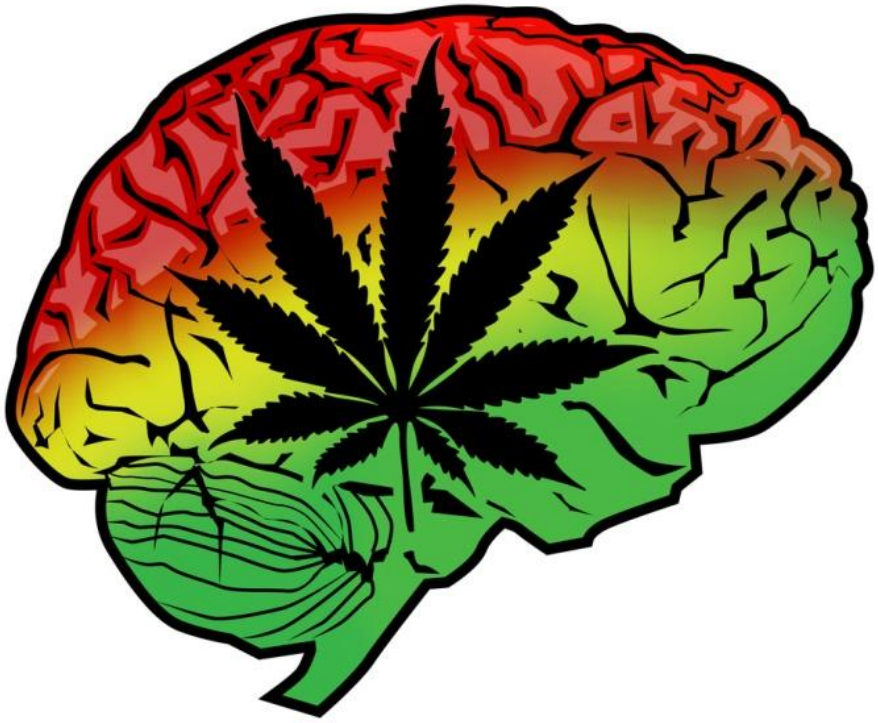
Appraising the Risks of Reefer Madness

By Sir Robin Murray, M.D.

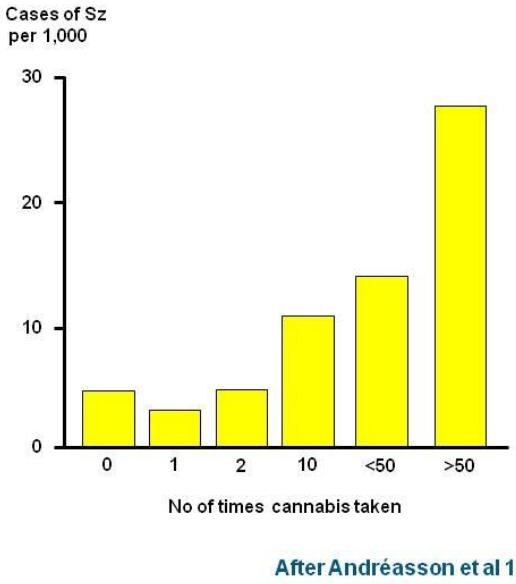


Editor's Note: Studies that have tied cannabis use to schizophrenia in the developing brain are just the tip of the iceberg when it comes to marijuana. Are different strains and synthetic cannabinoids especially dangerous? Are we doing enough to educate young people on the risks? Does marijuana use lower IQ? Where is the line between medical marijuana and recreational use? Our author, a noted British psychiatrist, offers a European perspective on these issues.

Beginning in the mid-1980s, European psychiatrists like me started seeing an increasing number of previously well-functioning teenagers who had developed hallucinations and delusions: the characteristic picture of schizophrenia. These troubled patients puzzled us because most had been bright and sociable and had no ties to the usual risk factors such as a family history of the disorder or developmental insult to the brain. Family and friends would often say, "Maybe it was all the cannabis they have been smoking," and we would confidently reassure them that they were mistaken and tell them that cannabis was known to be a safe drug.

