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# The use of cannabis for medical purposes

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It is rare to have heated public debate on the use of a drug as medicine. While the evidence-base on the indications, dosage and length of treatment for medicinal herbal cannabis (rather than synthetic or pharmaceutical preparations) has developed little in the past decade, its availability has greatly expanded, particularly in North America. As a result of the degree of public interest in the matter, the Centre made a submission to the recent NSW Parliament Legislative Council's Inquiry Into The Use Of Cannabis For Medical Purposes summarising the scientific literature. This Bulletin is based on that submission. There are a range of position papers available that discuss the relevant national and international agreements that touch on the availability of cannabis products for medicinal use and the complexities of designing a robust system of supply. This paper, therefore, focusses on the evidence regarding the efficacy of cannabinoids and crude plant in the management and treatment of medical conditions.

## Introduction

Prior to the development of modern science, cannabis was used as a medicine.[1] It enjoyed a brief period of popularity as a medicinal herb in Europe and the United States in the 1800s being prescribed for various conditions including menstrual cramps, asthma, cough, insomnia, birth labour, migraine, throat infection and withdrawal from opiate use.[2] Because of the problems with titrating the dose there were issues with patients being given too little or too much resulting in anything from no effect to adverse effects. Cannabis was removed from the register of medicines in the early twentieth century in the USA and made illegal at around the same time.

In the past 20 years there has been increasing international focus on the potential of cannabis as a treatment option for various medical conditions, mainly where traditional first line drugs have proven ineffective for particular subclasses of patients. The most common conditions include pain and nausea associated with cancer and its treatment, HIV and other wasting diseases, rheumatoid arthritis and peripheral neuropathic pain. It has also been used to treat the nightmares associated with post-traumatic stress disorder.[3] Accordingly, during this time pre-clinical and clinical research on humans into the effects of pharmaceutical preparations of cannabis has increased significantly.[4] A recent review of relevant randomised controlled trials of cannabinergic pain medicines found 38 published trials, wherein 71% found some efficacy.[5] These trials used approved cannabinoid medications, rather than smoked herbal cannabis, and found that while beneficial effects were achieved most trials were only short-term in duration and longer trials are needed in order to comprehensively gauge the therapeutic benefits of cannabinoids.

Over the past two decades cannabis has been made available, within various regulatory frameworks, for medicinal purposes in twenty two USA states and Washington DC, with no controls on the quality, dosage or safety of the product or its delivery system. In Australia, the debate about the legalisation of cannabis for medicinal or recreational purposes has also been growing.

## Cannabinoids

There are three broad types of the diverse class of chemical compounds known as cannabinoids:

1. phytocannabinoids (plant forms),
2. endogenous cannabinoids (produced naturally in the bodies of humans and animals), and
3. synthetic cannabinoids that are chemically produced by humans and not derived from plants.

1. The **phytocannabinoids** are comprised of the three best known varieties of the cannabis plant *Cannabis sativa, Cannabis indica* and *Cannabis ruderalis*. Cannabis sativa is by far the most common as it has the highest levels of the strongest psychoactive compound delta-9-tetrahydrocannabinol, commonly known as THC. Agricultural processes have succeeded in refining the types of cannabis plants (females bred alone, hydroponic methods) harvested to maximise the THC content. Indeed, trends in the cannabinoid profile of cannabis over the past two decades have biased contemporary cannabis towards high THC and low Cannabidiol (CBD) content. Recent NSW research into the cannabinoid profile of cannabis has indicated high levels of THC (around 15%) and negligible (<1%) levels of CBD.[6] While there is enormous variability in the level of these cannabinoids (commonly referred to as cannabis potency), some data do indicate that CBD may ameliorate or inhibit the psychotogenic, anxiogenic and memory-impairing effects of THC.[7]

2. **Endocannabinoids** are chemicals that occur naturally in the human body. Following the discovery of the bioactive compound in cannabis it was determined that THC acted by binding to specific plasma membrane proteins labelled the "cannabinoid receptors". Although the existence of several receptors for THC and/or its synthetic analogues are suspected based on pharmacological data, to date only two cannabinoid receptors have been cloned and both are members of the G-protein coupled receptor (GPCR) family. These receptors are called the CB1 receptor and the CB2 receptor. The CB1 and CB2 receptors have been found in the brain in the basal ganglia, cerebellum, neocortex, hypothalamus, hippocampus and cortex. They are also found in immune cells and tissues. Endogenous cannabinoid receptors have also been found in the reproductive organs and other areas of the body.

