Submission No 46

INQUIRY INTO USE OF CANNABIS FOR MEDICAL PURPOSES

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This is a review by Professor Wayne Hall and Professor Michael Farrell with a brief history of medical uses of cannabis; A summary of major putative medical uses and the evidence for the effectiveness of cannabis in each of these indications; A summary of evidence on the safety of medical cannabinoid and cannabis use; and an overview of the regulatory challenges faced by different methods of making cannabinoids, smoked cannabis, and cannabis extracts available for medical use

Submission to NSW Legislative Assembly General Purpose Standing Committee No. 4

INQUIRY INTO MEDICAL USES OF CANNABIS

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We give evidence in the following capacities:

Wayne Hall:

1. As an epidemiologist who has studied patterns of cannabis use and their adverse health effects on users (Hall and Degenhardt, 2009).

2. As Chair of NSW Premier's Working Party in 1999-2000 which examined medical uses of cannabis and ways of making cannabis available for medical use.

3. As someone familiar with the process involved in deciding whether to publicly subsidise pharmaceutical drugs in Australia, as a member (2001-2008) and Chair (2008-2011) of the Drug Utilisation Subcommittee of the Pharmaceutical Benefits Advisory Committee, and as an advisor to the Therapeutic Goods Administration on the adverse effects of neuropharmaceutical drugs (Hall et al, 2009).

Michael Farrell:

1 As Director of the National Drug and Alcohol Research Centre, University of New South Wales, where a wide range of research on cannabis and cannabis related harm has been conducted and where the National Cannabis Prevention and Information Centre is based. Professor Copeland will submit a separate report on behalf of NCPIC and its consortium members.

2 As an academic psychiatrist who has published widely on issues of psychiatric co-morbidity and epidemiological aspects of cannabis.

3 As a Former Senior Policy Advisor for the Department of Health in England I prepared the submission on Cannabis for the House of Lords Scientific Committee Enquiry on the Medicinal Use of cannabis.

4 As Chair of the Scientific Committee of the European Monitoring Centre on Drugs and Drug Abuse and the Early Warning Meeting on SPICE and related synthetic cannabinoid products.

Background

In the19th century before there were many active medications available for routine use, cannabis preparations played a significant role in medicine. It had a long history of use in India and the Middle East to treat pain, convulsions, spasm, nausea and induce sleep before its introduction into medical use in Britain in the mid 19th century (Grinspoon, 1993; Nahas, 1984; Mechoulam, 1986). Cannabis was prescribed in Britain and USA in the form of tinctures for various indications throughout most of the 19th Century (Kalant, 2001). Medical cannabis use declined with the development of more effective analgesic drugs in the early 20th century and difficulties experienced in standardising oral cannabis preparations for medical use (Kalant, 2001). The decline in medical use was accelerated by the somewhat arbitrary inclusion of cannabis under international drug control treaties in the 20th century as a drug that had no medical use and whose use posed similar risks as heroin and cocaine.

The widespread recreational cannabis use by young people in the USA in the 1960s and 1970s ensured that the medical use of cannabis has been entangled in policy debates about how to deal with nonmedical cannabis use (Bostwick, 2012). One consequence of this entanglement has been major difficulties in allowing medical cannabis use while prohibiting adult use of cannabis for any nonmedical purpose. Additional complications arise from the polarisation of expert and lay opinion on whether cannabis has medical uses, a dearth of evidence on the effectiveness of cannabis and cannabinoids for many of putatively therapeutic uses, and a lack of research on the adverse effects of long-term medical use of cannabis and cannabinoids. Our submission aims to explain why it has proven difficult: (1) to develop new medicinal drugs derived from cannabis or synthetic drugs; and (2) to find ways of allowing patients to use cannabis plant products for medical purposes.

In this submission ***cannabis*** refers to any product of the *cannabis sativa* plant, such as, marijuana (the flowering tops of the plant) and hash, the compressed resin, that are typically smoked by recreational users (Hall and Pacula, 2003; Hall and Degenhardt, 2009). The major psychoactive component in these cannabis preparations is the cannabinoid, tetrahydrocannabinol (THC) which produces its manifold psychological effects by acting on specific receptors in the brain, known as cannabinoid receptors (Iversen, 2007).

We use ***cannabinoids*** to refer to pharmaceutical drugs that are either derived from the cannabis plant (such as THC) or are synthetically produced that act on the same cannabinoid receptors in the brain on which THC, and the naturally occurring substance, anandamide, act.

Cannabinoids can include: cannabinoid agonists – synthetic or semisynthetic drugs that produce psychoactive effects similar to those of THC; cannabinoid antagonists - drugs that block the effects of THC on receptors; and cannabinoid inverse agonists– drugs that produce effects that are the opposite of those produced by THC (IOM, 1999; Iversen, 2007). We focus on cannabinoid agonists in this submission. These are the most contentious class of medical cannabinoids because they produce psychological effects that are similar to those sought by recreational users. By contrast, cannabinoid antagonists and inverse agonists do not produce the psychoactive effects sought by recreational users. They also do not have the same therapeutic effects that are claimed for either the cannabis plant or for cannabinoids that are THC agonists. We are aware that this is an area in which new agents may be developed given the potential for pharmaceutical industry interest.

