Submission No 56

INQUIRY INTO USE OF CANNABIS FOR MEDICAL PURPOSES

Organisation: National Cannabis Prevention and Information Centre

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Please find attached a submission to the inquiry from Jan Copeland (PhD). While she is the Director of the National Cannabis Prevention and Information Centre at the University of New South Wales the views expressed are those of the author and do not reflect those of the Australian Government or consortium members.

Conflict of interest: NI:
Jan Copeland has led an NH&MRC project using Sativex in the management of cannabis withdrawal. The medication was provided by GW Pharmaceuticals in the United Kingdom. She received no direct or indirect financial support and has no financial interest in that or any other pharmaceutical company.

Submission to the NSW Parliament Legislative Council's Inquiry into the Use of Cannabis for Medical Purposes

Submission on behalf of:

The National Cannabis Prevention and Information Centre (NCPIC) is an Australian Government Initiative that was officially opened in April 2008. It was established in 2007 in response to the recognition of cannabis as an important drug of concern within the Australian community. The Centre is a consortium of high quality organisations from around the country including drug and alcohol, mental health and criminal justice research organisations and service providers and is located at the University of New South Wales. The consortium is highly skilled in the provision of evidence-based drug information and intervention.

The NCPIC mission is to reduce the use of cannabis in Australia by preventing uptake and providing the community with evidence-based information and interventions.

It specifically aims to:

- provide the Australian community with access to evidence-based information on cannabis and related harms;
- provide community access to, and awareness of, evidence-based information to prevent uptake, and continuation, of cannabis use; and
- supply service providers with evidence-based interventions to respond to people experiencing cannabis-related problems.

NCPIC's perspective

The Centre's mandate does not extent to questions of cannabis policy and legislative options or to date on the issue of medicinal cannabis. Given the growth of the medical marijuana "pharmacies" in the US and now legalisation of cannabis in two American states, the influence of the very powerful and well funded pro-cannabis lobby groups have had a marked influence on the community perception of the harms associated with cannabis use among American adolescents. This has been followed by an increase in the levels of use among high school students in that country, such that daily use of cannabis is now at a 30 year peak level among high school students.[1] The messages emphasising cannabis' safety are also echoed by Australian lobby groups for the cause of legal and/or medicinal cannabis. As these also include prominent and credible members of the Australian legal, academic and medical communities they must be balanced with evidence regarding harms and consideration of the negative as well as any putative positive consequences of regulated availability.

To follow we will briefly outline trends in cannabis use in Australia, cannabis preparations, overview of the evidence on cannabis related harms, evidence of potential benefits of cannabinoids as medicines, followed by a conclusion.

Cannabis use trends

Australia is among the highest prevalence countries for cannabis use, with up to a third of the population ever having used the drug.[2] Dependence is a key predictor of

the societal burden from cannabis use disorders.[3] Public health costs of cannabis abuse and dependence include lower educational achievements, and poorer mental and physical health outcomes, as well as subtle cognitive deficits relating to attention and memory, as well as respiratory disorders.[4] Treatment admissions for cannabis use disorders have risen considerably over the last few years, globally and within Australia. In 2010-11, cannabis was a drug of concern in almost half (42%) of all treatment episodes. It was the principal drug of concern for more than one in five (22%) overall but this approached half (47%) of episodes among 10-19 year olds and 28% for 20-29 year olds.[5] Given the status of cannabis as the world's most prevalent illicit drug of abuse, and an estimated 10 - 20% of users meeting dependence criteria, it is important public health priority.[6]

Cannabis preparations

There are three broad types of the diverse class of chemical compounds known as cannabinoids: phytocannabinoids (plant forms), endogenous cannabinoids (produced naturally in the bodies of humans and animals) and synthetic cannabinoids that are chemically produced by humans and not derived from plants.

The phytocannabinoids are comprised of the three best known varieties *Cannabis sativa, Cannabis indica* and *Cannabis ruderalis. Cannabis sativa* is by far the most common as it has the highest levels of the strongest psychoactive compound delta-9-tetrahydrocannabinol, commonly known as THC.