My view began to shift when a colleague, Peter Allebeck from the Karolinska Institute in Stockholm, launched his own investigation. He had been struck similarly by seeing well-adjusted young people develop schizophrenia for no apparent reason. The wonderful Swedish national records system enabled him to trace the outcome of 45,750 young men who had been asked about their drug use when they were conscripted into the Swedish army. From analysis of these data, Allebeck and his colleagues[1] reported in 1987 that conscripts who had used cannabis more than fifty times were six times more likely to develop schizophrenia over the next fifteen years than those who had never used it (Figure1).

Figure 1 - Risk of schizophrenia in conscripts followed up for 15 years



Because only one study existed, most psychiatrists reassured themselves that the cannabis users probably were destined for schizophrenia before they started smoking. As a result, Allebeck's findings were mostly ignored. Even the prestigious medical journal *The Lancet*, which had published Allebeck's paper, carried an editorial in 1995 that restated the prevailing medical view that "the smoking of cannabis, even long term, is not harmful to health."[2]

Nevertheless, with the help of a young psychiatrist, Anton Grech, I began looking at patients who had smoked cannabis and been admitted to the Maudsley Hospital in London with a diagnosis of psychosis. Our aim was to see what happened to the ones who continued to use cannabis. If, as some suggested, psychotic patients used cannabis to "self-medicate" or otherwise help them to cope with their illness, then one might expect the persistent cannabis users to have a better outcome. But we found the opposite; four years later, the patients who continued to use cannabis were much more likely to still have delusions and hallucinations.[3] Many studies have replicated the findings.[4-6]

So, if smoking cannabis exacerbates established psychosis, might it play a causal role too? This question provided the impetus for various research groups to try to replicate the Swedish army study by following-up samples of young people in the general population, divided into cannabis users and non-users. Since 2002, a series of ten such studies have reported that individuals who used cannabis at the baseline evaluation had a greater risk of subsequently developing psychotic symptoms and indeed full-blown schizophrenia than non-users.[7-18] Other studies of cannabis users who had sought medical care showed that they had a marked increased risk of subsequent schizophrenia.[19-20] Such unanimity is rare in psychiatric epidemiology.[21]

A Hostile Reaction

Much of the scientific establishment greeted these findings with hostility, as did people advocating a more liberal attitude regarding cannabis use. My colleagues and I were accused of being closet prohibitionists; some suggested we were experiencing our own kind of "reefer madness." Critics suggested that people using cannabis were doing so because they were odd and destined to develop schizophrenia anyway.[22]

But in a study of young people who had been scrutinized intensely from birth in Dunedin, New Zealand, we were able to exclude those who already appeared psychosis-prone at age eleven. We still found a link between cannabis use and later schizophrenia, even when we excluded the effects of other drugs known to increase risk of psychosis.[7] Another criticism was that maybe some people were taking cannabis in an attempt to ameliorate symptoms of psychosis or its precursors. However, a second New Zealand study, this time from Christchurch, showed that once minor psychotic symptoms developed, people tended to smoke less.[8]

Eventually the sheer volume of data convinced European and Australian psychiatrists of a link. Cannabis is now generally accepted as a cause of schizophrenia [23-24] (though less so in North America, where this topic has received little attention). Argument does continue over just how significant cannabis-associated psychosis is. In different countries, the proportion of schizophrenia attributed to cannabis use ranges from 8 to 24 percent, depending, in part, on the prevalence of cannabis use.[25]

Excess Becomes a Major Concern

Most people enjoy cannabis in moderation and suffer few or no adverse effects. People take comfort in knowing that some of the most celebrated role models on the planet—Paul McCartney, Oprah Winfrey, and Barack Obama, for example—have admitted to smoking cannabis with no ill effect. But the scientific consensus is that, although there is no convincing evidence of a link to anxiety[26] or depression,[27] cannabis *can* lead to psychosis when consumed in large amounts. The bottom line: daily users who smoke large amounts are increasing their risk of schizophrenia.