   The two most studied endocannabinoids are anandamide (N-arachidonoylethanolamine) and 2-arachidonoylglycerol (2-AG)).[8] These endogenous cannabinoids operate at the CB1 and CB2 receptors. The mechanisms that operate at these receptors are very complex and our understanding of the way cannabinoids function in the body is progressing. Of the more than 80 cannabinoids that have been identified in the cannabis plant, only the metabolism of THC, cannabidiol (CBD) and cannabinol (CBN) have been researched to any extent. CBN has no affinity for CB1 and CB2 receptors but acts as an indirect antagonist of cannabinoid agonists.[9] Recently it was found to be an antagonist at the putative new cannabinoid receptor, GPR55, in the caudate nucleus and putamen.[10] CBD has also been shown to act as a 5-HT1A receptor agonist, an action which explains its antidepressant, anti-anxiety, and neuroprotective effects.[11-15] Additionally, CBD has been shown to inhibit cancer cell growth in cell cultures with low potency in non-cancer cells, although this inhibitory mechanism is not yet fully understood.[16]

3. **Synthetics** Pharmaceutical preparation of the plant for research and clinical purposes has enabled the constituent components to be adjusted for research purposes to investigate which combinations of the constituents provide the best treatment for differing medical conditions. This is critical as it is the psychoactive components and the balance of the constituents and the route of administration of the drug that create the risk of harm to self and others

(dependence, cognitive impairment, psychological impairment in terms of paranoia, anxiety, depression and impaired judgement when driving or working, hepatic, respiratory and cardiac harms). There have been different cannabis products developed and these include Dronabinol/Marinol, Cesamet, Cannador, and Sativex. Donabinol/Marinol is an oral synthetic cannabinoid preparation that has been used since 1985. Cesamet/Nabilone is a synthetic cannabinoid analogue purported to be more potent than natural THC.[4] Cannador is an oral capsule containing a cannabis extract, with reportedly a 2:1 ratio of THC to CBD[4], however the exact THC to CBD ratio has not yet been standardised.[2] Finally nabiximols, marketed as Sativex is a botanical oromucosal cannabinoid based spray, with one spray delivering a fixed dose of 2.7 mg THC and 2.5 mg CBD.[2]

## Cannabis as medicine

Almost all of the modern research literature on cannabinoids as medicine have utilised pharmaceutical preparations of THC and/or CBD. There have been no published human trials employing the accepted gold standard design of a randomised controlled trial using smoked whole plant. The cannabinoid pharmaceutical preparations that have been developed have been used to treat a range of conditions such as chronic/acute pain, nausea, HIV and cancer-related wasting and spasticity associated with Multiple Sclerosis.

- **Chronic/acute pain**

  Cannabis preparations have been used to treat many different types of pain including neuropathic pain, postoperative pain, chronic unexplained pain, fibromyalgia, rheumatoid arthritis, and the pain associated with Multiple Sclerosis and cancer.[17-24] Most of the studies have used cannabis in cases where traditional front-line medications have proven ineffective.[4] The studies focusing on pain have found some benefits, particularly for neuropathic pain, although there is some question about the generalizability of the results due to self-selection bias and other weaknesses of the studies reported.[25, 26] This fact, combined with the side-effects that have been recorded, necessitate further examination of these substances for this indication.

- **Nausea and vomiting in patients with cancer and to stimulate appetite in patients with HIV or cancer**

  Synthetic cannabis preparations have been used to treat nausea and vomiting in cancer and HIV patients[27, 28] and as an appetite stimulant therapy for the weight loss associated with these conditions. A recent Cochrane review of the studies conducted on HIV/AIDS patients call for stronger evidence to support the use of this substance in these conditions.[27] A review of randomised clinical trials of synthetic cannabinoids versus placebo or conventional anti-emetic drugs concluded that while side effects were more intense, patients reported superior anti-emetic effects from cannabinoids.[65]

> there have been no published clinical trials of smoked cannabis plant as a cure for cancer or other medical conditions

- **Spasticity, muscle cramps and nerve pain associated with Multiple Sclerosis and Parkinson's disease**

  This is the area that has received the most research attention in recent years. Numerous studies have examined the impact of cannabis preparations on spasticity and pain associated with Multiple Sclerosis and Parkinsons Disease.[29-33] Overall there has been mixed results in terms

of objective and subjective reports of symptom relief.[26,30] Recently nabiximols (Sativex) has been trialled in these conditions with some success and minor adverse effects[34], particularly for the relief of spasm symptoms. As a result, nabiximols is registered in many countries for this indication, where first line treatments have not been effective.

