

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 arrhythmias. 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.

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

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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 Nahas²⁸ 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 Zealand³⁵ and the British Lung Foundation⁴ 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 study³⁸ 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 editorial³⁹ 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 heart⁶¹⁻⁶⁵, 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 vasospasm⁷¹ as well as slowing and flow reversal in the middle cerebral artery⁷² 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 arrhythmias do exist⁵⁷ 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 density⁸⁶; 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- κ B 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), cardiovascularity (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 (polydactyly, 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 distractibility¹¹²; 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 CB1¹³⁰ and non-CB1/2 receptor-mediated¹³¹ mechanisms. Indeed, it has been shown that oxidation¹³⁵ 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 cannabitol),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 users¹²⁷ 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 cells¹⁴⁹ 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.

References

1. United Nations Office of Drugs and Crime. World Drug Report 2008. Vienna: UN ODC; 2008.
2. Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* 2007; 370:319–328.
3. Nordentoft M, Hjorthoj C. Cannabis use and risk of psychosis in later life. *Lancet* 2007; 370:293–294.
4. British Lung Foundation. Cannabis: a smoking gun. http://www.lunguk.org/Resources/British%20Lung%Foundation/Migrated%20Resources/Documents/A/A_Smoking_Gun.pdf. Accessed 20 June 2009. London; 2005.
5. Henquet C, Murray R, Linszen D, van Os J. The environment and schizophrenia: the role of cannabis use. *Schizophr Bull* 2005; 31:608–612.

6. Konings M, Henquet C, Maharajh HD, Hutchinson G, Van Os J. Early exposure to cannabis and risk for psychosis in young adolescents in Trinidad. *Acta Psychiatr Scand* 2008; 118:209–213.
7. Cohen M, Solowij N, Carr V. Cannabis, cannabinoids and schizophrenia: integration of the evidence. *Aust NZ J Psychiatry* 2008; 42:357–368.
8. Coulston CM, Perdices M, Tennant CC. The neuropsychology of cannabis and other substance use in schizophrenia: review of the literature and critical evaluation of methodological issues. *Aust NZ J Psychiatry* 2007; 41:869–884.
9. Coulston CM, Perdices M, Tennant CC. The neuropsychological correlates of cannabis use in schizophrenia: lifetime abuse/dependence, frequency of use, and recency of use. *Schizophr Res* 2007; 96:169–184.
10. Degenhardt L, Tennant C, Gilmour S. The temporal dynamics of relationships between cannabis, psychosis and depression among young adults with psychotic disorders: findings from a 10-month prospective study. *Psychol Med* 2007; 37:927–934.
11. Esterberg ML, Goulding SM, McClure-Tone EB, Compton MT. Schizotypy and nicotine, alcohol, and cannabis use in a non-psychiatric sample. *Addict Behav* 2008; 34:374–379.
12. Freedman R. Cannabis, inhibitory neurons, and the progressive course of schizophrenia. *Am J Psychiatry* 2008; 165:416–419.
13. Hashimoto T, Bazmi HH, Mirmics K, Wu Q, Sampson AR, Lewis DA. Conserved regional patterns of GABA-related transcript expression in the neocortex of subjects with schizophrenia. *Am J Psychiatry* 2008; 165:479–489.
14. Henquet C, Van Os J. The coherence of the evidence linking cannabis with psychosis. *Psychol Med* 2008; 38:461–462; author reply 2–4.
15. Hides L, Dawe S, Kavanagh DJ, Young RM. Psychotic symptom and cannabis relapse in recent-onset psychosis. Prospective study. *Br J Psychiatry* 2006; 189:137–143.
16. Linszen D, van Amelsvoort T. Cannabis and psychosis: an update on course and biological plausible mechanisms. *Curr Opin Psychiatry* 2007; 20:116–120.
17. Luzi S, Morrison PD, Powell J, di Forti M, Murray RM. What is the mechanism whereby cannabis use increases risk of psychosis? *Neurotox Res* 2008; 14:105–112.
18. Fergusson DM, Horwood LJ. Early onset cannabis use and psychosocial adjustment in young adults. *Addiction* 1997; 92:279–296.
