From: Drug Advisory Council of Australia Inc.
To: Committee, Education & Health Standing;
Subject: DRUG SUBMISSION
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Attachments: Chronic Toxicology of Cannabis Reece.pdf

Drug Advisory Council of Australia Inc.
PO Box 251,
Balwyn, Vic, 3103.

27 July 2009

Dr. J. Woollard MLA,
Chairman,
Education & Health Standing Committee,
Parliament of Western Australia,
laehsc@parliament.wa.gov.au

Dear Dr. Woollard,

SUBMISSION
ADEQUACY & APPROPRIATENESS OF PREVENTION & TREATMENT SERVICES FOR ALCOHOL &
ILLICIT DRUG PROBLEMS IN WESTERN AUSTRALIA

Thank you for your letter dated 29 June 2009 requesting a submission from our
Council.

We welcome the offer that you have made and we confine our comments to illicit
drugs however, the system we promote has been successfully applied to alcohol
rehabilitation.

Accordingly, we wish to refer your committee to a number of references being-

1. Sweden's successful drug policy: a review of the evidence September 2006 issued by the United Nations Office of Drugs and Crime and available at www.unodc.org
2. The Winnable War on Drugs September 2007 issued by the House of Representatives Standing Committee on Family and Human Services.
3. Cannabis- suicide, schizophrenia and other ill effects March 2009 issued by Drug Free Australia available at www.drugfree.org.au
4. Chronic toxicology of cannabis attached to this submission.

These primary resources will give your committee the evidence you require to address the evidence base in your terms of reference.

Our web site at www.daca.org.au has a large amount of information and the source of research that can be used by the committee for your recommendations
regarding prevention and treatment.

Our Council advises your Committee to recommend the replacement of the current
harm minimization approach to prevention and treatment and replace it with an
adoption of world's best practice.

We recommend that the drug policies of Sweden be adopted which focus on prevention of any illicit drug use by teenagers by provision of truthful information on the long term harms as evidenced by recent scientific research.

Sweden also users its legal system to divert illicit drug users into detoxification and rehabilitation that has the clear objective of ceasing illicit drug use quickly and permanently.

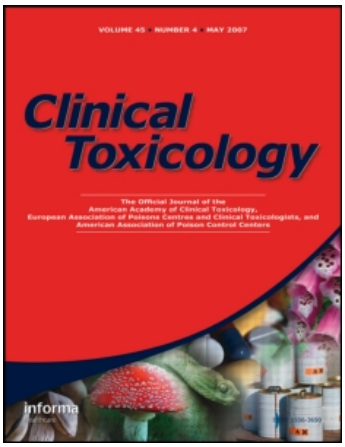
Our Council recommends the abandonment of illicit drug maintenance programs.

Our Council also recommends that detoxification and rehabilitation services be audited to determine the effectiveness of services in achieving the objective of ceasing illicit drug use. These audits should be made public.

We would be pleased to provide your committee with any further information that
it may require to assist you with your inquiry.

Yours Sincerely,

David Perrin,
Executive Officer,
Drug Advisory Council of Australia.



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Chronic toxicology of cannabis

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REVIEW

Chronic toxicology of cannabis

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Introduction. Cannabis is the most widely used illicit drug worldwide. As societies reconsider the legal status of cannabis, policy makers and clinicians require sound knowledge of the acute and chronic effects of cannabis. This review focuses on the latter. *Methods.* A systematic review of Medline, PubMed, PsychInfo, and Google Scholar using the search terms "cannabis," "marijuana," "marihuana," "toxicity," "complications," and "mechanisms" identified 5,198 papers. This list was screened by hand, and papers describing mechanisms and those published in more recent years were chosen preferentially for inclusion in this review. *Findings.* There is evidence of psychiatric, respiratory, cardiovascular, and bone toxicity associated with chronic cannabis use. Cannabis has now been implicated in the etiology of many major long-term psychiatric conditions including depression, anxiety, psychosis, bipolar disorder, and an amotivational state. Respiratory conditions linked with cannabis include reduced lung density, lung cysts, and chronic bronchitis. Cannabis has been linked in a dose-dependent manner with elevated rates of myocardial infarction and cardiac arrythmias. It is known to affect bone metabolism and also has teratogenic effects on the developing brain following perinatal exposure. Cannabis has been linked to cancers at eight sites, including children after *in utero* maternal exposure, and multiple molecular pathways to oncogenesis exist. *Conclusion.* Chronic cannabis use is associated with psychiatric, respiratory, cardiovascular, and bone effects. It also has oncogenic, teratogenic, and mutagenic effects all of which depend upon dose and duration of use.