- **Glaucoma**

  There is some evidence to suggest a therapeutic effect of cannabis preparations for the relief of glaucoma. Typically oral or intravenous dosing has been used and this produces a short-lasting effect. Continual dosing overcomes this handicap, however, it also produces unwanted side effects. Water soluble preparations are yet to be forthcoming.[35] Available medications are generally more effective than cannabis preparations for this condition. In a study of 20 opthamologists approved to prescribe cannabis as either oral THC or smoked whole plant for end-stage glaucoma, found that over two years no patients consented to receive smoked cannabis and only 9 oral THC. Less than half of these patients (4/9) achieved their therapeutic goal and all patients experienced side effects.[66]

- **Cannabis withdrawal**

  Recently in Australia, nabiximols has been trialled for the inpatient management of cannabis withdrawal and found to be safe and to have a positive effect on withdrawal symptoms, period of withdrawal and treatment retention.[36] Much more research is required into the use of cannabinoids in the management of cannabis withdrawal and cravings management.

- **Epilepsy**

  The endogenous cannabinoid system is known to be involved in regulating neuroexcitation. Laboratory studies of cannabinoids, particularly cannabidivarin (CBDV) and CBD have demonstrated anti-convulsive properties, however, the human clinical research is very small and contradictory.[8] THC alone in any form is considered unlikely to yield therapeutic benefit for patients with epilepsy.[67] There are currently trials underway assessing CBD for the management of severe early-life seizure disorders such as Dravet and Lennox-Gastaut syndrome.

- **Inflammatory bowel disease**

  While there have been various anecdotal reports of the use of cannabis for inflammatory bowel diseases and plausible putative biological mechanisms for its method of action, there are no large randomised controlled trials. Once again, there is a need for rigorous studies to establish which cannabinoids, at which doses and mode of administration will maximise beneficial effects for Crohn's Disease and related conditions and avoid potential harmful effects.[69]

## Issues to be considered

While its advocates make strong claims for smoked herbal cannabis as a first line treatment, and even cure, for a range of conditions including cancer[37], cannabis and cannabinoids were primarily intended to be used as an adjunctive or second line therapy where standard treatment is ineffective or poorly tolerated.[25] Studies of medicinal cannabis users in the US report that non-specific chronic pain is the most commonly reported reason for use.[42] As a result of the early stage of the evidence base for the appropriate indications, dosage, length of treatment and regulatory regimes, the relevant medical workforces are currently conflicted.[38]

## Regulation

There are many issues to be considered in the regulation of medicinal cannabis[39, 40] and many lessons to be learned from current regimes internationally.[41]

A particular issue for Australia, is our random roadside drug testing for THC and zero tolerance laws regarding testing positive for THC when driving. This makes it necessary for those receiving medicinal cannabis in any form, including nabiximols to refrain from driving for some hours after dosing.[68]

## Delivery

One of the challenges in the move to legalise cannabis for medicinal purposes is overcoming the problems associated with inhaling cannabis smoke alone, or mixed with tobacco. Legalising the smoking of cannabis for medicinal purposes means that all of the risk factors of smoking (cardiovascular and respiratory and addiction to tobacco when mixed with the cannabis) remain. The harms associated with cannabis use include the enormous variation in the product in terms of the levels of THC and other cannabinoids, and unknown contamination from pesticides, heavy metals and microbes, as well as the delivery system (smoking with or without tobacco and vaporisation).

## Diversion and risks to vulnerable populations

While it is early days in the availability of medicinal cannabis in most states in the US, there is some evidence to suggest that as availability increases in the community, children and adolescents are gaining easier access to the drug. This places these young people in the position of risks to physical and mental health in the longer term that have been documented in many studies.[43, 44] In the USA, there is mixed evidence on the effects of the availability of medicinal cannabis on levels of cannabis use in the general population.[25, 45, 46] Two groups that have been identified as vulnerable include infants and animals. Edible cannabis products are frequently sweet and attractive to children such as brownies, ice cream and sodas. This is extremely concerning as it is much easier for infants and young children to overdose on THC leading to coma and the need for urgent medical care.[47] This risk also extends to domestic pets with cases of severe illness and death associated with cannabis butter in particular.[48] In addition, making products highly palatable is a marketing ploy successfully used by the alcohol industry to recruit young drinkers and is a concerning aspect of the cannabis commercialisation industry.

