# WHO Expert Committee on Drug Dependence Pre-Review

.....

# Cannabis plant and cannabis resin

## Section 3: Toxicology

World Health Organization

*This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization*

## Acknowledgments

This report was prepared by the Secretariat of the Expert Committee on Drug Dependence (ECDD) within the Department of Essential Medicines and Health Products (EMP) of the World Health Organization (WHO), Geneva, Switzerland. The WHO staff involved in the production of this document, developed under the overall guidance of Mariângela Simão (Assistant Director General, Access to Medicines, Vaccines, and Pharmaceuticals), Suzanne Hill (Director, Essential Medicines and Health Products), Gilles Forte, (Secretary of the Expert Committee on Drug Dependence) were Dilkushi Poovendran (Technical Officer, WHO Essential Medicines and Health Products) and Wil De Zwart (Technical Officer, WHO Essential Medicines and Health Products).

This report was commissioned as a background document for a preliminary review for the 40th Expert Committee on Drug Dependence (ECDD). WHO would like to acknowledge the contributions of the following individuals who authored this report:

*Chemistry*
Giuseppe Cannazza (University of Modena and Reggio Emilia), Italy
Cinzia Citti (University of Modena and Reggio Emilia), Italy

*Pharmacology*
Jenny Wiley (RTI International), USA

*Epidemiology*
Vidhi Thakkar (Centre for Addiction and Mental Health), Canada
Omer S.M. Hasan (Centre for Addiction and Mental Health), Canada
Jakob Manthey (Institute for Clinical Psychology and Psychotherapy), Germany
Jurgen Rehm (Centre for Addiction and Mental Health), Canada
Astrid Otto (Centre for Addiction and Mental Health), Canada
Charlotte Probst (Centre for Addiction and Mental Health), Canada
Julian Sauer (Centre for Addiction and Mental Health), Canada

*Toxicology*
Jonathon Arnold (Pharmacology Expert Opinions), Australia

*Therapeutic Use*
Kevin P. Hill (Harvard Medical School), USA
Judith Spahr, (Thomas Jefferson University) USA
Charles V. Pollack. (Thomas Jefferson University) USA
Brock Bakewell (Thomas Jefferson University), USA

The Member State questionnaire report was prepared by Jurgen Rehm, Astrid Otto, and Jakob Manthey.
Technical editing was provided by Ann Morgan and Susan Kaplan.
Administrative support was provided by Afrah Vogel and Christine Berling.

# Contents

# 1. Toxicology

Most of the evidence for possible toxicity associated with cannabis use comes from observational, population-based studies, which are not as rigorous as the placebo-controlled, randomized–controlled trials (RCTs) used to evaluate therapeutic efficacy. The limitations of observational, population-based studies must be kept in mind when evaluating the possible toxicity of cannabis. Such studies are limited by multiple confounders and an inability to produce evidence from which to unequivocally infer causation. In addition, most of the available evidence of adverse effects involves cannabis use within an illegal, recreational context, where the cannabis that is self-administered is of unregulated quality and is administered by smoke inhalation. The increasing use of medicinal cannabis, particularly of regulated cannabis products that are consumed orally, will provide future opportunities to assess whether toxic effects of cannabis are minimized in the context of medicinal use.

## 1.1 Lethal dose

Cannabis is a relatively safe drug, which is not associated with acute fatal overdoses. A recent consensus report by the National Academies of Science, Engineering and Medicine (NASEM) concluded that there is insufficient evidence to support or refute associations between cannabis use and increased risk of all-cause mortality and overdose lethality in humans *(1)*. Lethality studies in animals show the doses needed to induce mortality are well beyond what could possibly be consumed by a human *(2)* - see Report 3 for specific data on lethal doses in animals for the main psychoactive constituent of cannabis, Δ9-tetrahydrocannabinol (Δ9-THC).

## 1.2 Effects on the cardiovascular system

Cannabis ingestion acutely promotes transient tachycardia and increased supine blood pressure in humans *(1, 3)* (also see Report 3 for the specific effects of purified Δ9-THC on cardiovascular function). With repeated exposure, tolerance develops to these effects, and, in some instances, repeated cannabis exposure lowers blood pressure and heart rate beneath the baseline *(4)*.

