Current evidence for the integration of medicinal cannabis into clinical practice

There is a growing body of evidence exploring the therapeutic efficacy of medicinal cannabis as well as its integration into clinical practice. Two major limitations to designing proper clinical studies are regulatory licensing hurdles and the lack of development and supply of a true placebo. Despite these barriers, research efforts have intensified in recent years with a focus on structured randomised controlled trials and large-scale systematic reviews. This document summarises current evidence for the use of medicinal cannabis and the most common active cannabinoids tetrahydrocannabinol (THC) and cannabidiol (CBD) in a range of therapy areas.

Evidence in selected therapy areas

Chronic pain
There is some evidence to suggest cannabinoids may offer a modest, clinically meaningful effect on pain[1]. A review and meta-analysis included 28 chronic pain trials with 2,454 participants all but one of which were placebo controlled[2]. The average number of patients who achieved a 30% or greater reduction in pain using cannabinoids was greater than with placebo. The trials included patients with pain from different aetiologies, including central and peripheral neuropathic pain, cancer pain, fibromyalgia, rheumatoid arthritis, MS, and others.

A systematic review of randomised controlled trials published between 2010 and 2014 found cannabinoids (nabilone, oral cannabis sprays, and inhaled cannabis) to be an effective analgesic in the treatment of non-cancer pain[3]. A patient level meta-analysis comparing inhaled cannabis to placebo in neuropathic pain demonstrated a statistically significant, greater than three-fold OR (odds ratio) of a 30% reduction in pain with a number needed to treat of only 5.6[4].

A randomised controlled study investigating the effect of inhaled cannabis on diabetic peripheral neuropathy demonstrated a dose-dependent reduction in pain, with high doses significantly better than low or medium doses[5]. Another study found that vaporised cannabis reduced central neuropathic pain in a dose-dependent fashion, though false-discovery-rate P values were not significant[6,7].

In the United States, between 1999 and 2010, states that enacted medical cannabis legislation had significantly lower opioid overdose mortality rates[8]. Recent analyses of prescription data from the United States, looking at states that have introduced a medical cannabis access regime, demonstrate a significant reduction in the prescription of conventional pain medicines[9,10].

Chemotherapy-induced nausea and vomiting
A review of 28 studies that included 1,772 participants suffering from chemotherapy-induced nausea and vomiting (CINV) found a greater benefit of cannabinoids for the treatment of nausea and vomiting than an active comparator or placebo, though the improvement was not always statistically significant[2]. A Cochrane review of 23 randomised controlled trials demonstrated a non-significant relative risk of 2.0 [95% CI, 0.74-5.4] for the outcome of absence of nausea and vomiting in the treatment of CINV compared to standard treatment[11]. A study of 64 patients found that the cannabinoid dronabinol was as effective at treating CINV as the commonly used antiemetic ondansetron[12]. Most of these studies tested pharmaceutical preparations of THC such as nabilone or dronabinol.

Multiple sclerosis
Nabiximols (THC/CBD oromucosal spray), and oral THC may be effective treatments to reduce patient-reported spasticity. This conclusion is based on systematic reviews of patients with MS[1,2] and an additional trial of nabiximols[13]. The European Federation of Neurological Societies task force lists cannabinoids as Level A for effectiveness in MS-related central pain and recommends cannabinoids as second- or third-line treatment for refractory cases[14].

Sleep disorders
A systematic review of two randomised controlled trials testing cannabinoids (nabilone, dronabinol) for the treatment of sleep disorders found that there was low quality evidence for an association[2]. Several studies measuring the effects of cannabinoids on other disorders report a concomitant positive effect on sleep outcomes[15].

PTSD
An open-label, non-placebo-controlled clinical trial with 47 participants found that nabilone treatment eliminated self-reported nightmares in 72% of PTSD patients[16]. A small study of Canadian military personnel with PTSD who were nonresponsive to traditional treatments also showed that nabilone provided significant relief of their trauma-related nightmares[17]. A systematic review of observational studies and previous systematic reviews found either insufficient evidence for benefits and harms or that, compared to non-use, cannabis was not effective to reduce symptoms of PTSD[18]. Regular cannabis use is linked to a heightened risk of anxiety, though causality is uncertain[19].

Anxiety disorders
A clinical review of 10 human clinical trials and 5 neuroimaging trials of CBD concluded that, "Overall, current evidence indicates that CBD has considerable potential as a treatment for multiple anxiety disorders, with need for further study of chronic and therapeutic effects in relevant clinical populations[20]."

Epilepsy
In a double-blind, placebo-controlled trial with children and young adults with Dravet syndrome, which causes drug-resistant epileptic seizures, CBD was found to decrease the median frequency of convulsive seizures from 12.4 to 5.9 per month, compared to a decrease of 14.9 to 14.1 with placebo[21]. The frequency of total seizures of all types was significantly reduced with cannabidiol (p=0.03).