Nevertheless, the vast majority of users won't become psychotic. Indeed, when young people who have developed schizophrenia after years of smoking cannabis are asked whether they think their habit may have contributed, they often say, "No, my friends smoke as much as I do, and they're fine." It appears that some people are especially vulnerable.

Not surprisingly, people with a paranoid or "psychosis-prone" personality are at greatest risk, alongside people with a family history of psychosis.[28] Research also suggests that inheriting certain

variants of genes that influence the dopamine system, which is implicated in psychosis, may make some users especially susceptible; examples of such genes include AKT1, DRD2, and possibly COMT.[29-31]

Another important question is: Are some types of cannabis more risky than others?

The Changing Nature of Cannabis

The cannabis plant is thought to originate from either central Asia or the foothills of the Himalayas. It produces compounds known as cannabinoids in glandular trichomes, mostly around the flowering tops of the plant. Recreational cannabis is derived from trichomes and has been traditionally available as herb (marijuana, grass, weed) or resin (hashish, hash); the former most common in North America and the latter in Europe. Cannabis acts on the CB1 cannabinoid receptor, part of the endocannabinoid system, which helps to maintain neurochemical stability in the brain. The cannabis plant produces more than 70 cannabinoids, but the most important are tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is responsible for the "high" that users enjoy. It activates the cannabinoid CB1 receptor, which is one of the most widespread receptors in the brain.

The proportion of THC in traditional marijuana and resin in the 1960s was approximately 1 to 3 percent. The potency of cannabis began to rise in the 1980s, when cannabis growers such as David Watson, commonly known as "Sam the Skunkman," fled the Reagan-inspired "War on Drugs" and brought cannabis seeds to Amsterdam, where it could be sold legally in "coffee shops." Together with Dutch enthusiasts, they experimented to produce more potent plants. This set the trend for a slow but steady increase in a new variety of marijuana called sinsemilla, harvested from unpollinated female flowers (often called "skunk" because of its strong smell). By the early years of the twenty-first century in England and Holland, respectively, the potency of sinsemilla, as measured by the proportion of THC, had risen to between 16 and 20 percent, and it had taken over much of the traditional market from resin. [32-33]

In 1845, French psychiatrist Jacques-Joseph Moreau (nicknamed "Moreau de Tours") took cannabis himself in the appropriately named Club de Hashischins, and gave it to some of his students and

patients.[34] He concluded that cannabis could precipitate "acute psychotic reactions, generally lasting but a few hours, but occasionally as long as a week." However, since then surprisingly little formal scientific research has explored THC's effects in humans.

One of the first THC studies was conducted by Paul Morrison, a Scottish psychopharmacologist in our group at King's College London, who gave the ingredient intravenously to healthy and eager young volunteers.[35] Their reactions ranged from euphoria to suspicion, paranoia, and hallucinations. Later, he and Amir Englund[36] pretreated their volunteers with cannabidiol (CBD), the other main ingredient of traditional cannabis), before giving them intravenous THC; the effects of the latter were much diminished. Thus, CBD appeared to counter the psychotogenic effects of THC. A German clinical trial supports this idea: Marcus Leweke [37] found that CBD had antipsychotic actions equivalent to a standard antipsychotic, amisulpride, in patients with schizophrenia.

High-potency types of cannabis such as sinsemilla (skunk) differ from traditional forms not only in the amount of THC they contain but also in the proportion of CBD. Interestingly, plants bred to produce a high concentration of THC cannot also produce a lot of CBD, so the high THC types of cannabis contain little or no CBD.[32]

Might high potency types of cannabis be more likely, therefore, to induce psychosis than traditional forms? To examine this question, my wife, Marta Di Forti, a psychiatrist supported by the UK Medical Research Council, compared the cannabis habits of 410 patients who were admitted to the Maudsley Hospital with their first episode of psychotic disorder to those of 390 controls in the local population. Those who had been using high-potency cannabis (skunk) had a much higher risk of psychosis than users of resin.[25,38-39] People using skunk-like cannabis on a daily basis were five times more likely than non-users to suffer from a psychotic disorder while users of traditional resin did not differ from non-users. Another study which tested hair for cannabinoids showed that those users with both detectable THC and CBD in their hair had fewer psychotic symptoms than those with only THC.[40]