There is an uncertain association between cannabis use and heart attack but any association appears at best to be weak *(1).* A study of 3882 patients with acute myocardial infarction found that six of the patients had used cannabis 1 hour prior to the myocardial infarction event, resulting in a relative risk of 3.2 *(6).* However, a more recent larger scale study of 2 451 933 patients with acute myocardial infarction showed that recreational cannabis use caused only a small, yet significant increase in the risk of myocardial infarction (odds ratio (OR) = 1.03) *(7).* However, cannabis use was associated with a reduced

risk of atrial fibrillation in a recent population study (OR = 0.87) *(8).* Smoked cannabis may decrease the latency to exercise-induced angina in angina pectoris patients, most likely due to carbon monoxide in the smoke decreasing blood oxygenation and increasing cardiac ischaemia *(5).*

There is some limited population evidence to suggest that smoking cannabis increases the risk of ischaemic stroke, although it is hard to disentangle the contribution of tobacco smoking in this association *(1, 9).* When novel drug delivery modes other than smoking become more widely available (e.g. vaporization, sublingual or oral administration), associations between cannabis use and cardiovascular events may become less pronounced, or even absent. It is noteworthy that cannabis vapour contains less carbon monoxide than cannabis smoke. It has been reported that there was almost no carbon monoxide in cannabis vapour, whereas there was close to 5 ppm of carbon monoxide in cannabis smoke *(10).*

### 1.3 Effects on the respiratory system

Smoking has traditionally been the predominant route of cannabis administration as it enables efficient cannabinoid uptake by the lungs and rapid distribution to the CNS. Regular cannabis users may experience higher rates of chronic bronchitis (cough, increased sputum production, wheezy airways). This is due to the irritant effects of smoking on the airways, rather than cannabinoids per se damaging the airways *(1, 9).* Cannabis smoking acutely improves airway dynamics and forced expiratory capacity due to the bronchodilatory effects of Δ9-THC (also see Report 3 for the specific effects of purified Δ9-THC on respiratory function) *(11)*. The largest study to date on cannabis and respiratory function followed 5000 people over 20 years and reported a dose–response relationship: those using low levels of cannabis (3–5 joints per month) had improved respiratory function, whereas respiratory function in heavy users was impaired *(12).* Increasing use of vaporizers and other non-smoking modes of delivery is likely to reduce respiratory complications associated with cannabis as suggested by a recent study *(13).*

### 1.4 Effects on the immune system

There is a wealth of data from studies on cells and animals supporting the notion that cannabinoids have immunosuppressant and anti-inflammatory effects *(14).* However, there are only limited data from studies in humans, although these studies do support anti-inflammatory effects *(1).* For example, one study of 20 cannabis users showed that they had lower CD4+ T-cell concentrations of interleukin (IL)-17 (a pro-inflammatory cytokine) and an increase in IL-10 (an anti-inflammatory cytokine) relative to controls *(15).* Studies assessing the effects of cannabis in immunocompromised HIV patients have not demonstrated any clinically meaningful adverse effects on immune function and susceptibility to infection, although the data are limited *(1).*

Illicit and unregulated cannabis may sometimes be contaminated with various microbes including *Staphylococcus aureus*, *Escherichia coli* and Aspergillus. Aspergillus is a fungus that can cause pulmonary aspergillosis, which is potentially lethal to immunocompromised patients *(16).* Many cases of aspergillosis have been documented in cannabis users *(16, 17).* In countries such as the Netherlands, where there is a government-regulated cannabis supply, the cannabis flower products are treated (often with gamma irradiation) to remove microbial contamination to a pharmaceutically acceptable level, obviating this issue *(18).*

