Cannabinoids may improve severe epilepsy
but adverse events increase

Although 70-80% of people with epilepsy can control their seizures using antiepileptic drugs, the remainder do not respond completely and require an alternative.

There has been widespread interest in the medical use of cannabis and its active components (cannabinoids), particularly in severe, drug-resistant epilepsy. Laboratory and animal studies suggest they may reduce epileptic seizures, and they have shown promise in some studies in people with severe epilepsy.

In people with some types of severe, drug-resistant epilepsy, adding cannabidiol to their treatment may reduce seizure frequency and improve quality of life compared with placebo, according to a systematic review that aimed to bring together evidence on the safety and efficacy of cannabinoids as an add-on (adjunctive) treatment for drug-resistant epilepsy (Stockings et al, 2018).

The review looked at cannabinoids as adjunctive treatments for drug-resistant epilepsy. It included six randomised controlled trials with 555 participants and 30 observational studies with 2,865 participants. All trials compared cannabidiol, a medicinal-quality cannabinoid, with placebo. The most recent, larger randomised controlled trials used a dose of 10mg or 20mg/kg/day over 14 weeks; earlier trials used 100mg two to three times a day over four to 26 weeks. The average age of participants was 16.3 years, and most had severe forms of epilepsy that start in childhood.

Only one trial was at low risk of bias; the remainder were at high risk of bias or could not be judged due to poor reporting. Observational studies were mostly at serious or critical risk of bias, and those results are not included here. The trials are mainly funded by one manufacturer. The use of this drug, based on this evidence, should be very cautious.

The main findings of this study are summarised in Box 1.

**Box 1. What did the review find?**
- Cannabidiol increased the likelihood of becoming seizure-free (78% with cannabidiol vs 0.7% with placebo)
- The likelihood of reducing seizure frequency by 50% or more was moderately increased (43.5% cannabidiol vs 25.0% placebo)
- The incidence of adverse events was higher with cannabidiol (88.4%) than with placebo (69.7%); serious adverse events were 18.9% with cannabidiol vs 6.8% with placebo; treatment-related serious adverse events were 6.8% with cannabidiol vs 0.6% with placebo.
- Parents or carers reported an improvement in their child’s overall quality of life (59.8% with cannabidiol vs 34.5% with placebo)
- To read the full Signal report go to: Bit.ly/NIHRcannabinoids

**Implications for practice**
- There are limited options available for people whose epilepsy has not responded to existing drug treatments. For children and young people these options include a ketogenic diet (low in carbohydrates and high in fat), as well as vagal nerve stimulation (implantation of a device to suppress abnormal electrical brain activity associated with seizures); deep brain stimulation may also be an option in special circumstances (National Institute for Health and Care Excellence, 2018).
- This review suggests some benefits of cannabidiol in a selected population with drug-resistant epilepsy, however, bias may explain some or all results.
- The main clinical outcome in epilepsy should be complete seizure freedom and this is an exception in the studies reviewed: the authors estimated a number needed to treat of 171 before seizure freedom was seen; this is not very impressive. Much more convincing evidence is needed if cannabinoids are to become a standard treatment for epilepsy.
- Cannabidiol is not licensed for the treatment of epilepsy in the UK, and is not covered by UK guidelines. It has been given orphan designation by the European Medicines Agency for the treatment of several severe and rare forms of epilepsy that have not responded to other treatments. This means incentives are in place to encourage its development for these indications, and a pharmaceutical company has applied to do this.

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**References**
National Institute for Health and Care Excellence (2018) Epilepsies: Diagnosis and Management. nice.org.uk/CG137