Thus the increasing availability of high-potency types of cannabis explains why psychiatrists should be more concerned about cannabis now than they were in the 1960s and 1970s. The trend towards

greater potency is not slackening with new forms of resin and resin oil being reported to contain up to 60 percent.[41] These particular very potent forms remain unusual but synthetic cannabinoids (often termed "spice" or "K2") are now commonly advertised and sold on websites that keep within the law by labelling their products as incense—or adding "not for human consumption." While THC only partially activates the CB1 receptor, most spice/K2 molecules fully activate the receptor and therefore are more powerful. Consequently, acute adverse reactions are more common. A survey of 80,000 drug users showed that those who used synthetic cannabinoids were thirty times more likely to end up in an emergency room than users of traditional cannabis.[42] The agitation, anxiety, paranoia, and psychosis that can result from synthetic cannabinoids use have been dubbed "spiceophrenia."[43-44]

Dependence and Cognitive Impairment Remain Controversial

While psychological dependence and tolerence occur, the issue of physical dependence remains hotly debated. Advocates point to an apparent absence of acute withdrawal symptoms from cannabis (there have been no studies to date examining specifically high THC users). Under ordinary circumstances, withdrawal symptoms are absent because cannabis remains in the body for several weeks—so withdrawal is very gradual and not obvious, though anxiety, insomnia, appetite disturbance, and depression can develop. Some claim that 10 percent of people who experiment with cannabis will develop dependence and that rates of dependence among daily users are at least 25 percent. Whether or not such figures are true, cannabis dependence is an increasingly common cause of those seeking help in Australia, Europe, and North America.[45-47]

Another controversial issue is cognitive impairment. THC disrupts the hippocampus, the area of the brain crucial to memory. When Paul Morrison induced psychotic symptoms by giving intravenous THC to volunteers, transient cognitive impairment also emerged**.** Such impairment likely is why drivers under the influence of cannabis are at double the risk of traffic accidents.[47]

Heavy users show cognitive impairment, but disagreement continues over what happens when they stop. Some studies suggest they can recover fully, while others indicate that only partial recovery is possible.[48] One (as yet unreplicated) study that provoked enormous concern was a report by

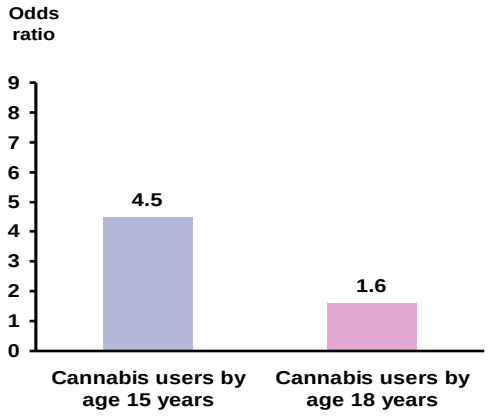
Madeleine Meier and her colleagues, based on the Dunedin study.[49] This suggested that persistent cannabis use over several decades causes a decline of up to eight points in IQ.

One possible explanation for the inconsistent cognitive findings is that the effects on cognition might depend on the age at which cannabis use began. Harrison Pope and colleagues examined long-term heavy cannabis users and found that it was those who initiated cannabis use before age seventeen who showed lower verbal IQ scores.[50] Meier also found greater decline in those in her Dunedin cohort who started using in adolescence.[49]

Other studies have implicated an association between adolescence cannabis use and poor educational achievement. Edmund Silins and colleagues reviewed more than 2,500 young people in Australia and found that that daily cannabis use before age seventeen was associated with "clear reductions" in the likelyhood of completing high school and obtaining a university degree.[51]

Researchers have raised similar questions regarding age of intiation and risk of psychosis. In our Dunedin study, we found that people who started to use cannabis at age eighteen or later showed only a small, non-significant increase in the risk of schizophrenia-like psychosis by age twenty-six. But among those starting at age fifteen or earlier, the risk increased fourfold.[7] (Figure 2) Other studies have reported similar disparities.[21]

