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Ms Sophie Dunstone
Committee Secretary
Legal and Constitutional Affairs Legislation Committee
The Senate, Parliament House, Canberra
3 March 2015

Dear Ms Dunstone

Re: **Inquiry into the Regulator of Medicinal Cannabis Bill 2014**

Please find a brief submission to the Committee's Inquiry into medical cannabis. I give evidence in the following capacities:

- As an epidemiologist who has conducted and reviewed research on patterns of recreational cannabis use and their adverse effects on users.

- As Chair of NSW Premier's Working Party (1999-2000) which examined medical uses of cannabis and proposed a trial of making cannabis available for medical use.

- As someone familiar with the regulation of pharmaceutical drugs 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 (2008-2010).

- As a member of the International Narcotics Control Board, May 2012-July 2014, the UN body charged with monitoring compliance of member states with the international drug control treaties.

I would be available to provide personal evidence if that would be of assistance to the Committee.

Yours sincerely

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Submission to Inquiry into the Regulator of Medicinal Cannabis Bill 2014

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This submission addresses the following topics:

1. Definitions of some key terms: cannabis; cannabinoids and cannabis extracts.
2. The major proposed medical uses for cannabis and cannabinoids and the evidence on their efficacy for these indications;
3. A summary of evidence on the safety of medical cannabinoid and cannabis use when used for short periods of time and over long periods of time; and
4. An overview of the regulatory challenges posed by different ways that Canada, the Netherlands and the United States have used to make cannabinoids, cannabis, and cannabis extracts available for medical use:
    a. Prescription of pharmaceutical cannabinoids
    b. Providing cannabis products for medical use
    c. Legalising recreational cannabis use.
5. Summary and a proposed way forward.

1. DEFINITIONS OF SOME KEY TERMS

In this submission paper ***cannabis*** refers to products of the *cannabis sativa* plant, such as marijuana (the flowering tops of the plant) and the compressed resin, hash. These products are usually smoked by recreational and medical cannabis users [1]. The principal psychoactive ingredient of the cannabis plant is tetrahydrocannabinol (THC) which acts on specific receptors in the brain, known as cannabinoid or CB1 receptors. These receptors also respond to a naturally occurring cannabinoid in the brain called anandamide [2].

The term ***cannabinoids*** is used to describe pharmaceutical drugs that act on the brain's cannabinoid system. These can be derived from the cannabis plant or chemically synthesised. If they produce similar effects to THC, they are called cannabinoid agonists [2,3].

Medicinal cannabis extracts are standardised preparations of the cannabis plant that deliver defined standard doses of cannabinoids. For example, the nabiximols, trade name Sativex, is a cannabis extract produced by combining equal amounts of extracts from two cloned cannabis plants that produce high levels of THC and cannabidiol (CBD), respectively. CBD is a cannabinoid that has few psychoactive effects but appears to moderate the psychoactive effects of THC that some patients find unpleasant [4]. Sativex is delivered as an oral sublingual spray to provide patients with defined doses of THC and CBD without having to smoke cannabis [4].

2. INDICATIONS FOR MEDICAL USE AND EVIDENCE OF EFFECTIVENESS

Advocates claim that cannabis and cannabinoids can be used to treat the following symptoms: nausea and vomiting as side effects of cancer treatment; poor appetite in patients with AIDS-related wasting; chronic pain and painful spasms in multiple sclerosis; epileptic convulsions; and glaucoma [2-6]. In each of these indications, cannabis and cannabinoids are used as an adjunctive or second line treatment. Adjunctive treatments are those used in combination with other medical treatments while second line treatments are those reserved for patients in whom standard treatments have proven ineffective or been poorly tolerated because of side effects [3].

Cannabinoids as anti-emetics

In the 1970s and 1980s controlled clinical trials found that THC was more effective in treating nausea produced by cancer chemotherapy and radiotherapy than either placebo or the anti-emetic drugs then in common use (see [3,7-9]). The major problem with this evidence is that there are now newer and more effective anti-emetic agents [3,10]. The anti-emetic effects of cannabinoids and these newer drugs have not been directly compared in clinical trials but indirect comparisons indicate that the newer agents achieve complete control of nausea in 90% of patients whereas cannabinoids achieved complete control in only 30% of patients [3,10]. This evidence indicates that cannabinoids are not a first line treatment for nausea and vomiting in cancer patients but they may still be adjunctive or second line treatments [3,5].

