Medicinal cannabis in the treatment of epilepsy

Executive Summary

- The Epilepsy Foundation recognises the need for more effective and safe therapies to assist patients and their families facing severe, intractable seizures.
- The effectiveness and safe use of medicinal cannabis products for epilepsy is currently lacking a sound evidence base.
- A recent trial of medicinal cannabis published in the New England Journal of Medicine offers cautious optimism on the role of medicinal cannabis for children with severe epilepsy. Further trials are due to report.
- Should evidence support that the benefits outweigh adverse events then best practice guidelines can be developed.
- The Epilepsy Foundation supports the need for further clinical trials to establish this evidence base.
- The unregulated manufacture, supply or possession of cannabis, in any form, is illegal in all states of Australia.
- Pharmaceutical cannabis products available for the treatment of pain and wasting associated with HIV and chemotherapy and for the treatment of spasticity in multiple sclerosis are not suitable for the treatment of severe refractory epilepsy or catastrophic epilepsy syndromes.
- Until the Therapeutic Goods Administration approves medicinal cannabis as an adjunct treatment for severe epilepsy, the Epilepsy Foundation urges all people living with epilepsy, their families and carers to consult with an epilepsy specialist and explore the many existing treatment options, so that they can make an informed decision. This would take into account the possible risks and benefits of the different treatment options, including any participation in clinical trials of medicinal cannabis.

Introduction

In 2016 Australian State and Federal governments responded to the calls from patients, families, their carers and clinicians for more effective therapies in severe, intractable epilepsies, by introducing legislation to facilitate the introduction of medicinal cannabis as a treatment for epilepsies as well as in other conditions.

Medicinal cannabis products remain an unapproved drug but now may be accessed via certain medical practitioners through the Special Access Scheme (SAS) or Authorised Prescriber Scheme.1

The unregulated manufacture of cannabis products, whether for medicinal or recreational purposes remains illegal in all Australian states. The Therapeutic Goods Agency (TGA) states: Cannabis remains a highly regulated drug in Australia and the use and supply of cannabis for non-medical purposes (for example, recreational use) is illegal in Australia, in accordance with applicable Commonwealth, state and territory laws.1

The active compounds found in the cannabis plant are referred to as cannabinoids. The cannabinoids that have attracted the most attention to date are cannabidiol (CBD), the major non-psychotropic compound, and tetrahydrocannabinol (THC) the compound that gives cannabis its psychotropic effect. Where the use of cannabis in epilepsy is concerned, CBD has been found by a number of small studies, as well as anecdotally, to reduce seizure activity. CBD use does not produce a ‘high’.

The American Academy of Neurology conducted a systematic review of the efficacy and safety of medical marijuana in selected neurological disorders and found that the use of oral cannabinoids are of unknown efficacy in epilepsy, that the risks and benefits of medical marijuana should be weighed carefully, and that the comparative effectiveness of medical marijuana versus already established therapies is unknown for epilepsy.2
In the United States in 2014, the Food and Drug Agency gave Orphan Drug Status\(^1\) to Epidiolex (cannabidiol) as an investigational drug therapy of Dravet and Lennox-Gastaut syndromes.\(^1\) Epidiolex was also given European Orphan Drug Status in 2017.\(^4\) There is an ongoing open label study (i.e. a clinical research study in which the participant, health care professional, and others know the drug and dose being given) that has recently released data for 27 patients treated for more than 12 weeks.\(^5\) Four patients were seizure free and approximately half the patients had a 50% reduction in seizures. Somnolence, fatigue, diarrhoea and altered appetite were each seen in more than 10% of these patients. These interim results look positive and we wait for further results to be published.

More recent reports of a Phase III, double-blind randomised placebo controlled trial of Epidiolex with 171 patients with Lennox-Gastaut Syndrome has shown a reduction in seizures frequency but increased treatment-related adverse events for those on the Epidiolex compared with the placebo.\(^5\) The results of a 2017 double-blind placebo controlled trial in 120 children and young adults with Dravet Syndrome were reported in the National English Journal of Medicine. Those in the CBD group demonstrated a decrease in seizures compared to the placebo group, but also reported increased adverse events. Commonly reported adverse events included drowsiness, ataxia and diarrhoea, and while more serious side effects were less common, some patients did experience a worsening of their seizures. Some of these adverse events were controlled by dose reduction but 8 patients on CBD withdrew from the trial.\(^6\)

Small clinical trials have therefore provided some evidence for the efficacy and safety of CBD for children with severe epilepsy. Despite these encouraging early findings, research data on the use of medicinal cannabis for epilepsy is limited. A 2014 Cochrane Review on Cannabinoids for Epilepsy examined published studies to assess the efficacy and safety of cannabinoids when used as monotherapy or add-on treatment for people with epilepsy. This review found that, overall, no reliable conclusions could be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy. Only four studies from 1978 to 1990 met the selection criteria of randomized control trials (the best level of evidence for new medications), whether blinded or not. Other difficulties with studies to date have included, small patient numbers, varying reports of seizure frequency and/or freedom, a lack of information on the cannabis compounds used, and a lack of longer term studies (most studies run between 4 weeks to 18 months), preventing an understanding of the long-term safety of these compounds.\(^7,8,9,10\) Furthermore, it should be noted that recent guidance documents released by the TGA state that “evidence is unavailable for first line or sole use of medicinal cannabis or cannabinoids in epilepsy.”\(^11\)