Medicinal cannabis extracts are preparations that are designed to deliver specified doses of cannabinoids by using standardised extracts of the cannabis plant. The most important of these in the medical cannabis debate is Sativex, a medical cannabis extract that is delivered as an oral sublingual spray. Sativex is produced by combining extracts from two cloned cannabis plants that have been bred to produce high levels of either THC or cannabidiol (CBD). CBD is a cannabinoid that is commonly found in cannabis plants which has few psychoactive effects by itself but appears to modulate or moderate the psychoactive effects of THC (Russo and Guy, 2006). Sativex combines these plants in equal amounts to produce a product with a 50:50 ratio of THC and CBD. Sativex is intended to allow patients to obtain a defined dose of THC without having to smoke cannabis along with CBD to reduce the psychoactive effects of THC that are often not welcomed by patients (Russo and Guy, 2006).

DOES CANNABIS HAVE MEDICAL USES?

Advocates of the medical uses of cannabis and cannabinoids argue that these products have potential medical use in relieving cancer pain and the side effects of cancer treatment, AIDS related wasting, chronic pain, and symptoms of multiple sclerosis (Di Marzo and de Petrocellis, 2006; IOM, 1999). Cannabis and cannabinoids are primarily intended to be used as either an adjunctive treatment (that is, in combination with other treatments) or as a second line treatment (that is, as a treatment reserved for use in patients in whom standard treatment has proven ineffective or been poorly tolerated because of side effects) (IOM, 1999).

The major therapeutic benefits claimed for cannabinoids are to: relieve nausea and vomiting in patients with cancer; to stimulate appetite in patients with cancer and AIDS; to relieve

acute and chronic, especially neuropathic pain, often in combination with other analgesics such as opioids; and to treat muscle cramps, spasticity and neuropathic (nerve) pain in patients with multiple sclerosis and Parkinson's disease (Institute of Medicine, 1999; Ben Amar, 2006; Iversen, 2007; Russo, 2003). Advocates of medical cannabis use often include a long list of other putative benefits, which as Hollister (2000) notes, resembles the indications claimed for 19th century patent medicines. We confine our discussion to the medical indications for which there is support from clinical trials and where a therapeutic effect is biologically plausible role given what is known about how the cannabinoids act on the human brain and body. We briefly review the clinical trial evidence on efficacy in each of these indications.

Cannabinoids as anti-emetics

Controlled clinical trials in the 1970s and 1980s compared the effectiveness of THC with a placebo or the anti-emetic drugs then used in cancer treatment (see Kalant, 2001; IOM, 1999). In these trials THC was as effective as the then commonly used anti-nausea drug, prochlorperazine but cannabis and THC only completely controlled nausea in a third of these patients (IOM, 1999).

A systematic review of these clinical trials (Tramer et al, 2001) concluded that cannabinoids were more effective than placebo or the active anti-emetic drugs with which it was compared. Tramer et al estimated that 6-8 patients needed to be treated with a cannabinoid to prevent one case of vomiting in a patient who received another anti-emetic. Patients in all these trials expressed a preference for cannabinoids when given a choice. Tramer et al recommended that further trials should be done evaluating the use of cannabinoids as adjunctive treatments in combination with newer, more effective anti-emetic drugs.

Another meta-analysis of trials comparing cannabinoids with placebo and other anti-emetic agents (Rocha et al, 2008) came to much the same conclusion. It also found that dronabinol (synthetic THC) was superior to placebo (n =185), RR=0.47 [0.19-1.16] and prochloperazine (n=325) RR=0.67 [0.47-0.96] in reducing nausea. The synthetic cannabinoids, nabilone (n = 277) RR=0.88 [0.72-1.08] and Levonantradol did not differ in effectiveness from proclorperazine or other neuroleptic drugs used to control nausea (n=194) RR=0.94 [0.75-1.18]. In the placebo trials, patients showed a strong preference for cannabinoids over placebo when offered the **choice** (n=1138) RR=0.33 [0.24-0.44].

It is clear from these studies that cannabinoids produce antiemetic effects but there is a major limitation on the evidence, namely that these trials which were done decades ago, and that the antiemetic drugs with which cannabinoids were compared in the 1980s have been replaced by much more effective anti-nausea agents that have dramatically reduced the severity of nausea and vomiting during cancer chemotherapy (Navari, 2009; IOM, 1999). There have been no controlled clinical trials that have directly compared the antiemetic effects of THC and other cannabinoids with these newer anti-emetic agents (Navari, 2009) but indirect comparisons suggest that cannabinoids are much less effective in that a much lower proportion of patients treated with cannabinoids achieve complete control over their nausea (IOM, 1999). These results are supported by a laboratory study that compared the anti-emetic effects of two strengths of smoked cannabis with that of the anti-emetic drug, odansetron, in controlling the severe nausea that is induced by the syrup of ipecac (a potent emetic drug that is used to treat persons who have been poisoned). Smoked cannabis only modestly reduced the severity of nausea and vomiting whereas ondansetron eliminated these symptoms (Soderpalm et al, 2001).