Appetite stimulation

THC and other cannabinoid agonists stimulate appetite in humans and animals [11,12]. Dronabinol (Marinol) was registered in the USA as an appetite stimulant in patients with terminal cancer and AIDS-related wasting in the early 1990s on the basis of several small scale clinical trials [8]. A Cochrane review of these studies concluded that the evidence was too weak to draw any inferences about efficacy or safety [13]. The use of cannabinoids to stimulate appetite in AIDS patients has largely been obviated by the advent of highly effective anti-retroviral drugs that prevent most HIV-infected persons from developing AIDS-related wasting.

Neuropathic pain and spasticity in multiple sclerosis

Analgesia is one of the oldest reasons for medical use of cannabis and one for which there is a biological rationale [14]. THC and other cannabinoid agonists act on similar pathways to the opioids but they also produce analgesia via distinct mechanisms which suggest that the analgesic effects of combinations of opioids and cannabinoids could be larger than the sum of their individual analgesic effects [15]. In double blind and placebo controlled clinical trials cannabinoids produce moderate analgesia equivalent to moderate doses of codeine [3,16].

The role of cannabinoids in controlling neuropathic pain has been evaluated in clinical trials in patients with multiple sclerosis (MS) [17]. Patients given Sativex reported greater subjective relief of painful muscle spasms than patients who received placebo. There were, however, only marginal reductions in observer ratings of muscle spasm after three weeks of treatment (e.g. [18]). Larger reductions were reported in observer ratings and patient reports of spasticity and pain in a 12 month follow up of the subset of the original patients who continued to use cannabinoids for over a year [19]. A meta-analysis of the controlled trials (involving 298 patients) [20] found that Sativex produced a larger reduction in pain (1.5 vs 0.8 points on a 10 point rating scale) than placebo after 3 weeks' treatment . This improvement was less than that defined as "clinically significant" on this scale (2 points).

A recent review of studies of the nabiximols (Sativex) in MS [17] concluded that most have shown a greater reduction in symptoms of spasticity in patients receiving Sativex than in those on placebo. The adverse effects were also generally mild to moderate, with the most common being dizziness, diarrhoea, fatigue, nausea, headache and somnolence. Podda and Constaninescu emphasised that Sativex was added to more traditional anti-spasticity drugs rather than being used as a stand-alone treatment.

The evidence on Sativex has not convinced regulatory authorities in Australia to support its medical use in MS. The Australian Therapeutic Goods Administration (TGA) argued that the benefits of Sativex had been over-estimated in clinical trials because the measure of pain was susceptible to bias and the studies had not been properly blinded [21]. The TGA also expressed concern about what it saw as the serious adverse effects in 10% of patients in these trials, namely, psychoses, fatigue and cognitive impairment, arguing that these effects are serious in patients with a degenerative neurological disorder like MS. The TGA only

approved Sativex in MS patients who failed to respond to other treatments and who showed a clinical response within 2 weeks of initiating treatment. The Australian Pharmaceutical Benefits Advisory Committee (PBAC) decided against publicly subsidising Sativex for MS patients [22]. It concluded that the modest clinical benefits and serious adverse side effects did not justify taxpayers paying the manufacturer's asking price.

Epilepsy

Cannabidiol (CBD) has anticonvulsant effects in animal models of epilepsy [23]. There have been four small randomised, placebo-controlled trials in which patients whose epilepsy had not responded to first line anti-convulsants were given CBD in addition to their usual anti-convulsant drugs [24]. The studies were small and a Cochrane review concluded that the results were inconclusive [25]. Recent clinical interest has focused on using CBD to treat a rare but serious childhood epilepsy syndrome, Dravet's syndrome. Epilepsy in Dravet's syndrome does not respond to conventional anti-convulsants and, if untreated, produces intellectual disability and death. Some parents have reported that cannabis extracts with high levels of CBD have controlled or greatly improved their children's epilepsy. Hill and colleagues [26] note that CBD is the most reliable anticonvulsant and appears to have no neurotoxic or motor side-effects. Randomised, controlled clinical trials are proposed to test its effectiveness [26,27].