Figure 2 - Risk of schizophrenia-like psychosis at age 26 years



After Arseneault et al 2002

Experimental studies in rodents have revealed that THC administration produced a greater impact on cognitive function in juvenile than in adult rats.[21] Also, some recent brain imaging studies of long-term, very heavy cannabis using people have claimed to find detectible brain changes especially in those who started in adolescence.[52-54] Although the imaging studies remain contentious, a possible explanation is that beginning cannabis use at an age when the brain is still developing might permanently impair the endocannabinoid system, and impact on other neurotransmitters such as dopamine system[21]—known to be implicated in both learning and in psychosis.

Implications

Cannabis attitudes are changing globally. Uruguay has legalized its use, as have four American states. In addition, seventeen states have decriminalized cannabis, while twenty-three others have passed "medical marijuana" laws on the basis that it helps people with chronic pain and symptoms associated with chemotherapy. A curious divide has opened up between North America and Europe. In the U.S., cannabis use in young people has increased since the mid-1990s as the number regarding use of cannabis as risky has fallen.[55] In contrast, use has fallen in many European countries, partly because of greater knowledge of the risks to mental health. In England for example, in 1998, 26 percent of people ages sixteen to twenty-four admitted to having used cannabis in the previous year. By 2013, that number had declined to 15 percent.[56]

As they consider the future of legal cannabis use, legislators and politicians need to balance the enjoyment of the many with the potential for harm. That challenge is displayed in the United Kingdom, where pro- and anti-cannabis lobbies have engaged in a raucous argument. In 2004, the government took the advice of the Advisory Council on the Misuse of Drugs that the use of cannabis had no serious adverse effects, and lowered restrictions on the drug. The following year, the Advisory Council reversed its view and accepted the evidence that linked cannabis to psychosis. Some newspapers that had campaigned for liberalization responded by turning on the "liberal" politicians. By 2007, the media clamour had reached such a pitch that the government increased restrictions again. Now pressure is building up once again for liberalization.[57]

In picking their way through the conflicting views, politicians and regulators need to recognize that "medicinal marijuana" has become largely a cover for introducing recreational use by the marijuana industry,[58] and that unscrupulous and increasingly wealthy doctors are involved. However, research into the numerous components of cannabis should be encouraged since, like research into opiates, it may produce drugs with important medical uses. Individual cannabinoid components can then be subject to trials measuring their effectiveness for a variety of ailments (e.g. multiple sclerosis, epilepsy) in the same way any other proposed drug is evaluated. When effective, it should be introduced for prescription by doctors; several cannabinoid drugs already have become available in this manner.

But we must be careful, since the evidence we have reviewed suggests that cannabis, like other psychotropic drugs, has negative as well as positive effects. When you consider that almost 200 million people worldwide use cannabis,[59] the number of people who suffer cannabis-induced psychosis is likely to be in the millions, and the number at risk for developing serious mental health problems becomes a huge concern.

Europeans are watching the evolution of the cannabis debate in the U.S. with great interest. Decriminalization and legalization of cannabis and synthetic cannabinoids are all on the table. Will legalization mean an increase in consumption? Will this result in greater use by those in their early teens who seem most susceptible to adverse effects? Will the mental health and addiction services be able to cope? How will educational campaigns regarding the risks of regular use of high-potency cannabis or synthetic cannabinoids play out? Might a simple genetic test reveal who is likely to suffer adverse mental effects? As cannabis use continues to win acceptance, as many questions as answers remain.

Bio

Sir Robin Murray, M.D., is professor of psychiatric research at the Institute of Psychiatry, Kings College, London. He has contributed to the understanding that schizophrenia is more than a genetic brain disease; environmental factors such as obstetric events, cannabis abuse, migration and adverse life events also increase the risk of the disorder. He is involved in testing new treatments for schizophrenia, and cares for people with psychosis at the Maudsley Hospital in London. He has written over 700

articles and is one of only five psychiatrists ever to have been elected a Fellow of the UK Royal Society (Freud was the first). A former president of the European Psychiatric Association and co-editor-in-chief of Psychological Medicine, he received a Knighthood from the Queen in 2011.

