Position statement - Medical use of cannabis

A joint position statement with 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. In addition, there is no current evidence that cannabis or cannabinoids reduce risk or prevent cancer occurrence or promote good health
- 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.
- Evidence from randomised, controlled trials is required to evaluate the impact of cannabis and cannabinoid products on cancer and side effects of chemotherapy
- Smoking the cannabis plant is a particularly harmful route of administration, largely because carcinogenic substances are inhaled into the lungs and cannabinoid levels present in the natural plant are unpredictable
- The side effects and unpredictable levels of cannabinoids delivered through smoking marijuana and use of the whole plant product make it inappropriate for therapeutic use
- Synthetic cannabis and natural cannabinoid extract products, particularly nabiximols delivered via an oral spray, offer advantages in providing symptom relief without harmful psychological or tetrahydrocannabinol (THC) related effects
- Synthetic cannabis and natural cannabinoid extract products delivered via an oral spray is a preferable route of administration for anti-emetic therapy
- Natural and synthetic forms of cannabis are currently illegal in Australia for therapeutic use to alleviate side effects of cancer and chemotherapy
- Cancer Council Australia and the Clinical Oncology Society of Australia welcome research into the potential benefits of cannabis and cannabinoids for cancer patients

Background

Managing illness induced by chemotherapy, especially in patients with advanced cancer who have responded poorly to conventional relief options, is a significant problem for cancer patients and their doctors.

The potential benefits of cannabis and cannabinoids for symptom relief have been subject to a number of government reviews and public debate in recent years. This includes the establishment in September 2014 of a New South Wales (NSW) Government working group that will report to the Premier on its recommendations. The NSW Government has also recently established the Terminal Illness Cannabis Scheme and has committed $9 million over the next five years towards clinical trials to further explore the use of cannabis and/or cannabis products, including the area of adults with chemotherapy-induced nausea and vomiting, where standard treatment is ineffective. Other jurisdictions, including the Commonwealth, have expressed an interest in evaluating the potential benefits of cannabis and cannabinoid use as a symptom-relief agent.

The use of natural and synthetic forms of cannabis is currently illegal in Australia.

Cannabis and cannabinoids are derived from the *Cannabis sativa* plant. Cannabis, also known as marijuana (and colloquially as “grass”, “pot”, “weed”, “hash” etc.), is made from the dried flowers and leaves of the *Cannabis sativa* plant. Cannabinoids are chemicals which act upon cannabinoid receptors, CB1 and CB2 in the body. Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most abundant and researched cannabinoids.

THC is the primary psychoactive component of cannabis and the most effective cannabinoid for alleviating nausea and vomiting, and for stimulating appetite[1][2]. However, the therapeutic use of THC is complicated by its psychoactive side effects. In recent years, there has been increased interest in non-psychoactive cannabinoid compounds such as CBD for therapeutic use to alleviate chemotherapy induced illness[3].

Access to therapeutic products in Australia

In Australia all authorised therapeutic substances are required to prove a high standard of safety, efficacy and quality, and demonstrate clinical effectiveness against standard treatment prior to use in practice[4]. Randomised controlled trials generate primary data which provides the strongest level of evidence to demonstrate the efficacy of a therapeutic product in a clinical setting. The Therapeutic Goods Administration (TGA) assesses this evidence before the product is made publicly available, and further assessment is undertaken by the Pharmaceutical Benefits Advisory Committee in considering whether a product should be recommended to receive government subsidy[4]. Clinical trials compare clinically relevant treatments, require a high participation rate to be representative of the affected population and support the production of significant results, and set relevant trial endpoints to capture clinically meaningful outcomes. Conducting a high quality trial is a complex, lengthy and an expensive process. The rigorous assessment of a new medication or modification of an existing product is required to ensure the Australian population can access the highest quality products with a reduced risk of adverse effects.

Clinical trials are governed by the *National Statement on Ethical Conduct in Human Research*[5] and the *Australian Code for the Responsible Conduct of Research*[6].

Natural and synthetic products

The therapeutic use of cannabis in its natural form is limited for a number of reasons.

Different strains of the *Cannabis sativa* plant contain varying levels of cannabinoids such as THC and CBD. This is also true of marijuana oil or hemp oil, since purified oils contain roughly the same ratios of compounds as the plants from which they are derived[7]. Although *Cannabis indica* (rather than Cannabis sativa) is sometimes recommended by some hemp oil advocates for its higher CBD and lower THC levels, these levels are neither consistent nor predictable.

In addition to being unpredictable, cannabinoid levels found in natural (plant-based) cannabis are generally lower than the therapeutic doses used in most clinical studies[8]. Therefore, to acquire a therapeutic benefit a cancer patient would require a purified and concentrated form of cannabis rather than the whole plant product.