3. THE RISKS OF MEDICAL CANNABINOID AND CANNABIS USE

Short term use

Wang et al [28] conducted a systematic review of the adverse effects reported in randomised controlled trials (RCT) of cannabinoids and cannabis extracts. They also examined case reports and observational studies of adverse outcomes in recreational cannabis users. They found that 97% of the adverse effects in the clinical trials were minor, with dizziness (20%) being the most common. They did not find a higher rate of serious adverse events in patients given cannabinoid drugs (either as plant extracts or THC preparations) than in those given placebo. Wang et al's conclusions agree with the US Institute of Medicine [3] which concluded that the acute adverse effects of cannabinoids were "within the risks tolerated for many medications".

Longer term use

Wang et al were unable to evaluate the risks of longer term medical use of cannabinoids (e.g. to treat the symptoms of chronic disorders, such as multiple sclerosis), because the clinical trials have all been short-term (from 8 hours to 12 months). As noted above, the Australian TGA expressed concern about the adverse effects of Sativex when used to treat neuropathic pain in patients with MS. It pointed out that cognitive impairment, fatigue and psychotic symptoms are more serious effects in patients who may be impaired by a degenerative neurological disease [21].

A small number of studies have been done on the emotional and cognitive effects of long-term Sativex use in patients with MS. In one trial, patients who were allocated to receive

Sativex for 50 weeks reported no statistically significant differences from placebo in their performance of cognitive and mood tests [29]. Participants in another RCT did not show any performance differences in the Paced Auditory Serial Addition Test, or score differences in the Beck Depression Inventory [30]. We need more studies like these to assess the safety of long term medical use of cannabinoids.

Population-based studies of recreational cannabis users provide tentative indications of possible adverse effects of long term cannabis use that we should examine in clinical follow up studies. These studies have examined (1) the effects in adolescence and early adulthood of regular (usually daily) and sustained cannabis smoking by young people; and (2) less commonly, the risks of long term health harms, such as cancers, that may arise from exposure to carcinogens in cannabis smoke over decades (see [1,31] for reviews). The relevance of these findings to medical cannabis use is uncertain because of the age of the users in these studies and the fact that *smoking* is the primary route of administration.

Recreational users who use daily can become dependent on cannabis [32]. The risk is higher if they begin smoking cannabis in adolescence and smoke the most potent cannabis products daily during young adulthood [33]. A substantial minority of cannabis dependent persons seek help to stop using cannabis [1]. The risks of dependence are probably higher in recreational users who smoke potent forms of cannabis multiple times per day than they are in older adults who use smaller oral doses of cannabinoids for symptomatic relief [34]. There is nonetheless some evidence that patients taking Sativex daily over a period of months experience withdrawal symptoms when they cease using the drug [21]. It is uncertain how many of these patients will develop a full dependence syndrome or experience difficulty in ceasing their use. We need studies of the risks and consequences of cannabis dependence in long-term medical cannabis or cannabinoid users to see if this is the case.

Longitudinal studies of young adults also suggest that daily cannabis use can precipitate psychotic symptoms and disorders in individuals with a personal or family history of these disorders [35,36]. Again this evidence comes from studies of young adults who started daily cannabis use in adolescence and used regularly throughout young adulthood, the period when the risk of developing psychotic disorders is at its highest. As noted above the Australian TGA has emphasised reports of acute psychotic syndromes in patients given Sativex [21]. Given these reports it would be prudent to advise persons with a personal or family history of psychosis to either avoid using cannabis for medical purposes, or use it with care and monitor adverse psychological effects [37].

The cardiovascular risks of cannabinoid use are of greater potential concern to medical cannabis users. The risks of cardiovascular disease are higher among older adults than among younger recreational users [38] and there are epidemiological studies suggesting that cannabis *smoking* can precipitate myocardial infarction in older adults [1]. There are also a number of case reports of serious cardiovascular complications, including cardiac deaths, in young recreational cannabis users [39,40]. It would be prudent for older patients to avoid smoking cannabis and use oral cannabinoids or cannabis extracts.