On the available evidence, cannabinoids are not a first line treatment for nausea and vomiting in cancer patients but they may still have a role as adjunctive or second line treatments (Ben Amar, 2006; Institute of Medicine, 1999). The mechanisms by which cannabinoids reduce nausea and vomiting differ from those of more potent antiemetic drugs so they may be potentially be useful in enhancing anti-emetic effects in patients who do not respond fully to these newer agents (Navari, 2009; IOM, 1999). There may also be patients with this condition with a history of cannabis consumption who have a strong preference to use cannabis either alone or in combination with other anti-nausea medications.

Appetite stimulation

THC and other cannabinoid agonists stimulate appetite in humans and animals (Ungerleider, 1982; Berry and Mechoulam, 2002), a phenomenon described as the “munchies by recreational cannabis users. The major clinical use of this effect has been in stimulating appetite in patients with cancer and the clinical AIDS syndrome. Dronabinol (Marinol) was registered in the USA in the early 1970s as an appetite stimulant for use in AIDS-related wasting (Tramer, 2001; Beal, 1995).

The need to use appetite stimulants in AIDS treatment, however, has largely been obviated by the advent of anti-retroviral drugs. Combinations of these drugs prevent most HIV infected

persons from developing AIDS-related wasting. Cannabinoid agonists may still have an adjunctive role in stimulating appetite in cancer patients.

Analgesia

Analgesia is one of the oldest uses of cannabinoids for which there is a good biological rationale. In animal models of acute and chronic pain, cannabinoids appear to reduce pain and inflammation (Guindon and Hohmann, 2008). The receptors on which THC and other cannabinoid agonists act influence similar pathways to those that on which morphine acts to control pain. Cannabinoids also produce analgesia via pharmacologically distinct mechanisms from opioids which means that opioids and cannabinoids could potentially have additive or synergistic analgesic effects (effects that are larger than the sum of the individual drug effects) (Christie, 2003).

Cannabinoids have shown some analgesic effects in double blind and placebo controlled clinical trials producing analgesic effects equivalent to those of codeine (IOM, 1999). Clinical trials of the cannabis extract Sativex suggest that cannabinoids may be useful in managing neuropathic pain, that is, pain arising from abnormalities and diseases of the nervous system (such as multiple sclerosis) rather than from tissue damage, such as pain following surgery (IOM, 1999; Russo, 2008). Sativex has been approved in Canada for use in treating pain that has proven resistant to opioids (Russo, 2008).

Pain and Spasticity in Multiple Sclerosis

The medical indication for cannabinoids that has received most research attention in recent years has been pain and muscle spasticity in patients with multiple sclerosis (MS). Patients with MS have reported that these symptoms have been reduced by smoking cannabis (Consroe, 1997) and there is some support for these reports from studies of the effects of cannabinoids in animal models of MS (Pertwee, 2002; Grant et al, 2012; Smith, 2003).

Patient reports that cannabis reduces spasticity and pain have received more mixed support from controlled clinical trials of cannabis extracts and THC in MS (Podda and Constaninescu, 2012). These trials have reported greater subjective relief of symptoms in patient ratings of spasticity in those receiving cannabinoids than in those given placebo but there have been only marginal reductions in observer ratings of spasticity after three weeks of treatment (e.g. Zajicek et al, 2003). There were larger reductions in both objective ratings and

self-reported spasticity, pain and disturbed sleep in a 12 month follow up of the subset of these patients who continued to use cannabinoids over a year (Zajicek et al, 2005).

The effectiveness of Sativex in treating symptoms of MS has been assessed in six placebo controlled clinical trials. A meta-analysis of these trials (which collectively involved 298 patients) (Iskedjian et al, 2007) found that Sativex produced a modest reduction in pain assessed on a 10 point rating scale after 3 weeks of treatment. Patients who received Sativex and the placebo did not differ in their baseline pain ratings (6.4 and 6.5 for active vs placebo) but there was a 1.5 point reduction in the pain rating of the patients who received Sativex or another cannabinoid compared to an 0.8 point reduction in those who received placebo (Iskedjian et al, 2007). By convention, a "clinically significant" effect has been defined as a reduction of 2 points on this pain scale. The authors (employees of the company that licenses Sativex) argued that a 1.5 reduction was clinically significant because the confidence interval around it included a 2 point difference. We do not think that this argument is very compelling but these trials did use small numbers of patients and the duration of treatment with Sativex was only 3 weeks.