## 1.5 Mutagenicity and cancer

A wealth of preclinical literature demonstrates that cannabinoids reduce cancer cell proliferation, inducing apoptosis in these cells, as well as inhibiting cancer cell migration and angiogenesis in numerous cancer cell types *(19).* There is moderately strong epidemiological evidence that cannabis use does not increase the risk of cancers of the lung, head and neck (reviewed in *(1)*). A systematic review of six case–control studies on 2159 lung cancer patients and 2985 controls found a statistically nonsignificant trend towards cannabis smoking (> 1 joint per day) increasing lung cancer risk *(20).* A systematic review and meta-analysis of nine case–control studies comparing 5732 patients with head and neck cancer with 8199 controls found cannabis use did not increase the risk of head and neck cancers (including upper head and neck squamous cell carcinoma, and upper digestive tract, nasopharyngeal and oral cavity cancers) *(21).* Cannabis smoking has been reported to increase the risk of testicular cancer 2.5-fold *(22–24).* Any association between cannabis use and cancer reported in epidemiological studies is confounded by the act of smoking, as pyrolysed plant material typically contains carcinogens. Again, the development of safer cannabis drug delivery technologies may well mitigate cancer risks by avoiding smoke inhalation during delivery.

## 1.6 Fertility and teratogenesis

There is strong population-based evidence that illicit cannabis smoking during pregnancy reduces the birthweight of offspring *(1).* A recent systematic review and meta-analysis showed that maternal cannabis users gave birth to babies with birthweights on average 109 g lower than non-cannabis-using mothers *(25).* Whether the lower birthweights can be specifically attributed to cannabinoids is unclear. It might be explained by the ingestion of carbon monoxide in cannabis smoke *(1).* Animal studies confirm that maternal exposure to Δ9-THC reduces birthweights, albeit only at very high doses (see Report 3 on Δ9-THC). There is limited evidence that cannabis use increases pregnancy complications such as stillbirth, spontaneous abortion and fetal distress (reviewed in *(1)*). One study examining 13 859 cases and 6556

controls found an association between cannabis use (for 1 month prior to pregnancy through to the third trimester) and birth defects. There was a significantly increased risk of: anencephaly (OR = 2.2), oesophageal atresia (OR = 1.4), diaphragmatic hernia (OR = 1.4) and gastroschisis (OR = 1.2) *(26).* At present, there is insufficient evidence to determine whether in exposure to cannabis in utero is associated with impaired cognitive development or propensity to substance abuse, although some preclinical research with Δ9-THC suggests this *(1).*

## 1.7 Effects on cognitive function

Acute cannabis use impairs certain types of cognitive function and can interfere with attention, learning and memory (reviewed in *(1)*). A modest proportion of people who start using cannabis in adolescence and consume the drug for decades, show reductions in IQ (as much as an 8-point reduction in those who started as early as 13 years and had used it to the age of 38 years) *(29).* However, those who had commenced cannabis use in early adulthood and had been abstinent for a year did not display any reduction in IQ, suggesting a lack of residual effects.

A recent systematic review and meta-analysis of 69 cross-sectional studies with 2152 cannabis users and 6575 controls found only a small effect size for reduced cognitive functioning in frequent or heavy cannabis users *(30).* Given the small effect size, the study's authors questioned the clinical significance of such cognitive impairments for the majority of cannabis users. No relationship could be found between the age of onset of cannabis use and cognitive function. Furthermore, no association between cannabis use and reduced cognitive function could be found in studies with a greater than 72-hour abstinence period, suggesting that the effects of cannabis use on cognition were reversible. Reductions in the odds of completing high school have been associated with adolescent cannabis use, but the evidence is contentious due to numerous confounders (gender, socioeconomic status, education, polydrug abuse) *(1, 31).*

Some studies, involving small numbers of participants, have reported structural abnormalities in brain regions important to cognitive function, mood and reward *(32–34).* However, such effects appear to be absent in larger studies that controlled for confounders such as alcohol use, tobacco use, gender, age and other variables *(35, 36).*

