CANNABINOIDS IN EPILEPSY

In Australia approximately 25,000 people are diagnosed with epilepsy each year(1) affecting up to 240,000(2) adults and children at any given time. Characterised by recurrent seizures, epilepsy is an umbrella term that covers multiple disorders and causes ranging from genetic syndromes, strokes, infections and traumatic brain injuries. Orrin Devinsky, Comprehensive Epilepsy Centre New York University Paediatric Neurologist, explains that 'while many drugs can limit seizures, no drugs can prevent underlying cause of epilepsy or the development of epilepsy'(3). With just over a third of patients failing to find an antiepileptic medication (AED) to control their seizure activity or finding the medications intolerable due to side effects, many people live with the impact of medication resistant epilepsy on their everyday lives and that of their families(4).

Media reports and personal experiences posted on social network sites have ignited the interest of parents, people with epilepsy and scientists (5). Families having exhausted all conventional treatment options tentatively embarked on a journey with cannabis based products with the aim to ease their child's suffering in the time they had left. As a result some children experienced seizure freedom for the first time in their lives while other families tell of their child reaching milestones no one ever thought possible. All attributed to the botanical herb cannabis.

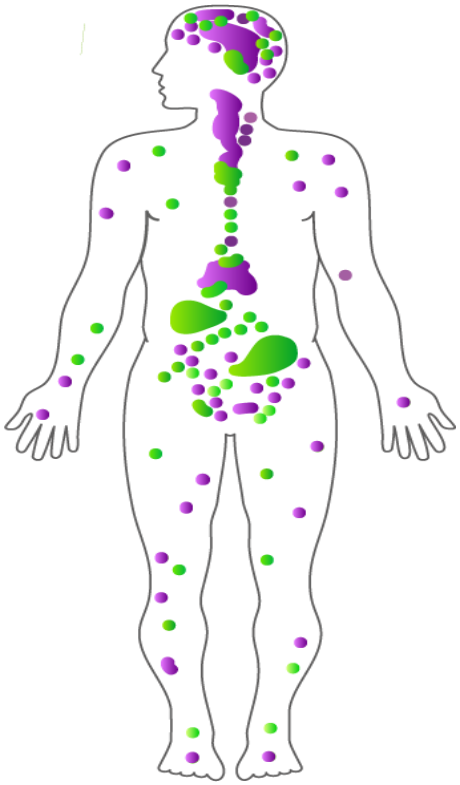
Cannabis has been use for thousands of years, and physicians have documented reports from the mid-1800's of cannabis medicinal products as a successful treatment for epilepsy(3). From 1906 control and restriction over medicinal cannabis products increased. Cannabis was listed as a Schedule 1 Drug in Australia, meaning cannabis is considered a drug with a high potential for abuse and no medical uses which severely restricted its use in medicine and clinical research. This Scheduling is set to change at a federal level in Australia within the coming months.

A recent survey conducted by Epilepsy Action Australia revealed that 14% of the 983 people included in the analysis of the survey were currently using cannabis based products for medicinal purposes with 86% reporting that medicinal cannabis was helpful in managing their seizure activity(4). Professor Nicholas Lintzeris from The Lambert Initiative of Sydney University stated that "this result mirrors results from recent Australian studies in other fields such as chronic pain and palliative care"(5). The interest and the need are there, we just require the science and legislation to catch up.

Endocannabinoid System

'The endocannabinoid system is a biochemical control system which is involved in the regulation of numerous physiological processes'(7) so named after the compounds found to bind to the receptors. Two receptors have been identified to date CB1 and CB2 receptors (7, 8, 3).

'Endocannabinoids and their receptors are found throughout the body: in the brain, organs, connective tissues, glands, and immune cells. In each tissue, the cannabinoid system performs different tasks, but the goal is always the same: homeostasis, the maintenance of a stable internal environment despite fluctuations in the external environment.' (7). *Dr Dustin Sulak*



CB1 and CB2 receptor function is to receive chemical signals to control cellular activity and play an important role in signal processing in the brain (15).

CB1

'**CB1 Receptors** are abundant in the central nervous system particularly in the cortex, basal ganglia, hippocampus and cerebellum' (9, 15) however are sparse within the brainstem (10, 15).

CB2

CB2 Receptors are abundant throughout the body however are present in much lower levels compared to CB1 receptors in the brain (9, 15).

Epilepsy

Research in epilepsy and cannabinoids is in its infancy despite the work of scientists in Israel, Canada, Spain and the United States. Little translational work has been published however scientists have 'demonstrated in animal models that the CB2 receptor raises the excitation threshold of nerve cells in the hippocampus'(16) which has potential application in epilepsy. It is thought that 'the CB2 receptor works like a set screw by which such communication processes can be adjusted'(16).