A recent review of studies of the safety and efficacy of nabiximols (Sativex) in controlling symptoms of MS has been reported by Podda and Constaninescu (2012). These authors concluded: that most of the trials have shown a greater reduction in severity of symptoms of spasticity in patients receiving Sativex than in those on placebo. The adverse effects reported in these trials were generally mild to moderate, with the most common being dizziness, diarrhea, fatigue, nausea, headache and somnolence. They cautioned, however, that in the majority of these trials patients had used Sativex as an add-on therapy to improve the efficacy of more traditional anti-spasticity drugs. No study provided evidence that Sativex was effective as a monotherapy or stand-alone treatment.

Glaucoma

Glaucoma is a leading cause of blindness that is often caused by elevated intra-ocular pressure (IOP) (Jarvinen et al, 2002). Cannabis and THC taken orally or intravenously reduce IOP by 25% Crawford and Merrit, 1979) but this effect lasts only three to four hours. High doses of THC have to be used daily to reduce IOP, a pattern of use that produces psychoactive effects that many patients find unacceptable (IOM, 1999; Crawford and Merritt, 1979; Jarvinen et al, 2002). There has been very little interest in trialing THC or cannabinoids that have to be delivered in this way for glaucoma (IOM, 1999). Water soluble cannabinoids

that can be delivered directly into the eye show more promise of producing therapeutic effects without unwanted psychoactive effects (Jarvinen et al, 2002) but pharmaceutical companies have not been interested in developing and clinically researching such drugs.

WHAT ARE THE RISKS OF THERAPEUTIC CANNABINOID USE?

Patients in therapeutic trials of cannabinoids often complain about dizziness, dysphoria, depression, hallucinations and paranoia. The use of cannabis or cannabinoid use also impairs psychomotor performance, making it prudent for patients who use medicinal cannabinoids to avoid driving (Asbridge et al, 2012; Hall and Degenhardt, 2009). The US Institute of Medicine (1999) concluded that these acute adverse effects were "within the risks tolerated for many medications" and noted that patients developed tolerance to many of these effects with continued use.

Wang and colleagues' (2008) systematic review of research on adverse effects of medical cannabis use supported the IOM's conclusion. They conducted a meta-analytic review of adverse effects reported in randomised controlled trials (RCT) of cannabinoids and cannabis extracts. They also examined case reports of adverse events among cannabis users and observational studies of adverse events among recreational cannabis users. They found that 97% of the adverse effects reported in the clinical trials were minor, with dizziness (20%) the most common. They did not find a higher risk of serious adverse events in patients who used cannabinoid drugs (either plant extracts or THC preparations) compared to placebo.

These findings provide reassurance that the medical use of cannabinoids and cannabis extracts for short term symptomatic relief is reasonably safe. This would include their use to control nausea and vomiting in cancer treatment, appetite stimulation, and the relief of acute pain after surgery. The Wang et al review was unable to provide information on the risks of longer term use of cannabinoids to treat symptoms of chronic disorders, such as multiple sclerosis, because the clinical trials have all been short-term (from 8 hours to 12 months).

Observational population-based cohort studies of recreational cannabis users potentially provide an indication of possible adverse effects of long term cannabis smoking in recreational users. However, these studies have largely examined (1) the effects in adolescence and early adulthood of regular and sustained cannabis use by young people; and

(2) more rarely, long term adverse health effects, such as cancers, that may arise from prolonged exposure to carcinogens in cannabis smoke over years or decades (see Hall and Degenhardt, 2009 for a review). It is uncertain how relevant the adverse outcomes observed in younger recreational cannabis smokers are to the medical use by older adults of oral cannabis preparations or cannabinoids.

The adverse health consequences of long term cannabis use that are likely to be of most concern to clinicians and patients are: the risks of developing cannabis dependence, the exacerbation of cardiovascular disease, precipitation of psychotic disorders, and development of cancers (Degenhardt and Hall, 2008; Hall and Degenhardt, 2009).

Recreational users who use regularly (near daily) can become dependent on cannabis (Hall and Swift, 2006), but this evidence comes from studies of users who began using cannabis in adolescence and early adulthood, and who often smoked the most potent cannabis products daily (Anthony, 2006). These users smoke cannabis with a greater frequency and intensity than older adults who are likely to use smaller doses of cannabinoids for symptom relief (Bostwick, 2012). A substantial minority of cannabis dependent persons seek help from addiction treatment services to cease their use (Hall and Degenhardt, 2009). However we know nothing about, and are not aware of any significant published literature on, the risks and severity of any adverse consequences of cannabis dependence that may develop in long-term medical cannabis or cannabinoid users.

There are associations between cannabis use and psychosis risk, with evidence from longitudinal studies suggesting that cannabis can precipitate psychotic symptoms and disorder in individuals who vulnerable to developing these disorders because of a personal or family history of these disorders (Degenhardt and Hall, 2006; Moore et al, 2007). Again, however, this evidence comes from studies of young adults who initiated daily cannabis use in adolescence and continued to use regularly throughout young adulthood, the period with the highest risk of developing psychotic disorders. There are no data on the risk of psychosis among older medical cannabis users – who will have lived through the highest risk period for developing a psychosis. The prudent advice would be that persons who have personal or family history of psychosis or other psychiatric disorders should avoid using cannabis for medical purposes (Hall and Degenhardt, 2006).