A number of natural and synthetic cannabinoid products have been developed for use in a medical setting and act in the same way in the body as the plant product. Currently there are three main products:

- dronabinol, a synthetic form of THC;[9]
- nabilone, a synthetic form of THC;[10] and
- nabiximols, a chemically pure 50:50 mixture of THC and CBD[2][11].

Cannabinoid products such as these have been approved for therapeutic use in some countries. Dronabinol has been available in the United States of America (United States) by prescription since 1985[9][12], and nabilone has been approved for use in the United Kingdom[10]. Naboximols is the only cannabinoid product, natural or synthetic, approved by the TGA in Australia[13].

Therapeutic benefits of cannabis use

Symptom relief

The majority of evidence for the therapeutic benefit of cannabis and cannabinoids addresses their use in relieving the symptoms of cancer and cancer treatments such as chemotherapy[14].

In the late 1990s the NSW Government formed a working party on the use of cannabis for medical purposes which, in 2000, reported that medical conditions for which cannabis may be of medical benefit include[2]:

- as an appetite stimulant for cancer and HIV related wasting;
- pain unrelieved by conventional treatments;
- neurological disorders, such as multiple sclerosis; and
- nausea and vomiting in cancer patients undergoing chemotherapy which do not respond to conventional treatment.

These conclusions, suggesting the use of cannabinoids would benefit cancer patients, were consistent with a report prepared in 1998 by the Drug and Alcohol Services Council of South Australia for the Ministerial Council on Drug Strategy[15] and a 1999 report by the United States Institute of Medicine[16]. The report by the United States Institute of Medicine recommended that more research should be conducted, with a specific focus on situations where all currently marketed medications are unable to provide relief[16]. The report also found that some of the effects of cannabinoids, such as reduced anxiety, sedation, and euphoria, may be helpful for certain patients and situations, but distressing for others[16].

The Australian Medical Association (AMA) acknowledges that, given the available evidence, cannabis could be of medical benefit as an appetite stimulant and as an anti-emetic. However, the AMA also supports the need to conduct comprehensive research producing clinically meaningful outcomes to determine the benefits for neurological disorders and pain relief, as well as guiding safe and effective routes of administration[17].

Currently, evidence from clinical trials to support the use of cannabis and cannabinoids to relieve symptoms of chemotherapy and pain is limited. Clinical trials have investigated medical cannabis products for a range of indications.

A randomised controlled phase III trial conducted using cannabis extract and purified THC on patients with advanced incurable cancer found no impact on their appetite or quality of life[18], while a systematic review found that cannabinoids were effective anti-emetics for controlling chemotherapy related sickness[19]. Cannabinoids reviewed in the study provided a slightly superior outcome to conventional anti-emetics after chemotherapy, and were preferred by participants. However, potentially serious adverse effects, even when taken short-term orally or intramuscularly, could limit their widespread use.

Multiple studies have demonstrated that using THC and CBD together has an analgesic effect for neuropathic, multiple sclerosis (MS) and HIV-related pain[20][21][22]. The use of THC and CBD combination therapy demonstrated efficacy in treating neuropathic pain and spasticity without the psychotropic side effects of cannabis. The study did not report any clinically relevant adverse events and in animal studies, no signs of strong dependency after withdrawal.

A 2004 National Drug and Alcohol Research Centre survey of Australian adults who had used cannabis for medical purposes reported the use of cannabis to relieve a number of medical conditions including pain and nausea[23].

Studies of synthetic cannabis and natural cannabinoid extract products

In North America and some European countries, dronabinol, nabilone and nabiximols are currently in use for the treatment of chemotherapy-related nausea and vomiting in people who have not responded to conventional treatment. Dronabinol and nabiximols are also used to treat loss of appetite and weight loss in cancer patients[9][10][24]. Additionally, nabiximols are used as an adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain[25].

A clinical trial is currently underway in Australia to determine the efficacy of administrating nabiximols via an oral spray to relieve persistent chronic pain in patients with advanced cancer who have not responded to conventional medicines[26].

Cancer treatment

It should be noted that the current discussion in Australia about the potential benefits of cannabis and cannabinoids relates only to symptom relief. Symptom relief is a separate issue from cancer treatment, i.e. the potential to halt or reverse tumour growth. Currently there is no evidence from controlled studies that cannabinoids can cure or treat any cancer types in humans.