## 1.8 Mental health

A frequently cited adverse effect of cannabis use is increased risk of psychosis, where the user experiences disordered thinking, hallucinations and delusions. There are frequent reports of acute cannabis intoxication precipitating a short-lasting psychotic state that reverses once the effects of the drug have abated *(37).* Human population studies have linked cannabis use to schizophrenia, which is characterized by hallucinations, delusions and cognitive dysfunction, with cannabis increasing the risk of developing the disorder by around 2-fold *(1, 37).* The relationship between cannabis use and risk of schizophrenia appears to be dose-dependent: heavier cannabis use increases the risk of developing schizophrenia *(1).* There is also some evidence that cannabis use during adolescence may bring forward the age of schizophrenia onset *(38).* It has been argued that reducing the incidence of cannabis-induced schizophrenia would be difficult, because it has been estimated that 4700 young people would need to be dissuaded from cannabis use to prevent a single case of schizophrenia *(42).*

The argument that cannabis causes schizophrenia is contentious, however, as some have observed that sharp increases in global cannabis use in recent decades has not increased the incidence of schizophrenia *(39).* However, other studies have linked increased prevalence of cannabis use in specific localities with increased incidence of schizophrenia *(40, 41).*

Importantly, most of the evidence that cannabis causes schizophrenia comes from studies of during-adolescence users, and adolescence is the period of highest risk for developing schizophrenia. The rates of cannabis-induced psychosis may be lower in patients who commence cannabis use in adulthood. The vast majority of people who use cannabis will never develop a psychotic disorder, and those who do are likely to have some genetic vulnerability to cannabis-induced psychosis *(43).*

The NASEM report on cannabis noted moderate evidence that cannabis use increases manic symptoms in bipolar disorder patients; the risk of developing depression (albeit a small increased risk); suicidal ideation, suicide attempts and completions in heavy users; and, the development of social anxiety disorders *(1).*

## 1.9 Driving under the influence of drugs

There is an array of evidence to support the idea that people driving under the influence of cannabis are more likely to be involved in a car accident (reviewed in *(1)*), although the level of risk is generally not as great as with alcohol *(31)*. A large systematic review that incorporated results for 239 739 participants from 21 case–control and culpability studies in 13 countries, showed that cannabis use caused a low-to-

moderate (20–30%) increase of being in an accident *(1, 44).* The relatively low risk may be due to cannabis users overestimating their level of impairment and recruiting strategies to compensate for the effects of cannabis on their driving performance *(45).* By contrast, alcohol-intoxicated individuals underestimate their level of impairment. Laboratory studies show that cannabis acutely impairs certain types of cognitive function and psychomotor skills and can diminish driving performance under certain conditions *(46, 47).* These cognitive and performance deficits are less apparent in experienced cannabis users due to tolerance, and may even be absent *(48).* Some studies suggest that drivers under the influence of cannabis drive more slowly, make fewer attempts to overtake, and leave greater distances between themselves and the vehicle in front *(49).* However, other studies have shown that cannabis use impairs reaction time, lane control, speedometer monitoring, hand and body steadiness and braking time as well as promoting inappropriate responses in an emergency scenario *(50–53).*

# 2. Adverse reactions in humans

Cannabis consumption causes euphoria, laughter and talkativeness. It is an appetite stimulant, and may promote dry mouth and dizziness as well as increasing visual, olfactory and auditory perceptions *(1, 54, 55).* Conjunctival reddening occurs, due to vasodilation of blood vessels in the eyes. Time perception may be altered and some users may experience anxiety and panic reactions *(56)*. Cannabis intoxication can impair attention and short-term memory function *(57)* and can precipitate psychotic reactions in vulnerable individuals *(58).* The pharmacological effects of cannabis are subject to tolerance following repeated exposure and therefore many of the marked reactions observed in naive users are diminished in frequent users.