Keywords Cannabis; Psychopathology; Respiratory pathology; Psychosis; Depression; Chronic bronchitis; Chronic asthma; Genotoxicity; Oncogenesis; Toxicity; Toxicology

Introduction

According to the United Nations Office of Drugs and Crime, there are some 165 million users of cannabis worldwide, making it the most widely used illicit drug.[1] This review examines the psychiatric, respiratory, cardiovascular, and bone effects associated with chronic cannabis use and the neurodevelopmental, genotoxic, mutagenic, and oncogenic effects of cannabis.

Methodology

A systematic review of Medline, PubMed, PsychInfo, Google Scholar, Scopus, Proquest, Web of Knowledge, and Ebsco-Host using the search terms "cannabis," "marijuana," or "marihuana" identified 14,065 papers, excluding duplicates. When the search terms "toxicity," "complications," and "mechanisms" were added, the list narrowed to 5,198 papers. This list was screened by hand, and original papers describing mechanisms and those published in more recent years were chosen preferentially. Review papers are cited where appropriate to introduce a large or detailed field for the interested reader. Few case reports are included and they are specifically flagged where they occur; those that are cited have been included largely because they suggest important pathophysiological mechanisms.

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Psychiatric and social disorders

An authoritative meta-analysis of cannabis-related psychopathology has been published,[2] with an accompanying editorial.[3] Another review found an elevated risk of psychosis in many studies, with an odds ratio (OR) of about 2.3.[4] A similar meta-analysis from the Netherlands found a pooled OR for psychosis of 2.1.[5] Several studies from diverse cultures have confirmed the elevated risk of psychosis and schizophreniform spectrum disorders[5–17] following high levels of cannabis use, particularly when cannabis consumption has commenced at a young age.[14,18] Cannabis use has been found to exacerbate pre-existing psychotic disorders.[5,15]

There is a similar and increasing literature around both bipolar disorder[19–21] and depression.[22–25] Although the psychoneurological effects of cannabis are usually stereotypically characterized as a depressant, both its use and the

withdrawal state are accompanied frequently by psychomotor agitation, which has been implicated causally with interpersonal violence.[26] Interestingly, in a series of forensic examinations of suicide, cannabis use was associated with the most violent means of death, particularly severe motor vehicle accidents.[27]

In 1972 Nahas[28] drew attention to the devastating effects of cannabis in Egypt as quantified by carefully prepared and formally psychologically documented surveys from that country. Higher levels of anxiety, impaired memory, poor concentration, impaired learning ability, and psychomotor impairment including reduced quality and quantity of work were seen in these users. In addition, a common dependency syndrome was observed, which made exit from the dependent state both difficult and rare.[28] Geographical microclustering of cannabis use has been demonstrated, which has the effect of establishing local socially normative use patterns.[29] Both in northern Africa and in New Zealand communities exist where cannabis use is common, and intellectual impairment, psychomotor slowing, poor work capacity, and severe social deprivation are entrenched.[30–32]

Lee and colleagues[33,34] have published several descriptions of heavy, problematic, and refractory cannabis use in remote indigenous communities of the Northern Territory and across northern Australia more generally. A substantial proportion (31–62%) of users' median weekly income and up to 10% of the total community income were spent on cannabis. Ninety percent smoked cannabis heavily (more than six cones daily) and were not able to cease use. Severe mental illness was commonplace, as were depression, suicidal ideation, auditory hallucinations, and imprisonment. There was less participation in employment, education, or training. Community violence escalated when cannabis supplies from distant centers were interrupted. Most users had not "matured out" of dependent cannabis use even 5 years later. It is particularly noteworthy that these same communities had largely successfully defeated alcohol abuse, primarily by tight restrictive policies aimed at severely curtailing alcohol supply. The authors concluded that cannabis was both an important cause and a consequence of ongoing severe social disadvantage and deprivation.