The cancer risks of long term cannabis smoking are unclear because studies have produced inconsistent findings and in many of these studies it has been difficult to separate the effects of cannabis smoking from those of tobacco smoking [1,41]. The cancer risks of cannabis use may be of little concern to older patients with a limited life expectancy, such as those with terminal cancer. They may be of more concern in patients with MS or chronic pain who may use cannabis daily over years and possibly decades. Again it would be prudent for long-term medical cannabis users to avoid smoking cannabis and use oral cannabinoids or cannabis extracts.

4. PHARMACEUTICAL CANNABINOIDS FOR MEDICAL USE

A synthetic form of THC, dronabinol, was registered for medical use as an anti-emetic and appetite stimulant in the USA in 1985. Nabilone, a synthetic cannabinoid with similar effects to THC, was approved for use in AIDS-related wasting in 1992. But neither of these drugs has been widely used because patients have found it difficult to obtain therapeutic doses that did not also produce unwanted adverse side effects [3,42]. This largely reflects the drawbacks of using the oral route to take THC: when taken orally THC has a delayed onset of effect and patients either receive insufficient THC for therapeutic benefit or too much and experience adverse side effects [2,42].

Pharmaceutical companies have not developed new cannabinoids, or new methods of delivering them, that overcome the problems with dronabinol and nabilone. This has been for a number of reasons. First, it is costly to develop and test new cannabinoids [3] and difficult to recoup these costs when the conditions for which they may be medically used are uncommon [3]. Second, regulations controlling the medical use of prohibited substances make it difficult to conduct basic and clinical research on drugs that are chemically similar to, or derived from a prohibited drug. Third, these regulations also impose restrictions on medical use of any cannabinoids that may be approved for human use, thereby discouraging physicians from using them [3,34,43].

Cannabis extracts such as Sativex have been trialled in the UK [2,4]. After controlled clinical trials, Sativex has been approved for use in patients with MS in Canada, Czech Republic, Denmark, Germany, New Zealand, Spain, Sweden and the UK (http://www.gwpharm.com/Sativex.aspx). Sativex has been approved for clinical use in the UK but it has not been approved for publicly subsidised use under the National Health System. It remains to be seen if Sativex (and other cannabis extracts) are more acceptable to patients than dronabinol and nabilone have been.

5. ALLOWING MEDICAL CANNABIS USE

The unavailability of pharmaceutical cannabinoids or cannabis extracts prompted US advocates of medical cannabis use to circumvent the traditional pharmaceutical regulatory route to medical use. In the 1990s these advocates campaigned to pass referenda in some US states that would allow patients to smoke cannabis for medical reasons. The challenge for US state governments has been in finding ways to allow patients to access cannabis products for medical use while recreational cannabis use has remained illegal.

Medical Marijuana Initiatives in the USA

In 1996 Californian voters passed a citizen initiated referendum, Proposition 215 (by 56% to 44%). This allowed patients to use marijuana for a broad set of medical indications that included those supported by evidence (namely, nausea, weight loss, pain and muscle spasm) as well as an open-ended category, namely, any 'serious medical condition" that a medical practitioner believed could be relieved by using marijuana [44].

Since 1996 a total of 23 US states and the federal District of Columbia have legislated to allow the medical use of marijuana, either by passing a referendum proposal or at the initiative of the legislature [45]. Not all these schemes allow access to marijuana for medical purposes in the same liberal fashion as California. State medical cannabis laws and regulations vary in how many and what type of patients they allow to use marijuana and the conditions under which they are allowed to obtain the drug [46].

The approved indications for medical cannabis use vary from the very narrow to the very broad [47]. Some states define medical use as the use of cannabis to treat indications for which there is evidence of efficacy from controlled trials (i.e. nausea in cancer, appetite stimulation in AIDS and analgesia). A few states have followed California's example in defining a broadly inclusive set of indications that allow medical use for any condition that a physician believes may benefit from the use of marijuana [47-49]. States also differ in whether they require physicians to examine a patient and advise them about the risks of using marijuana and whether they need to monitor patients who use marijuana [48].