**The current situation in Australia with medicinal cannabis and epilepsy**

The situation in Australia is changing at a very fast pace. Much has been put in place by the TGA to provide the basis for prescribing medicinal cannabis. Medicinal cannabis is imported at the moment but is regulated by the TGA. Patients will need a prescription from the treating doctor to obtain medicinal cannabis. This will come under the Special Access Scheme (SAS). If the prescribed medicine is more than 2% THC (the part of cannabis that creates a “high”) then it is considered very restricted and the doctor needs to apply for an additional Schedule 8 permit. This is unlikely to impact on people with epilepsy as medicinal cannabidiol here will contain 2% or less THC, which means that it is a Schedule 4 drug and does not require anything more than the SAS permit.

In Victoria, the government is providing access to cannabidiol on a compassionate scheme for some 29 young children with uncontrolled seizures. This is being closely monitored by their treating specialists and data is being collected on the results. In Queensland, medicinal cannabis is available for a number of conditions including uncontrolled epilepsy and can be prescribed by both specialists and general practitioners after applying through the TGA SAS and to the Queensland Dept. of Health. Similar arrangements are enacted in other states.

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1. Orphan drug status is given to drugs which are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the US, or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug.
In October 2016 Federal Parliament passed legislation to enable applications for licences and permits for the cultivation, production and manufacture of medicinal cannabis products in Australia. This industry will be highly regulated. It will also mean a new pharmaceutical industry for Australia and a consistently high standard of medicinal cannabis products. Barriers to the use of all medicinal cannabis products in Australia at present are the shortage of supply of imported product and the associated cost.

Recent guidance documents released by the TGA include a number of recommendations for individuals considering medicinal cannabis for epilepsy, multiple sclerosis, chronic pain, palliative care and nausea and vomiting related to chemotherapy or HIV/AIDS. The guidance document for people with epilepsy includes the following recommendations (among others):

- Epilepsy treatment with medicinal cannabis or cannabinoids is only recommended as an adjunctive treatment – that is, in addition to existing anti-epileptic drugs.
- There is insufficient evidence to provide recommendations for adults aged over 25 years.
- Patients and prescribing clinicians should be aware of likely adverse events such as diarrhoea, drowsiness, and changes to appetite. Adverse events such as a worsening of seizures, convulsions, severe diarrhoea or behavioural difficulties may affect the aims of the epilepsy treatment and increase the likelihood of treatment withdrawal, and should be evaluated on a case by case basis. If treatment is likely to be long-term, it is important that any side-effects from medicinal cannabis are not greater than side effects experienced with other anti-epileptic drugs and that their response to treatment is regularly assessed.
- In the absence of strong evidence for dosing and specific preparations of medicinal cannabis in epilepsy treatment, it is recommended that CBD be used and re-evaluated after twelve weeks of therapy, to ascertain whether there has been any benefit from its introduction.
- Prescribing clinicians should also be aware of the potential drug-drug interactions with CBD and anti-epileptic drugs.

The future of medicinal cannabis in epilepsy treatment in Australia

In the future, Australia will have a safe consistent supply of medicinal cannabis for a number of conditions including epilepsy. As the Australian industry develops there will be more trials conducted which will be of particular importance to encourage in the case of children and young people with epilepsy as this ensures the highest standards of care.

The Epilepsy Foundation urges all people living with epilepsy, their families and carers to consult with an epilepsy specialist and explore the many existing treatment options, so that they can make informed decisions with their specialist that weighs the risks and benefits of the different treatment options, including any participation in clinical trials of medicinal cannabis.

While these results are encouraging we need to exercise caution because of the lack of evidence around the efficacy and safety of using medicinal cannabis in children and the potential impact it can have on the developing brain in regard to memory, cognition, and the potential for psychosis in later years. Even more caution should be exercised with regard to using marijuana bought illicitly since the ingredients in it will be unknown and untested. Patients and families need to give careful consideration to such issues.

The use of medicinal cannabis and driving motor vehicles

This section refers to CBD, THC and non-prescribed cannabis products. While prescribed medicinal cannabis products in epilepsy are limited to children at present, this situation will change and cannabis is likely to be prescribed to people of driving age.

Prescribed CBD is not an illicit drug under the Road Safety Act in Victoria. However, CBD would be considered a drug by the Road Safety Act if it deprives the person consuming it of any of his/her mental or
physical capacities, in other words being impaired by the CBD. This is the case with any drug, prescribed or not.

Prescribed THC is an illicit drug for the purposes of the Road Safety Act and any presence of THC in blood is a driving offence. CBD does not necessarily show up in any of the standard roadside tests, however THC does.

When being prescribed a medicinal cannabis product it is important to use it in accordance with the prescribing doctor’s directions and to seek advice as to driving a motor vehicle while using that specific product.

There are discussions taking place amongst the States to develop a nationally consistent approach to driving and medicinal cannabis but at this point in time each State has some variations about which drivers will need to inform themselves.

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References