Clinical Evidence for Medicinal Cannabis: Epilepsy, Cancer and Multiple Sclerosis

A Report Developed by the University of Sydney Community Placement Program in Partnership with MGC Pharmaceuticals

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1. Executive Summary

In recent years, medicinal cannabis has gone from being a niche and obscure area of medical scientific research into "one of the fastest moving frontiers in pharmacology".[1] The potential value of cannabis as medicine has been demonstrated in relation to a number of serious conditions and symptoms including cancer, epilepsy, multiple sclerosis, chronic pain, muscle spasticity and nausea.

The clinical evidence regarding medicinal cannabis has received less attention than it merits, and scientists, clinicians, patients and carers seeking access to this evidence have found it difficult to separate good research from the wealth of anecdotal and less rigorously obtained experimental results. This report aims to summarise the strongest available scientific research on the use of cannabis as a medicine for the treatment of epilepsy, cancer and multiple sclerosis; the symptoms of these conditions; and the side-effects of their current treatment.

We will begin by explaining the current state of clinical medicinal cannabis research; the historical trends in this research; and the challenges and barriers faced by researchers in this field. We will then summarise the evidence currently available in support of cannabis for the treatment of the specified conditions and symptoms. Finally, we will summarise the evidence currently available on the unwanted side-effects and 'adverse events' caused by medicinal cannabis.

The evidence presented in this paper has been limited as much as possible to high quality, placebo controlled clinical trials with published results. Where relevant, we have also included other sources of evidence including results from animal trials, uncontrolled or small clinical studies, and model-based evidence. We have specified the quality and reliability of this research throughout the report.

Clinical Evidence

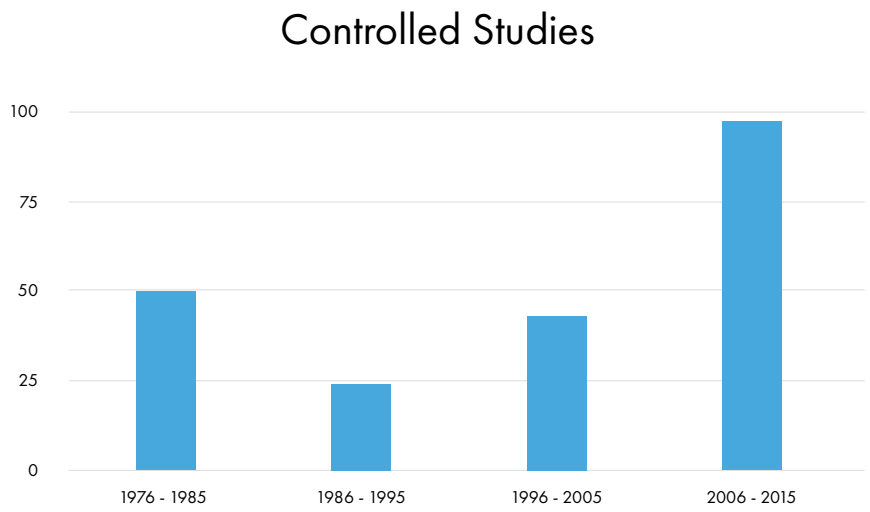
Clinical evidence on medicinal cannabis is patchy. Despite the concerted efforts of many dedicated individuals and institutions, properly controlled clinical trials on cannabis treatments are still relatively rare.

It is worth noting that a lack of available evidence does not indicate a lack of medical potential for cannabis. There is a lack of evidence because there has been a lack of research. In the absence of large-scale and well-funded studies, a huge body of anecdotal evidence has been built. It is partly due to this body of evidence, and the commitment and passion of the people involved in its development, that the mainstream scientific and political communities have begun to take notice of the potential which medicinal cannabis holds.

But patients, carers and medical professionals deserve more certainty than this. For many doctors, the current evidence is not sufficient for them to feel comfortable recommending medicinal cannabis to their patients. For many patients making choices about how they treat their serious health conditions, this lack of evidence makes them cautious in choosing medicinal cannabis treatments.