The cardiovascular risks of chronic cannabis or cannabinoid use are potentially of greater concern for medical cannabis users. The risk of serious cardiovascular disease increases with age and the older adults who are most likely to use cannabis for medical purposes are also more likely to have underlying cardiovascular disease (Degenhardt and Hall, 2008). There is moreover some evidence that cannabis *smoking* can precipitate myocardial infarctions in older adults (Hall and Degenhardt, 2009). It would accordingly be prudent for older adults to avoid smoking cannabis for medical purposes and instead use oral cannabinoids or cannabis medical extracts because the latter are much less likely to have serious adverse effects on cardiovascular risk in older adults than smoking cannabis.

The cancer risks of long term cannabis smoking are uncertain because studies of recreational cannabis users have to date produced inconsistent findings. Moreover, in many of these studies it has been difficult to separate any adverse effects of cannabis smoking from those of tobacco smoking because most regular cannabis smokers in these studies have also smoked tobacco (Hall and Degenhardt, 2009). If cannabis smoking does prove to be a cause of cancer, then long-term medical cannabis users would be advised to avoid smoking. This risk would not apply to long term medical users of oral cannabinoids or cannabis extracts. The availability of THC in a variety of nonsmoked delivery forms reduces the necessity for patients to smoke cannabis.

These uncertainties about the potential adverse effects of sustained use of cannabinoids and cannabis preparations for medical users need to be clearly communicated to patients considering their use. Long term follow-up studies of patients who use cannabis preparations and medical cannabinoids are needed to provide better information on these issues.

CHALLENGES IN MAKING CANNABIS AVAILABLE FOR MEDICAL USE

Pharmaceutical Cannabinoids

Dronabinol (synthetic THC) was registered for medical use as an anti-emetic and appetite stimulant in the USA in 1985 and nabilone (a synthetic cannabinoid with similar effects to THC) has been approved for similar indications. Unfortunately, neither of these drugs has been widely used because patients have found it difficult to titrate their doses of these drugs (IOM, 1999), that is, patients find it difficult to achieve a dose that produces the desired therapeutic effects without adverse side effects (Grotenhermen, 2004). Oral delivery of THC typically produces a delayed onset of the effect because of processing by the liver. The result is that patients either get insufficient drug to be of benefit or they experience unpleasant side effects (Grotenhermen, 2004; Iversen, 2007).

Smoking is the preferred method of cannabis use among recreational users because it enables users to better titrate their dose. However, smoked cannabis is unlikely to obtain regulatory approval for medical purposes because smoking (IOM, 1999) delivers carcinogens and other substances that are biologically toxic to the lung, along with THC and cannabinoids (Hall and Degenhardt, 2009; IOM, 1999; Tashkin, 2001).

Pharmaceutical companies have not developed any newer cannabinoids that overcome the problems with approved oral cannabinoids because there are substantial disincentives to them doing so (IOM, 1999). Natural cannabis products cannot easily be patented so synthetic drugs would need to be developed. The costs for developing and clinically testing new cannabinoids are like those of neuropharmaceuticals, i.e. drugs that are costly to develop and register for medical use (IOM, 1999). There also needs to be a large market of potential patients to justify these costs. As outlined above, the indications for medical cannabinoids are not very common and much more effective drugs have been developed for the best supported and most common indication, nausea and vomiting (Hall et al, 2001; IOM, 1999). An additional disincentive is that in the USA, strict regulatory requirements must be met before registering a drug that is derived from, or chemically related to, a prohibited substance (Cohen, 2008; IOM, 1999; Bostwick, 2012). Similar restrictions would apply after registration, discouraging routine use by physicians.

The current best hope of new pharmaceutical cannabinoids lies with Sativex, the sublingual cannabis extract that has been developed and trialled in the UK over the past decade (Iversen,

2007; Russo and Guy, 2006). The manufacturers of Sativex have been able to patent the plant clones and the process used to produce their extract rather than the natural extract itself. Sativex has been registered for clinical use in Canada, Czech Republic, Denmark, Germany, New Zealand, Spain, Sweden and the UK (http://www.gwpharm.com/Sativex.aspx). Sativex has not yet been registered for use in Australia. Until it has been registered, Australian patients who wish to use cannabinoids for medical purposes have to smoke cannabis.

POTENTIAL MODELS FOR PROVIDING MEDICAL CANNABIS

MEDICAL MARIJUANA INITIATIVES IN THE USA

Between 1975 and 1992 the US Government allowed compassionate access to cannabis to patients under the Investigational New Drug (IND) program (Pacula et al, 2003). A number of US states also legislated to allow the medical use of cannabis under similar conditions to the Federal IND. Eight state programs were authorised by the Federal government but very small numbers of patients entered them (Pacula et al, 2003).