19. Jarvis K, DelBello MP, Mills N, Elman I, Strakowski SM, Adler CM. Neuroanatomic comparison of bipolar adolescents with and without cannabis use disorders. *J Child Adolesc Psychopharmacol* 2008; 18:557–563.
20. Merikangas KR, Herrell R, Swendsen J, Rossler W, Ajdacic-Gross V, Angst J. Specificity of bipolar spectrum conditions in the comorbidity of mood and substance use disorders: results from the Zurich cohort study. *Arch Gen Psychiatry* 2008; 65:47–52.
21. van Rossum I, Boomsma M, Tenback D, Reed C, van Os J. Does cannabis use affect treatment outcome in bipolar disorder? A longitudinal analysis. *T J Nerv Ment Dis* 2009; 197:35–40.
22. Wichers M, Schrijvers D, Geschwind N, Jacobs N, Myin-Germeys I, Thiery E, Derom C, Sabbe B, Peeters F, Delespaul P, Van Os, J. Mechanisms of gene-environment interactions in depression: evidence that genes potentiate multiple sources of adversity. *Psychol Med* 2008; 1–10.
23. Bovasso GB. Cannabis abuse as a risk factor for depressive symptoms. *Am J Psychiatry* 2001; 158:2033–2037.
24. Lee KS, Clough AR, Jaragba MJ, Conigrave KM, Patton GC. Heavy cannabis use and depressive symptoms in three Aboriginal communities in Arnhem Land, Northern Territory. *Med J Aust* 2008; 188:605–608.
25. Konings M, Maharajh HD. Cannabis use and mood disorders: patterns of clinical presentations among adolescents in a developing country. *Int J Adolesc Med Health* 2006; 18:221–233.
26. Moore TM, Stuart GL, Meehan JC, Rhatigan DL, Hellmuth JC, Keen SM. Drug abuse and aggression between intimate partners: a meta-analytic review. *Clin Psychol Rev* 2008; 28:247–274.
27. Eksborg S, Rajs J. Causes and manners of death among users of heroin, methadone, amphetamine, and cannabis in relation to postmortem chemical tests for illegal drugs. *Subst Use Misuse* 2008; 43:1326–1339.
28. Nahas GG. Effects of hashish consumption in Egypt. *N Engl J Med* 1972; 287:310.
29. Wells JE, Degenhardt L, Bohnert KM, Anthony JC, Scott KM. Geographical clustering of cannabis use: results from the New Zealand Mental Health Survey 2003–2004. *Drug Alcohol Depend* 2009; 99:309–316.
30. Voirin N, Berthiller J, Benhaim-Luzon V, Boniol M, Straif K, Ayoub WB, Ayed FB, Sasco AJ. Risk of lung cancer and past use of cannabis in Tunisia. *J Thorac Oncol* 2006; 1:577–579.
31. Berthiller J, Straif K, Boniol M, Voirin N, Benhaim-Luzon V, Ayoub WB, Dari I, Laouamri S, Hamdi-Cherif M, Bartal M, Ayed FB, Sasco AJ. Cannabis smoking and risk of lung cancer in men: a pooled analysis of three studies in Maghreb. *J Thorac Oncol* 2008; 3:1398–1403.
32. Aldington S, Harwood M, Cox B, Weatherall M, Beckert L, Hansell A, Pritchard A, Robinson G, Beasley R, Cannabis and Respiratory Disease Research Group. Cannabis use and risk of lung cancer: a case-control study. *Eur Respir J* 2008; 31:280–286.
33. Lee KS, Conigrave KM, Patton GC, Clough AR. Cannabis use in remote Indigenous communities in Australia: endemic yet neglected. *Med J Aust* 2009; 190:228–229.
34. Lee KS, Clough AR, Conigrave KM. High levels of cannabis use persist in Aboriginal communities in Arnhem Land, Northern Territory. *Med J Aust* 2007; 187:594–595.
35. Taylor DR, Hall W. Respiratory health effects of cannabis: position statement of the Thoracic Society of Australia and New Zealand. *Int Med J* 2003; 33:310–313.
