

# Medicinal Cannabis- the discussion so far

Medicinal cannabis is sometimes referred to as medical cannabis or medical marijuana. Medicinal cannabis comes as a pill, oil, nasal spray or some other form of cannabis plant extract. It is used to relieve the symptoms of some medical conditions. Medicinal cannabis is being researched worldwide due to its potential to help a number of conditions, but its use is very highly regulated in Australia. Products approved for use in Australia include nabiximols<sup>1</sup> and synthetic cannabinoids. These products are formulated so they have the greatest medical effect and the fewest possible side effects. In some countries, crude cannabis (raw cannabis plant material) and cannabis oil are used as therapies. These are both illegal in Australia.

A Deakin University online article makes the point that "despite the widespread support for medical cannabis, economic, cultural and moral agendas make the arguments for and against the legalisation of medical marijuana incredibly complex. Professor of Psychology in Deakin University's Faculty of Health, Professor Peter Miller, says that the stigma around drugs makes their integration into medicine incredibly difficult."<sup>2</sup>

Cannabis has a significant history as an illegal drug. As such, much of what is known about the adverse effects of cannabis comes from studies of recreational users. Research has shown that:

*"Short-term use of cannabis has led to impaired short-term memory; impaired motor coordination; altered judgment; and paranoia or psychosis at high doses. Long-term or heavy use of cannabis, especially in individuals who begin using as adolescents, has led to addiction; altered brain development; cognitive impairment; poor educational outcomes (e.g., dropping out of school); and diminished life satisfaction. Long-term or*

*heavy use of cannabis is also associated with chronic bronchitis and an increased risk of chronic psychosis-related health disorders, including schizophrenia and variants of depression, in persons with a predisposition to such disorders. Vascular conditions, including myocardial infarction, stroke, and transient ischemic attack, have also been associated with cannabis use."*<sup>3</sup>

## The Endocannabinoid System

The endocannabinoid system (ECS) can explain why natural cannabinoids in hemp and other plants have therapeutic effects. "Cannabinoid" is the term given to any compound that interacts with the endocannabinoid system, including the cannabinoids found naturally in human and animal bodies (called endocannabinoids) and the ones found naturally in plants (called phytocannabinoids).

*"Although Endocannabinoids are distinct from those produced in the cannabis plant, they share many similar properties and effects. This is because they interact with the same pathways in the brain and body called cannabinoid receptors. Scientists believe there are many different endocannabinoids, but the most studied and understood are 2-AG and anandamide."*<sup>4</sup>

The endogenous cannabinoid or Endocannabinoid System (ECS) is named after the plant that led to its discovery in the 1990s. The discovery occurred during research aimed at understanding how tetrahydrocannabinol (THC), the primary intoxicating substance in cannabis, affected the body. What researchers discovered was a remarkably complex network of cannabinoid receptors (CB<sub>1</sub>) expressed in cells of both the central and peripheral nervous system. Endocannabinoids and their receptors are found throughout the body including inside

<sup>1</sup> A herbal preparation containing a defined quantity of specific cannabinoids formulated for oromucosal spray administration with potential analgesic activity. Nabiximols contains a standardized extract of tetrahydrocannabinol (THC), the non-psychoactive cannabinoid cannabidiol (CBD), other minor cannabinoids, flavonoids, and terpenes from two cannabis plant varieties. Cannabinoids interact with G protein-coupled cannabinoid 1 (CB<sub>1</sub>) receptors in the central nervous system, resulting in analgesic, euphoric, and anticonvulsive effects.

<sup>2</sup> Are you for or against medical marijuana? This, Deakin University, <http://this.deakin.edu.au/society/are-you-for-or-against-medical-marijuana>

<sup>3</sup> Mary Barna Bridgeman & Daniel T Abazia (2017), Medicinal Cannabis: History, Pharmacology, And Implications for the Acute Care Setting, P & T (Pharmacy & Therapeutics), Volume 42, no. 3, 180-188, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5312634/>

<sup>4</sup> What Are Cannabinoids? (2017), <https://www.leafscience.com/2017/10/25/what-are-cannabinoids/> Shutterstock

the brain, organs, connective tissues, glands, and immune cells. In each tissue, the ECS performs different tasks, but the goal is always the same: homeostasis, the maintenance of a stable internal environment despite fluctuations in the external environment.