## Harms

Harms resulting from smoking cannabis that have been reported in numerous studies include:

- addiction[49]
- adverse psychological effects including impaired judgement and thinking[50]
- delusional thoughts, anxiety and depression, psychosis (all conditions that may persist)[51-54]
- persistent cognitive decline[43]
- physical problems including circulation (such as stroke and heart attack) and lung problems (chronic cough, sputum production, wheezing and bronchitis) and some cancers [55-58]
- financial problems[59]

- interpersonal problems including conflict with friends and family and loss of social connections[59]
- increased risk of suicide among some groups[44, 60]
- car accidents and accidents at work[61-63]

Younger age of initiation of cannabis use, as well as longer duration of use, increase the risk to individuals of the above adverse consequences.

## Potential benefits of cannabinoids

A number of studies using both smoked and pharmaceutical preparations of cannabis have been published over the last 30 years. Some modest success with this drug class has been reported treating a range of conditions, predominantly in the treatment of the symptoms of Multiple Sclerosis. A variety of human clinical trials have been performed using nabiximols in community settings, representing over 2000 subjects with 1000 patient years of exposure, with no evidence of tolerance, significant intoxication, or any form of withdrawal syndrome.[24] Nabiximols has also been shown to have some success as an adjunctive treatment with patients suffering from brachial plexus avulsion,[23] neuropathic pain in Multiple Sclerosis (MS)[17], rheumatoid arthritis[18], peripheral neuropathic pain[21] and pain associated with advanced cancer.[20] Various studies in MS patients have shown that there is no habituation to the treatment and no withdrawal effect given the low doses used with nabiximols.[24] To date, nabiximols presents the best hope for pharmaceutical cannabinoids as a second or third line treatment or as an adjunctive therapy.

## Conclusions

When considering whether or not to legalise cannabis for medicinal purposes a distinction must be made between 1) the therapeutic potential of specific constituent compounds found in the cannabis plant delivered in controlled doses via non-toxic delivery systems, and 2) the effects of smoking cannabis on both the user and the wider society. As an Australian cost-benefit analysis of a legalised-regulated model of cannabis availability predicted a 35% increase in the prevalence of use, this should also be considered in any model for regulated medicinal use.[64]

Drug approval must be considered in the context of public health, particularly for controlled substances. Cannabis has been proven to be an addictive drug. Consuming cannabis has been shown to cause cognitive impairment as well as increasing vulnerability to psychological harms among users. Consuming cannabis and then driving or working also increases the risk to the user and also to the general public through traffic accidents and workplace incidents. Smoking cannabis has been associated with cardiac and respiratory tract morbidity as well as a form of testicular cancer.

Considering the results of the many clinical and experimental studies in humans involving pharmaceutical preparations of cannabis extracts, it is logical that selected and targeted manipulation of the cannabinoid system is preferable to treatment with a whole, unregulated, variable dose and contaminated cannabis product with an unsafe delivery system. The only way research can be communicated clearly about cannabis is to use reliable and standardised methods to understand the composition of various cannabis preparations. ‘Ideally a comprehensive

overview of the cannabinoid content (i.e. the chemical fingerprint) of cannabis preparations used in studies should therefore be a standard part of scientific reports on the effects of cannabis'.[2]

Pharmaceutical preparations of cannabis can be delivered safely, are tested and subjected to strict regulatory control both in their preparation and administration, thereby reducing the harm potential both to the user and the wider society. As nabiximols are now licensed by the Australian Therapeutic Goods Administration for those with Multiple Sclerosis associated muscle spasticity, this is the most promising type of cannabinoid preparation for clinical research, and if proven safe and effective, for medical prescription under supervision.

## Conflict of interest declaration

Jan Copeland has led an NH&MRC project using nabiximols (Sativex) in the management of cannabis withdrawal. The medication was provided by GW Pharmaceuticals in the United Kingdom. Drs Clement and Copeland are also currently conducting a study of the feasibility of the use of CBD in the management of cannabis withdrawal. Neither have received any direct or indirect financial support nor have any direct/known financial interest in any pharmaceutical company.

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