36. British Lung Foundation. Cannabis: A Smoking Gun. London: British Lung Foundation; 2005.
37. Tashkin DP. Smoked marijuana as a cause of lung injury. *Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace/ Fondazione clinica del lavoro, IRCCS [and] Istituto di clinica fisiologica e malattie apparato respiratorio, Università di Napoli, Secondo ateneo* 2005; 63:93–100.
38. Aldington S, Williams M, Nowitz M, Weatherall M, Pritchard A, McNaughton A, Robinson G, Beasley R. Effects of cannabis on pulmonary structure, function and symptoms. *Thorax* 2007; 62:1058–1063.
39. Lange P. Cannabis and the lung. *Thorax* 2007; 62:1036–1037.
40. Research confirms cannabis poses a serious health risk to the lungs. British Lung Foundation, 2007. <http://www.lunguk.org/media-and-campaigning/media-centre/archive-press-releases-and-statements/july2007/Researchconfirmscannabisposesaserioushealthrisktothelungs.htm>. Accessed 20 June 2009.
41. Johnson MK, Smith RP, Morrison D, Laszlo G, White RJ. Large lung bullae in marijuana smokers. *Thorax* 2000; 55:340–342.
42. Thompson CS, White RJ. Lung bullae and marijuana. *Thorax* 2002; 57:563.
43. Reece AS. Cannabis as a cause of giant cystic lung disease. *Q J Medicine* 2008; 101:503.
44. Zhang ZF, Morgenstern H, Spitz MR, Tashkin DP, Yu GP, Marshall JR, Hsu TC, Schantz SP. Marijuana use and increased risk of squamous cell carcinoma of the head and neck. *Cancer Epidemiol Biomarkers Prev* 1999; 8:1071–1078.
45. Hashibe M, Straif K, Tashkin DP, Morgenstern H, Greenland S, Zhang ZF. Epidemiologic review of marijuana use and cancer risk. *Alcohol (Fayetteville, NY)* 2005; 35:265–275.
46. Roth MD, Marques-Magallanes JA, Yuan M, Sun W, Tashkin DP, Hankinson O. Induction and regulation of the carcinogen-metabolizing enzyme CYP1A1 by marijuana smoke and delta (9)-tetrahydrocannabinol. *Am J Respir Cell Mol Biol* 2001; 24:339–344.
47. Sarafian TA, Magallanes JA, Shau H, Tashkin D, Roth MD. Oxidative stress produced by marijuana smoke. An adverse effect enhanced by cannabinoids. *Am J Respir Cell Mol Biol* 1999; 20:1286–1293.
48. Jones RT. Cardiovascular system effects of marijuana. *J Clin Pharmacol* 2002; 42:58S–63S.
49. Varga K, Lake KD, Huangfu D, Guyenet PG, Kunos G. Mechanism of the hypotensive action of anandamide in anesthetized rats. *Hypertension* 1996; 28:682–686.

50. Sidney S. Cardiovascular consequences of marijuana use. *J Clin Pharmacol* 2002; 42:64S–70S.
51. Strougo A, Zuurman L, Roy C, Pinquier JL, van Gerven JMA, Cohen AF, Schoemaker RC. Modelling of the concentration – effect relationship of THC on central nervous system parameters and heart rate – insight into its mechanisms of action and a tool for clinical research and development of cannabinoids. *J Psychopharmacol (Oxford)* 2008; 22:717–726.
52. Mukamal KJ, Maclure M, Muller JE, Mittleman MA. An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. *Am Heart J* 2008; 155:465–470.
53. Lambrecht GL, Malbrain ML, Coremans P, Verbist L, Verhaegen H. Acute renal infarction and heavy marijuana smoking. *Nephron* 1995; 70:494–496.
54. Reece AS. Severe multisystem dysfunction in a case of high level exposure to smoked cannabis. *BMJ Case Reports* 2009; in press.
55. Zachariah SB. Stroke after heavy marijuana smoking. *Stroke* 1991; 22:406–409.
56. Mateo I, Pinedo A, Gomez-Beldarrain M, Basterretxea JM, Garcia-Monco JC. Recurrent stroke associated with cannabis use. *J Neurol Neurosurg Psychiatry* 2005; 76:435–437.
57. Russmann S, Winkler A, Lovblad KO, Stanga Z, Bassetti C. Lethal ischemic stroke after cisplatin-based chemotherapy for testicular carcinoma and cannabis inhalation. *Eur Neurol* 2002; 48:178–180.