*"The homeostatic action of cannabinoids on so many physiological structures and processes is the basis for the hypothesis that the endocannabinoid system is nothing less than a naturally evolved harm reduction system."<sup>5</sup>*

There is proof that specific diseases—like arthritis, depression, fibromyalgia, IBS, and migraines—have been connected to lower levels of natural endocannabinoids and other changes in the endocannabinoid system's activity.

This discovery had led researchers to coin the term "endocannabinoid deficiency" to describe the health of a person's ECS and potentially to use it as a way to measure overall health as well.

However, there is still a lot to learn about how the ECS works as a whole and how cannabinoids can be used for specific ailments. It is telling that even a strongly pro-medicinal cannabis website has noted that:

*"The ECS is far from being fully understood or fully 'mapped'. In fact, having only been discovered in the 1990's, there is still a lot that scientists and physicians need to learn about it in order to have a more complete understanding of how cannabis works in the body, and more importantly, how we might be able to manipulate it to effectively treat almost any medical condition."<sup>6</sup>*

Nonetheless, the ECS has a very wide scope of influence due to an abundance of cannabinoid receptors located anywhere from immune cells to neurons.

Given the prevalence of ECS receptors throughout the human body, it is clearly plausible that drugs that target endocannabinoid receptors, like THC (or

derivatives), have the potential to target specific effects on specific organs. This could include products that produce beneficial effects and minimise any adverse effects.

Maroon and Bost note that:

*"Research on the ECS is fervently ongoing with wide-ranging discoveries. The roles of endogenouscannabinoid,phytocannabinoids, and synthetic pharmacological agents acting on the various elements of the ECS have a potential to affect a wide range of pathologies, including food intake disorders, chronic pain, emesis, insomnia, glaucoma, gliomas, involuntary motor disorders, stroke, and psychiatric conditions such as depression, autism, and schizophrenia."<sup>7</sup>*

## What we know

A number of recent studies and reviews by reputable researchers on the therapeutic effects of cannabinoids have not been sufficient in coming to firm conclusions in many areas of benefit claimed for the use of medicinal cannabinoids. There are some areas of research that show promising results, but these are not always substantiated by subsequent studies.

In a comprehensive review of recent medical literature on the Health Effects of Cannabis and Cannabinoids, the American National Academies of Sciences, Engineering and Medicine concluded that:

*"There was conclusive or substantial evidence that Cannabis or cannabinoids are effective for the treatment of pain in adults; chemotherapy-induced nausea and vomiting and spasticity associated with multiple sclerosis. Moderate evidence was found for secondary sleep disturbances. The evidence supporting improvement in appetite, Tourette syndrome, anxiety, posttraumatic stress disorder, cancer, irritable bowel syndrome, epilepsy and a variety of neurodegenerative disorders was described as limited, insufficient or absent."<sup>8</sup>*

With regards to effective pain management,

5 Robert Melamede (2005), Harm reduction-the cannabis paradox, Harm Reduction Journal, Volume 2, no. 17, <https://harmreductionjournal.biomedcentral.com/articles/10.1186/1477-7517-2-17>

6 The Endocannabinoid System: Explained (2018), MarijuanaBreak, <https://www.marijuanabreak.com/endocannabinoid-system>

7 Joseph Maroon & Jeff Bost (2018), Review of the neurological benefits of phytocannabinoids, Surgical Neurology International, Volume 9, no. 91, <http://surgicalneurologyint.com/surgicalint-articles/review-of-the-neurological-benefits-of-phytocannabinoids/>