References

1. Andreasson S, Allebeck P, Engstrom A, Rydberg U. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. Lancet. 1987;2(8574):1483-6. Epub 1987/12/26.

2. Deglamorising cannabis. Lancet. 1995;346(8985):1241. Epub 1995/11/11.

3. Grech A, Van Os J, Jones PB, Lewis SW, Murray RM. Cannabis use and outcome of recent onset psychosis. European psychiatry : the journal of the Association of European Psychiatrists. 2005;20(4):349-53. Epub 2005/07/16.

4. Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet. 2007;370(9584):319-28. Epub 2007/07/31.

5. Zammit S, Moore TH, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, et al. Effects of cannabis use on outcomes of psychotic disorders: systematic review. The British journal of psychiatry : the journal of mental science. 2008;193(5):357-63. Epub 2008/11/04.

6. Foti DJ, Kotov R, Guey LT, Bromet EJ. Cannabis use and the course of schizophrenia: 10-year follow-up after first hospitalization. The American journal of psychiatry. 2010;167(8):987-93. Epub 2010/05/19.

7. Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ. 2002;325(7374):1212-3. Epub 2002/11/26.

8. Fergusson DM, Horwood LJ, Ridder EM. Tests of causal linkages between cannabis use and psychotic symptoms. Addiction. 2005;100(3):354-66. Epub 2005/03/01.

9. McGrath J, Welham J, Scott J, Varghese D, Degenhardt L, Hayatbakhsh MR, et al. Association between cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults. Archives of general psychiatry. 2010;67(5):440-7. Epub 2010/03/03.

10. van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H. Cannabis use and psychosis: a longitudinal population-based study. American journal of epidemiology. 2002;156(4):319-27. Epub 2002/08/16.

11. Henquet C, Krabbendam L, Spauwen J, Kaplan C, Lieb R, Wittchen HU, et al. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. BMJ. 2005;330(7481):11. Epub 2004/12/03.

12. Stefanis NC, Delespaul P, Henquet C, Bakoula C, Stefanis CN, Van Os J. Early adolescent cannabis exposure and positive and negative dimensions of psychosis. Addiction. 2004;99(10):1333-41. Epub 2004/09/17.

13. Ferdinand RF, Sondeijker F, van der Ende J, Selten JP, Huizink A, Verhulst FC. Cannabis use predicts future psychotic symptoms, and vice versa. Addiction. 2005;100(5):612-8. Epub 2005/04/26.

14. Weiser M, Knobler HY, Noy S, Kaplan Z. Clinical characteristics of adolescents later hospitalized for schizophrenia. American journal of medical genetics. 2002;114(8):949-55. Epub 2002/11/29.

15. Rossler W, Hengartner MP, Angst J, Ajdacic-Gross V. Linking substance use with symptoms of subclinical psychosis in a community cohort over 30 years. Addiction. 2012;107(6):1174-84. Epub 2011/12/14.

16. Griffith-Lendering MF, Wigman JT, Prince van Leeuwen A, Huijbregts SC, Huizink AC, Ormel J, et al. Cannabis use and vulnerability for psychosis in early adolescence--a TRAILS study. Addiction. 2013;108(4):733-40. Epub 2012/12/12.

17. Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. BMJ. 2002;325(7374):1199. Epub 2002/11/26.

18. Manrique-Garcia E, Zammit S, Dalman C, Hemmingsson T, Andreasson S, Allebeck P. Cannabis, schizophrenia and other non-affective psychoses: 35 years of follow-up of a population-based cohort. Psychological medicine. 2012;42(6):1321-8. Epub 2011/10/18.

19. Niemi-Pynttari JA, Sund R, Putkonen H, Vorma H, Wahlbeck K, Pirkola SP. Substance-induced psychoses converting into schizophrenia: a register-based study of 18,478 Finnish inpatient cases. The Journal of clinical psychiatry. 2013;74(1):e94-9. Epub 2013/02/20.