More research is certainly needed. Some high quality clinical trials have delivered positive and exciting results, and the frequency of these studies is increasing in tandem with the growing acceptance of the actual and potential value of cannabis as a medicine. According data available via the International Association for Cannabinoid Medicines online database[2], the number of controlled studies[3] published on cannabis treatments per decade has been increasing exponentially since 1986:

And with more than 100 open clinical trials[4] currently being conducted on medicinal cannabis around the world[5], this trend looks set to continue.



Not only does cannabis appear to have great clinical potential, but compared to the drugs currently used to treat some of these conditions (especially painkillers such as ketamine and opioids), it is also often much safer for patients. According to some of the research, this means certain patients have the potential to achieve both better treatment outcomes and fewer undesirable and dangerous side-effects by using medicinal cannabis.[6] [7] This nett clinical benefit is further supported by recent analysis conducted in the U.S. showing a correlation between access to medicinal cannabis and lower demand for prescription opioids.[8]

Challenges and Barriers

The history of societal attitudes towards cannabis is well known. Sadly, this is one of the primary reasons for the lack of medical scientific research on the benefits of medicinal cannabis. The data from the International Association for Cannabinoid Medicines, although limited, certainly matches the patterns of U.S. attitudes towards cannabis. The financial and time costs associated with scientists getting access to cannabis and the substantial administrative burdens placed on research institutions has effectively discouraged high quality medicinal cannabis research for decades. This is illustrated by Dr Alexander Wodak of the Australian Drug Law Reform Initiative as quoted in the Regulator of Medicinal Cannabis Bill 2014,

> "In the United States cannabis is still on schedule 1, which means it is as dangerous as heroin and more dangerous than cocaine, which is on schedule 2. That gives you an idea of how serious the obstacles are. But getting funding, getting approval from an ethics committee and, most importantly of all, getting supplies of lawful medicinal cannabis in Australia, the United States and many other countries at the moment is virtually impossible" [9]

These barriers have meant that instead of engaging in difficult and costly clinical medicinal cannabis research, medical scientists have tended to focus on surveys of patients self-administering illicit cannabis to treat their conditions. Studies conducted in this way cannot meet the high methodological standards required for confident adoption by many in the medical profession.

As well as these regulatory and legal barriers, cannabis researchers are also challenged by the trade-off which needs to be made between accurately testing individual chemical components of the cannabis plant and understanding how these various chemicals interact with each other to produce particular effects. There is evidence to suggest that many cannabinoids, terpenes and flavonoids have combinational and synergistic interactions[10] but the kinds of scientific tests required to produce consistent clinical results are most compelling when the number of variables are as limited as possible. This is why much of the more rigorous clinical medicinal cannabis research has been conducted using isolated, individual cannabinoids extracted from the plant or synthesised.[11]

Summary of Evidence

Intractable childhood epilepsy has been one of the most publically-supported conditions in Australia's path towards legalised medicinal cannabis. But although much of the clinical research currently being conducted is focused on these conditions (including Dravet and Lennox-Gastaut syndromes), relatively little clinical evidence is currently available.

Based on the available evidence, there is cautious optimism that medicinal cannabis will prove to be an effective treatment for intractable childhood epilepsy. This evidence has not yet been developed to a standard which satisfies all medical professionals but based on the severity of these conditions, the ineffectiveness of conventional treatments, and the wealth of preliminary clinical and anecdotal evidence, CBD-based cannabis medicines will be made available to people living with chronic childhood epilepsy in Australia from 2017.

Although research into the use of cannabis to directly treat certain cancers is still nascent, cancer was selected for this report due to its seriousness and prevalence, and the strength of the evidence supporting cannabis use for the alleviation of pain, nausea and vomiting and the improvement of appetite and mood in cancer patients.

The effectiveness of medicinal cannabis in treating the symptoms of pain, nausea, vomiting and appetite in cancer patients is recognised by the Clinical Oncology Society of Australia, but more research is still needed in these areas. There is currently insufficient clinical evidence to support the use of medicinal cannabis in preventing or treating cancer.