The restrictiveness of the Federal IND program prompted advocates of medical marijuana in the USA to campaign for the passage of citizen-initiated referenda that would allow "medical marijuana" to be used in some states. Advocates of these medical marijuana initiatives argued that only smoked cannabis could meet the medical needs of patients. The initiatives allowed patients to smoke cannabis for medical purposes without requiring approval by a pharmaceutical regulatory process.

The first referendum was in 1996 when Californian voters passed Proposition 215 (by 56% to 44%). This allowed the medical use of marijuana for a broad set of medical indications that included those supported by evidence (nausea, weight loss, pain and muscle spasm) as well as an open-ended catch-all category: any 'serious medical condition" for which marijuana provided relief (Conboy, 2000). Citizen-initiated referenda have since been used to legislate to allow medical uses of marijuana in 11 US states and another 7 states have legislated to allow medical use of marijuana (Medical Marijuana Pro and Con, 2012).

The US medical marijuana initiatives provide patients with access to medical marijuana but at the cost of creating new regulatory problems. First, laws that allow physicians to prescribe cannabis conflict with US Federal law which bans the use of cannabis for any purpose and the latter pre-empt the former (Bostwick, 2012; Conboy, 2000). The US Supreme Court ruled

in 2001 that persons who sold or supplied cannabis for medical use were not protected from Federal criminal prosecution by state laws that permit medical marijuana use (Bostwick, 2012). The Bush administration enforced Federal laws against cannabis in these states but the Obama administration decided in 2009 not to enforce Federal laws against patients or doctors in states that allowed medical cannabis use (Hoffman and Weber, 2010). The administration continued to enforce Federal laws against the cultivation and supply of cannabis on a commercial scale (Eddy, 2009).

Second, securing a legal supply of cannabis can be difficult in States that allow cannabis to be prescribed. Patients often have to secure their supply from the black market or in some states they are allowed to grow their own or have a carer grow it on their behalf. In California the state government has allowed Cannabis Buyers' Clubs to sell cannabis to patients suffering from a range of medical conditions provided that they have a doctor's "prescription". These clubs have not, however, been licensed to produce cannabis so they have to obtain it from the illicit market (Hoffman and Weber, 2010). The effect of these forms of liberalization has been to create a quasi-legal system of cannabis production and distribution in many parts of California and some of this cannabis is sold to recreational users (Cohen, 2010; Regan, 2011; Samuels, 2008).

Third, medical cannabis laws create medico-legal problems for physicians who are asked to prescribe cannabis. The Bush government threatened to strip physicians of their license to practice if they prescribed cannabis. But even when this threat was removed, physicians were reluctant to prescribe because of fears of legal liability for any harms experienced by patients for whom they prescribed cannabis (Hoffman and Weber, 2010; Pacula et al, 2003). In the absence of data from controlled trials, physicians also find it difficult to decide to whom they should prescribe cannabis, in what amounts, and for how long (Barnes, 2000; Cohen, 2006; Hall and Degenhardt, 2003).

Fourth, indications for medical use vary widely between US states (Hoffman and Weber, 2010). Some states have narrowly defined indications as those for which there is some evidence of efficacy (e.g. nausea, appetite stimulation and analgesia) whereas Californian legislation uses a broadly inclusive set of indications that in fact allow medical use for any condition that a physician believes may benefit from the use of marijuana (Cohen, 2010; Hoffman and Weber, 2010; Regan, 2011). States also vary in whether they require physicians to examine a patient and advise them about the risks of using marijuana (Cohen, 2010).

Providing such advice is difficult for physicians in the case of indications for which there is some evidence of efficacy, given uncertainty about the quality and quantity of cannabis that should be used; it is more difficult in the case of medical conditions for which there is no evidence of efficacy or safety (Hoffman and Weber, 2010).

Fifth, studies of medical marijuana patients in the most liberal Californian system suggest that cannabis compassion clubs largely function as marijuana maintenance programs rather than providing medical treatment for patients with cancer and other chronic diseases. For example, an analysis of 4117 patients using clubs in the San Francisco-Bay Area during 2001-2007 found that 77% were male and their average age was 32 years. Most (89%) had started using cannabis before the age of 19 and 90% were daily smokers who used between and 1/8th and ¼ of an ounce per week (O'Connell and Bou-Matar, 2007). There were no data on the medical indications for which these patients used cannabis but their age and sex suggest that they were unlikely to have cancer or neurological diseases. There were similar findings in another survey of 1746 medical marijuana patients in California in 2006: three quarters were male, only 13% were older than 55 years, and two thirds were daily cannabis smokers (Reinarman et al, 2011). The most commonly reported uses were to control various kinds of pain and to help with sleep. A substantial minority reported that they used cannabis as a substitute for alcohol and prescription drugs (Reinarman et al, 2011).