Issues for Prescribers

Medical marijuana schemes remove the threat of criminal sanctions for patients but create problems for prescribers. Laws allowing physicians to prescribe cannabis conflict with US Federal law which does not allow the use of cannabis for any purpose. Under the US Constitution Federal laws pre-empt state laws [34,44]. The Bush administration threatened to strip doctors of their licenses to practice if they recommended marijuana to their patients. Even when the US courts removed this threat, physicians remained reluctant to recommend cannabis because of concerns that they would be legally liable for any harms experienced by their patients [47,50]. In the absence of data, physicians also found it difficult to decide to whom they should recommend cannabis, in what amounts, and for how long [51,52]. These

challenges were ignored by a small number of physicians who advertised their preparedness to provide patients with a medical recommendation for a fee.

Obtaining medical cannabis

Where do patients who have a physician's letter of recommendation obtain their cannabis? Patients either had to secure their cannabis from the black market or in some states were allowed to grow cannabis for their own medical use or have a carer grow it on their behalf. The Bush administration enforced Federal laws against cannabis cultivation and supply in medical marijuana states but in 2009 the Obama administration indicated that it would refrain from doing so [47]. The Obama administration enforced Federal laws against the large scale commercial cultivation of cannabis but tolerated commercial cannabis "dispensaries" in states that allowed medical marijuana use, provided that they only sold marijuana to patients who had a doctor's letter of recommendation [53].

The number of dispensaries increased rapidly in California, Colorado and Washington State after the 2009 decision. The dispensaries were not licensed to produce cannabis and so had to obtain it from the illicit market [47]. States that allowed dispensaries created a quasi-legal cannabis distribution system, much like the coffee shops in the Netherlands. The combination of a commercial cannabis supply system and very liberal criteria for what constituted medical cannabis use effectively allowed recreational users to obtain and use cannabis without fear of prosecution if they had a doctor's letter recommending medical use [48,49,54].

This is clear from studies of approved medical marijuana users in California. A survey of 4117 "patients" in the San Francisco Bay Area in 2001-2007 reported that 77% were male with an average age of 32 years. Most (89%) started using cannabis before the age of 19, and 90% were daily smokers who used between and $1/8^{th}$ and ¼ of an ounce per week [55]. There were no data on the medical indications for which they used cannabis but, given their age and sex, it is unlikely that they had cancer or serious neurological diseases. Another survey of 1746 medical marijuana patients in California in 2006 found that three quarters were male, only 13% were older than 55 years, and two thirds were daily smokers and had done so since adolescence [56].

A survey of self-reported "medical marijuana use" in a representative sample of the Californian population confirms the findings in dispensary clients [57]. In total 7% of Californian adults reported "medical cannabis use" with the highest rate (10%) among adults aged 18-24 years. The lowest rate (1.5%) was among persons over the age of 65 years, the age group in which one would expect to find persons with cancers, neurological disorders, and chronic pain. These findings indicate that there is a "porous boundary" between recreational and medical cannabis use in California [34,48,49,56].

The medical marijuana program in Canada

In April 2001 the Canadian Government legislated to allow patients to access cannabis for medical purposes [58-60]. The legislation allowed cannabis to be supplied by the government (who obtained it from a single commercial supplier), and it also allowed a registered patient (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 or epilepsy; or (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" [59,61].

Under the Canadian government-approved medical marijuana access program doctors have been reluctant to prescribe cannabis for medico-legal reasons [59,62]. The Canadian Medical Association (CMA) and the Canadian Medical Protection Agency advised physicians not to prescribe cannabis [59,63], arguing that there was no clinical evidence that it was effective for most of the approved indications and that prescribers would be legally liable for any adverse effects that their patients experienced [64].

Patients complained about the quality and the cost of the government supplied cannabis, arguing that black market cannabis was cheaper and better quality [59,64]. They also complained about the cumbersome and lengthy process to obtain approval to use cannabis [64]. The scheme cost an estimated C$30M between 1999 and 2007 when it only supplied cannabis to several thousand patients [59]. The number of approved patients grew to 37,884 by January 2014, a three-fold increase since December 2011. The majority of these lived in British Columbia (18,383) and Ontario (11,071).

The high costs and small patient numbers raise a major concern about equity of access to pharmaceuticals. The Canadian medical cannabis scheme provides an unapproved drug of uncertain safety and efficacy for many of its supposed indications, at substantial cost, to a small number of patients. It does so when Canadian provincial governments (which fund drugs in Canada) do not always fund approved pharmaceutical drugs for which there is evidence of efficacy.