The clinical evidence supporting medicinal cannabis as a treatment for multiple sclerosis is some of the strongest in the field, especially in the relief of muscle spasticity and associated pain. This condition was also selected due to the maturity of pharmaceutical-grade cannabis products for MS, and their standardised use in many clinical trials to date.

Based on the available evidence, medicinal cannabis has been demonstrated to be a viable treatment option for the management of muscle spasticity and pain in people living with MS. There is limited and provisional research suggesting medicinal cannabis may also assist in the treatment of incontinence from MS.

2. Epilepsy

There are few published controlled studies on the use of medicinal cannabis for the treatment of epilepsy in human subjects. There are two minor studies from the 1980s with small numbers of participants:

Year	Title	Medication	Route	Participants	Outcome
1980	Chronic administration of cannabidiol to healthy volunteers and epileptic patients.	Cannabidiol	Oral	15	Improvement noted
1986	Anticonvulsant effect of cannabidiol.	Cannabidiol	Oral	12	No effect

However, a number of in-vitro and animal studies over the years have shown the potential of cannabis and related substances in the treatment of epilepsy.[12] [13] [14] The cannabinoids found to be most promising in treating epileptic conditions are cannabidiol (CBD), cannabidivarin (CBDV) and tetrahydrocannabivarin (THCV).[15]

In 2012 research in this area received a major boost from a single case: that of Charlotte Figi, a Colorado girl born in 2006 whose parents' highly-publicised use of a particular high-CBD strain of cannabis ("Charlotte's Web") to treat her Dravet Syndrome has had a major effect on regulation and legislation worldwide.

As of the 25 of July 2016, the U.S. National Institutes of Health web site listed no fewer than 28 clinical trials for the application of cannabidiol in the treatment of epilepsy and other seizures, all of which started after 2012, and which plan to use a total of over 2,700 participants. Of these trials, over a third are at Phase 3.[16]

A number of clinical trials are now starting to bear fruit, including one open-label trial[17] which showed a one third reduction in seizures. The state of research in this area was summarised by Epilepsy Action Australia in 2014:

> "We … understand that human clinical trials for CBD and epilepsy are in early phases, and that while CBD has been examined as a potential anti-epileptic in humans, these early studies have not been followed up with larger and more convincing clinical trials over a longer period … EAA supports funding of paediatric study and clinical trials of CBD medication in Australia, with compassionate use of the product extended to children currently being treated with CBD tinctures and oils" [18]

Since then even more research has begun in Australia: The Lambert Initiative research group was set up in 2015 as a result of a donation of AUD$34M to the University of Sydney by Barry Lambert, whose granddaughter suffers from Dravet Syndrome. The Lambert initiative's targets include paediatric epilepsy and also cancer, chronic pain, obesity, anorexia, addictions, mental health and dementia[19]. Large scale State Government clinical trials on intractable paediatric epilepsy are currently under way in New South Wales[20] which recently became the first State in the country to receive a Federal medicinal cannabis cultivation license. Premier Mike Baird has said he hopes Australia can lead the way in this research.[21]

3. Cancer

Cannabinoids have been studied in the treatment of cancer for some decades. Clinical studies have looked at the reduction of chronic pain, nausea and lack of appetite that resulted from cancer and its treatment. There have also been some molecular and animal studies which show some potential for cannabinoids to kill certain kinds of cancers, although this research is still preliminary.

Pain

There is evidence that the use of cannabinoids reduces chronic pain, whether due to cancer or other causes. A systematic meta-analysis of studies examining the use of cannabinoids for the alleviation of chronic pain from cancer available up to April 2015 conducted by Whiting et al concluded that there was "moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain".[22] The review formally assessed study quality, as well as study heterogeneity (agreement between studies on the level of effect), and reviewed over 23,000 documents; in this context, 'moderate-quality' represents an impressive outcome.

