10 March 2015

Submission to **Inquiry into the Regulator of Medical Cannabis Bill 2014**

I am pleased to have the opportunity to interact with the Senate Committee on this important topic.

Whilst I am firmly of the view that international experience has established the case for making appropriate cannabis available to relieve suffering in a number of 'medical' conditions, there are a number of important safeguards which need to be taken into account. It will be the first time in Australia, since the approval of morphine as a prescription pharmaceutical, of authorising one of the 'illicit' drugs for use in 'medical' conditions. The current drugs are 'illicit' under the Single Convention on Narcotic Drugs of 1961 as amended in 1972 and the UN Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988.

The Single Convention requires signatories to: *Limit exclusively to medical and scientific purposes the production, manufacture, export, import distribution of, trade in, use or possession of drugs; eradicate all unlicensed cultivation; suppress illicit manufacture and traffic and cooperate with each other in achieving the aims of the Convention*. It is important to note the specific provision in respect of 'medical and scientific purposes' covers morphine and its derivatives, and it should be noted that a number of signatories to the Convention have approved use of cannabis for 'medical' conditions, (including Canada, Netherlands, Belgium, Italy, Czech Republic, Israel) and currently 23 of the US States.

If Australia moves similarly, it will be important to ensure for both public health and legal reasons that the change takes account of meeting the general obligations of the Convention in respect of any damaging use of the 'medicinally' approved drug being used for recreational purposes in the general population and that those receiving it for their medical condition have reason for confidence that use will not be damaging to them. Regulated supply of cannabis would be an important next step in the whole field of illicit drug reform.

Specific concerns

C. sativa or indica both have a large number of psychometrically active components amongst *more than 90 cannabinoid compounds* and another group of compounds - *'terpenoids'* - some of which interact with the principal cannabinoids. The most potent cannabinoid in its influence on mood (relaxation and euphoria) is *delta*-9-tetrahydrocannabinol (THC). The effect of high dosage is termed '*stoned'* in the vernacular. It also has significant analgesic effects. Over the past 10-15 years, marijuana has been bred to produce a high content of this product to serve the market demand for its ef-

fects. This is derived particularly from the reproductive seed and adjacent leaves of the plant This type of product is colloquially termed *skunk.* It acts on the endogenous CB1 and CB2 receptors, the former being widely represented in the brain. CB2 on the other hand is wieldy distributed in body tissues and cells, responding to the body's own endo-cannabinoids influencing immunity and inflammation.

The second most extensively studied component has been cannabidiol (CBD) which counteracts, to a significant extent, the excitatory effects of THC mediated through its influence on excitation of the body's endogenous cannabinoid receptors CB1and CB2, substantially modifying the effects of stimulation by THC. It derives especially from the stalk of the leaves and is commonly contained in the marketed product of *hash* or *hashish*. It has strong anti-emetic and analgesic effects and may also have anti-inflammatory effects. It is reported to improve symptoms of developing psychosis. There is much recent research in this field.

Clinical reports of benefits in terms of pain relief and improvement in general well-being in the late stages of cancer, and relief from nausea in the course of cancer chemotherapy, represent the strongest case for action to make the therapy available. To this is added pain associated with some neurological conditions and recent reports strongly indicative of marked improvement in sufferers some forms of juvenile epilepsy resistant to conventional anti-epilepsy medication when treated with cannabis with a known high content of CBD.

Clinical trials with CBD enriched preparations, and CBD alone, are currently in progress in juvenile epilepsy in the US and UK. Relatively few formal trials of use of cannabis in other conditions have been reported, although a number are known to be in progress or planned relating to pain and nausea associated with cancer an chemotherapy, pain associated with neurological conditions and post-traumatic stress disorder. The lack of trials is primarily due to the illegal status of use of cannabis. A further factor has been uncertainty of the variable components of cannabis in preparations used, including THC and CBA and the many other constituents commonly present in cannabis.

Trials of a commercially available concentrate *Sativex* from a UK company GW Pharmaceuticals in multiple sclerosis has both THC and CBD in close to equal concentrations. A further product *Epidiolex,* is highly concentrated CBD. The Dutch company Bedrocan BV, an offshoot of their Medical Cannabis Office of the Health Department, now markets five selective products, two of which are high in CBD, one of which has very little THC. The other three are high in THC. It is an approved provider of medical cannabis in Canada where its products are on sale to approved medical cannabis recipients. There remains doubt as to whether the selective products are as effective as cannabis itself in some applications. Each of the commercial products are protected by patents and use entails considerable cost. Italy is currently embarking on its own development of a product to save cost after use of a Dutch product for the first year of its medical marijuana project.