Agricultural processes have succeeded in refining the types of cannabis plants (females bred alone, hydroponic methods) harvested to maximise the THC content. Indeed, trends in the cannabinoid profile of cannabis over the past two decades have biased contemporary cannabis towards high THC and low CBD content. Recent NSW research has indicated high levels of THC (around 15%) and negligible (<1%) CBD.[7] While there is enormous variability in the level of these cannabinoids (commonly referred to as cannabis potency), some data do indicate that CBD may prevent or inhibit the psychotogenic, anxiogenic and memory-impairing effects of THC.[8-10]

Pharmaceutical preparation of the plant for research and clinical purposes has enabled the constituent components to be adjusted for research purposes to investigate which combinations of the constituents might provide the best treatment for differing conditions. This is critical as it is the psychoactive components and the balance of the constituents and the route of administration of the drug that create the largest risk of harm to self and others (dependence, cognitive impairment, psychological impairment in terms of paranoia, anxiety and impaired judgement when driving or working, hepatic, respiratory and cardiac disease).

Cannabis the drug

An understanding of the main actions of cannabis is required in order to fully understand the findings in relation to the harms and benefits of cannabis and cannabis derivatives. There are more than 70 phytocannabinoids, and these

substances are considered to be the main biologically active components of the plant.[3] Smoking cannabis is the most common and widely used method of administration of the substance and it is an effective method for THC to quickly reach the brain and exert the desired psychoactive effects. When smoked, about half of the THC is inhaled and most of what is inhaled enters the bloodstream via the lungs. Once in the bloodstream, THC travels to the brain very quickly. The psychoactive effects of cannabis begin within minutes of smoking, and peak within half an hour with blood serum levels peaking between 0.5-4 hours after inhalation.[11-13] When swallowed, cannabis causes similar psychoactive effects but takes longer to reach the bloodstream than when smoked, so that the onset of the effect is delayed by between one and three hours. This delay in psychoactive effect can result in people ingesting more cannabis than desired. Once metabolised by the liver, THC and its metabolites are distributed to other parts of the body and accumulate in fatty tissue, due to their fat-soluble nature. Although THC and its metabolites are released into the blood for days following the administration of the drug, there is little evidence that this causes intoxication to re-occur without re-administering the drug. [11-13]

Once THC and other cannabinoids reach the brain, they bind to endogenous cannabinoid receptors known as CB1 receptors.[13] The CB1 receptors are found in the frontal regions of the cerebral cortex, basal ganglia, cerebellum, and limbic structures such as the amygdala, hypothalamus and hippocampus. These areas are involved in the control of movement, appetite, emotion, memory and cognitive functioning.

Another type of cannabinoid receptor, the CB2 receptor, has been identified and is not found in the brain but in other parts of the body. Cannabinoid receptors can be found in most parts of the brain as well as the immune system and other organs of the body.[3]

Although the metabolic processes of THC have been well researched, comparatively little is known about the metabolism of the other cannabinoids. Only the metabolism of cannabidiol (CBD) and cannabinol (CBN) have been researched to some extent. Cannabidiol has no affinity for CB1 and CB2 receptors but acts as an indirect antagonist of cannabinoid agonists.[15] Recently it was found to be an antagonist at the putative new cannabinoid receptor, GPR55, a GPCR expressed in the caudate nucleus and putamen.[16] Cannabidiol has also been shown to act as a 5-HT1A receptor agonist, an action which explains its antidepressant, anti-anxiety, and neuroprotective effects.[17-22] Cannabidiol has also been shown to inhibit cancer cell growth with low potency in non-cancer cells., although the inhibitory mechanism is not yet fully understood.[23]

Cannabis is considered to be a drug of addiction with approximately 8-10% of those who try it becoming addicted.[6] Addiction includes cannabis abuse or dependence and will soon be listed in the fifth version of the Diagnostic and Statistical Manual of Mental Disorders. Cannabis abuse and dependence are characterised by clinical significant impairment or distress resulting from recurrent use resulting in failure to fulfil major role obligations, use in situations which are hazardous, use requiring

markedly increased amounts to achieve the same intoxication, use in larger amounts than intended, use despite persistent efforts to cut down, much time spent in activities necessary to gain cannabis, cannabis withdrawal and use to relieve withdrawal symptoms and use despite knowledge of the physical and psychological problems arising from that use. The abuse/dependence potential of cannabis is attributed to the rewarding and reinforcing effects of THC on the endocannibinoid system.

Harms and risks associated with cannabis use

There is now a large and growing evidence base demonstrating that regular use of cannabis in either smoked or eaten form has serious implications for the individual and for society. These implications involve adverse psychological, physical, financial and interpersonal effects for the user and adverse consequences for public health and society in terms of the burden of disease on the public purse and the public health systems.