Two recent controlled studies are summarised here. They both look at the use of cannabinoids in patients where opioids are not sufficient for pain relief:

Title	Participants	Medication	Outcome
Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial.	263	Nabiximols (Sativex), sublingual	"Nabiximols ... may be a useful add-on analgesic for patients with opioid-refractory cancer pain."
Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC Extract in Patients With Intractable Cancer-Related Pain.	177	tetrahydrocannabinol: cannabidiol (THC:CBD) extract	"This study shows that THC:CBD extract is efficacious for relief of pain in patients with advanced cancer pain not fully relieved by strong opioids."

Nausea

Dozens of controlled studies were carried out in this area prior to 2001, but despite positive results the area received less research attention after that. Two more recent small controlled studies showed that cannabis-based medicines were more effective than placebo, and were similar in effect to another medicine normally used to counter nausea:

Title	Participants	Medication	Outcome
Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting.	16	Whole-plant cannabis-based medicine	"Compared with placebo, CBM added to standard antiemetic therapy was well tolerated and provided better protection against delayed CINV."
Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Cancer-Related Pain.	64	Dronabinol (Delta-9-tetrahydrocannabinol)	"Dronabinol or ondansetron was similarly effective for the treatment of CINV."

Appetite

A number of studies looked at the application of cannabis in the treatment of appetite suppression in HIV/AIDS, with positive results. However, studies looking at appetite loss due to chemotherapy are less uniformly positive:

Title	Participants	Medication	Outcome
Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: r esults of a randomized, double-blind, placebo-controlled pilot trial.	46	Delta-9-tetrahydrocannabinol	"Compared with placebo, THC-treated patients reported improved (P = 0.026) and enhanced (P < 0.001) chemosensory perception and food 'tasted better' (P = 0.04). Premeal appetite (P = 0.05) and proportion of calories consumed as protein increased compared with placebo (P = 0.008)."
Improving Quality of Life With Nabilone During Radiotherapy Treatments for Head and Neck Cancers: A Randomized Double-Blind Placebo-Controlled Trial	56	Nabilone	"At the dosage used, nabilone was not potent enough to improve the patients' quality of life over placebo."
Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-in-Cachexia-Study-Group	164	Cannabis extract, Delta-9-tetrahydrocannabinol	"[Cannabis extract] at the oral dose administered was well tolerated by these patients with [cancer-related anorexia-cachexia syndrome]. No differences in patients' appetite or [quality of life] were found either between [cannabis extract], THC, and [placebo] or between [cannabis extract] and THC at the dosages investigated."
Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study.	469	Dronabinol (Delta-9-tetrahydrocannabinol)	"In the doses and schedules we studied, megestrol acetate provided superior anorexia palliation among advanced cancer patients compared with dronabinol alone. Combination therapy did not appear to confer additional benefit."

Tumours

Controlled clinical trials on the antitumoral effects of cannabinoids have not been conducted. As a result, there is insufficient evidence to support the use of cannabis treatments in this context. However, according to a leading researcher in this area, Dr Guillermo Velasco, and his colleagues,

> "It is well-established that cannabinoids exert palliative effects on some cancer-associated symptoms. In addition evidences obtained during the last fifteen years support that these compounds can reduce tumor growth in animal models of cancer. Cannabinoids have been shown to activate an ER-stress related pathway that leads to the stimulation of autophagy-mediated cancer cell death. In addition, cannabinoids inhibit tumor angiogenesis and decrease cancer cell migration."[23]

In 2006, a pilot Phase I clinical trial involving a group of 9 patients with actively growing brain cancer tumours (glioblastoma) who had not responded to standard therapy received intracranial administrations of THC.[24] Although the patient group was very small and no control group was used, the results of this study indicated that "some patients responded - at least partially - to THC treatment in terms of decreased tumour growth rate, as evaluated by magnetic resonance imaging".[25] Other research has also identified that the powerful anti-inflammatory capacities of cannabinoids could assist with chronic inflammation associated with new cancer cell growth (neoplasia) and "as a consequence, reducing inflammation as a way of impacting cancer presents a new role for these compounds".[26]