Respiratory effects

Both the Thoracic Society of Australia and New Zealand[35] and the British Lung Foundation[4] have issued major statements in recent years acknowledging the known deleterious effects of cannabis on the lungs. Cannabis is smoked differently from tobacco. Users commonly inhale deeply to a maximal breath and then retain the smoke in the lungs, which generates higher pressures during breath holding and on expiration.[35–37]

Cannabis smoke stimulates inflammation in the airways so that its long-term use is associated with the development of chronic bronchitis. A New Zealand study[38] demonstrated large airway inflammation and obstruction and hyperinflation but was seldom associated with macroscopic emphysema, with a dose equivalence of one cannabis joint to 2.5–5 cigarettes. These findings were supported by an accompanying editorial[39] and press release.[40] Decreased lung density has also been noted with increased lung volumes, signs of destruction of lung tissue, cyst formation, and emphysematous change with secondary pneumothorax because of bullous rupture.[41–43]

Cannabis smoke is known to contain several potent carcinogens including anthrocyclines, nitrosamines, polycyclic aromatic hydrocarbons, terpenes, and vinyl chloride.[4,35,44–47] As a consequence, cannabis use is associated with cancer of the lung.[30–32]

Cardiovascular effects

Cannabis exposure is known to cause phasic systemic vasodilation, mild hypertension, and tachycardia often associated with postural hypotension, and a reduced duration and increased heart rate response to exercise.[48–51] Some but not all these effects are mediated by the autonomic nervous system. Tolerance to many of these acute effects with time appears. In most young healthy patients such changes are clearly generally well tolerated,[48,50] but this is not universally true and several exceptions cited below are of considerable pathophysiological interest. Such generic reassurances cannot be provided to patients with pre-existing coronary or atherosclerotic disease.[50,52]

Several case reports associate cannabis use with infarctions of kidney,[53] brain,[54–60] heart[61–65], and digits,[66,67] and of priapism in humans with sickle cell disease.[68] An association between cannabis use and pedal gangrene has also been described in a 27-year old.[67] Some 50 cases of cannabis arteritis have been reported in the literature.[67] Cannabis use can acutely trigger myocardial infarction,[69] which has also been documented in a 25-year-old man with no other cardiac risk factors and normal coronary arteries at angiography.[62] Coronary no-flow phenomenon has been observed after acute cannabis use.[57] Cardiomyopathy has also been reported in a young man.[70] One large study of 1,913 adults conducted in the United States found both a significant association between myocardial infarction and cannabis use, and a dose–response effect, with adjusted hazard ratios of 2.5 and 4.2 for less than weekly and weekly use, respectively.[52]

Reversible cerebral vasospasm[71] as well as slowing and flow reversal in the middle cerebral artery[72] has also been documented and attributed to cannabis use. On the contrary, the same authors also reported an increase of blood flow in the cerebral frontal lobes.[73] Several case reports have described a cannabis-associated inflammatory angiitis,[61,74,75] which can be so severe as to mimic Buerger's disease (thromboangiitis obliterans or "disappearing artery syndrome").

In a study in 19 patients, alterations of the cardiac pressure cycle were found with a highly significant prolongation of

both electromechanical systole (by 17 ms) and left ventricular ejection time, in the context of a reduced pre-ejection period (systolic pressure upstroke), a tachycardia of 132 bpm, and unchanged brachial systemic pressures.[76] These more abrupt cardiac pressure changes imply increased cardiac work in the context of a prolonged QTc interval and reduced opportunity for myocardial perfusion (the "Buckberg index"), which is limited to the diastolic phase of the cardiac cycle.[77,78] Hence, this scenario combines both an adverse mechanical and electrical profile in the context of reduced coronary perfusion and an altered endothelial, coagulation, angiogenic,[79] and inflammatory milieu.

Cannabis has also been linked with elevated rates of cardiac arrhythmias in several case reports.[80] Generally, these are supraventricular and trivial,[81–83] but well-documented cases of lethal ventricular arrythmias do exist[57] and one such was recently reported from a man who survived and whose episode was recorded on his implantable defibrillator.[84]

Elevated plasma concentrations of the endocannabinoid 2-arachidonylglycerol status have been associated in an Italian study of 62 patients with an exacerbation of the cardiovascular risk profile with worse concentrations of total cholesterol, high-density lipoprotein cholesterol, body mass index, intra-abdominal obesity, and adiponectin.[85]