20. Callaghan RC, Cunningham JK, Allebeck P, Arenovich T, Sajeev G, Remington G, et al. Methamphetamine use and schizophrenia: a population-based cohort study in California. The American journal of psychiatry. 2012;169(4):389-96. Epub 2011/12/24.

21. Casadio P, Fernandes C, Murray RM, Di Forti M. Cannabis use in young people: the risk for schizophrenia. Neuroscience and biobehavioral reviews. 2011;35(8):1779-87. Epub 2011/05/03.

22. Macleod J, Oakes R, Copello A, Crome I, Egger M, Hickman M, et al. Psychological and social sequelae of cannabis and other illicit drug use by young people: a systematic review of longitudinal, general population studies. Lancet. 2004;363(9421):1579-88. Epub 2004/05/18.

23. Arseneault L, Cannon M, Witton J, Murray RM. Causal association between cannabis and psychosis: examination of the evidence. The British journal of psychiatry : the journal of mental science. 2004;184:110-7. Epub 2004/02/03.

24. Radhakrishnan R, Wilkinson ST, D'Souza DC. Gone to Pot - A Review of the Association between Cannabis and Psychosis. Frontiers in psychiatry. 2014;5:54. Epub 2014/06/07.

25. Di Forti M, Iyegbe C, Stilo SA, Murray RM, et al. The proportion of first episode psychosis attributable to cannabis use. Lancet Psychiatry. In Press

26. Kedzior KK, Laeber LT. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population--a meta-analysis of 31 studies. BMC psychiatry. 2014;14:136. Epub 2014/06/03.

27. Manrique-Garcia E, Zammit S, Dalman C, Hemmingsson T, Allebeck P. Cannabis use and depression: a longitudinal study of a national cohort of Swedish conscripts. BMC psychiatry. 2012;12:112. Epub 2012/08/18.

28. Henquet C, Di Forti M, Morrison P, Kuepper R, Murray RM. Gene-environment interplay between cannabis and psychosis. Schizophrenia bulletin. 2008;34(6):1111-21. Epub 2008/08/30.

29. Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, et al. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. Biological psychiatry. 2005;57(10):1117-27. Epub 2005/05/04.

30. Di Forti M, Iyegbe C, Sallis H, Kolliakou A, Falcone MA, Paparelli A, et al. Confirmation that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users. Biological psychiatry. 2012;72(10):811-6. Epub 2012/07/27.

31. Colizzi M, Di Forti M, Gaughran F, Stilo S et al Interaction between a functional variant in DRD2 and cannabis use in psychosis. Schizophrenia Bulletin.In revision

32. Potter DJ, Clark P, Brown MB. Potency of delta 9-THC and other cannabinoids in cannabis in England in 2005: implications for psychoactivity and pharmacology. Journal of forensic sciences. 2008;53(1):90-4. Epub 2008/02/19.

33. Pijlman T, Rigter SM, Hoek I,Goldsmidt MJ, and Niesink RJ Strong increase in total delta-THC in cannabis preparations sold in Dutch coffee shops. Addiction Biology (June 2005) 10, 171 – 180.

34. Moreau, J. J. Hashish and Mental Illness (Raven, New York, 1973).

35. Morrison PD, Zois V, McKeown DA, Lee TD, Holt DW, Powell JF, et al. The acute effects of synthetic intravenous Delta9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. Psychological medicine. 2009;39(10):1607-16. Epub 2009/04/02.

36. Englund A, Morrison PD, Nottage J, Hague D, Kane F, Bonaccorso S, et al. Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. J Psychopharmacol. 2013;27(1):19-27. Epub 2012/10/09.

37. Leweke FM, Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Translational psychiatry. 2012;2:e94. Epub 2012/07/27.

38. Di Forti M, Morgan C, Dazzan P, Pariante C, Mondelli V, Marques TR, et al. High-potency cannabis and the risk of psychosis. The British journal of psychiatry : the journal of mental science. 2009;195(6):488-91. Epub 2009/12/02.

39. Di Forti M, Sallis H, Allegri F, Trotta A, Ferraro L, Stilo SA, et al. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. Schizophrenia bulletin. 2014;40(6):1509-17. Epub 2013/12/19.