This had led to a new round of research and early phase clinical trials funded by GW Pharmaceuticals to assess the potential of incorporating cannabis medicines into cancer treatment regimes.[27] Other significant research projects include the recent announcement from the University of Canberra which will see clinical trials of cannabis treatments for melanoma patients.[28] The Lambert Initiative also intends to conduct further cellular and animal testing on the efficacy of certain cannabinoids in the treatment of brain and lung cancers, with a view towards human clinical trials in the future.[29]

It is important to stress that however promising this research might appear, the available evidence in support of using cannabis to treat, prevent or cure cancer is very weak. Using cannabis to treat pain, nausea and appetite in cancer patients is much more strongly supported, as stated by the Cancer Council of NSW and the Clinical Oncology Society of Australia:

> "There is no current evidence that cannabis or cannabinoids are effective at inhibiting tumour growth or to treat or cure cancer in humans … There is some evidence that cannabis and cannabinoids in controlled delivery may have a benefit to cancer patients where conventional treatments are unsuccessful in providing relief in the following areas: for relieving nausea and vomiting in patients undergoing chemotherapy; as an adjunctive analgesic in patients with moderate to severe pain; and/or as an appetite stimulant for patients experiencing weight loss and muscle wasting"[30]

4. Multiple Sclerosis

Studies on the use of medicinal cannabis for MS have focussed on three areas: muscle spasticity, pain and incontinence. There have been other studies on spasticity from other causes (e.g. injury) and studies on pain due to cancer, which further support the usefulness of medicinal cannabis in the treatment of MS related pain.

Spasticity

There is evidence that the use of cannabinoids reduces muscle spasticity.

The previously cited meta-analysis by Whiting et al also concluded that there was "moderate-quality evidence to support the use of cannabinoids for the treatment of ... spasticity".[31] Again, the size and methodology of that paper means that 'moderate-quality' represents an impressive outcome. Of particular note is a pattern observed by Whiting et al that the particular choice of cannabinoids used in these clinical trials did not appear to make a significant difference to the outcome.[32]

In addition, some recent large studies have given mixed results:

Title	Participants	Medication	Outcome
Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial.	657	Oral cannabis extract, Delta-9-tetrahydrocannabinol	"Treatment with cannabinoids did not have a beneficial effect on spasticity when assessed with the Ashworth scale."
A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols (Sativex®), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis.	527 (241 in randomised phase)	Sativex	"Intention-to-treat (ITT) analysis showed a highly significant difference in favour of nabiximols (P=0.0002)."
Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up.	502	Oral cannabis extract, Delta-9-tetrahydrocannabinol	"These data provide limited evidence for a longer term treatment effect of cannabinoids."
Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial.	498	Dronabinol	"Our results show that dronabinol has no overall effect on the progression of multiple sclerosis in the progressive phase."

Clearly more research is needed to understand the ways in which cannabinoids improve muscle spasticity in MS patients.

Pain

The evidence for pain relief from cannabinoids in the treatment of MS is good.

Three large recent studies are presented here:

Title	Participants	Medication	Outcome
Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial.	657	Oral cannabis extract, Delta-9-tetrahydrocannabinol	"...though there was a degree of unmasking among the patients in the active treatment groups, objective improvement in mobility and patients' opinion of an improvement in pain suggest cannabinoids might be clinically useful."
Multiple Sclerosis and Extract of Cannabis: results of the MUSEC trial.	279	Cannabis extract	"...the rate of relief from body pain was also consistently higher in the [cannabis extract] group than in the placebo group"
Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis.	64	Whole-plant cannabis-based medicine	"Cannabis-based medicine is effective in reducing pain and sleep disturbance in patients with multiple sclerosis related central neuropathic pain and is mostly well tolerated."