Bones

Cannabinoid receptors are present on bones. Physiological studies have shown that cannabinoids have an important role in the regulation of bone density[86]; blockade or modulation of CB1 cannabinoid activity protects from bone loss.[87] Heavy cannabis use in humans is associated with substantial bone loss.[54] Interestingly, CB2 stimulation appears to be causally associated with stimulation of both endosteal and periosteal bone growth by mechanisms involving inhibition of osteoclastogenesis, osteoblast stimulation, and favorable modulation of the RANKL (receptor activated NF-kB ligand) – osteoprotegerin system, matrix metalloproteinase inhibition, inhibition of adrenergic sympathetic signaling to bone, and inhibition of bone marrow monocyte-directed hemopoiesis[88–99] (the bone marrow-derived monocyte is believed to be the immediate precursor of the multinucleate osteoclast). Cannabis use is also known to be associated with profound loss of alveolar bone from the jaws,[100–103] often in the context of severe erosive periodontitis.[104,105]

Maternal cannabis use and fetal development

Not all the studies in this field have returned results confirming a link between maternal cannabis use and later deleterious changes in the offspring.[106] However, maternal cannabis use has been shown to reduce body weight at birth.[107] Many birth abnormalities were identified in a large Hawaiian sample over 6 years. Of 54 birth defects studies, 39% were noted in cannabis-exposed babies.[108] Many of these defects were major and involved the brain (encephalocoele, hydrocephaly, microcephaly, anophthalmia/microphthalmia), cardiovasculature (tetralogy of Fallot, ventricular septal defect, atrial septal defect, and right and left heart atretic syndromes), gastrointestinal system (pyloric stenosis, intestinal atresias and stenoses, and gastroschisis), and limbs (polydatyly, syndactyly, and reduction deformities of the upper and lower limbs); oro-facial clefts were also reported. One large American study found a somewhat elevated risk of anencephaly (OR = 1.7, CI = 0.9–3.4).[109] The association with gastroschisis has been confirmed by other investigators.[110]

The dominant theme to emerge from studies of perinatal exposure is that of impaired executive cortical functioning reflected in reduced attention and analytical behavior and visuospatial analysis and hypothesis testing;[111] parent-rated behavioral problems, language comprehension, and distractibility[112]; and inattention, hyperactivity, impulsivity, and substance use disorders.[113] Indeed, close agreement between human and animal studies of perinatal exposure has been shown.[113] Such changes emerge from as early as the first weeks of life and persist in children in longitudinal studies into the school ages. Importantly, cannabis seemed to potentiate other causes of disadvantage such as smoking, low protein nutrition, and early age of first maternal pregnancy, and child sexual abuse implying that cannabis use by disadvantaged groups compounds other functional deficits.[112,114] Lower school age child IQ was also noted in another large longitudinal follow-up study.[115] It is important to note, however, that such reductions in intellectual performance, executive function, memory, sustained attention, and verbal ability are also seen in samples of low-risk upper middle class children of school age.[116] Equally, it is important to note that careful studies controlling for such pertinent confounding psychosocial variables find strong persistent effects of cannabis exposure.[117]

Maternal prenatal cannabis use has been found to predict later cannabis use during adolescence both as age of onset and frequency of use, a relationship that persisted after adjustment for many other risk factors.[118]

Genotoxicity, mutagenicity, and oncogenesis

Cannabis use is associated with cancer of the lung[30–32] (OR = 2.3, 4.1, and 5.7), head and neck[44,119] (OR = 4.1, 2.6, and 3.1), larynx (OR = 1.7 and 2.3), prostate (OR = 3.1)[120], cervix (OR = 1.4),[120] testes (OR = 1.7),[121] and brain (OR = 2.8).[122] Cannabis has also been linked with tumors of the urothelial tracts.[123–125] Several authors have also found evidence of a dose–response relationship, either with dose, duration, or the combined lifetime total duration of cannabis consumption.[31,32,44,121] A report from Tunisia showed an eightfold rise in lung cancer risk, but initially did not demonstrate a dose–response relationship; tobacco is frequently mixed with cannabis in that country.[30] A later expanded revision of these

data from the same area in northern Africa was able to demonstrate a relationship with the total dose duration of cannabis exposure.[121]

Of great concern is the evidence of inheritable tumors such as childhood neuroblastoma (OR = 1.8, 4.7),[126] rhabdomyosarcoma,[45] and leukemia (OR = 11), particularly non-lymphoblastic leukemia,[127] in cannabis-exposed pregnant mothers.