58. Moussouttas M. Cannabis use and cerebrovascular disease. *Neurologist* 2004; 10:47–53.
59. Termote B, Verswijvel G, Gelin G, Palmers Y. Cannabis-induced brain ischemia. *JBR-BTR* 2007; 90:218–219.
60. Renard D, Gaillard N. Brain haemorrhage and cerebral vasospasm associated with chronic use of cannabis and buprenorphine. *Cerebrovasc Dis* 2008; 25:282–283.
61. Citron BP. Angiitis in drug abusers. *N Engl J Med* 1971; 284:111.
62. Charles R, Holt S, Kirkham N. Myocardial infarction and marijuana. *Clin Toxicol* 1979; 14:433–438.
63. Kotsalou I, Georgoulis P, Karydas I, Fourlis S, Sioka C, Zoumboulidis A, Demakopoulos N. A rare case of myocardial infarction and ischemia in a cannabis-addicted patient. *Clin Nucl Med* 2007; 32:130–131.
64. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. *Circulation* 2001; 103:2805–2809.
65. Montisci M, Thiene G, Ferrara SD, Basso C. Cannabis and cocaine: a lethal cocktail triggering coronary sudden death. *Cardiovasc Pathol* 2008; 17:344–3446.
66. Noel B, Ruf I, Panizzon RG. Cannabis arteritis. *J Am Acad Dermatol* 2008; 58:S65–S67.
67. Peyrot I, Garsaud AM, Saint-Cyr I, Quitman O, Sanchez B, Quist D. Cannabis arteritis: a new case report and a review of literature. *J Eur Acad Dermatol Venereol* 2007; 21:388–391.
68. Birnbaum BF, Pinzone JJ. Sickle cell trait and priapism: a case report and review of the literature. *Cases J* 2008; 1:429.
69. Cappelli F, Lazzeri C, Gensini GF, Valente S. Cannabis: a trigger for acute myocardial infarction? A case report. *J Cardiovasc Med* 2008; 9:725–728.
70. Ting JY. Reversible cardiomyopathy associated with acute inhaled marijuana use in a young adult. *Clin Toxicol (Phila)* 2007; 45:432–434.
71. Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser MG. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. *Brain* 2007; 130:3091–3101.
72. Mathew RJ, Wilson WH, Humphreys DF, Lowe JV, Wiethe KE. Middle cerebral artery velocity during upright posture after marijuana smoking. *Acta Psychiatr Scand* 1992; 86:173–178.
73. Mathew RJ, Wilson WH, Humphreys DF, Lowe JV, Wiethe KE. Regional cerebral blood flow after marijuana smoking. *J Cereb Blood Flow Metab* 1992; 12:750–758.
74. Disdier P, Granel B, Serratrice J, Constans J, Michon-Pasturel U, Hachulla E, Conri C, Devulder B, Swiader L, Piquet P, Branchereau A, Jouglard J, Moulin G, Weiller PJ. Cannabis arteritis revisited – ten new case reports. *Angiology* 2001; 52:1–5.
75. Ducasse E, Chevalier J, Dasnoy D, Speziale F, Fiorani P, Puppinc P. Popliteal artery entrapment associated with cannabis arteritis. *Eur J Vasc Endovasc Surg* 2004; 27:327–332.
76. Kanakis C Jr, Pouget JM, Rosen KM. The effects of delta-9-tetrahydrocannabinol (cannabis) on cardiac performance with and without beta blockade. *Circulation* 1976; 53:703–707.
77. Olinger GN, Mulder DG, Maloney JV Jr, Buckberg GD. Phasic coronary flow: intraoperative evaluation of flow distribution, myocardial function, and reactive hyperemic response. *Ann Thorac Surg* 1976; 21:397–404.
78. Olinger GN, Po J, Maloney JV Jr, Mulder DG, Buckberg GD. Myocardial revascularization in high-risk coronary patients. *West J Med* 1976; 124:265–271.
79. Kogan NM, Blazquez C, Alvarez L, Gallily R, Schlesinger M, Guzmán M, Mechoulam R. A cannabinoid quinone inhibits angiogenesis by targeting vascular endothelial cells. *Mol Pharmacol* 2006; 70:51–59.