The majority of scientific research investigating the effect of cannabinoids on cancer cells has been conducted using cancer cells grown in a laboratory setting or using animal models. There is evidence that the cannabinoid receptors, CB1 and CB2 play a role in tumour growth and progression in animal models, and may be a promising therapeutic target in cancer treatment[27]. Various cannabinoids (both natural and synthetic products) have a wide range of effects in the laboratory, including[27][28]:

- inducing cell death;
- inhibiting cells cell division;
- preventing new blood vessels from growing into tumours; and
- stopping cancer cells from moving or invading neighbouring tissue

One clinical trial has published results on the use of the cannabinoid THC to treat cancer in humans. Using a syringe pump, via an infusion catheter, nine people with glioblastoma multiforme received THC administered directly to the site of the tumour. All patients died within a year, with a median survival of 24 weeks, which is consistent with survival rates at diagnosis for glioblastoma multiforme patients[29]. Some participants had a minor response to treatment including, improvement in their clinical symptoms and short term progression free tumour growth prior to further decline in health. As this was an early stage trial without a control group, the study is unable to conclude whether THC had an impact on patient survival.

Additional international research in this area include an early-stage trial testing a synthetic cannabinoid called dexanabinol in patients with advanced solid tumour cancer[30], and an early-stage trial, currently on hold, testing a nabiximols called Sativex for treating people with brain tumours[31].

Side effects

The effects of cannabis and cannabinoids can differ significantly with different doses and between individuals[14].

Short term

The short term effects of natural cannabis include loss of inhibition, anxiety or paranoia, difficulty concentrating, elevated heart rate, dry mouth and throat, vomiting, and hallucinations[32].

Some people find the emotional and mental side effects of cannabis frightening. A few experience temporary psychosis (loss of contact with reality) as a result of taking certain cannabinoids[7].

A systematic review found that potentially serious adverse effects, even when taken short term orally or intramuscularly, are likely to limit widespread use of cannabinoids as anti-emetic drugs for controlling chemotherapy

related sickness[19].

In most cases, the side effects of the purified cannabis extracts are mild and can be managed with careful dosing.

Long term

Based on multiple studies, researchers found that smoking the cannabis plant delivers harmful substances and may be an important risk factor in the development of respiratory diseases and cancer of the lungs, mouth, and tongue, and an increased risk of bronchitis[33][34].

Marijuana smoke contains known carcinogens, however epidemiological studies exploring the link between marijuana and cancer risk have been inconsistent, and most recent epidemiological studies have not found a substantial effect on cancer risk[35][36]. A case control study demonstrated an association between marijuana smoking and HPV-16-positive head and neck squamous cell carcinoma. Participants who were HPV-16-positive, non-smokers of tobacco but had a history of smoking marijuana for five or more joint years presented with a squamous cell carcinoma of the head or neck 11 times greater than HPV-16 positive participants who were sporadic or non-smokers of marijuana[37]. The United States Institute of Medicine report stated that because marijuana contains a number of active compounds, it cannot be expected to provide precise effects unless the individual components are isolated[16].

Smoking cannabis is associated with stroke, myocardial infarction, and arteritis of the limb[38][39]. There is a dose-dependent association between smoking cannabis and an increase in the presence of myocardial infarction. Smoking the cannabis plant decreases the amount of oxygen available to the heart resulting in an increased resting heart rate and blood pressure[38][39]. In a systematic review, 58% of patients with cannabis-associated arteriopathy underwent limb amputation[38].

Most of what is known about the adverse effects of smoked cannabis comes from studies of long-term recreational users rather than medical users. People who smoke cannabis for medicinal purposes usually use smaller quantities over shorter time periods compared to recreational users[40]. Medical programs that involve smoking cannabis, such as in Canada and the Netherlands, present an opportunity to conduct follow-up studies to investigate the risk of these adverse events in this population[40].

Additional adverse health effects associated with chronic cannabis use include cannabis dependence (addiction), depression and decreased concentration, memory and impaired cognitive function[32].

Side effects of synthetic cannabis and natural cannabinoid extract products

A systematic review of the adverse effects associated with the use of synthetic cannabis products found that there was no increased risk of serious adverse events, such as vomiting and urinary tract infections[12]. Non-serious adverse events such as dizziness, dry mouth, confusion, anxiety and nausea have been associated with the use of synthetic cannabis products[9][10][11][12].

Nabiximols via oral spray offer advantages in treating the symptoms without the associated 'high'[41]. It also allows patients who require anti-emetic therapy, but who cannot swallow, an alternative to control side effects of chemotherapy or radiotherapy induced nausea and vomiting. Synthetic forms of THC, especially dronabinol and nabilone, can increase heart rate and decrease blood pressure, which can be especially problematic in people with pre-existing heart conditions[7][42].

In addition, synthetic cannabis and natural cannabinoid extract products can increase the risk of psychiatric and cardiovascular conditions and the effects of some sedatives, sleeping pills, or alcohol, including sleepiness and poor coordination[7][42].