8 Donald I Abrams (2018), The therapeutic effects of Cannabis and cannabinoids: An update from the National Academies of Sciences, Engineering and Medicine report, European Journal of Internal Medicine, Special Issue: Cannabis in Medicine, Edited by Victor Novack, Volume 49, pp. 1-50, [https://www.ejinme.com/article/S0953-6205\(18\)30003-7/fulltext](https://www.ejinme.com/article/S0953-6205(18)30003-7/fulltext)

another meta-analysis of clinical trials of cannabis and cannabinoids for pain found:

*"Modest evidence supporting the use of cannabinoid pharmacotherapy for pain. Recent epidemiological studies have provided initial evidence for a possible reduction in opioid pharmacotherapy for pain as a result of increased implementation of medical cannabis regimens."<sup>9</sup>*

Contrary to the American National Academies of Sciences, Engineering and Medicine review cited above, which reported insufficient evidence supporting a benefit for epilepsy, WHO's Expert Committee on Drug Dependence (ECDD) report on therapeutic applications of cannabidiol (CBD), which focused on the use of CBD for reducing seizures in patients with epilepsy, found clinical evidence for this application was the strongest.

In trials, CBD has been shown to be an effective treatment for at least some forms of epilepsy, such as Dravet syndrome, a complex childhood epilepsy associated with drug-resistant seizures and a high mortality rate. In addition to observational studies and case reports, the report reviewed findings from two trials examining the effects of CBD in patients with severe, intractable, childhood-onset, treatment resistant epilepsy. Both trials—an open-label study of 214 patients and a randomised controlled trial of 120 patients—showed a reduction in convulsive-seizure frequency during the treatment period in patients who received CBD compared with either pre-treatment seizure frequency or with patients who received placebo. Since the publication of the ECDD's preliminary report, a trial of 171 patients with treatment-resistant Lennox-Gastaut syndrome has provided evidence supporting the efficacy of CBD as an add-on therapy for drop seizures.<sup>10</sup>

Alex Halperin<sup>11</sup> has made the point that:

*"Following media reports, which have touted it as a miracle cure, there's a growing community of parents who attempt to*

*treat their children's seizure disorders with CBD oil. They've largely had to treat these devastating illnesses based on word of mouth or information they find online. This is one example where cannabis pharmaceuticals make more sense. The best-known example is probably the UK firm GW Pharmaceuticals. The company's first drug, Sativex, an oral spray with a 1:1 ratio of THC and CBD, has been approved in 30 countries, mainly in Europe, for MS-associated spasticity. In June 2018, after years of clinical trials, the U.S. Food and Drug Administration approved Epidiolex (cannabidiol) [CBD] oral solution for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients two years of age and older. This is the first FDA-approved drug that contains a purified drug substance derived from marijuana. It is also the first FDA approval of a drug for the treatment of patients with Dravet syndrome."<sup>12</sup>*

A study on the effects of medical cannabis in the elderly concluded that:

*"The therapeutic use of cannabis is safe and efficacious in the elderly population. Cannabis use may decrease the use of other prescription medicines, including opioids. Gathering more evidence-based data, including data from double-blind randomized-controlled trials, in this special population is imperative."<sup>13</sup>*

Oncology academics Maida and Daeninck note that:

*"The most studied and established roles for cannabinoid therapies include pain, chemotherapy-induced nausea and vomiting, and anorexia. Moreover, given their breadth of activity, cannabinoids could be used to concurrently optimize the management of multiple symptoms, thereby reducing overall polypharmacy. The use of cannabinoid therapies could be effective in improving quality of life and possibly modifying malignancy by virtue of direct effects and in improving compliance or adherence with*

9 Kevin P Hill, Matthew D Palastro, Brian Johnson & Joseph W Ditre (2017), Cannabis and Pain: A Clinical Review, Cannabis and Cannabinoid Research, Volume 2, no. 1, <https://www.liebertpub.com/doi/10.1089/can.2017.0017>

10 Clearing the haze around medicinal cannabis: Editorial (2018), The Lancet Neurology, Volume 17, issue 3, [https://www.thelancet.com/journals/laneur/article/PIIS1474-4422\(18\)30049-8/fulltext](https://www.thelancet.com/journals/laneur/article/PIIS1474-4422(18)30049-8/fulltext)

11 Alex Halperin is a freelance business reporter in L A where he covers the marijuana industry, writes the newsletter WeedWeek and co-hosts the WeedWeek Podcast. His work has appeared in The Guardian, The Washington Post, The Atlantic, Mother Jones, Fast Company and many other publications.