The psychological effects of cannabis use in the research literature include psychosis and psychotic symptoms, paranoia, depression and anxiety. In terms of the individual and psychological consequences the birth cohort studies (based on 20 years of data)[25,26] and the studies of targeted cohorts of adolescents[27,28] as well as various other studies have been able to demonstrate definitively the relationship between cannabis use and the development of psychosis. The strength of these analyses is

that they are from large, representative samples participating in multiple waves of a longitudinal study that have measured a large number of demographic, psychosocial and health-related variables that allow greater specificity of casual variables in the analyses. Furthermore numerous other longitudinal and other types of studies have demonstrated the link between cannabis use and mental health disorders including anxiety and mood disorders including different diagnoses of depression.[29] The literature demonstrates both that using cannabis leads to greater vulnerability for mental health disorders and that people with a vulnerability to mental health disorders use cannabis to self-medicate for those conditions.[30]

A recent study has assessed changes in IQ and specific cognitive abilities between adolescence and the age of 38 in 1,037 New Zealanders enrolled in the Dunedin birth cohort that found early and persistent cannabis users showed an eight-point decline in IQ compared to those who hadn't used cannabis in this way. This was an especially strong finding as further analysis eliminated the effects of SES on IQ by only examining the relationship between cannabis use and IQ decline in children who came from middle-class homes. They found the same IQ decline in cannabis users who started in adolescence and persisted using into young adulthood within middle-class cannabis users. Further, the alternative hypothesis that the IQ of low SES participants would be boosted by schooling and decline faster after they left school was excluded as they found that average IQs were unchanged in low SES participants between beginning

school and adolescence. Most critically, low SES was not related to IQ decline between adolescence and young adulthood.[31]

Similarly, there is a robust association between cannabis use and educational achievement. Pooling of prospective cohort data from Australia and New Zealand found that there were significant associations between age of onset of cannabis use and all outcomes such that rates of attainment were highest for those who had not used cannabis by age 18 and lowest for those who first used cannabis before age 15. There was no consistent trend for cannabis use to have greater effect on the academic achievement of males but there was a significant gender by age of onset interaction for university enrolment. This interaction suggested that cannabis use by males had a greater detrimental effect on university participation than for females. Pooled estimates suggested that early use of cannabis may contribute up to 17% of the rate of failure to obtain the educational milestones of high school completion, university enrolment and degree attainment.[32]

Adverse physical effects have been found as a result of smoking cannabis include respiratory problems-chronic cough, sputum production, wheezing and bronchitis than non-users,[33,34] even after controlling for tobacco use, cardiovascular events such as stroke and heart attack problems and hepatic disease.[35]

In addition to the direct effects of the drug on the psychological and physical health of the user, cannabis use increases the risk of injury or death whilst driving[36,37] or operating equipment at work.[38] Cannabis use is also associated with significant financial and interpersonal implications including difficulties with family and friends, difficulties at school and at work, and poorer academic achievement.[26,39] There is some evidence to suggest that cannabis use increases risk of suicide, particularly amongst the young.[29]

In addition to the impact on the user of cannabis, cannabis use poses significant public health consequences (lower birth weight of infants exposed to cannabis in utero,[40] incidents in the traffic or at work as a result of a third party negligence whilst under the influence of cannabis. Many laboratory studies and field studies have established the risks associated with driving under the influence of cannabis.[41] According to the 2010 National Drug Strategy household Survey 21.5% of males and 13.2% of females reported driving under the influence of an illicit drug with cannabis being the most likely of these.[2]

The early onset (during early adolescence) of cannabis use poses particularly high risks of serious adverse health consequences that persist into adulthood.[42] The cost of addiction treatment, hospital treatment for the health or motor vehicle and workplace accidents and education about the harms associated with cannabis use and the safe

use of pharmaceutical preparations must also be considered when discussing regulatory policy.

Potential benefits of cannabinoids

Cannabis, most likely originating from central Asia, has been used in medicinal form since ancient Egyptian times.[43] It enjoyed a brief period of popularity as a medicinal herb in Europe and the United States in the 1800s being prescribed for various conditions including menstrual cramps, asthma, cough, insomnia, birth labour, migraine, throat infection and withdrawal from opiate use.[3] Because of the problems with titrating a dose there were issues with patients being give too little or too much resulting in anything from no effect to adverse side effects. Cannabis was removed from the register of medicines in the early 1900s in the USA and made illegal at around the same time. Although the origins of prohibition enjoy some controversy, cannabis prohibition coincided with the general prohibition to alcohol and other "habit forming substances and poisons" in the USA.[44]

In the past 20 years pre-clinical and clinical research on humans into the effects of pharmaceutical preparations derived from cannabis has increased significantly.[45] A recent review of relevant randomised controlled trial of cannabinergic pain medicines found 38 published trials, wherein 71% found some efficacy.[46] These trials used approved medications, rather than smoked herbal cannabis, and found that while beneficial effects were found most trials were only short-term.

