**Marijuana and Medicinal Cannabis in the treatment of epilepsy**

Patients, families, carers and doctors recognise the need, sometimes a desperate need, for additional, more effective and better tolerated therapies for epilepsy. Medical treatment decisions should always be based on knowledge of potential risks and proven benefits of the therapy. Anecdotal reports of patients with epilepsy experiencing dramatically beneficial responses to treatment with derivatives of marijuana, “medical marijuana” or “medicinal cannabis” as it is often known, have brought renewed attention to its potential as an anti-epileptic therapy1. Importantly, there are also many reports of people who experience worsening of seizure control with the use of marijuana.

Marijuana contains many different compounds. The most active compounds are the cannabinoids, which include THC (9-tetrahydrocannabinol) and CBD (cannabidiol). THC is the main cannabinoid responsible for the psychoactive and addictive effects of marijuana. THC may be harmful for people with epilepsy and put them at increased risk of psychiatric problems such as psychosis.

The main cannabinoid that is promising as a treatment for epilepsy is CBD. Many reviews emphasise that the current data for CBD in epilepsy are limited, and no definite conclusions can be drawn until further formal clinical trials are published 2-5. The controlled clinical trials reported thus far are for the severe epilepsies of childhood (in particular Dravet and Lennox-Gastaut syndromes), rather than more common types of epilepsy. Further, the safety profile of long term treatment with cannabinoids is not well established.

One pharmaceutical CBD (Epidiolex™) has been given Orphan Drug status by the Food and Drug Agency of the United States as an investigational drug therapy for patients with Dravet and Lennox-Gastaut syndromes. A recent open-label non-randomised study in 214 children and young adults with severe uncontrolled epilepsies reported a mean 34% reduction in monthly seizure rate over a 12 week study period6. Serious adverse effects were reported in 12% of patients possibly related to CBD intake. The most common severe adverse event reported was status epilepticus, affecting 6% of individuals.

In 2016 GW Pharmaceuticals announced (by media release) positive results of the first randomised, double blinded, placebo controlled Phase III clinical trial of it Epidiolex for the treatment of Lennox Gastaut Syndrome. Epidiolex was added as an adjunct to the patient’s current treatment resulting in a significant reduction in seizure frequency over a 14 week period in the treatment group compared patients in whom placebo treatment was added (p=0.0135).

This trial follows a media announcement in March 2016 of a positive result for the same agent in a Phase III, double blind, placebo controlled study for Dravet’s Syndrome. This work has recently (May 2017) been published in the New England Journal of Medicine7  providing the first class one evidence for the use of medical cannabidiol in a subset of patients with epilepsy. The percentage of patients who had at least a 50% reduction in convulsive seizure frequency was 43% in the treatment group and 27% with placebo (p=0.8). Adverse events that occurred more frequently in the treatment group included diarrhoea, vomiting, somnolence and abnormal liver function tests.

More broadly, the adverse effects on health from marijuana intake include effects on brain development, risk of addiction, cognitive impairment during times of intoxication, subsequent psychiatric illness and increased risk of motor vehicle accidents5. Currently, we have limited understanding of the long term effects of marijuana intake, including whether it is teratogenic (effects on the unborn baby). Further, the increase in the THC concentration of marijuana in the United States is estimated to have risen from 3% to 12% over the last 30 years. This may lead to increased toxicity8.

There are now imported cannabidiol products available in Australia that can be accessed via the Special Access Scheme (SAS). However these products are not approved or registered with the Therapeutics and Goods Administration (TGA) and at current standard dosing, as suggested by the limited trial data available, would cost individuals and/or their families approximately $40,000 per annum.

How should neurologists advise patients regarding “medical marijuana” (medicinal cannabis) for the treatment of epilepsy until there is sufficient, good quality evidence from clinical trials to allow informed decisions for best management? Firstly, the extent of uncertainty regarding efficacy (whether it works in all people with epilepsy, or just a small subset of people with severe epileptic encephalopathies) and safety of CBD should be explained to patients and families.

Secondly, definitive answers regarding efficacy and safety of marijuana and specific cannabinoids to treat people with epilepsy needs to be obtained from properly constructed and ethically approved double-blind randomized placebo-controlled trials, in both children and adults, in different types of epilepsy. Despite the promising class I evidence recently published for Dravet’s Syndrome, even this requires replication.

Thirdly, individual doctors should determine their position on how the use these substance to obtain a therapeutic benefit should be appropriately managed. Finally, patients need to be aware of the limitations with respect to availability, including the lack of a TGA registered and approved product and the prohibitive costs of current imported products.

In summary, the Epilepsy Society of Australia has the following position:

a) In general, the use of CBD and related agents in epilepsy should be in the context of a human ethics committee approved research trial, as efficacy and safety are still being evaluated. These agents are at a stage of development of an investigational drug.

b) There is now evidence to support the use of certain cannabidiols in severe drug resistant epilepsies (e.g. epileptic encephalopathies) where prescription outside of a clinical trial may be considered, where a suitable compound meeting consistent concentration, bioavailability and stability standards as applicable by the Therapeutic Goods Administration approved medicines is available.

c) Recommendations regarding use will likely change with information obtained from clinical trials of these drugs.

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