangulated with other methods to develop a robust evidence base.[14]

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## Competing interests statement

We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: none.

## Copyright statement

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