These findings suggest at the very least a blurring of boundaries between recreational and medical cannabis use among patrons of the California medical marijuana program (Bostwick, 2012; Cohen, 2010; Regan, 2011; Reinarman et al, 2011). It seems likely that many medical cannabis users in that state have been recreational cannabis users who continue to use recreationally while also using cannabis for medical and quasi-medical purposes, such as controlling pain, helping with sleep and improving mood. Very few use cannabis to treat symptoms of cancer or any of the neurological conditions in which there is some evidence of efficacy for cannabinoids. These patients are more likely to tolerate, if not welcome, the psychoactive effects of cannabis than older medical cannabis users in clinical trials who have had no prior experience with the drug (Bostwick, 2012).

MEDICAL MARIJUANA IN CANADA

In April 2001 the Canadian Government legislated to allow patients to have access cannabis for medical purposes (Bogdanoski, 2010; Lucas, 2008). This legislation was passed in response to legal challenges in the Canadian Supreme Court to Federal laws that prohibited

any use of cannabis, including medical use (Lucas, 2008). The legislation allowed cannabis to be supplied by the government (who sourced it from a single commercial supplier), or allowed registered patients (or a carer) to grow cannabis under licence. Patients were eligible for the program if they: (1) had a terminal illness and a life expectancy of less than 12 months; (2) had MS, spinal cord injury or disease, cancer pain, AIDS, arthritis and epilepsy; and (3) had " symptoms associated with a serious medical condition other than those described in categories 1 and 2 where among other things conventional treatments have failed to relieve symptoms of the medical condition or its treatment" (Lucas, 2008; Moffat, 2002).

The Canadian government estimated that there were 290,000 Canadians in province of British Columbia using cannabis for medical purposes in the past year (Lucas, 2008). As of June 2007, only 1816 applicants for compassionate access to medical cannabis had been approved; only 20% of these patients (356) had their cannabis supplied by the government, the remaining 80% preferred to grow their own, largely because of dissatisfaction with the quality and cost of the government supplied cannabis (Lucas, 2008; Lucas, 2012). According to Lucas 30,000 Canadian medical cannabis users obtain their medical cannabis through compassion clubs (Lucas, 2012). Canadian medical cannabis users surveyed by Lucas, (2012) were older (most over 35 years) but otherwise similar to those in California. Most (78%) were males, they had been regular cannabis users for 10 or more years, were primarily daily smokers although they many have used cannabis in other ways. The reasons for medical cannabis use most often mentioned were to relieve chronic pain and depressed mood (Lucas, 2012).

Even under the Canadian government-approved medical marijuana access program doctors are reluctant to prescribe cannabis for medico-legal reasons (Lucas, 2008). The Canadian Medical Association (CMA) and the Canadian Medical Protection Agency advised physicians not to prescribe cannabis (Abraham, 2002; Lucas, 2008) arguing that there was no clinical evidence that it was effective for most of the approved indications and practitioners who prescribed cannabis would be legally liable for any adverse effects that their patients experienced (Lucas, 2012).

There have been other problems with the Canadian scheme. First, patients have complained about the quality and the cost of the government supplied cannabis, arguing that illegally produced cannabis was cheaper and much better quality (Lucas, 2008; 2012). Second, patients have complained about the cumbersome (29 page form) and lengthy process (often

up to a year) that has been required to obtain approval to use medical cannabis under the scheme (Lucas, 2012). Third, it cost an estimated C$30M between 1999 and 2007 to supply cannabis to several thousand patients (Lucas, 2008). These costs raise a major concern about equity of access to pharmaceuticals. The medical marihuana scheme provides an unapproved drug of uncertain safety and efficacy for many indications, at substantial cost, to a small number of patients, when other pharmaceutical drugs with better evidence of efficacy that have been through the regulatory process may not be provided by the Canadian government.

MEDICAL CANNABIS IN THE NETHERLANDS

The Netherlands has also legislated to allow medical use of cannabis and supplies a cannabis product suitable for oral use through pharmacies on the prescription of a physician (Bogdanoski, 2010). It is unclear how many patients have accessed the scheme but there are media reports that Dutch physicians have been reluctant to prescribe cannabis, presumably for medico-legal reasons. As in Canada, patients have complained about the quality and costs of the government supplied cannabis which is prepared for oral use rather than for smoking.

One important difference between the programs in Canada and the Netherlands is the different regulatory regimes that apply to recreational cannabis use. Such use remains prohibited in Canada whereas in the Netherlands recreational cannabis use has been effectively decriminalized and a de facto legal retail cannabis market is tolerated in coffee shops in major cities (Room et al, 2010). In the Netherlands, patients who want to use cannabis may find it easier to buy cheaper and better quality cannabis in a form that can be smoked from coffee shops and they can do so without any risk of arrest. For these reasons, the medical cannabis program in the Netherlands is even more likely to be a very expensive program that serves a small number of patients and raises the same equity issues as the program in Canada.

CUTTING THE GORDIAN KNOT: SHOULD WE LEGALISE CANNABIS?

