The Medicine Cabinet: Medicinal Cannabis – why the fuss?

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Medicinal cannabis became a controlled substance in the Poisons Standard on 1st November 2016 and thus is a Schedule 8 controlled medication but cannabidiol is schedule 4 (prescription medication). Prescribing medicinal cannabis requires state legislation and at present the only licensed product is Sativex® which is an oromucosal spray but currently there is no local sponsor and as such the product needs to be imported on a personal use and TGA Special Access Scheme (SAS) category B authorisation.

Each cannabis or marijuana plant (*cannabis sativa or indica or ruderalis*) contains up to 104 different chemical compounds called cannabinoids, terpenes and phenolic compounds (Patel, Williams & Wallace 2017; Andre, Hausman & Gueriero 2016). Cannabinoids are a diverse group of phytochemicals which have a wide range of pharmaceutical effects due to their action on the cannabinoid receptors that alter the neurotransmitter release in the brain. Science is still learning the effect of each of these chemicals. The most notable of the cannabinoids is tetrahydrocannabinol (THC) which is the primary psychoactive compound in cannabis and also shown in animal studies to have both anticonvulsant and proconvulsant properties. This means that under some circumstances it can increase seizure rates and sometimes reduce seizure rates. Cannabidiol (CBD) is another major constituent of cannabis which tends to have more medicinal benefit in terms of our current understanding and less side effects, especially in terms of psychiatric symptoms. There are multiple strains of cannabis and there are multiple cannabinoids within each strain. The correct treatment requires the right drug for the right symptom for the right person, which is difficult when so many different

chemicals are in the one plant, many working in different ways and different doses for different conditions.

Currently, there is no approved manufacturer of medicinal cannabis in Australia and worldwide there is scarce supply with Israel being one of the most advanced groups in the production of specific strains. Legislation that passed on 30th October 2016 was needed to allow Australian cultivators to begin to produce medicinal cannabis for clinical trials and research. Shipments of medicinal cannabis have been allowed into Australia as an interim measure while the domestic medicinal cannabis industry continues to develop.. The cultivation and manufacture of medicinal cannabis will be controlled by the Office of Drug Control (ODC) similar to that for locally grown Opium poppies (*Papaver somniferum*).

Why can't we use the home grown variety? (TGA Medicinal cannabis factsheet)
The (Therapeutic Goods Administration) TGA outline that for cannabis to be used in clinical trials and for it to be registered as a pharmaceutical there are several steps that need to occur.

1. The product needs to be uniform, i.e. each time the dose is given the same active ingredients need to be present
2. The active ingredients have to be safe and not contaminated
3. Manufacture needs to adhere to strict principles of quality control.

Access to medicinal cannabis is available through:
1. Selected clinical trials and
2. Personal import through SAS (Special Access Scheme) and authorised prescribers schemes administered by the TGA .

This will ensure that the same safeguards and legislation will apply to medicinal cannabis as to other experimental or emerging medications. The Australian government aims to maintain high standards of safety for patients who want to access medicinal cannabis and it's use under suitably qualified clinicians and /or through appropriate clinical trials.

Current literature

1. Cannabidiol in treatment resistant epilepsy

Devinsky et al (2016) led an open-label interventional trial on patients aged 1-30 years with severe intractable childhood-onset, treatment resistant epilepsy from 11 centres across the USA. The research was sponsored by a pharmaceutical company. The researchers conducted a safety study to test whether cannabidiol (CBD) as an add-on treatment to conventional antiepileptic drugs would be safe, tolerated and efficacious in children and young adults with highly treatment resistant epilepsy.

The product tested was 99% pure oil-based cannabidiol extract of constant composition. 100mg/ml. doses were titrated to a maximum dose of 50mg per kg per day in 30% of patients during the 12 week observation period. Adverse effects were reported in 79% of patients with the most common being somnolence, decreased appetite, diarrhoea, fatigue, convulsions, appetite changes, status epilepticus, lethargy, changes in concentrations of concomitant antiepileptic drugs, gait disturbance and sedation. On further analysis diarrhoea and weight loss occurred more frequently in patients taking more than 15mg/kg/d.