Young children may be particularly vulnerable to the effects of cannabis. There are several recent case reports of young children accidentally ingesting cannabis and experiencing respiratory depression, tachycardia and temporary coma *(1, 59–61).* This increasing risk of overdose and related adverse effects in paediatric populations may be greater in US states that have legalized cannabis use *(1).*

# 3. References


1. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*2017: Washington (DC).
2. Lachenmeier, D.W. and J. Rehm, *Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach.* Sci Rep, 2015. **5**: p. 8126.
3. Sultan, S.R., S.A. Millar, S.E. O'Sullivan, and T.J. England, *A Systematic Review and Meta-Analysis of the In Vivo Haemodynamic Effects of Delta(8)-Tetrahydrocannabinol.* Pharmaceuticals (Basel), 2018. **11**(1).
4. Benowitz, N.L. and R.T. Jones, *Cardiovascular effects of prolonged delta-9-tetrahydrocannabinol ingestion.* Clin Pharmacol Ther, 1975. **18**(3): p. 287-97.
5. Aronow, W.S. and J. Cassidy, *Effect of smoking marihuana and of a high-nicotine cigarette on angina pectoris.* Clin Pharmacol Ther, 1975. **17**(5): p. 549-54.
6. Mittleman, M.A., R.A. Lewis, M. Maclure, J.B. Sherwood, and J.E. Muller, *Triggering myocardial infarction by marijuana.* Circulation, 2001. **103**(23): p. 2805-9.
7. Desai, R., U. Patel, S. Sharma, P. Amin, R. Bhuva, M.S. Patel, N. Sharma, M. Shah, S. Patel, S. Savani, N. Batra, and G. Kumar, *Recreational Marijuana Use and Acute Myocardial Infarction: Insights from Nationwide Inpatient Sample in the United States.* Cureus, 2017. **9**(11): p. e1816.
8. Adegbala, O., A.C. Adejumo, O. Olakanmi, A. Akinjero, E. Akintoye, S. Alliu, E. Edo-Osagie, and A. Chatterjee, *Relation of Cannabis Use and Atrial Fibrillation Among Patients Hospitalized for Heart Failure.* Am J Cardiol, 2018.
9. Jouanjus, E., V. Raymond, M. Lapeyre-Mestre, and V. Wolff, *What is the Current Knowledge About the Cardiovascular Risk for Users of Cannabis-Based Products? A Systematic Review.* Curr Atheroscler Rep, 2017. **19**(6): p. 26.
10. Newmeyer, M.N., M.J. Swortwood, O.A. Abulseoud, and M.A. Huestis, *Subjective and physiological effects, and expired carbon monoxide concentrations in frequent and occasional cannabis smokers following smoked, vaporized, and oral cannabis administration.* Drug Alcohol Depend, 2017. **175**: p. 67-76.
11. *Schedules of controlled substances: temporary placement of three synthetic cannabinoids into Schedule I. Final order.* Fed Regist, 2013. **78**(95): p. 28735-9.
12. Pletcher, M.J., E. Vittinghoff, R. Kalhan, J. Richman, M. Safford, S. Sidney, F. Lin, and S. Kertesz, *Association between marijuana exposure and pulmonary function over 20 years.* JAMA, 2012. **307**(2): p. 173-81.
13. Shiplo, S., M. Asbridge, S.T. Leatherdale, and D. Hammond, *Medical cannabis use in Canada: vapourization and modes of delivery.* Harm Reduct J, 2016. **13**(1): p. 30.
14. Klein, T.W. and G.A. Cabral, *Cannabinoid-induced immune suppression and modulation of antigen-presenting cells.* J Neuroimmune Pharmacol, 2006. **1**(1): p. 50-64.
15. Abo-Elnazar, S., M. Moaaz, H. Ghoneim, T. Molokhia, and W. El-Korany, *Th17/Treg imbalance in opioids and cannabinoids addiction: relationship to NF-kappaB activation in CD4+ T cells.* Egypt J Immunol, 2014. **21**(2): p. 33-47.
16. Hamadeh, R., A. Ardehali, R.M. Locksley, and M.K. York, *Fatal aspergillosis associated with smoking contaminated marijuana, in a marrow transplant recipient.* Chest, 1988. **94**(2): p. 432-3.
17. Ruchlemer, R., M. Amit-Kohn, D. Raveh, and L. Hanus, *Inhaled medicinal cannabis and the immunocompromised patient.* Support Care Cancer, 2015. **23**(3): p. 819-22.
18. Hazekamp, A., *Evaluating the Effects of Gamma-Irradiation for Decontamination of Medicinal Cannabis.* Front Pharmacol, 2016. **7**: p. 108.
19. McAllister, S.D., L. Soroceanu, and P.Y. Desprez, *The Antitumor Activity of Plant-Derived Non-Psychoactive Cannabinoids.* J Neuroimmune Pharmacol, 2015. **10**(2): p. 255-67.