A specific condition, cluster headaches, has recently been studied as cannabis use is frequent among those presenting for specialist treatment in France. A study 139 participants with cluster headaches concluded that the efficacy of cannabis for this condition was limited and at this stage its use should not be recommended.[47]

There have been different cannabis products tested and these include Donabinol/Marinol, Cesamet, Cannador, Sativex and smoked/vaporized herbal cannabis.

- *Donabinol/marinol*: a oral synthetic cannabinoid preparation that has been used since 1985 for the treatment of nausea and vomiting associated with cancer treatment after the failure of other anti-nausea agents.[45] It has also been used with anorexic patients and to treat HIV patients for weight loss associated with the disease. It has also been studied as an analgesic and/or antispasmodic and whilst it has proved successful in reducing cancer pain at specific doses, the side effects were prominent. It has proven to be effective in certain type of pain for instance central neuropathic pain in Multiple Sclerosis.[48] In a large trial of multiple sclerosis patients it did not show objective improvement in spasticity but it showed objective improvement in mobility and subjective improvements in spasticity, spasm, pain and sleep quality which remained at 1 year follow-up.[49]
- *Cesamet/Nabilone:* a synthetic cannabinoid analogue purported to be more potent than natural THC.[45] It has been used with cancer patients as an anti-

nausea medication, to reduce spasticity related pain and to treat nightmares associated with PTSD.[50,51]

- *Cannador*: an oral capsule containing a cannabis extract, with reportedly a 2:1 ratio of THC to CBD,[45]however the exact THC to CBD ratio has not yet been standardised.[3] It has been shown to facilitate objective improvements in spasticity as well as subjective improvements in spasticity, spasm, pain and sleep quality in patients with multiple sclerosis. These effects were maintained at 1 year follow-up.[50]

  Sativex/nabixomols: *Sativex* is an oromucosal cannabinoid based spray developed and marketed for the relief of neuropathic pain and to aid with spasticity in multiple sclerosis. The *Sativex* spray contains THC, as used in the previously discussed studies, but in addition it contains approximately equal proportions of cannabidiol (CBD), with one spray delivering a fixed dose of 2.7 mg THC and 2.5 mg CBD. CBD is a non-psychoactive cannabinoid that can comprise up to 40% of the active ingredients of the cannabis plant. However, the amounts of CBD in cannabis vary greatly, with 1:1 THC:CBD ratios common in hashish prepared in developing countries but negligible CBD amounts found in high potency hydroponically grown cultivars. In various animal and human laboratory studies, CBD has been found to attenuate the intoxicating and psychotomimetic effects of THC, and CBD given alone has also been reported to relieve anxiety and nausea and to have anti-inflammatory and antipsychotic effects. A variety of human clinical trials have been performed using *Sativex*

spray in community settings, representing over 2000 subjects with 1000 patient years of exposure, for other indications than cannabis dependence with no evidence of tolerance, significant intoxication, or any form of withdrawal syndrome.[51-57] *Sativex* has also been shown to have some success as an adjunctive treatment with patients suffering from brachial plexus avulsion,[52] central neuropathic pain in multiple sclerosis,[53,54] rheumatoid arthritis,[55] peripheral neuropathic pain[56] and pain associated with advanced cancer.[56,57] In the Multiple Sclerosis (MS) studies some adverse effects have been observed which include dizziness, nausea and feeling intoxicated in 50% of patients.[53] Twenty five per cent of subjects withdrew from the study due to adverse events which also included impaired judgement, speech disorder, abnormal coordination, hallucinations and oral symptoms including discomfort.[53] Various studies in MS patients have shown that there is no habituation to the treatment and no withdrawal effect.[59]

Recently in Australia, *Sativex* has been trialed for the inpatient management of cannabis withdrawal and found to be safe and efficacious.[58]

- *Vaporised herbal cannabis:* Several studies have examined the efficacy of smoked or vaporised cannabis for the treatment of pain in predominantly already experienced cannabis smokers.[60-63] All of the studies reported improvements in subjective experience of pain. However adverse effects were identified in all of the studies and included headache, dry eyes, burning

sensation in areas of neuropathic pain, dizziness, numbness and cough,[63] cognitive impairment,[61] concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation, and thirst[60] and feeling uncomfortably 'high'.[62] There were also methodological weaknesses that challenge the validity of these findings.[45] A very recent trial with 39 participants with central and peripheral neuropathic pain compared placebo with low dose (1.3% THC) and medium dose (3.5%) vaporized cannabis. They found that both cannabis conditions led to an analgesic response compared with placebo but there was no difference between the two levels of cannabis. The participants remained on traditional medications and the study was run as an experimental trial in a laboratory rather than a clinical study, so it represents very preliminary but interesting evidence.