A systematic review reported that although patients only perceive synthetic cannabinoids and natural cannabinoid extract products as slightly more effective than traditional anti-emetics, they also preferred cannabinoid use for future chemotherapy[19].

Routes of administration

The effects of cannabis vary depending on how cannabis compounds enter the body.

THC is processed by the liver, which produces a secondary psychoactive compound. When marijuana smoke is inhaled, cannabinoids enter the bloodstream and to the brain quickly which can create a high, uncontrolled dose of cannabis. The secondary psychoactive compound is produced in smaller amounts when marijuana is taken orally and the effects are longer lasting[43]. Smoking cannabis is not recommended, as the smoke contains at least 50 of the same carcinogens as tobacco[44]. Furthermore, the smoked natural plant product does not satisfy requirements to be classed as a therapeutic good in Australia[2].

Dronabinol and nabilone are taken orally in capsule form[9][10]. The oral capsule form can be problematic if a patient has difficulty swallowing and holding down capsules, as the beneficial components of the dronabinol and nabilone are then unable to be well absorbed into the body[2]. Therefore eligible patients in the United Kingdom and United States, where these synthetic forms are available, do not view this route of administration favourably and it limits the use of oral synthetic cannabis products in this form.

Nabiximols is administered as an oral spray which is absorbed in the patient's mouth. This is a more acceptable method of administration of anti-emetic therapy for patients who have difficulty swallowing or digesting tablets[41][45]. It is expected that the oral spray form of nabiximols will be the preferred medicinal cannabinoid product, because the spray delivery system prevents THC from entering the blood too quickly, and the formulation enhances the therapeutic benefits, while minimising unwanted psychological and other THC-related effects[45].

Current public policy and legislation

The use of cannabis for medical use or any other purposes is currently prohibited in all Australian states and territories, although penalties for possession and use differ between jurisdictions. Access to cannabis for research purposes is dependent on the approval of Commonwealth and/or State or Territory Health Authorities and the outcome of an ethical review on the proposed research.

Cannabis is listed as an illicit drug under Australian federal law. This law is outlined in the Crimes (Traffic in Narcotic Drugs and Psychotropic Substances) Act 1990 and the Customs Act 1901[2]. Cannabis is encompassed by law under the Narcotics Drugs Act 1967 and the Therapeutic Goods Act 1989[2].

Australia is a signatory on two United Nations international agreements relating to the use of cannabis for medical purposes: the Single Convention on Narcotic Drugs (1961); and the Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances (1988). The agreements aim to combat drug abuse through coordinated international action, specifically to discourage drug trafficking. The Single Convention was implemented to limit possession, use, trade in, distribution, import, export, manufacture and production of drugs exclusively to medical and scientific purposes[2]. The 1988 Convention listed additional behaviour and mood-altering drugs to the Single Convention and distinguished between drugs which are totally prohibited and those, such as cannabis, which have the potential to be used for restricted medical purposes[2].

Cannabis, and THC and synthetic cannabinoids which are not scheduled elsewhere, are Schedule 9 prohibited substances under the Standard for the Union Scheduling of Medicines and Poisons (SUSMP). Schedule 9 substances under the SUSMP are substances which may be abused or misused, the manufacture, possession, sale or use of which should be prohibited by law except when required for medical or scientific research, or for analytical, teaching or training purposes with approval of Commonwealth and/or State or Territory Health Authorities[13]. They are the most heavily regulated poisons.

Dronabinol, nabilone and nabiximols are listed as Schedule 8 (controlled drug) substances. Schedule 8 substances are substances which 'should be available for use but require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical and psychological dependence'[13]. On an individual patient basis, access to Schedule 8 substances unregistered in Australia can be applied for through the Special Access

Scheme. However, as the SUSMP is implemented through individual state/territory drugs, poisons and controlled substances legislation, additional restrictions to access may be applied.

On the 26 November 2012, the TGA listed nabiximols (Sativex) on the Australian Registration of Therapeutic Goods (ARTG) for 'treatment, for symptom improvement in patients with spasticity due to multiple sclerosis who have not responded adequately to other anti-spasticity medicine who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy'[46] In Australia, Schedule 8 substances such as nabiximols, if listed on the ARTG, can be obtained through a doctor who holds a permit to prescribe Schedule 8 substances pending individual state/territory access legislation.

Neither cannabis and cannabinoids, nor their synthetic forms, are currently approved for cancer-related therapeutic use in Australia. In the most recent Australian Institute of Health and Welfare National Drug Strategy Household Survey, 74% of participants supported clinical trials investigating the benefits of cannabis use for the treatment of medical conditions while 69% supported legislative change that permitted medical use of cannabis[47].

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