TGA guidance documents and systematic reviews

Australian medicinal cannabis guidance documents
The Australian Commonwealth Department of Health in conjunction with state and territory governments has developed a series of medicinal cannabis clinical guidance documents for prescribers. These guidance documents reviewed evidence for the use of medical cannabis in several therapy areas[22]. While there is some preliminary evidence for the use of medicinal cannabis in several therapy areas, the guidance documents highlight the need for further high-quality clinical evidence to be developed. The following recommendations for selected therapy areas were made as part of the guidance documents:

- **Prevention or management of nausea and vomiting**
  High-THC medicinal cannabis products can sometimes be effective for nausea and vomiting and should only be prescribed only after newer standard approved treatments have failed and where otherwise not contraindicated.
- **Epilepsy paediatric and young adult patients**
  Epilepsy treatment with medicinal cannabis or cannabinoids is only recommended as an adjunctive treatment – that is, in addition to existing anti-epileptic drugs.
- **Palliative care**
  As there are very few studies on medicinal cannabis treatment in palliative care, it should be used only after standard treatments have failed.
- **Multiple sclerosis**
  There is some evidence that dronabinol or THC extracts may be effective at reducing pain associated with multiple sclerosis. There is also some evidence (although inconsistent) that nabiximols and other THC/CBD extracts may reduce muscle spasticity and improve patient quality of life.
- **Chronic non-cancer pain (CNCP)**
  The use of medications, including medicinal cannabis, is not the core component of therapy for CNCP. Patient education is a critical component of therapy for CNCP, particularly with respect to expectations of drug therapy.

The full guidance documents and further information regarding their development are available from the TGA at: ***www.tga.gov.au/medicinal-cannabis-guidance-documents***

The Health Effects of Cannabis and Cannabinoids – The Current State of Evidence and Recommendations for Research

The United States National Academies of Sciences, Engineering, and Medicine has developed a comprehensive systematic review of the therapeutic use of medicinal cannabis[2]. The expert committee reviewed 10,000 published papers in scientific journals and concluded the following:

- **Conclusive or substantial evidence that cannabis or cannabinoids are effective treatments**
  For chronic pain in adults, as antiemetics in the treatment of chemotherapy-induced nausea and vomiting, and to improve patient-reported muscle spasticity in multiple sclerosis (MS).
- **Moderate evidence that cannabis or cannabinoids are effective for improving outcomes**
  For patients with sleep disturbances associated with obstructive sleep apnoea syndrome, fibromyalgia, chronic pain, and MS.
- **Limited evidence that cannabis or cannabinoids are effective for improving outcomes**
  For appetite and decreasing weight loss associated with HIV/AIDS, clinician-measured MS spasticity symptoms, symptoms of Tourette syndrome, anxiety symptoms, and symptoms of post-traumatic stress disorder (PTSD).

Safety and side effects of medicinal cannabis

When cannabis is inhaled, THC and other cannabinoids are rapidly absorbed. Maximum brain concentrations usually occur within 15 minutes. These effects plateau for 2–4 hours before declining[23,24]. Ingested cannabis has a longer onset of action (1–3 hours) and the effects may last 6–8 hours[25].

Cannabis is metabolised via the hepatic cytochrome pathway and excreted via the biliary tract into faeces, along with urinary excretion of acid metabolites. Because the cytochrome P450 enzyme system is implicated in the metabolism of THC and CBD, there is a theoretical possibility of drug-drug interactions with cannabis. In clinical trials where nabiximols has been taken concomitantly with other drugs metabolised by the cytochrome P450 enzyme system, no clinically apparent drug-drug interactions have been seen in these trials at clinical doses.

While cannabis has a relatively small chance of significant drug-drug interactions, it can have an additive effect when added to other CNS depressants. For this reason, patients currently taking benzodiazepines, hypnotics, or opioids should be monitored closely and consideration to start at a lower dose should be made.

Despite smoking being the most common means of consuming cannabis, this is not a recommended method and healthcare providers have a duty to counsel patients against smoking all plant substances, including cannabis.

Most people who use cannabis do not develop problems with dependence. Data examining recreational use suggests that 9% of adults who use cannabis develop a dependence while that number rises to 17% for those who begin using before the age of 18[26–28].

Cannabis dependence, both physical and psychological, can develop, especially with chronic use[29–31]. Withdrawal symptoms related to physical dependence show up within 1–2 days when cannabis use is suddenly stopped and wane within 1–2 weeks[15,32]. Common symptoms of withdrawal include increased dreaming and other sleep disturbances, irritability, appetite changes, weight loss, headache, anger, and aggression[30,31,33]. It should be noted that this data is from recreational use and is not controlled for medical users.