80. Korantzopoulos P, Liu T, Papaioannides D, Li G, Goudevenos JA. Atrial fibrillation and marijuana smoking. *Int J Clin Pract* 2008; 62:308–313.
81. Charbonney E, Sztajzel JM, Poletti PA, Rutschmann O. Paroxysmal atrial fibrillation after recreational marijuana smoking: another ‘holiday heart’? *Swiss Med Wkly* 2005; 135:412–414.
82. Kosior DA, Filipiak KJ, Stolarz P, Opolski G. Paroxysmal atrial fibrillation in a young female patient following marijuana intoxication – a case report of possible association. *Med Sci Monit* 2000; 6:386–389.
83. Lehavi A, Shay M, Gilony C, Even L. Marijuana smoking and paroxysmal atrial fibrillation. *Harefuah* 2005; 144:2–3, 72.
84. Baranchuk A, Johri AM, Simpson CS, Methot M, Redfearn DP. Ventricular fibrillation triggered by marijuana use in a patient with ischemic cardiomyopathy: a case report. *Cases J* 2008; 1:373.
85. Cote M, Matias I, Lemieux I, Petrosino S, Almérás N, Després J-P, Di Marzo V. Circulating endocannabinoid levels, abdominal adiposity and related cardiometabolic risk factors in obese men. *Int J Obes (2005)* 2007; 31:692–699.
86. Idris AI, van’t Hof RJ, Greig IR, Ridge SA, Baker D, Ross RA, Ralston SH. Regulation of bone mass, bone loss and osteoclast activity by cannabinoid receptors. *Nat Med* 2005; 11(7):774–779.
87. George KL, Saltman LH, Stein GS, Lian JB, Zurier RB. Ajulemic acid, a nonpsychoactive cannabinoid acid, suppresses osteoclastogenesis in mononuclear precursor cells and induces apoptosis in mature osteoclast-like cells. *J Cell Physiol* 2008; 214(3):714–720.
88. Bab I, Ofek O, Tam J, Rehnelt J, Zimmer A. Endocannabinoids and the regulation of bone metabolism. *J Neuroendocrinol* 2008; 20(Suppl. 1):69–74.
89. Bab I, Zimmer A. Cannabinoid receptors and the regulation of bone mass. *Br J Pharmacol* 2008; 153:182–188.
90. Bab IA. Regulation of skeletal remodeling by the endocannabinoid system. *Ann N Y Acad Sci* 2007; 1116:414–422.
91. Buckley NE. The peripheral cannabinoid receptor knockout mice: an update. *Br J Pharmacol* 2008; 153:309–318.
92. George KL, Saltman LH, Stein GS, Lian JB, Zurier RB. Ajulemic acid, a nonpsychoactive cannabinoid acid, suppresses osteoclastogenesis in mononuclear precursor cells and induces apoptosis in mature osteoclast-like cells. *J Cell Physiol* 2008; 214:714–720.
93. Johnson DR, Stebulis JA, Rossetti RG, Burstein SH, Zurier RB. Suppression of fibroblast metalloproteinases by ajulemic acid, a nonpsychoactive cannabinoid acid. *J Cell Biochem* 2007; 100:184–190.
94. Lunn CA, Reich EP, Fine JS, Lavey B, Kozlowski JA, Hipkin RW, Lundell DJ, Bober L. Biology and therapeutic potential of cannabinoid CB2 receptor inverse agonists. *Br J Pharmacol* 2008; 153(2):226–239.
95. Napimoga MH, Benatti BB, Lima FO, Alves PM, Campos AC, Penadós-Santos DR, Severino FP, Cunha FQ, Guimaraes FS. Cannabidiol decreases bone resorption by inhibiting RANK/RANKL expression and pro-inflammatory cytokines during experimental periodontitis in rats. *Int Immunopharmacol* 2008; 9(2):216–222.

96. Tam J, Trembovler V, Di Marzo V, Petrosino S, Leo G, Alexandrovich A, Regev E, Casap N, Shteyer A, Ledent C, Karsak M, Zimmer A, Mechoulam R, Yirmiya R, Shohami E, Bab I. The cannabinoid CB1 receptor regulates bone formation by modulating adrenergic signaling. *FASEB J* 2008; 22:285–294.