12 Alex Halperin (2018), Is marijuana a medical miracle? The truth is, we still don't know, The Guardian Australian Edition, <https://www.theguardian.com/society/2018/jan/15/medical-marijuana-does-it-work-miracle-drug-evidence>

13 Ran Abuhasira, Lihi Bar-Lev Schleider, Raphael Mechoulam, Victor Novack (2018), Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly, European Journal of Internal Medicine, Special Issue: Cannabis in Medicine, Edited by Victor Novack, Volume 49, pp. 1-50, [https://www.ejinme.com/article/S0953-6205\(18\)30003-7/fulltext](https://www.ejinme.com/article/S0953-6205(18)30003-7/fulltext)

disease-modulating treatments such as chemotherapy and radiation therapy."<sup>14</sup>

## Caution is required

Like any other drugs, the use of cannabinoids is not purely benign. Owing to metabolism in the liver, THC and other Cannabinoids have the potential to interact with other drugs. We do not yet understand enough about the full extent of the adverse effects of interactions. Overall impact has not been well studied, however there are a number of medications that have already been noted as contraindicated for medicinal cannabis use. These include but are not limited to Warfarin; Benzodiazepines; Haloperidol (Haldol—Johnson & Johnson); Atorvastatin (Lipitor—Pfizer); and Simvastatin. In some studies:

*"Compared to placebo, medical cannabinoids have been shown to cause multiple different adverse events in patients, from visual disturbance or hypotension (1 in 3-10) to hallucination or paranoia (1 in 20). Stopping due to adverse effects occurs in 1 in every 8-20 patients. Regardless of the type of medical cannabinoid used, adverse events are common and likely underestimated. Given the extensive harms, potential benefits must be impressive to warrant a trial of therapy."*<sup>15</sup>

A major problem with ascertaining benefits as opposed to adverse effects in medicinal cannabis use is, as Dr. Kenneth Mukamal, Associate Professor of Medicine at Harvard-affiliated Beth Israel Deaconess Medical Center, has noted:

*"There are almost no uses of medical marijuana that have been subjected to the kind of rigorous testing you'd want for a pharmaceutical... This does not mean that it has no benefits, but only that the lack of human studies prevents us from being sure if medical marijuana can really help."*<sup>16</sup>

At this stage cannabis is touted to be safer than some other medications prescribed to treat the same symptoms. For example, medicinal

cannabis is preferred when compared to the widespread harms and mortality caused by substances like alcohol and opioids for pain management. Opioids are highly addictive and are typically not recommended for long-term use in treating chronic pain. The problem is that the effectiveness of medicinal cannabis in pain relief and its long-term effects still need to be proven. Clearly more research is needed to add to the body of evidence that will cut across claims that are based on either exaggerated claims of benefit or exaggerated negative claims about harmful effects.

## What we need to know

A German review found that research into the use of cannabis for medical treatment has been limited, especially in comparison to the intensive research process before traditional drugs receive regulatory approval. The review says that:

*"What limited research there is does not support the claims made by proponents of medicinal cannabis."*<sup>17</sup>

The main reason for this discrepancy is that studying cannabis under rigorous circumstances has been difficult, not least due to its status as a prohibited drug. Also:

*"The plant itself isn't patented, so even ignoring the legal access issues, there may be a lack of industry enthusiasm in conducting clinical trials. The other issue is the challenge of a proper placebo control, particularly for non-oral forms of use. Given the psychoactive effects and the widely heralded effects on conditions that can only be assessed subjectively, like nausea, fatigue or appetite, a proper placebo is essential to separate out actual from placebo effects. While some commercial products have been developed and marketed with standardized ingredients and quality control (e.g., nabilone), these products are exceptions. However, these purified and standardized products have allowed for proper placebo controls and more rigorous assessments of effectiveness."*<sup>18</sup>