Overview

Recreational cannabis use has been shown to have serious and costly adverse health and social consequences for the individual and the population at large with young people, women and indigenous people being particularly vulnerable to the deleterious effects of cannabis use. Apart from an age vulnerability effect, the issues that also contribute to the harms associated with cannabis use include the enormous variation of the product in terms of THC level, and unknown contamination from pesticides, heavy metals and microbials, as well as the delivery system (smoking with or without tobacco and vaporisation).

Cannabis has been made available for medicinal purposes in eighteen US states and Washington DC, however, without controlling for the quality or safety of the product. The problems that have arisen with this approach are manifold.[43] Firstly because the cannabis that has been legalised is the same plant substance that is taken by recreational users and the mode of delivery of the drug has remained the same (i.e. it is predominantly smoked). This means that all of the risk factors of smoking (cardiovascular and respiratory, addiction to tobacco when mixed with the cannabis) are present. The *Journal of Global Drug Policy and Practice* reported that in 2011 over 85% of the 40,000 people enrolled in the medical marijuana program in Oregon USA were using it for purported chronic pain.[56] In addition, there is some evidence to suggest that children and adolescents are gaining easier access to the drug on the basis of some medical condition and this places these young people in the position of risks to physical and mental health in the longer term that have been documented above. In the USA, cannabis use is higher in states where cannabis has been legalised for medical purposes.[57]

Considering the results of the many clinical and experimental studies in humans involving pharmaceutical preparations of cannabis extracts it is logical that selected and targeted manipulation of the cannabinoid system is preferable to treatment with a whole, unregulated, variable dose and contaminated cannabis product with an unsafe delivery system. The only way research can be communicated clearly about cannabis is to use reliable and standardised methods to understand the composition of various

cannabis preparations.[3] Ideally a comprehensive overview of the cannabinoid content (i.e. the chemical fingerprint) of cannabis preparations used in studies should therefore be a standard part of scientific reports on the effects of cannabis.[3] Even so, the mixed results of many studies particularly those examining pain in MS and some of the unwanted effects call for much more research to be undertaken on the safety and efficacy of these products.

Australia has *per se* laws regarding cannabis use for drivers, and this would make it necessary for those receiving medicinal cannabis in any form, to refrain from driving. This is perhaps fortunate as a Californian study in 2010, revealed that a total of 14.4% of weekend night time drivers tested positive for illegal drugs, with 8.5% testing positive to THC. A comparison with the 2007 data found an increase in THC-positive drivers in 2010, but no increase in illegal drugs other than cannabis. Drivers who reported having a medical cannabis permit were significantly more likely to test positive for THC.[65]

Conclusions

When considering whether or not to make cannabis available for medicinal purposes there must be a distinction made between 1) the therapeutic potential of specific constituent compounds found in the cannabis plant delivered in controlled doses via non-toxic delivery systems and 2) the effects of smoking cannabis on both the user and the wider society. As an Australian cost benefit analysis of a legalised-regulated

opinion of cannabis availability predicted a 35% increase in the prevalence of use, this should also be considered in any model for regulated medicinal use.[66]

Drug approval must be considered in the context of public health, particularly for controlled substances. Cannabis has been proven to be an addictive drug. Consuming cannabis has been shown to cause cognitive impairment as well as increasing vulnerability to psychological harms in the users. Consuming cannabis and then driving or working also increases the risk to the general public through traffic incidents and workplace incidents. Smoking cannabis has been associated with cardiac and respiratory tract morbidity.

Pharmaceutical preparations of cannabis extracts on the other hand can be delivered safely, are tested and subjected to strict regulatory control both in preparation and administration, thereby reducing the harm potential both to the user and the wider society. As nabiximols (*Sativex*) is now licensed by the Australian Therapeutic Goods Administration for those with Multiple Sclerosis associated muscle spasticity unresponsive to other medications, it is the most promising cannabinoid preparation for clinical research - and if proven safe and effective, for medical prescription under supervision. A clear distinction needs to be drawn, however, between the regulated, therapeutic preparation of cannabinoids and smoking the whole plant for the putative relief of symptoms associated with a range of conditions.

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Conflict of interest

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