Side effects of medicinal cannabis

Side Effect	Most common	Common	Rare
Drowsiness/fatigue	■		
Dizziness	■		
Dry mouth	■		
Cough, phlegm, bronchitis (smoking only)	■		
Anxiety	■		
Nausea	■		
Cognitive effects	■		
Euphoria		■	
Blurred vision		■	
Headache		■	
Orthostatic hypotension			■
Toxic psychosis/paranoia			■
Depression			■
Ataxia/dyscoordination			■
Tachycardia (after titration)			■
Cannabis hyperemesis			■
Diarrhoea			■

Adapted from MacCallum and Russo 2008[25]

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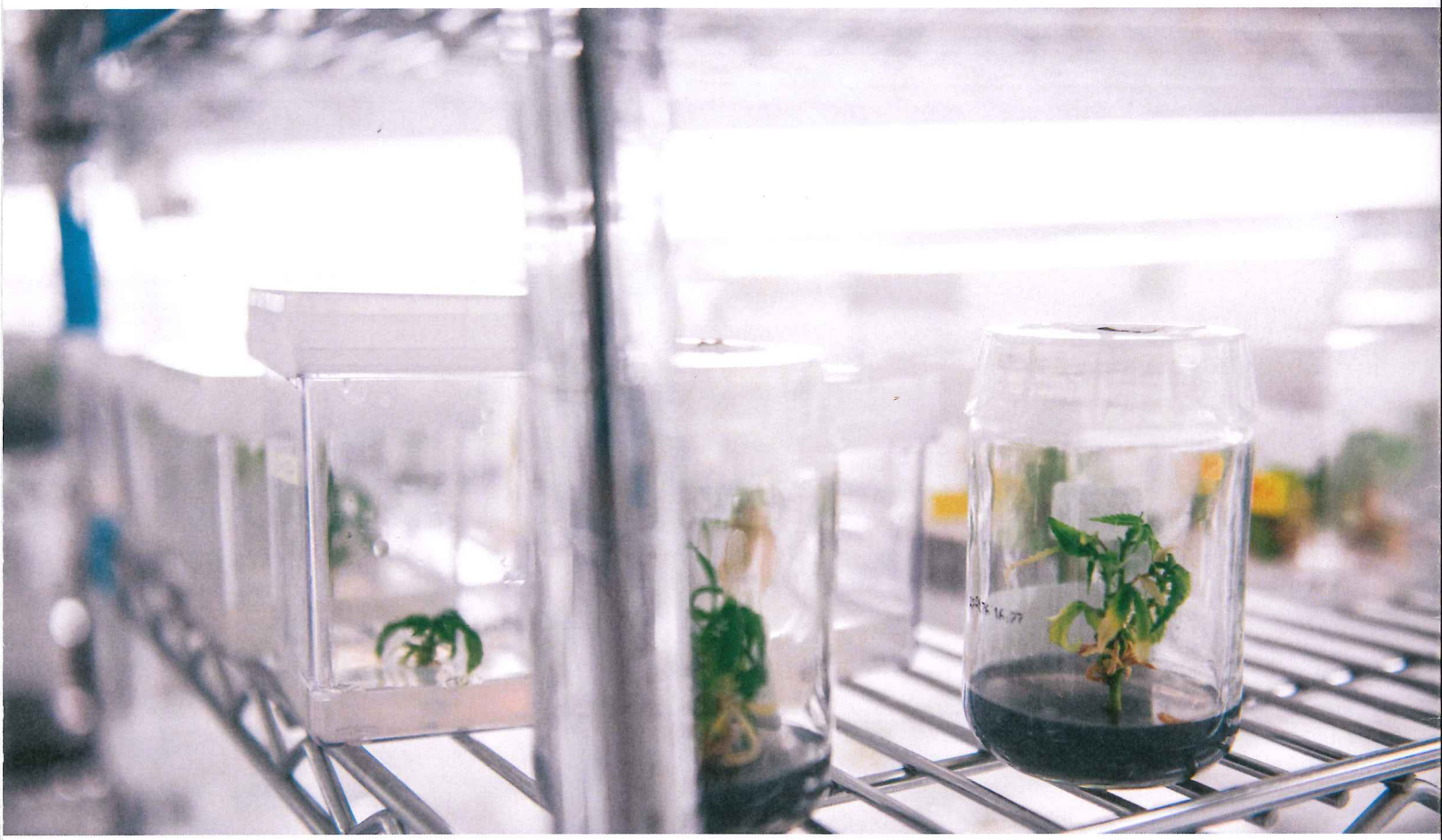
McCann Health CASP15970. March 2019. SPT/003/03-19.



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