Incontinence

Another area where cannabinoids may help in the treatment of MS is in incontinence, although this evidence is not as strong as that for the treatment of pain and spasticity:

Title	Participants	Medication	Outcome
The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMS-LUTS).	630	Cannabis extract, Delta-9-tetrahydrocannabinol	"The findings are suggestive of a clinical effect of cannabis on incontinence episodes in patients with MS."
Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis.	135	Sativex	"Although the primary endpoint did not reach statistical significance, we conclude that Sativex did have some impact on the symptoms of overactive bladder in patients with MS, providing evidence of some improvement in symptoms associated with bladder dysfunction in these subjects."

A 2015 systematic review of randomised controlled trials found that "several cannabinoids showed effectiveness or probable effectiveness for spasticity, central pain, and painful spasms in multiple sclerosis".[33] Overall, the current evidence supporting medicinal cannabis treatments for people living with MS appears to be reasonably well supported.

5. Adverse Events

When considering a particular treatment option, patients, carers and medical professionals need to weigh the potential for a positive improvement against the prospect of other treatments and the potential for adverse events (AEs). These are undesirable reactions to treatments which can range from very mild discomforts to serious life threatening reactions.

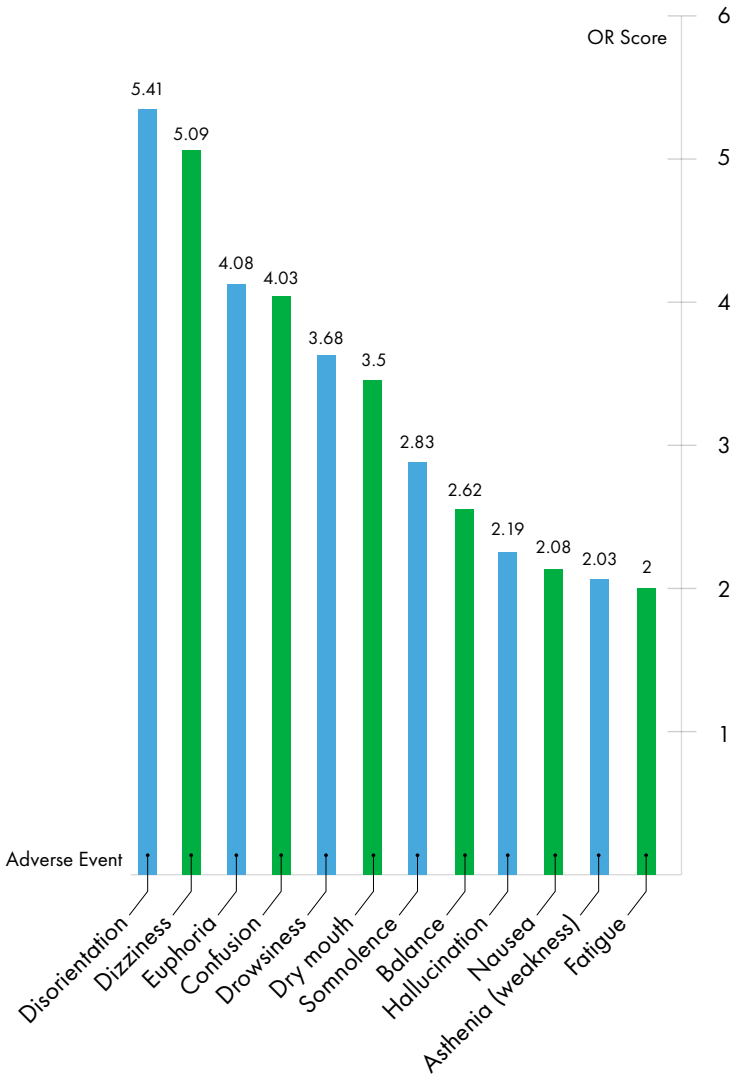
For example, the most promising non-cannabinoid pharmaceutical currently available for treating Dravet syndrome is Stiripentol. In a 2009 study, AEs from this treatment "were reported in about half the patients and included drowsiness, slowing of mental function, ataxia [loss of some bodily control], diplopia [double vision], loss of appetite with weight loss, nausea, and abdominal pain".[34] In many cases children with Dravet syndrome will be prescribed complex combinations of multiple pharmaceuticals.