Patients with Dravet and Lennox-Gastaut syndromes were the largest cohort of patients. Post hoc analysis revealed 50% of the patients with Dravet syndrome had 50% or greater reduction in motor seizures, with one patient who became seizure free during treatment. In patients with Lennox-Gastaut syndrome there was a median reduction in motor seizures of 36.8%.

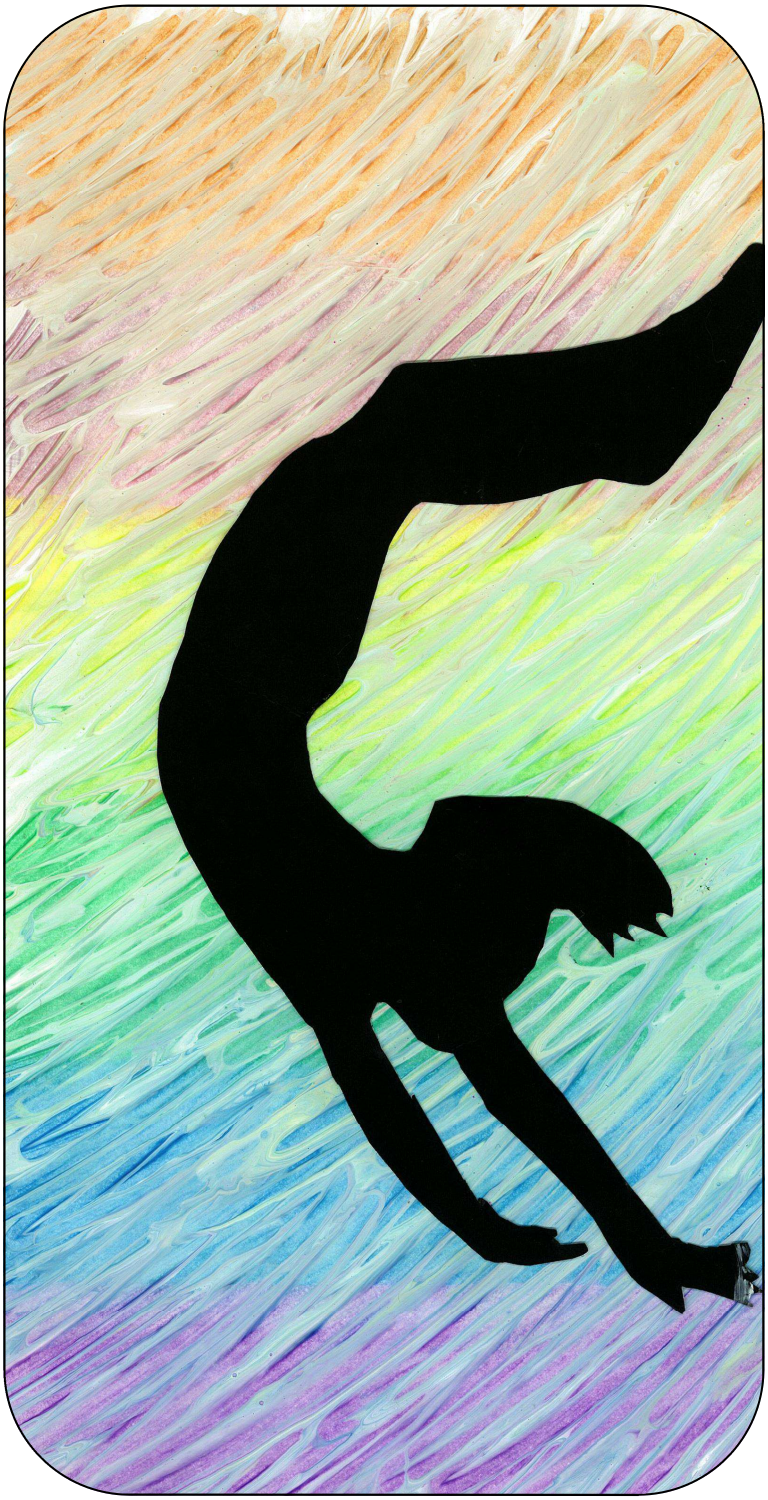
2. Cannabidiol in Dravet syndrome

Devinsky et al (2017) led multinational double blinded placebo control trial where 120 children were randomly assigned to cannabidiol solution at dose of 20mg/kg/day in addition to their standard antiepileptic treatment over a 14 week treatment period. This was a pharmaceutical company sponsored study. There were 177 patients screened and 120 underwent randomisation with the mean age of 9.7 years and 90% completed the treatment period. The primary end point was reduction in number of seizures with 108 patient included for protocol analysis.

