

In Australia approximately 25,000 people are diagnosed with epilepsy each year (1) affecting up to 250,000 (2) adults and children at any given time.

Epilepsy is a disorder of the brain, characterised by the tendency to have recurrent unprovoked seizures. It is primarily managed with antiepileptic drugs (AED's), while 2 in 3 people gain seizure control with medication, a third of people with epilepsy continue to have seizures. This is called medication resistant epilepsy and it impacts not only the quality of life for the person with epilepsy but also the lives of their families. (4,20) Ongoing seizures also mean a higher likelihood of seizure related risks and injuries and many people with epilepsy also experience intolerable side effects from AEDs.

There is great interest in the development of new treatments for people with epilepsy as these figures have not changed despite the development of many new AEDs in the last 30 years.

Medicinal cannabis

Cannabis has been used for centuries to treat seizures. (3). The plant *Cannabis sativa* is composed of more than 500 compounds and those that are unique to the cannabis plant are called cannabinoids. THC (Tetrahydrocannabinol) and CBD (Cannabidiol) are two of the most abundant cannabinoids present in cannabis plant.

Over the past decade there has been an increasing interest in the use of cannabinoids to treat a range of epilepsy syndromes following reports of some remarkable responses in individual patients. (21)

In 2016, Epilepsy Action Australia conducted an Australia-wide survey which by revealed that 14% of the 983 people surveyed were using cannabis-based products for medicinal purposes and 86% of those utilising medicinal cannabis reported it was helpful in managing their seizure activity (4). Professor Nicholas Lintzeris from The Lambert Initiative of Sydney University stated at the time that "this result mirrors results from recent Australian studies in other fields such as chronic pain and palliative care" (5).

Endocannabinoid System

The human body contains a network of receptors that play an important role in regulating and maintaining our internal health and well-being. These receptors are better known collectively as our endocannabinoid system (ECS).

There are two main types of receptors in the ECS:

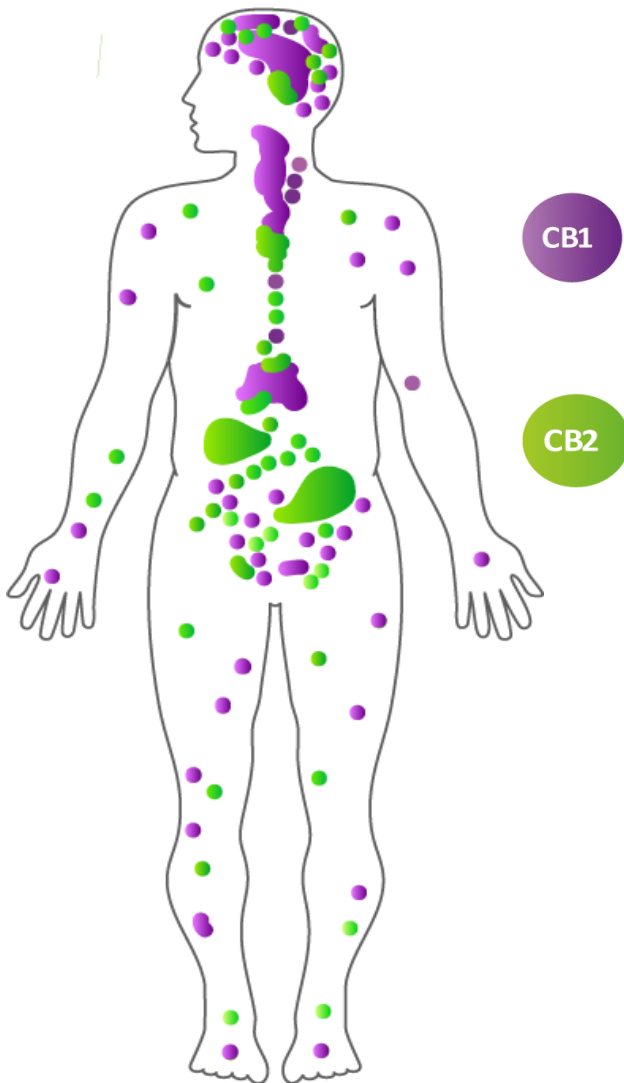
- CB1 receptors - commonly found in the brain and spinal cords
- CB2 receptors - exist mostly within the peripheral nervous system, such as our immune cells and gastrointestinal system.

Cannabinoids such as THC and CBD can mimic our body's naturally produced compounds called "endocannabinoids". Endocannabinoids are a critical part of the ECS and bind to CB1 and CB2 receptors and activate signals for communication. (22)



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

Cannabinoids have also been found to have effects outside the CB1/CB2 receptor system (17) and studies are attempting to identify and understand other potential receptors such as GPR18, GPR55, GPR119, TRPV1, 5-HT3, GlyR, PPAR α , PPAR γ and CBD3.

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Cannabidiol and Epilepsy Research

Cannabidiol (CBD) is the substance featured in most published evidence related to medicinal cannabis as a treatment for epilepsy. This evidence is when it is used as an add-on to current treatments in medication-resistant epilepsy in children and young adults up to 25 years where use of several AED's has not controlled their seizures.

In half of the people studied with paediatric-onset medication-resistant epilepsy, CBD products reduced seizure frequency by 50 per cent or more and seizure freedom was achieved in a small number. (23) Several studies have reported improved quality of life in paediatric and adult groups, but overall, there are few studies of how effective CBD is in treating adult epilepsy.