20. Zhang, L.R., H. Morgenstern, S. Greenland, S.C. Chang, P. Lazarus, M.D. Teare, P.J. Woll, I. Orlow, B. Cox, Cannabis, Z. Respiratory Disease Research Group of New, Y. Brhane, G. Liu, and R.J. Hung, *Cannabis smoking and lung cancer risk: Pooled analysis in the International Lung Cancer Consortium.* Int J Cancer, 2015. **136**(4): p. 894-903.
21. de Carvalho, M.F., M.R. Dourado, I.B. Fernandes, C.T. Araujo, A.T. Mesquita, and M.L. Ramos-Jorge, *Head and neck cancer among marijuana users: a meta-analysis of matched case-control studies.* Arch Oral Biol, 2015. **60**(12): p. 1750-5.
22. Daling, J.R., D.R. Doody, X. Sun, B.L. Trabert, N.S. Weiss, C. Chen, M.L. Biggs, J.R. Starr, S.K. Dey, and S.M. Schwartz, *Association of marijuana use and the incidence of testicular germ cell tumors.* Cancer, 2009. **115**(6): p. 1215-23.
23. Lacson, J.C., J.D. Carroll, E. Tuazon, E.J. Castelao, L. Bernstein, and V.K. Cortessis, *Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk.* Cancer, 2012. **118**(21): p. 5374-83.
24. Trabert, B., A.J. Sigurdson, A.M. Sweeney, S.S. Strom, and K.A. McGlynn, *Marijuana use and testicular germ cell tumors.* Cancer, 2011. **117**(4): p. 848-53.
25. Gunn, J.K., C.B. Rosales, K.E. Center, A. Nunez, S.J. Gibson, C. Christ, and J.E. Ehiri, *Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis.* BMJ Open, 2016. **6**(4): p. e009986.
26. van Gelder, M.M., A.R. Donders, O. Devine, N. Roeleveld, J. Reefhuis, and S. National Birth Defects Prevention, *Using bayesian models to assess the effects of under-reporting of cannabis use on the association with birth defects, national birth defects prevention study, 1997-2005.* Paediatr Perinat Epidemiol, 2014. **28**(5): p. 424-33.
27. Solowij, N., K.A. Jones, M.E. Rozman, S.M. Davis, J. Ciarrochi, P.C. Heaven, D.I. Lubman, and M. Yucel, *Verbal learning and memory in adolescent cannabis users, alcohol users and non-users.* Psychopharmacology (Berl), 2011. **216**(1): p. 131-44.
28. Solowij, N., R.S. Stephens, R.A. Roffman, T. Babor, R. Kadden, M. Miller, K. Christiansen, B. McRee, and J. Vendetti, *Cognitive functioning of long-term heavy cannabis users seeking treatment.* JAMA, 2002. **287**(9): p. 1123-31.
29. Meier, M.H., A. Caspi, A. Ambler, H. Harrington, R. Houts, R.S. Keefe, K. McDonald, A. Ward, R. Poulton, and T.E. Moffitt, *Persistent cannabis users show neuropsychological decline from childhood to midlife.* Proc Natl Acad Sci U S A, 2012. **109**(40): p. E2657-64.
30. Cobb, S.J., S. Slomiak, T., J.D. Jones, A.F.G. Rosen, T.M. Moore, and R.C. Gur, *Association of Cannabis With Cognitive Functioning in Adolescents and Young Adults: A Systematic Review and Meta-analysis.* JAMA Psychiatry, Published online April 18, 2018.
31. Hall, W., *What has research over the past two decades revealed about the adverse health effects of recreational cannabis use?* Addiction, 2015. **110**(1): p. 19-35.
32. Gilman, J.M., J.K. Kuster, S. Lee, M.J. Lee, B.W. Kim, N. Makris, A. van der Kouwe, A.J. Blood, and H.C. Breiter, *Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users.* J Neurosci, 2014. **34**(16): p. 5529-38.
33. Solowij, N., M. Yucel, C. Respondek, S. Whittle, E. Lindsay, C. Pantelis, and D.I. Lubman, *Cerebellar white-matter changes in cannabis users with and without schizophrenia.* Psychol Med, 2011. **41**(11): p. 2349-59.
34. Yucel, M., N. Solowij, C. Respondek, S. Whittle, A. Fornito, C. Pantelis, and D.I. Lubman, *Regional brain abnormalities associated with long-term heavy cannabis use.* Arch Gen Psychiatry, 2008. **65**(6): p. 694-701.
35. Gillespie, N.A., M.C. Neale, T.C. Bates, L.T. Eyler, C. Fennema-Notestine, J. Vassileva, M.J. Lyons, E.C. Prom-Wormley, K.L. McMahon, P.M. Thompson, G. de Zubicaray, I.B. Hickie, J.J. McGrath, L.T. Strike, M.E. Renteria, M.S. Panizzon, N.G. Martin, C.E. Franz, W.S. Kremen, and M.J. Wright,