It should be noted that not all epidemiological studies have been positive,[128] with some studies failing to demonstrate such a link, possibly because cannabis exposure in the study population was limited.[45] For example, a study conducted in Los Angeles did not observe an association with lung cancer, which the authors attributed to the relatively few cases exposed to significant amounts of cannabis.[129] Similarly, a New Zealand study of head and neck cancer was recently found to be negative, a finding attributed by the authors to uncontrolled confounding and inadequate sampling of the New Zealand population.[128]

Cannabinoids liberate radical species both by receptor binding (nitrogen-centered species[130–132]) and by uncoupling mitochondrial oxidative phosphorylation via stimulation of the matrix protein uncoupling protein 2.[133,134] Nitric oxide generation at the cell membrane occurs via both CB1[130] and non-CB1/2 receptor-mediated[131] mechanisms. Indeed, it has been shown that oxidation[135] of the DNA base guanosine to oxo-guanosine is a *normal* part of endocannabinoid signaling. This potentially very serious and inherently mutagenic defect is overcome during normal signaling by activation of the base excision DNA repair pathway within cells. The capacity of such DNA repair pathways is well known to be limited, so the possibility exists that with pathological overstimulation, as might occur during substantial cannabis use, the resulting major genetic defects would become fixed and eventually translated into altered mRNAs, micro-RNAs, genetic expression, and protein sequences.

Cannabis is known to stimulate the oncogenic MAP kinase pathway,[136] which is potently oncogenic, and to be involved particularly in the genesis of non-lymphocytic leukemias.[137] A strongly positive association between cannabis consumption and this tumor has been found.[127] Cannabinoids block topoisomerase II, an enzyme that untwists and makes accessible the dominant coding DNA strand and plays a vital role in DNA repair, meiotic chromosomal replication, mRNA transcription, and DNA hypermutation in prelymphocytes.[138,139] Cannabinoids also impair RAD-51, another enzyme involved in the accurate repair of DNA breaks. Mice chromosomal studies imply that cannabinoids also interfere with the normal maintenance of the ends of chromosomes.[140]

Chromosomal ends or telomeres are made up of many copies of a 6-nt repeat structure (T–T–A–G–G–G) and are protected by a complex of proteins collectively called "shelterin."[141,142] Telomeres are maintained by an enzyme called telomerase, which is absent from most cells but is present in stem cells, gonads (testes and ovaries), and cancers.[143,144] The length of the telomeres has been shown recently to be proportional to the age, the health, and the reproductive fitness of stem cells in a variety of *in vivo* tissue niches.[145] It is of concern that the chromosomal damage was shown in mice not only for tetrahydrocannabinol but also for cannabidiol (and cannabinol),[140] a non-psychoactive cannabinoid that has been added to commercial cannabis sprays supposedly to confer safety![146]

The involvement of cannabinoids with at least three enzymes involved in DNA repair raises questions about their potential genetic toxicity, a subject that remains largely uninvestigated. Gonadal stem cell and genetic toxicity have implications for cell growth inhibition, fetal malformations, and inheritable defects including cancers. Indeed, evidence of cannabis-induced altered DNA expression,[147] a higher incidence of 21 birth defects,[107] and an 11-fold rise in inherited leukemias in the offspring of cannabis users[127] have been documented. Other studies have produced similar findings,[148] including tissues of the germ line.[149] The presence of such major chromosomal abnormalities in sperm cells but not in circulating white blood cells[149] is consistent with the inhibition by cannabinoids of telomerase, which is well known to be present in stem cells, germ cells, and cancer cells but not in the nuclei of normal tissue.[150–152]

Conclusions

In summary, now there is evidence for the implication of cannabis in various psychiatric, respiratory, cardiovascular, and bone pathologies.[153,154] The reports of social disruption, disorganization, and deprivation consequent on widespread heavy cannabis use from a number of communities around the world are of substantial concern. The features associated with chronic cannabis use imply that a clear public health cautionary message is warranted along the lines employed for other environmental intoxicants such as tobacco, which should be targeted strategically to young and otherwise vulnerable populations.

Declaration of interest: There is no conflict of interest to declare.

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