Grinspoon and Bakalar (1993) have argued that the simplest way to enable patients to use cannabis for medical purposes is to legalise all cannabis use, including recreational use. Legalisation of cannabis use, they point out, would enable patients who wanted to use cannabis for medical purposes to do so, without requiring a medical prescription, and at their own risk. It would also make it legal to purchase or grow cannabis without fear of criminal

prosecution. This solution would cut the Gordian knot of regulatory issues that are faced by cannabis prescription programs and medical marijuana initiatives.

There are major political and legal obstacles to implementing such a policy in Australia or in any other developed country that is a signatory to the Single Convention which prohibits the nonmedical use of cannabis (Room et al, 2010). The majority of the public opposes legalisation of recreational cannabis use so the community would need a much stronger justification for legalisation of cannabis than the claim that it would enable a small number of patients (100,000 at most in NSW Hall et al, 2001) to legally access cannabis for medical purposes. Much more weight would almost certainly be given to public concerns about the effects that legalisation would have rates of recreational cannabis use and cannabis-related harm among young people (Hall and Babor, 2000; Hall and Pacula, 2003; Kilmer et al, 2010). Advocates of legalisation would face a considerable burden of persuasion, given our experience with alcohol and tobacco, in convincing the community that legalising cannabis would not increase its use and cannabis-related harm (Hall and Babor, 2000; Hall and Pacula, 2003).

SUMMING UP: MEDICAL MARIJUANA CONUNDRUMS

Controlled clinical trials indicate that cannabinoids have some efficacy in controlling emesis in cancer patients, in stimulating appetite in AIDS patients and in relieving pain. Much of this evidence comes from studies that are 30 years old and for many of these indications the medical need for cannabinoids has been reduced by the development of more effective drugs. If the cannabinoids have a medical role in these indications, it is as second or third line treatments, or as an adjunctive treatment.

The pharmaceutical synthetic cannabinoids that have been approved for medical use (e.g. dronabinol) have not been widely used because patients find it difficult to titrate their dose and avoid adverse side effects. These drugs have not been very profitable for the companies that produced them. The lack of profitability, the small potential market for cannabinoids, and regulatory costs and burdens, have been major disincentives to pharmaceutical companies developing more effective synthetic cannabinoids (IOM, 1999).

Currently, the best hope for new pharmaceutical cannabinoids being made available for medical use lies with the cannabis extract, Sativex. This is a standardised medicinal cannabis extract that has been patented and approved for medical use in multiple sclerosis and pain a

number of countries because it has shown modest efficacy in clinical trials in controlling the symptoms of MS. It remains to be seen if Sativex proves more acceptable to patients and to advocates of “medical marijuana” than dronabinol and nabilone have.

Medical marijuana advocates in the USA and elsewhere have insisted that only smoked cannabis can meet the needs of patients. Cannabis can only be legally used for medical purposes use if it is supplied on prescription but a smoked form of a plant is unlikely to ever be approved by the pharmaceutical regulatory process in Australia, or anywhere else.

Medical marijuana initiatives have attempted to provide patients with access to smoked cannabis by using the popular vote in referenda to circumvent the requirements of the pharmaceutical regulatory system. This has created new problems. First, physicians have been reluctant to prescribe cannabis because of uncertainty about the indications in the absence of clinical research on its safety and efficacy, and fears of legal liability for any harms patients experience. Second, securing legal supply of cannabis has been a problem, unless the government supplies the drug, or patients are allowed to grow their own. Deciding pharmaceutical policy by popular referendum sets an undesirable precedent (Cohen, 2006).

Governments that have attempted to create special access schemes for cannabis by legislating to allow cannabis to be prescribed for medical use have also faced problems. Doctors in these countries have been reluctant to prescribe cannabis for medico-legal reasons. Patient uptake has often been low because of a combination of complaints about the poor quality and high costs of the government supplied cannabis, and the cumbersome bureaucratic process that has been required for approval. These governments have unwittingly found themselves funding an expensive special access program for a plant-based drug that few patients want to use. The prosecution of wheelchair-bound patients who claim to have benefitted from using cannabis has complicated public discussion by disposing the public to express compassionate attitudes towards such individuals, as expressed in majority support for citizen-initiated referenda in 11 US states.

Overall we believe that it is desirable to uphold the regulatory and quality control process of the existing Pharmaceutical System for reasons that go beyond the medical cannabis debate. The creation of special access schemes for medical cannabis should be avoided because they may undermine the integrity of the pharmaceutical regulatory system by creating a precedent that may be used to introduce other drugs into medical practice without evaluations of their safety and efficacy. These schemes also raise equity issues: is it fair for governments to

subsidize the medical use of a drug that is, at best, modestly effective for some purposes (e.g. vomiting and nausea) and of uncertain efficacy for others (e.g. chronic pain, depression, muscle spasm), when governments often decide not to subsidize other pharmaceuticals for which there is better evidence of efficacy?

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