*Testing associations between cannabis use and subcortical volumes in two large population-based samples.* Addiction, 2018.

36. Weiland, B.J., R.E. Thayer, B.E. Depue, A. Sabbineni, A.D. Bryan, and K.E. Hutchison, *Daily marijuana use is not associated with brain morphometric measures in adolescents or adults.* J Neurosci, 2015. **35**(4): p. 1505-12.
37. Radhakrishnan, R., S.T. Wilkinson, and D.C. D'Souza, *Gone to Pot - A Review of the Association between Cannabis and Psychosis.* Front Psychiatry, 2014. **5**: p. 54.
38. Large, M., S. Sharma, M.T. Compton, T. Slade, and O. Nielssen, *Cannabis use and earlier onset of psychosis: a systematic meta-analysis.* Arch Gen Psychiatry, 2011. **68**(6): p. 555-61.
39. Degenhardt, L., W. Hall, and M. Lynskey, *Testing hypotheses about the relationship between cannabis use and psychosis.* Drug Alcohol Depend, 2003. **71**(1): p. 37-48.
40. Ajdacic-Gross, V., C. Lauber, I. Warnke, H. Haker, R.M. Murray, and W. Rossler, *Changing incidence of psychotic disorders among the young in Zurich.* Schizophr Res, 2007. **95**(1-3): p. 9-18.
41. Boydell, J., J. van Os, A. Caspi, N. Kennedy, E. Giouroukou, P. Fearon, M. Farrell, and R.M. Murray, *Trends in cannabis use prior to first presentation with schizophrenia, in South-East London between 1965 and 1999.* Psychol Med, 2006. **36**(10): p. 1441-6.
42. Hickman, M., P. Vickerman, J. Macleod, J. Kirkbride, and P.B. Jones, *Cannabis and schizophrenia: model projections of the impact of the rise in cannabis use on historical and future trends in schizophrenia in England and Wales.* Addiction, 2007. **102**(4): p. 597-606.
43. Silveira, M.M., J.C. Arnold, S.R. Laviolette, C.J. Hillard, M. Celorrio, M.S. Aymerich, and W.K. Adams, *Seeing through the smoke: Human and animal studies of cannabis use and endocannabinoid signalling in corticolimbic networks.* Neurosci Biobehav Rev, 2017. **76**(Pt B): p. 380-395.
44. Rogeberg, O. and R. Elvik, *The effects of cannabis intoxication on motor vehicle collision revisited and revised.* Addiction, 2016. **111**(8): p. 1348-59.
45. MacDonald, S., R. Mann, M. Chipman, B. Pakula, P. Erickson, A. Hathaway, and P. MacIntyre, *Driving behavior under the influence of cannabis or cocaine.* Traffic Inj Prev, 2008. **9**(3): p. 190-4.
46. Ramaekers, J.G., G. Kauert, P. van Ruitenbeek, E.L. Theunissen, E. Schneider, and M.R. Moeller, *High-potency marijuana impairs executive function and inhibitory motor control.* Neuropsychopharmacology, 2006. **31**(10): p. 2296-303.
47. Ramaekers, J.G., M.R. Moeller, P. van Ruitenbeek, E.L. Theunissen, E. Schneider, and G. Kauert, *Cognition and motor control as a function of Delta9-THC concentration in serum and oral fluid: limits of impairment.* Drug Alcohol Depend, 2006. **85**(2): p. 114-22.
48. Ramaekers, J.G., E.L. Theunissen, M. de Brouwer, S.W. Toennes, M.R. Moeller, and G. Kauert, *Tolerance and cross-tolerance to neurocognitive effects of THC and alcohol in heavy cannabis users.* Psychopharmacology (Berl), 2011. **214**(2): p. 391-401.
49. Sewell, R.A., J. Poling, and M. Sofuoglu, *The effect of cannabis compared with alcohol on driving.* Am J Addict, 2009. **18**(3): p. 185-93.
50. Crancer, A., Jr., J.M. Dille, J.C. Delay, J.E. Wallace, and M.D. Haykin, *Comparison of the effects of marihuana and alcohol on simulated driving performance.* Science, 1969. **164**(881): p. 851-4.
51. Hansteen, R.W., R.D. Miller, L. Lonero, L.D. Reid, and B. Jones, *Effects of cannabis and alcohol on automobile driving and psychomotor tracking.* Ann N Y Acad Sci, 1976. **282**: p. 240-56.
52. Klonoff, H., *Marijuana and driving in real-life situations.* Science, 1974. **186**(4161): p. 317-24.
53. Rafaelsen, O.J., P. Bech, J. Christiansen, H. Christrup, J. Nyboe, and L. Rafaelsen, *Cannabis and alcohol: effects on stimulated car driving.* Science, 1973. **179**(76): p. 920-3.
54. Whiting, P.F., R.F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A.V. Hernandez, J.C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijnen, *Cannabinoids for Medical Use: A Systematic Review and Meta-analysis.* JAMA, 2015. **313**(24): p. 2456-73.