Compounds

There are three main forms of cannabinoids, Endocannabinoids, Phytocannabinoids and Synthetic cannabinoids [15].

Endocannabinoids are the substances that your body naturally make to stimulate the CB1 and CB2 receptors as well as those not yet identified within the endocannabinoid system. Endocannabinoids that have been identified include Anandamide, 2-AG, Noladin ether [15, 8, 3].

Phytocannabinoids are cannabinoids synthesised in plants that can interact or indirectly stimulate CB1 and CB2 receptors such as THC, CBD, CBG, CBDV, THCV, CBC, CBN, THCVA to name a few [15, 8].

Synthetic cannabinoids are created in the lab usually focusing on single compounds or a combination of isolated compounds such as Nabilone, HU-210, AB-PINACA, JWH-018 [15, 8].

The cannabis plant consists of more than 100 phytocannabinoids and over 400 trace compounds including terpenes which work synergistically and can be found in various ratios in the differing strains of the plant. Known as the entourage effect, these compounds work together, magnifying the therapeutic benefits of the plant's individual components [8, 3].

Just a few of the compounds of interest and the focus of studies in disease specific animal models to uncover therapeutic potential include THC, CBD, CBDA, CBDV, THCA, THCV, CBG CBGA, CBN, CBC. [11]

Preclinical research identifies a range of possible therapeutic effects from phytocannabinoids

Cannabinoid	Intoxicates?	Possible Medicinal Application
THC	√	*Nausea and Vomiting, Muscular Spasms, PTSD, Pain, Cancer, Inflammation,*
CBD	X	*Epilepsy, Psychosis, Anxiety, PTSD, Addiction, Dementia, Cancer, Insomnia*
CBDA	X	*Epilepsy, Nausea and Vomiting, Cancer*
CBDV	X	*Epilepsy*
THCA	X	*Nausea and Vomiting, Epilepsy*
THCV	X	*Diabetes, Obesity, Pain, Inflammation, Epilepsy*
THCVA	X	*Under investigation*
CBG	X	*Glaucoma, Cancer, Inflammation, Anxiety, Huntingdon's Disease*
CBGA	X	*Under investigation*
CBN	X	*Anxiety, Insomnia, Epilepsy, Anti-bacterial effects*
CBC	X	*Pain, Inflammation, Cancer*

[15]

Drug to Drug Interactions

Cannabinoids are chemical compounds either naturally occurring in the whole cannabis plant or synthetically created in a lab. No matter the form, cannabinoids, specifically Cannabidiol (CBD) can compete with other medications, such as anti epileptic drugs (AED) in the liver to be metabolised through particular pathways such as the CYP450 (10,11,12).

There are a number of AEDs that are metabolised through the CYP450 pathway and when taken in combination, blood levels can increase, fluctuate or diminish. It is important to be aware of this potential effect and discuss this with your prescribing doctor to guide you in monitoring and adjusting your current AED treatment regime when considering or commencing cannabinoid products (10,11,12).

Drug	Potential change in blood levels
Carbamazepine	↑
Clobazam	↑
Clonazepam	↑
Ethosuximide	↑
Felbamate	↑
Lacosamide	↔
Lamotrigine	↓
Levetiracetam	↔
Oxcarbazepine	↑

Drug	Potential change in blood levels
Phenobarbital	↑
Pregabalin	↔
Rufinamide	↓
Stiripentol	↓
Tigagabine	↑
Topiramate	↑
Valproate	↑
vigabatrin	↔
zonisamide	↑

KEY: ↑ Increase ↓ decrease ↔ fluctuates or no change (10,11,12)
NB: Limited research has been conducted in the drug to drug interaction and this information will change as more information is published. This is not intended as medical advice. Always speak with the prescribing doctor before making any adjustments to your AED therapies.

Medicinal Cannabis: The evidence gap

Despite more than 2000 years of historical use up until the early 1900's prohibition of cannabis, today we have limited case studies and reports from families of their experiences of using various high CBD, low THC or THCA cannabis oils and tinctures in individuals with epilepsy. As prohibition is lifted in some jurisdictions and funding for research becomes available for other than 'addiction medicine' studies, there is an emerging understanding of the cannabis plant and its pharmacology. Animal studies are indicating therapeutic potential with a few clinical studies in humans show similar results. What is needed to provide sufficient evidence to bring medicinal cannabis into mainstream medicine in a form that is acceptable to patients and doctors is randomised clinical studies not only on single compounds but full spectrum extracts for the entourage effects

to be studied (15).

As our knowledge evolves and attitudes change, we believe the answer is a broad approach to providing cannabis therapies to people living with epilepsy and amnesty for those currently experiencing improvements in seizure control and quality of life whilst the science, legislation and processes catch up to the grass roots movement of parents acting in the best interest of their children.

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