Because of these problems many Canadian patients obtain their cannabis from private suppliers. The Canadian government estimated that 290,000 Canadians in the province of British Columbia used cannabis for medical purposes in the past year [59] but that only 1816 persons had been approved to use medical cannabis in the province and only 20% (356) of these obtained cannabis from the government. The remaining 80% either grew their own or obtained it from unapproved dispensaries [59,60,64].

According to Lucas, 30,000 Canadian patients obtained medical cannabis from compassion clubs in 2012 [64]. These patients were older (most over 35 years) but otherwise very similar to patients using dispensaries in California: 78% were males, who had been daily cannabis

smokers for 10 years or more, and they reported using cannabis to relieve chronic pain as well as depression [64,65].

In 2014 changes were made to Canadian medical cannabis policy [60]. The Government delegated decisions about patient eligibility to doctors who provided a letter of recommendation for medical use. Medical use was allowed for any patient whom a doctor believed would benefit from using cannabis. The government also licensed a number of companies to grow and sell cannabis to patients who had letters of recommendation. Fischer et al argue, however, that the Canadian system is now very like the Californian medical marijuana system in defining medical use broadly and leaving this definition to doctors and patients. The licensed suppliers operate for profit and so have an interest in expanding their market. These features of the revised system may create de facto legalisation of recreational cannabis use for any Canadian prepared to obtain a medical recommendation.

Medical cannabis in the Netherlands

The Netherlands legislated to allow the medical use of cannabis in 2003. Cannabis is provided in a form suitable for oral use by pharmacies on the prescription of a physician [58]. Dutch physicians apparently shared the reluctance of their Canadian colleagues to prescribe cannabis, presumably for medico-legal reasons. Dutch patients have also complained about the quality and cost of the government supplied cannabis. Unlike Canadian patients, however, those in the Netherlands have the option of purchasing cannabis from coffee shops because recreational cannabis use and de facto retail cannabis sales have been decriminalised [66].

Hazecamp and Herdink [67] have reported the number of patients who accessed the Dutch scheme between 2003 and 2010. During this period 3 per 100,000 new patients received a prescription each year and the annual use varied between 8 and 10 per 100,000 between 2005 and 2010. These rates were much lower than estimated rates in Canada (35 per 100,000) and in California (500 per 100,000). Dutch patients were much older than US medical cannabis users on average (55.6 years vs 40.7 years) and used lower daily doses (0.68 g vs 2.4-3.8 g). Hazekamp and Herdink did not have data on the medical indications for use but the other drugs these patients were prescribed suggest that it was more often used for chronic pain rather than AIDS and cancer. The small number of medical cannabis patients in the Netherlands means that this special access program raises similar equity issues to those of the original Canadian medical cannabis program.

6. SHOULD WE LEGALISE RECREATIONAL CANNABIS USE?

Grinspoon and Bakalar [68] argued that the simplest way to enable patients to use cannabis for medical purposes was to legalise any adult use of cannabis. This would enable patients who wanted to use cannabis for medical purposes to do so, at their own risk, without needing a medical prescription. It would also be legal to grow, supply and purchase cannabis. Legalisation would sever the Gordian knot of regulatory issues raised by cannabis prescription programs and medical marijuana initiatives.

Until very recently the major political and legal obstacle to legalisation was the UN Single Convention which prohibits the nonmedical use of cannabis [66]. This policy has consistently enjoyed majority public support in most developed countries [66] but this recently changed in the USA with the passage of citizen-initiated referenda that legalised recreational cannabis use in Colorado and Washington in 2012 and in Alaska and Oregon in 2014 [69]. Colorado and Washington implemented legal cannabis markets for recreational use in 2013 and 2014 respectively [70,71].

The fact that cannabis use has been legalised in these US states creates an interesting issue for the regulation of medical cannabis use. Colorado will allow medical cannabis users to pay a lower rate of tax on their cannabis than recreational users. This has created an incentive for tax evasion that recreational users appear to have recognised, judging by a large increase in the number of persons registered to use cannabis for medical reasons in Colorado after the passage of cannabis legalisation. This policy will prevent Colorado from receiving the large tax income windfall that advocates of legalisation used to persuade voters to support cannabis legalisation.

