**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 therapy. 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. The 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 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 period. 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.

More recently GW Pharmaceuticals announced (by media release) positive results of the first randomised, double blinded, placebo controlled Phase III clinical trial of 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 this year of a positive result for the same agent in a Phase III, double blind, placebo controlled study for Dravet’s Syndrome. Formal publication of the results is awaited in a peer-reviewed journal.

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 accidents. 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 toxicity.

How should neurologists and other medical practitioners 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 people with epilepsy) and safety of CBD should be explained to patients and families. Secondly, the patient or family should be encouraged to inform a treating doctor if this alternative therapy is being commenced (and the lack of legal implications in doing so emphasised). This means that if a significant change in the patient’s health occurs, it can be properly assessed. Thirdly, 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. Finally, individual doctors should determine their position on how the use of an illicit substance to obtain a therapeutic benefit should be appropriately managed.

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 may be select cases of severe drug resistant epilepsies (eg. 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.

References:
1. The case for medical marijuana in epilepsy. Maa E, Figi P Epilepsia 2014;55: 783-6