Concerns about possible toxic effects of THC need careful consideration in the light of clear evidence of the precipitation of psychotic symptoms with high intake of conventional cannabis rich in THC. Many publications report such an increase in THC content of widely used forms of marijuana.[1] On the other hand, a very recent study of 410 adults with first onset of psychosis in South London and 370 volunteer controls without features of psychosis (conducted by the highly respected Maudsley Institute) showed a strong correlation of psychosis with heavy use of *skunk* marijuana (high in THC) whilst even heavy users of *hash* marijuana (with both THC and CBD) showed no correlation with development of psychosis. The difference was attributed to the high THC content of *skunk* with the protective effect of CBD present in *hash.*[2] 53% of first episode psychosis people took the skunk-like cannabis, 30% taking it daily, whilst in the control group 63% had used cannabis. 42% took hash, 19% took skunk, 11% taking it daily. The high level of cannabis consumption in South London is noted. Of those using cannabis, 60% used the hash-like product. 30% used the more potent and expensive skunk-like product. In both groups, a significant number proceed to weekend and then daily use, so presumably both contained very significant THC content producing the *'stoned'* effect that most recreational users seek, but the hash-like product would have also contained CBD.

These findings are consistent with other studies concluding association of heavy cannabis use with emergence of schizophrenia or other forms of psychosis, especially in people with certain genetic constitutions. The presence of CBD is protective in symptom relief from psychotic symptoms and may halt progression despite the presence of THC. Other studies suggest that people with a specific genetic disposition (at the AKT1 gene) are particularly susceptible to psychosis triggered by THC [3], whereas other users over many years may suffer no such ill-effects. AKT1 is one of a number of genetic elements known to be associated with schizophrenia.[4]

Many publications on the differences in effect of THC and CBD on the human brain and subjective experience have been reported over the past 10 years. Many of the studies touch at length on the mechanisms of interaction between CBD and THC. [5] [6] [7]

---

[1] Kuepper R, van Ost J, Lieb R et al 2011 Brit. Med. J 342: d783

[2] Di Fordi M, Marconi A, Carra E et al 2015 Lancet Psychiatry 2:233-238

[3] Di Forti K, Iyegbe C Sallis H et al 2012 Bio. Psychiatry 15:811-6

[4] van Winkel R 2011 Arch Gen Psychiatry 68:148-157

[5] Bhattacharrya S, Morrison PD, Fusar-Poli et al 2010 Neuropharmacology 35:764-774

[6] Niesink RJM van Laar MW 2013 Front. Psychiatry doi :10.3389/fpsyt.2013.00130

[7] Russo EB 2011 Br J Pharmacol 163:1344-1364

Much will be learned in the coming years about both the benefits arising from medical cannabis programs and possible hazards, although it is already clear that the demand from patients with painful conditions is high. It would be important to ensure that a cannabis preparation for 'medical' conditions has a significant presence of CBD, because of the possible complication of triggering psychosis in people with an inherent susceptibility. Further studies with purified or enriched CBD preparations will no doubt be reported once legislation permits both research with cannabis and its use in clinical treatment is established.

A further public health issue is the proven negative effect on development of frontal lobe functions in cannabis users aged between 15 and 25.[8] People this age range must not have access to 'medical' cannabis except in demanding situations when low content of THC may be appropriate.

Designation of conditions appropriate for medical cannabis will no doubt extend beyond pain associated with advanced cancer, nausea and distress associated with intense chemotherapy, painful neurological conditions and possibly post-traumatic stress disorder and adult Attention Deficit Hyperactivity Disorder although formal clinical trials might well provide clear evidence in these last two conditions. Late AIDS was seen as a further condition to benefit, but retroviral drug medication has reduced to relevance of they group.

Legislation will need to designate processes for approval of further recipient groups, which will no doubt emerge. It is suggested that the initial categories of pain in cancer, nausea and distress with cancer chemotherapy, painful neurological conditions and refractory juvenile epilepsy also provide for further categories when strongly recommended by two or more recognised specialists with a commitment to data collection and reporting or formal clinical trials.

I attach to this submission my article on 'Medical' Cannabis published in the Medical Journal of Australia on 2 February on 2 February 2015.

Emeritus Professor David Penington AC, DM FRCP, FRACP

---

[8] Sillins E,Horwood LJ Patton GC et al 2014 Lancet Psychiatry 1:286-293