I would argue that medical cannabis use should only be given a tax advantage for medical indications in which there is evidence of efficacy. But this would require a system of approval and registration that could be expensive to run, creating a regulatory expense that cannabis legalisation was supposed to remove. It would be arguably simpler if medical users purchased cannabis at the same price that everyone else pays. This will in probably be considerably cheaper, in any case, under a legal regime than it has been in dispensaries operating under a nominal policy of prohibition.

7. SUMMING UP

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 and spasticity. There are now much more effective drugs available for these indications. If cannabinoids have a medical role in these cases, it is as second or third line treatments, or as an adjunctive treatment.

Pharmaceutical synthetic cannabinoids have been approved for medical use (e.g. dronabinol) but they have not been widely used because patients find it difficult to achieve therapeutic doses. These drugs have not been very profitable for the companies that produced them. The small market for cannabinoids, the lack of profitability, and the regulatory costs and burdens of their clinical use, are major disincentives to the development of more effective cannabinoids [3].

A pharmaceutical cannabis extract, Sativex, has been approved for medical use in multiple sclerosis and neuropathic pain in a number of countries. It has shown modest efficacy in clinical trials in controlling these symptoms but regulators in Australia have found the evidence unconvincing. It remains to be seen if Sativex proves more acceptable to patients than dronabinol and nabilone.

Medical marijuana advocates in the USA have used referenda to enable patients to smoke cannabis. These initiatives have created problems for physicians who have been reluctant to prescribe cannabis because of uncertainty about clinical indications, and fears of being legally liable for any harm that patients experience.

Securing legal supply of cannabis has been a problem for medical cannabis users. Some governments have responded by creating special access schemes for medical cannabis. Even under these systems, physicians have been reluctant to prescribe cannabis for medico-legal reasons and patients have often complained about the quality and cost of the government supplied cannabis, and the cumbersome approval process. These governments find themselves funding an expensive special access program for a plant-based drug of unknown efficacy that very few patients want to use.

In some US states medical cannabis schemes has been used as a "Trojan horse" for the legalisation of recreational cannabis use. This outcome has been facilitated by (1) defining the criteria for medical cannabis use very broadly, (2) allowing the decisions as to whether a patient meets these criteria to be made by doctors and patients, without any independent scrutiny; and (3) allowing commercial businesses to supply cannabis to approved patients. Canadian medical cannabis policy may now be moving in the same direction. If governments do decide to legalise adult cannabis use it would be better, on the grounds of honesty and transparency, if they did so after an informed public debate rather than doing so by inadvertence .

If we wish to maintain the integrity of the pharmaceutical regulatory system it would be best to avoid creating special access schemes for medical cannabis. They run the risk of creating a precedent that will be used to introduce other drugs into medical practice in the absence of evaluations of safety and efficacy. Government supply of cannabis via such special access schemes also raises equity issues. It is arguably unfair for governments to subsidise the medical use of a drug that is, at best, modestly effective for some purposes (e.g. vomiting and nausea) and probably for others (e.g. chronic pain, depression, muscle spasm), when they decide not to subsidise other pharmaceuticals for which there is better evidence of efficacy.

8. WHAT DO I PROPOSE?

An informed policy towards the medical use of cannabinoids requires much better evidence than we currently have.

First, we need clinical trials of the safety and efficacy of CBD and other cannabinoids in treating intractable epilepsy and chronic pain. Evidence from these trials is essential for rational decisions to be made about the medical use of cannabinoids.

Second, in the interim, state governments could allow medical necessity as a defence against criminal prosecution for patients with defined conditions who use cannabis. They could do so either by legislation, or they could direct the police not to enforce criminal penalties for cannabis use where a credible medical necessity defence can be offered. Either would arguably be in compliance with the international drug control treaties or at the very least consistent with approaches adopted by a number of other countries. The uncertainties about the potential adverse effects of sustained use of cannabis for medical use would need to be clearly communicated to these patients.

Third, if we decide to allow medical cannabis use outside clinical trials this should be for registered patients and for a time limited period (e.g. 5 years) rather than an open ended commitment. Governments should fund long term follow-up studies of patients who use cannabis preparations and medical cannabinoids over periods of years to assess: the risks of developing cannabis dependence; exacerbating cardiovascular disease; precipitating psychotic disorders; and developing cancer [1,38].

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