97. Patinkin D, Milman G, Breuer A, Fride E, Mechoulam R. Endocannabinoids as positive or negative factors in hematopoietic cell migration and differentiation. *Eur J Pharmacol* 2008; 595:1–6.
98. Rossi F, Siniscalco D, Luongo L, De Petrocellis L, Bellini G, Petrosino S, Torella M, Santoro C, Nobili B, Perrotta S, Di Marzo V, Maione S. The endovanilloid/endocannabinoid system in human osteoclasts: possible involvement in bone formation and resorption. *Bone* 2008; 44:476–484.
99. Tam J, Ofek O, Fride E, Ledent C, Gabet Y, Müller R, Zimmer A, Mackie K, Mechoulam R, Shohami E, Bab I. Involvement of neuronal cannabinoid receptor CB1 in regulation of bone mass and bone remodeling. *Mol Pharmacol* 2006; 70:786–792.
100. Newman MG, Takei HH, Carranza FA. Carranza's Clinical Periodontology. London: W.B. Saunders & Co.; 2002.
101. Reece AS. Dentition of addiction in Queensland: poor dental status and major contributing drugs. *Aust Dent J* 2007; 52:144–149.
102. Versteeg PA, Slot DE, van der Velden U, van der Weijden GA. Effect of cannabis usage on the oral environment: a review. *Int J Dent Hyg* 2008; 6:315–320.
103. Nogueira-Filho Gda R, Cadide T, Rosa BT. Cannabis sativa smoke inhalation decreases bone filling around titanium implants: a histomorphometric study in rats. *Implant Dent* 2008; 17:461–470.
104. Hujoel PP. Destructive periodontal disease and tobacco and cannabis smoking. *JAMA* 2008; 299:574–575.
105. Thomson WM, Poulton R, Broadbent JM, Moffitt TE, Caspi A, Beck JD, Welch D, Hancox RJ. Cannabis smoking and periodontal disease among young adults. *JAMA* 2008; 299(5):525–531.
106. Fried PA. Postnatal consequences of maternal marijuana use. *NIDA Res Monogr* 1985; 59:61–72.
107. Davitian C, Uzan M, Tigaizina A, Ducarme G, Dauphin H, Poncelet C. Maternal cannabis use and intra-uterine growth restriction. *Gynecol Obstet Fertil* 2006; 34:632–637.
108. Forrester MB, Merz RD. Risk of selected birth defects with prenatal illicit drug use, Hawaii, 1986–2002. *J Toxicol Environ Health* 2007; 70:7–18.
109. van Gelder MM, Reefhuis J, Caton AR, Werler MM, Druschel CM, Roeleveld N. Maternal periconceptional illicit drug use and the risk of congenital malformations. *Epidemiology* 2009; 20:60–66.
110. Weinsheimer RL, Yanchar NL. Impact of maternal substance abuse and smoking on children with gastroschisis. *J Pediatr Surg* 2008; 43:879–883.
111. Fried PA, Smith AM. A literature review of the consequences of prenatal marijuana exposure. An emerging theme of a deficiency in aspects of executive function. *Neurotoxicol Teratol* 2001; 23:1–11.
112. O'Connell CM, Fried PA. Prenatal exposure to cannabis: a preliminary report of postnatal consequences in school-age children. *Neurotoxicol Teratol* 1991; 13:631–639.
113. Sundram S. Cannabis and neurodevelopment: implications for psychiatric disorders. *Hum Psychopharmacol* 2006; 21:245–254.
114. Nelson EC, Heath AC, Lynskey MT, Bucholz KK, Madden PA, Statham DJ, Martin NG. Childhood sexual abuse and risks for licit and illicit drug-related outcomes: a twin study. *Psychol Med* 2006; 36(10):1473–1483.
115. Goldschmidt L, Richardson GA, Willford J, Day NL. Prenatal marijuana exposure and intelligence test performance at age 6. *J Am Acad Child Adolesc Psychiatry* 2008; 47:254–263.