40. Morgan CJ, Curran HV. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. The British journal of psychiatry : the journal of mental science. 2008;192(4):306-7. Epub 2008/04/02.

41. European Monitoring Centre for Drugs and Drug Addiction. New developments in Europe's cannabis market. 2014

42. Winstock AR, Barratt MJ. Synthetic cannabis: a comparison of patterns of use and effect profile with natural cannabis in a large global sample. Drug and alcohol dependence. 2013;131(1-2):106-11. Epub 2013/01/08.

43. Papanti D, Schifano F, Botteon G, Bertossi F, Mannix J, Vidoni D, et al. "Spiceophrenia": a systematic overview of "spice"-related psychopathological issues and a case report. Human psychopharmacology. 2013;28(4):379-89. Epub 2013/07/25.

44. Spaderna M, Addy PH, D'Souza DC. Spicing things up: synthetic cannabinoids. Psychopharmacology. 2013;228(4):525-40. Epub 2013/07/10.

45. Khan SS, Secades-Villa R, Okuda M, Wang S, Perez-Fuentes G, Kerridge BT, et al. Gender differences in cannabis use disorders: results from the National Epidemiologic Survey of Alcohol and Related Conditions. Drug and alcohol dependence. 2013;130(1-3):101-8. Epub 2012/11/28.

46. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *Drug Treatment Overview for Netherlands*. Lisbon: EMCDDA; 2013. Available at: http:// www.emcdda.europa.eu/data/treatment-overviews/Netherlands (accessed 23 July 2014). (Archived athttp://www.webcitation.org/6S4yjPY59 on 25 August 2014).

47. Hall W. What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? Addiction. 2015;110(1):19-35. Epub 2014/10/08.

48. Solowij N. Cannabis and Cognitive Functioning Published by Cambridge University Press, 2006 ISBN 10: 0521591147 ISBN 13: 9780521591140.

49. Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. Proceedings of the National Academy of Sciences of the United States of America. 2012;109(40):E2657-64. Epub 2012/08/29.

50. Pope HG, Jr., Gruber AJ, Hudson JI, Cohane G, Huestis MA, Yurgelun-Todd D. Early-onset cannabis use and cognitive deficits: what is the nature of the association? Drug and alcohol dependence. 2003;69(3):303-10. Epub 2003/03/14.

51. Silins E, Horwood LG, Patton GC, Fergusson DM et al Young adult sequelae of adolescent cannabis use:an integrative analysis. Lancet Psychiatry 2014; 1: 286–93.

52. Gilman JM, Kuster JK, Lee S, Lee MJ, Kim BW, Makris N, et al. Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2014;34(16):5529-38. Epub 2014/04/18.

53. Yucel M, Solowij N, Respondek C, Whittle S, Fornito A, Pantelis C, et al. Regional brain abnormalities associated with long-term heavy cannabis use. Archives of general psychiatry. 2008;65(6):694-701. Epub 2008/06/04.

54. Filbey FM, Aslan S, Calhoun VD, Spence JS, Damaraju E, Caprihan A, et al. Long-term effects of marijuana use on the brain. Proceedings of the National Academy of Sciences of the United States of America. 2014;111(47):16913-8. Epub 2014/11/12.

55. Johnston LD, O'Malley PM, Miech RA, et al. Monitoring the Future: national survey results on drug use, 1975-2013 —overview, key findings on adolescent drug use. Ann Arbor: Institute for Social Research,University of Michigan, 2014 (http://monitoringthefuture.org/pubs/monographs/mtf-overview2013.pdf).

56. Drug misuse: Findings from the 2013/14 Crime Survey for England and Wales. Home Office. UK Government.

57. UK Drug Policy Commission. A Fresh Approach to Drugs, 2012

58. Sevigny EL, Pacula RL, Heaton P. The effects of medical marijuana laws on potency. The International journal on drug policy. 2014;25(2):308-19. Epub 2014/02/08.

59. United Nations. Commission on Narcotic Drugs. Report to the 56th session. World situation on Drug Abuse. Vienna 11-15th March. 2013.