14 V Maida, P Daeninck (2016), A user's guide to cannabinoid therapies in oncology, Current Oncology: A Canadian cancer research journal, Volume 23, no. 6, <http://www.current-oncology.com/index.php/oncology/article/view/3487>

15 Scott Gavura (2018), Medical Marijuana: Where is the evidence? Science-Based Medicine: Exploring issues & controversies in science and medicine, <https://sciencebasedmedicine.org/medical-marijuana-where-is-the-evidence/>

16 Medical marijuana: Know the facts: While the drug therapy is becoming more widely available, the science is still not clear on how it may help (2017), Harvard Health Publishing, Harvard medical School, <https://www.health.harvard.edu/staying-healthy/medical-marijuana-know-the-facts>

17 Ned Stafford (2018), Medicinal cannabis should not be used ahead of approved drugs, says German review, BMJ, Volume 361, <https://www.bmj.com/content/361/bmj.k2326>

18 Scott Gavura (2018), Medical Marijuana: Where is the evidence? Science-Based Medicine: Exploring issues & controversies in science and medicine, <https://sciencebasedmedicine.org/medical-marijuana-where-is-the-evidence/>

Consequently, there are significant gaps in information about the benefits of medicinal cannabis and these include:

- Contraindications and drug interactions.
- Knowledge about the adverse events and long-terms risks.
- How cannabis affects the brains of different users.
- Also, of an estimated 400 compounds there are only two - THC and CBD - that much is known about. That means there's a lot to learn about which compounds might contribute to psychoactive effects and which might potentially have medical uses.

The practical use and legalisation of medicinal cannabis is happening faster than science can keep up with. There is little standardisation and quality control of the products produced across the world. Medicinal cannabis needs to meet the same standards of quality, effectiveness, and safety expected of any other prescription drug. That standard has not yet been met.

## Conclusion

The legalisation of medicinal cannabis is viewed favourably by many Australians, including members of the medical community and politicians. This is largely based on limited research in a number of areas which show good results for medicinal cannabis and on anecdotal reports of efficacy. The 2016 National Drug Strategy Household Survey (NDSH Survey) shows that Australians largely support the decriminalisation of cannabis and the use of medicinal cannabis, and a growing number support full legislation of cannabis. The survey showed that there were significant changes in people's attitudes

towards cannabis: more people supported cannabis being used in clinical trials to treat medical conditions (from 75% in 2013 to 87%), and supported a change in legislation permitting the use of cannabis for medical purposes (from 69% in 2013 to 85%).<sup>19</sup>

A recent study also found more than half of surveyed Australian GPs are in favour of prescribing medicinal cannabis. The survey of 640 Australian general practitioners found almost two-thirds have had patients ask about the drug. More than half the doctors said they'd like to be able to prescribe medicinal cannabis, but they don't know enough about it, are uncomfortable discussing it with patients, and feel overwhelmed by the bureaucratic access scheme.<sup>20</sup>

The best evidence suggests that medicinal cannabis may be a reasonable treatment option for a limited number of conditions only when safer, more effective, and better tolerated treatment options have been tried first. On the whole there is not enough evidence for many of the perceived beneficial effects of medicinal cannabis, and many of these perceived benefits may instead be due to the placebo effect. Hopefully, clinical trials will become more common and further cannabis-based drugs can be rigorously evaluated.

<sup>19</sup> Australian Institute of Health and Welfare (2017), National Drug Strategy Household Survey 2016: detailed findings. Drug Statistics series no. 31. Cat. no. PHE 214, Canberra: AIHW. <https://www.aihw.gov.au/getmedia/15db8c15-7062-4cde-bfa4-3c2079f30af3/21028a.pdf.aspx?inline=true>

<sup>20</sup> More than half of surveyed GPs are in favour of prescribing medicinal cannabis (2018), ABC Radio AM, <http://www.abc.net.au/radio/programs/am/more-than-half-gps-favour-prescribing-medicinal-cannabis/9937822>

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