116. Fried PA. Prenatal exposure to marijuana and tobacco during infancy, early and middle childhood: effects and an attempt at synthesis. *Arch Toxicol Suppl* 1995; 17:233–260.
117. Fried PA. Postnatal consequences of maternal marijuana use. *NIDA Res Monogr* 1998; 59:61–72.
118. Day NL, Goldschmidt L, Thomas CA. Prenatal marijuana exposure contributes to the prediction of marijuana use at age 14. *Addiction* 2006; 101:1313–1322.
119. Hashibe M, Ford DE, Zhang ZF. Marijuana smoking and head and neck cancer. *J Clin Pharmacol* 2002; 42:103S–107S.
120. Sidney S, Quesenberry CP Jr, Friedman GD, Tekawa IS. Marijuana use and cancer incidence (California, United States). *Cancer Causes Control* 1997; 8:722–728.
121. Daling JR, Doody DR, Sun X, Trabert BL, Weiss NS, Chen C, Biggs ML, Starr JR, Dey SK, Schwartz SM. Association of marijuana use and the incidence of testicular germ cell tumors. *Cancer* 2009; 115:1215–1223.
122. Efrid JT, Friedman GD, Sidney S, Klatsky A, Habel LA, Udaltsova NV, Van den Eeden S, Nelson LM. The risk for malignant primary adult-onset glioma in a large, multiethnic, managed-care cohort: cigarette smoking and other lifestyle behaviors. *J neuro-oncol* 2004; 68(1):57–69.
123. Moiche Bokobo P, Atxa de la Presa MA, Cuesta Angulo J. Transitional cell carcinoma in a young heavy marijuana smoker. *Arch Esp Urol* 2001; 54:165–167.
124. Chacko JA, Heiner JG, Siu W, Macy M, Terris MK. Association between marijuana use and transitional cell carcinoma. *Urology* 2006; 67:100–104.
125. Nieder AM, Lipke MC, Madjar S. Transitional cell carcinoma associated with marijuana: case report and review of the literature. *Urology* 2006; 67:200.
126. Bluhm EC, Daniels J, Pollock BH, Olshan AF. Maternal use of recreational drugs and neuroblastoma in offspring: a report from the Children's Oncology Group (United States). *Cancer Causes Control* 2006; 17:663–669.
127. Robinson LL, Buckley JD, Daigle AE, Wells R, Benjamin D, Arthur DC, Hammond GD. Maternal drug use and risk of childhood nonlymphoblastic leukemia among offspring. An epidemiologic investigation implicating marijuana (a report from the Children's Cancer Study Group). *Cancer* 1989; 63:1904–1911.
128. Aldington S, Harwood M, Cox B, Weatherall M, Beckert L, Hansell A, Pritchard A, Robinson G, Beasley R; Cannabis and Respiratory Disease Research Group. Cannabis use and cancer of the head and neck: case-control study. *Otolaryngol Head Neck Surg* 2008; 138:374–380.
129. Hashibe M, Morgenstern H, Cui Y, Tashkin DP, Zhang ZF, Cozen W, Mack TM, Greenland S. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. *Cancer Epidemiol Biomarkers Prev* 2006; 15:1829–1834.
130. Jones JD, Carney ST, Vrana KE, Norford DC, Howlett AC. Cannabinoid receptor-mediated translocation of NO-sensitive guanylyl cyclase and production of cyclic GMP in neuronal cells. *Neuropharmacology* 2008; 54:23–30.
131. McCollum L, Howlett AC, Mukhopadhyay S. Anandamide-mediated CB1/CB2 cannabinoid receptor – independent nitric oxide production in rabbit aortic endothelial cells. *J Pharmacol Exp Ther* 2007; 321:930–937.
132. Howlett AC, Mukhopadhyay S, Norford DC. Endocannabinoids and reactive nitrogen and oxygen species in neuropathologies. *J Neuroimmune Pharmacol* 2006; 1:305–316.
133. Sarafian TA, Habib N, Oldham M, Seeram N, Lee R-P, Lin L, Tashkin DP, Roth MD. Inhaled marijuana smoke disrupts mitochondrial energetics in pulmonary epithelial cells in vivo. *Am J Physiol* 2006; 290:L1202–L1209.