Strong opioids such as morphine and fentanyl are often used to help treat severe cancer-related pain and their side effects can be debilitating and severe. But even weaker opioids can produce unwanted effects. A double-blind comparative trial of 117 cancer patients receiving either hydrocodone, codeine or tramadol published in 2007 reported that across these three groups, the most common side effects included somnolence (39.5% of patients), nausea (33.9%), constipation (29.9%), dizziness (27.7%) and vomiting (24.9).[35]

Medicinal cannabis treatments including THC have been shown to induce AEs in patients across all treatment groups. In one multicenter, double-blind, randomized, placebo-controlled, parallel-group study on patients with intractable cancer pain published in 2010 involving 177 participants, the most common adverse events were:[36]

	Proportion of patient group experiencing an event		
Description of Event	THC:CBD (%)	THC extract (%)	Placebo (%)
Somnolence	13	14	10
Dizziness	12	12	5
Confusion	7	2	2
Nausea	10	7	7
Vomiting	5	7	3
Raised gamma GT	3	9	2
Hypercalcemia	0	0	5
Hypotension	5	0	0

Whiting et al's meta-analysis provides a high-level aggregation of reported AEs across all medicinal cannabis clinical trials included in their review. This allows the identification of the kinds of AEs most associated with medicinal cannabis treatments across all included studies and conditions. This is represented as an 'odds ratio' (OR) score, with a higher OR indicating a closer correlation between medicinal cannabis treatments and particular AEs. The most strongly correlated AEs across this meta-analysis were:[37]



The prevalence and severity of AEs from medicinal cannabis treatments is believed to be partially related to the interactions between cannabinoids and other chemical compounds found in the cannabis plant. The most well researched combination is that of THC and CBD. Although this combination is often beneficial, this is not always the case. In a review of the available literature published in 2005, Russo & Guy found that,

> "CBD is demonstrated to antagonise some undesirable effects of THC including intoxication, sedation and tachycardia, while contributing analgesic, anti-emetic, and anti-carcinogenic properties in its own right … The hypothesis that the combination of THC and CBD increases clinical efficacy while reducing adverse events is supported"[38]

This paper does not set out to provide a comprehensive assessment of the tolerability or safety of all available treatments. But it is important when discussing the risks and side effects of medicinal cannabis that this is done in a proper context. Although some people do experience AEs from medicinal cannabis use, these are usually both less common and less severe than those resulting from other treatments. Cannabis treatments tend to be well tolerated and AEs are commonly mild to moderate in severity.

6. Conclusion

The field of medicinal cannabis has been constrained and, in many places, prohibited or actively discouraged through onerous regulatory, legal and social barriers. In spite of all of this, there is strong evidence demonstrating the effectiveness of medicinal cannabis in treating the symptoms of pain, nausea, vomiting and appetite in cancer patients. Medicinal cannabis has also been demonstrated to be a viable treatment option for the management of muscle spasticity and pain in people living with MS.

In this field, as in all of science, more research is needed. There is limited and provisional research suggesting medicinal cannabis may assist in the treatment of incontinence from MS. There is cautious optimism that medicinal cannabis will prove to be an effective treatment for intractable childhood epilepsy. While there is currently insufficient clinical evidence to support the use of medicinal cannabis in preventing or treating cancer, there is anecdotal evidence to suggest it may help.

Given the strength of the clinical evidence supporting the use of medicinal cannabis for certain conditions and symptoms, like nausea and vomiting, and the fact that this evidence has been available for many years, we might question why this treatment has not been available sooner. However, Australia is still comparatively advanced in this area: the vast majority of people worldwide live in places where medicinal cannabis continues to be – often punitively – prohibited.

As one of the few countries currently permitting the use of medicinal cannabis, and actively encouraging and funding its research, Australia is uniquely placed to lead the field of medicinal cannabis research and innovation. The work still yet to be done by our patients, carers, medical professionals, advocates, clinicians, scientists and researchers will provide the evidence required to transform people's lives both in Australia and around the world.

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