Strengthening the evidence for medicinal cannabis and cannabinoids

Alternative trial designs and patient registries can rapidly generate robust data on efficacy and safety

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Draft recommendations by the National Institute for Health and Care Excellence (NICE) did not recommend prescription of unlicensed cannabis based products to patients on the NHS. The potential benefits for people with chronic pain were considered too small relative to costs, and the quality of evidence was rated too low to recommend use in children with severe treatment resistant epilepsy.¹ At present, the only way to get cannabis products for medicinal use in the UK is through prescriptions issued by private clinics (which are prohibitively expensive) or the illicit market (which carries risk of prosecution as well as unknown product content, quality, and safety). Given the vocal requests for access to these products from patients and their carers,更强 evidence is urgently needed so that these products can be made available in situations where they are known to be effective and safe.

Cannabis based medicines vary in their content of Δ⁹-tetrahydrocannabinol (THC) and cannabidiol (CBD), which have contrasting mechanisms of action, efficacy, and safety.⁷ Some cannabis based medicines include both THC and CBD, which can interact with each other.⁷ Although evidence from randomised controlled trials is stronger for certain formulations (such as CBD for severe treatment resistant epilepsy⁵), patients have expressed a preference for treatments such as THC combined with CBD.¹ Gathering evidence for such treatments is a priority and can be expedited by using alternative trial designs and patient registries.

Alternative trial designs and patient registries

To compare varied cannabis based products efficiently, randomised controlled trials can follow adaptive designs.⁸ 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 trial arms testing potentially effective doses.

Cannabis based products have been investigated for a wide range of medical indications, some of which may share aetologies related to the endocannabinoid system.⁷ When multiple disorders are characterised by the same underlying mechanism, basket trials can investigate a single targeted intervention across multiple diagnostic categories.⁴ Alternatively, when different mechanisms are known to give rise to a common medical diagnosis, umbrella trials can stratify patients into different treatment arms based on the underlying disease mechanism, allocating targeted interventions to each group.⁸ Stratification can also occur at the level of the individual patient. N-of-1 trials allow randomised, double blind crossover comparisons of active and control treatments in a cyclical manner sequentially in the same patient.⁹ These trials can establish efficacy and safety within an individual, and the results from multiple patients can be combined with meta-analysis.

Such trials have been used to evaluate cannabis based products in people with chronic pain¹⁰ and could be used for other indications such as severe treatment resistant epilepsy. They are ideally suited to situations such as treatment for compassionate reasons, unlicensed use, and for patients who fail to respond to conventional treatments,¹¹ as is often the case for cannabis based medicines. Establishing individual patients as “responders” by using n-of-1 trials could provide evidence strong enough to justify continued prescription.

Randomised controlled trials are not the only source of evidence. The European Medicines Agency and the US Food and Drug Administration have approved many drugs without randomised trials.¹² Other sources of evidence used to support drug approvals include historical control studies and observational studies.¹² Where cannabis based medicines are provided on private prescription,³ patient registries should be set up to generate observational data on real world clinical practice and outcomes.
Such data can be rapidly obtained at minimal cost and may be combined with registries outside the UK—in countries such as Canada and Israel.

Need for industry cooperation

Initial public funding to support research into cannabis based products has been offered through dedicated calls from the National Institute for Health Research. However, the UK’s parliamentary health and social care committee has raised concerns about the unwillingness of industry to provide cannabis based products for research or to support or conduct clinical trials on their products. Greater support from industry could increase access to cannabis based products in a research context and help patients avoid the excessive costs of private prescriptions. Providing access to cannabis based products in trials with informed consent can offer participants balanced information on the possible benefits and risks, which are uncertain based on the evidence at present.

The current limited evidence for cannabis based products alongside clear patient demand requires new solutions. Further trials are urgently needed, and designs such as n-of-1 trials can provide rapid evidence to inform treatment and optimise clinical outcomes for individual patients. Like all research methods, randomised trials have their limitations, such as poor generalisability. Data should also be sought from alternative methods, such as observational data from patient registries, which can be triangulated with other findings to develop a robust evidence base. 

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