The convulsive-seizure frequency decreased from a median of 12.4 seizures per month at baseline to 5.9 over the entire treatment period. In the placebo group there was also a reduction decreasing from 14.9 to 14.1 seizures. 8 patients withdrew from the cannabidiol arm due to adverse effects which included vomiting, fatigue, pyrexia, upper respiratory tract infections, decreased appetite, convulsion, lethargy, somnolence, and diarrhoea.

3. Oral cannabis extract duration of use

Oral cannabis extract is increasingly being used in USA for the treatment of epilepsy. A study by Treat et al (2017) looked at the perceived benefit in a cohort of patients with paediatric epilepsy through a retrospective chart review. In this study, 119 patients were reviewed between December 2013 and July 2015, with 71% terminating their treatment during the study peri-



od. This study is looking at Colorado Medical Marijuana Registry program with a retrospective chart review.

The average age of patients were 7.5 years and the mean duration of treatment was 11.7 months (range 0.3-57). 49% of parents reported at least some improvement in seizures. The highest proportion of responders was for Lennox-Gastaut syndrome. The exact nature of the product used was not always recorded so this could not be analysed. The most common adverse events noted were worsening of seizures, somnolence, and gastrointestinal symptoms but greater than 40% of patients who had experienced adverse events continued with oral cannabis extract. Among the cohort in

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the study there was a low response rate similar to placebo rates for antiepileptic trials. Those patients whose families perceived there to be benefit, even with adverse events, continued on treatment the longest.

4. Cannabidiol and commonly used antiepileptics

Gaston et al (2017) have recently researched the interactions between cannabidiol and other commonly used antiepileptic drugs. Significantly changed serum levels of clobazam, rufinamide, topiramate, zonisamide and eslicarbazepine were recorded in clinical trials with cannabidiol (CBD) which may account for some of the adverse effects reported from the Treat et al (2017) trial. CBD modulates several cytochrome P450 enzymes (CYP) and thus the potential for drug interactions. CBD is a potent inhibitor of CYP 2C19, CYP2D6 and CYP2C9 and a potential inhibitor of CYP3 family.

Baseline AED levels were done and again at each visit where CBD dosing was adjusted. Clinically significant interactions were found with clobazam and eslicarbazepine but not with topiramate and rufinamide when adult and child arms of the study were combined. Serum levels of N-desmethylclobazam, topiramate, eslicarbazepine, zonisamide and rufinamide increased after CBD was initiated. The interaction between CBD and N-desmethylclobazam appears much more profound and is likely due to CBD's potent inhibition of CYP2C19 which is responsible for metabolism of N-desmethylclobazam. This resulted in prolongation of the half-life and accumulation, thus leading to sedation.

Also of note was the interaction between valproate and CBD leading to abnormally high AST and/or ALT levels after CBD treatment; on rechallenge without CBD there was no recurrence of the abnormalities.

Note: eslicarbazepine is not available in Australia

So where do I get it?

Currently the only authorised prescribers of medicinal cannabis in Australia include clinical trial investigators and prescribers under the TGA's Special Access Scheme. There are 3 clinical trials under way in NSW: one for severe epilepsy in children;a second for adults

in palliative care; and a third for chemotherapy related nausea and vomiting.

The epilepsy trial is using the overseas manufactured product Epidiolex® and there is also a compassionate use scheme for severe non responsive epilepsy. See https://www.medicinalcannabis.nsw.gov.au/clinical-trials/paediatric-epilepsy-trial

The research thus far has been limited by access to medicinal cannabis and also the complex nature of the make-up of cannabis and its many chemical compounds. Further research is needed across health areas for a better understanding of cannabis potential.

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