Guidance for the use of medicinal cannabis in Australia.		
Epilepsy	Products	Current evidence quality
To reduce and/or eliminate the number of seizures	CBD when used in conjunction with anti-epileptic drugs	Low to very low
	Oral cannabis extracts (OCEs)	Very low
	CBD:THC	Very low
	Cannabis sativa	Very low
Quality of life	CBD	Low
	Oral cannabis extracts (OCEs)	Very low
	CBD:THC	Very low
	Cannabis sativa	Very low
	THC	Very low

Ref: TGA 2017

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 two primary compounds have been confirmed as endocannabinoids, Anandamide and Arachidonoylglycerol (2-AG) (3, 8, 15). More studies are required to support the notion of Nolan Ether (2-AGE), Oleamide, N-Oleoyl dopamine, N-Archidonoyl ethanolamine, Haemopressin, EPEA, DHEA and NADA as endocannabinoids and how they interact with the endocannabinoid system. (Table 29)

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 (8,15).

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 (8,15).



Compounds (continued)

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 (3, 8).

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)

Potential Therapeutic Applications of CBD		
Cannabinoid	Intoxicating	Potential therapeutic application
THCA	No	Anti-inflammatory, Irritable Bowel Disorder
THC	Yes	Anti-emetic, anti-inflammatory, analgesic
THCV	No	Unknown
CBDA	No	Inflammation, nausea, psychosis and inhibitor of breast cancer migration
CBD	No	Alzheimer's dis, Anxiety, Cancer, Cardiovascular disease, Depression, Diabetic complications, Huntington's disease, Hypoxia-ischemia injury, Infection, Inflammatory disease, Inflammatory bowel and Crohn's disease Multiple Sclerosis, Nausea, Pain, Parkinson's disease, Psychosis, Rheumatoid arthritis, seizures, mitigation of side effects of high THC (A)
CBDV	No	Anticonvulsant, antiepileptic
CBGA	No	unknown
CBG	No	Gram-positive bacterial infections, inflammatory bowel disease
CBC	No	Enhances effect of CBD and THC, anti-inflammatory and analgesic effects
CBN	No	Sedative, anxiolytic
(Reference A) Ahmad S, Hill KP (2021) The Pharmacology of Cannabis Chapter 7, Table 7.9 Potential Therapeutic Applications of CBD, Medical Marijuana: A Clinical Handbook, Wolters Kluwer Philadelphia)		
(Reference for all others) Ahmad S, Hill KP (2021) Constituents of Cannabis Chapter 4, Medical Marijuana: A Clinical Handbook, Wolters Kluwer Philadelphia)		

Unwanted side effects

While cannabinoids are less likely to be associated with severe side effects, details of side effects with most cannabinoids are limited. Some studies (24,25) have shown significant side effects including sedation, increased seizure frequency and gastrointestinal disturbance such as decreased appetite, weight loss and diarrhoea in some in some people.



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	Drug	Potential change in blood levels
Carbamazepine	↑	Phenobarbital	↑
Clobazam	↑	Pregabalin	↔
Clonazepam	↑	Rufinamide	↓
Ethosuximide	↑	Stiripentol	↓
Felbamate	↑	Tigagabine	↑
Lacosamide	↔	Topiramate	↑
Lamotrigine	↓	Valproate	↑
Levetiracetam	↔	vigabatrin	↔
Oxcarbazepine	↑	zonisamide	↑

Table: Potential Interactions with AED's

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 of medicinal cannabis, there is still limited information about its potential benefits, but ongoing studies are generating an emerging understanding of the cannabis plant and its pharmacology.

With recent changes in medicinal cannabis regulation and legislation, accessibility and affordability has improved and is expected to further improve. Access to regulated cannabinoid based therapies is through the Therapeutic Goods Administration (TGA) Special Access Scheme (SAS) Category B process with access to a range of unapproved products warehoused in Australia or Category A for those with life threatening or terminal conditions requiring importation rather than accessing the unapproved products warehoused in Australia.



To date, the TGA has approved SAS applications including, but not limited to, the following conditions: (26)

- chemotherapy-induced nausea and vomiting
- refractory paediatric epilepsy
- palliative care indications
- cancer pain, neuropathic pain, chronic non-cancer pain
- spasticity and movement disorders from neurological conditions
- anorexia and wasting associated with chronic illness (such as cancer).
- sleep disorders
- Alzheimer's syndrome
- Autism syndromes
- Tourette's syndrome
- Ulcerative colitis
- Anxiety, PTSD

For medicinal cannabis, the amount of evidence is currently limited, and the products, doses and research methods used vary between studies. This makes it difficult to come to firm conclusions about how best to use medicinal cannabis products and how to determine the most appropriate and safe dose while minimising potential side-effects.

Because there is limited scientific evidence to support the use of medicinal cannabis in most conditions, and in many cases the evidence is for its use together with other medicines, it should be used only when approved treatments have been tried and have failed to manage conditions and symptoms. (27)

Access

Medicinal cannabis products are not registered for general distribution within Australia. Legislation and access differ slightly from state to state and continues to change. Please check your local state or territory Medicinal Cannabis regulations.

Under Australian therapeutic goods legislation, medical practitioners can request access to unregistered medicines for their patients in certain circumstances. Approval can be obtained from the TGA under the Special Access Scheme (SAS) or the Authorised Prescriber Scheme. (28)

As our knowledge evolves and attitudes change, we believe the answer is a broad approach to providing cannabinoid based therapies to people living with epilepsy, affordable access to bio-equivalent cannabis based therapies for those already utilising unregulated medicinal cannabis and temporary amnesty for those currently experiencing improvements in seizure control and quality of life until transition to a bio-equivalent evidence based prescribed product is possible.



Fact Sheet: Cannabinoids in Epilepsy

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