55. Zajicek, J.P., H.P. Sanders, D.E. Wright, P.J. Vickery, W.M. Ingram, S.M. Reilly, A.J. Nunn, L.J. Teare, P.J. Fox, and A.J. Thompson, *Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up.* J Neurol Neurosurg Psychiatry, 2005. **76**(12): p. 1664-9.
56. Walter, C., B.G. Oertel, L. Felden, U. Noth, J. Vermehren, R. Deichmann, and J. Lotsch, *Effects of oral Delta(9)-tetrahydrocannabinol on the cerebral processing of olfactory input in healthy non-addicted subjects.* Eur J Clin Pharmacol, 2017. **73**(12): p. 1579-1587.
57. Ranganathan, M. and D.C. D'Souza, *The acute effects of cannabinoids on memory in humans: a review.* Psychopharmacology (Berl), 2006. **188**(4): p. 425-44.
58. Sherif, M., R. Radhakrishnan, D.C. D'Souza, and M. Ranganathan, *Human Laboratory Studies on Cannabinoids and Psychosis.* Biol Psychiatry, 2016. **79**(7): p. 526-38.
59. Amirav, I., A. Luder, Y. Viner, and M. Finkel, *Decriminalization of cannabis--potential risks for children?* Acta Paediatr, 2011. **100**(4): p. 618-9.
60. Appelboam, A. and P.J. Oades, *Coma due to cannabis toxicity in an infant.* Eur J Emerg Med, 2006. **13**(3): p. 177-9.
61. Carstairs, S.D., M.K. Fujinaka, G.E. Keeney, and B.T. Ly, *Prolonged coma in a child due to hashish ingestion with quantitation of THC metabolites in urine.* J Emerg Med, 2011. **41**(3): p. e69-71.