134. Sarafian TA, Kouyoumjian S, Khoshaghidieh F, Tashkin DP, Roth MD. Delta 9-tetrahydrocannabinol disrupts mitochondrial function and cell energetics. *Am J Physiol* 2003; 284:L298–306.
135. Sarker KP, Obara S, Nakata M, Kitajima I, Maruyama I. Anandamide induces apoptosis of PC-12 cells: involvement of superoxide and caspase-3. *FEBS Lett* 2000; 472:39–44.
136. Todd F, McLean S, Krum H, Martin J, Copeland J. Cannabis. In: Hulse GWJ, Cape G, eds. *Management of Drug and Alcohol Problems*. Oxford: Oxford University Press; 2002:141–156.
137. Bentires-Alj M, Kontaridis MI, Neel BG. Stops along the RAS pathway in human genetic disease. *Nat Med* 2006; 12:283–285.
138. Kogan NM, Schlesinger M, Peters M, Marincheva G, Beeri R, Mechoulam R. A cannabinoid anticancer quinone, HU-331, is more potent and less cardiotoxic than doxorubicin: a comparative in vivo study. *J Pharmacol Exp Ther* 2007; 322:646–653.

139. Kogan NM, Schlesinger M, Priel E, Rabinowitz R, Berenshtein E, Chevion M, Mechoulam R. HU-331, a novel cannabinoid-based anti-cancer topoisomerase II inhibitor. *Mol Cancer Ther* 2007; 6:173-183.
140. Zimmerman AM, Zimmerman S, Raj AY. Effects of Cannabinoids on spermatogenesis in mice. In: Nahas GG, Sutin KM, Harvey DJ, Agurell S, eds. *Marihuana and Medicine*. Totowa, NJ: Humana Press; 1999:347-358.
141. de Lange T. Shelterin: the protein complex that shapes and safeguards human telomeres. *Genes Dev* 2005; 19:2100-2110.
142. Wang F, Podell ER, Zaug AJ, Yang Y, Baciú P, Cech TR, Lei M. The POT1-TPP1 telomere complex is a telomerase processivity factor. *Nature* 2007; 445:506-510.
143. Capper R, Britt-Compton B, Tankimanova M, Rowson J, Letsolo B, Man S, Houghton M, Baird DM. The nature of telomere fusion and a definition of the critical telomere length in human cells. *Genes Dev* 2007; 21:2495-2508.
144. Baird DM. Telomere dynamics in human cells. *Biochimie* 2008; 90:116-121.
145. Flores I, Canela A, Vera E, Tejera A, Cotsarelis G, Blasco MA. The longest telomeres: a general signature of adult stem cell compartments. *Genes Dev* 2008.
146. Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses* 2006; 66:234-246.
147. Sarafian T, Habib N, Mao JT, Tsu IH, Yamamoto ML, Hsu E, Tashkin DP, Roth MD. Gene expression changes in human small airway epithelial cells exposed to Delta9-tetrahydrocannabinol. *Toxicol Lett* 2005; 158:95-107.
148. Li JH, Lin LF. Genetic toxicology of abused drugs: a brief review. *Mutagenesis* 1998; 13:557-565.
149. Morishima A. Effects of cannabis and natural cannabinoids on chromosomes and ova. *NIDA Res Monogr* 1984; 44:25-45.
150. Canela A, Klatt P, Blasco MA. Telomere length analysis. *Methods Mol Biol* 2007; 371:45-72.
151. Samper E, Fernandez P, Eguia R, Martín-Rivera L, Bernad A, Blasco MA, Aracil M. Long-term repopulating ability of telomerase-deficient murine hematopoietic stem cells. *Blood* 2002; 99:2767-2775.
152. Franco S, Alsheimer M, Herrera E, Benavente R, Blasco MA. Mammalian meiotic telomeres: composition and ultrastructure in telomerase-deficient mice. *Eur J Cell Biol* 2002; 81:335-340.
153. Hall W. The adverse health effects of cannabis use: what are they, and what are their implications for policy? *Int J Drug Policy* 2009. epub ahead of print April 14, 2009.
154. Hall W, Lynskey M. The challenges in developing a rational cannabis policy. *Curr Opin Psychiatry* 2009; 22:258-262.