Can we make cannabis safer?

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A changing cannabis climate

The cannabis landscape is rapidly changing. Following the Single Convention on Narcotic Drugs in 1961, possession, distribution and use were criminalised and cannabis-related arrests increased significantly in Europe and North America, particularly among younger and ethnic minority populations [1]. In subsequent decades cannabis use has waxed and waned in different countries, but there has been an overall trend towards greater use in most parts of the world [2]. This may be because prohibitive measures (scheduling substances or law enforcement) having little or no effect on use, abuse or substance related harms, as suggested by a recent systematic review [3]. In the UK, the demand for treatment for cannabis-related problems increased by 56% in adults and 51% in those under 18 between the years 2005-06 and 2013-14 (Public Health England, 2014; 2015). Increased treatment-seeking for cannabis use problems has also been evident in the US [5], and in Europe, cannabis has become the primary illicit drug responsible for first-time entry to drug treatment, although in some countries this is mainly due to referrals from the criminal justice system [6].

Certain US states along with Uruguay have recently decided to allow cannabis to be sold for recreational purposes [7]. Canada has recently proposed to legalise recreational use and several European countries have already lessened or dropped their criminal sanctions on cannabis possession and use [8]. While it is likely that such moves will decrease the cost of crime associated with cannabis use, the effect they will have on cannabis consumption and the prevalence of cannabis associated harms is unclear.

In any event, moves toward legalization of medicinal or recreational cannabis are unlikely to decrease the number of people who use cannabis. However, they could facilitate measures to reduce population levels of harm – for example, by regulating cannabis potency and promoting safer (e.g. non-tobacco) routes of administration [9]. It is therefore incumbent on

those concerned about cannabis-related harms to consider other ways in which the use of cannabis might be made safer.

Cannabis is becoming more potent

Cannabis Sativa L. contains at least 120 different compounds known as cannabinoids which are specific to the cannabis plant with more than 600 other compounds such as terpenoids and flavonoids [10,11]. The most abundant of the cannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) which the plant produces in different ratios from the precursor cannabigerol (CBG), based on genes that code for certain enzymes (THCA-synthase and CBDA-synthase) [12]. Hence, increased THC content in cannabis will be at the cost of CBD content. Furthermore, preventing pollination of the female plant leads to a much more potent product as the plant converts the plants energy to producing more cannabinoids rather than seeds [13]. This type of cannabis is referred to as *sinsemilla* which means "without seed" in Spanish, but is commonly termed 'skunk' in the UK.

Over the past 4 decades cannabis potency (its percentage of THC) has on average doubled worldwide [14] and CBD levels remaining low or absent in most cannabis preparations [15–18]. Systematic cross-breeding of cannabis plants by black-market growers has yielded a market dominance of high-THC plants. By 2008, roughly 80% of cannabis sold on the UK black market was high-potency cannabis [16], an increase from 55% in 2004-2005 [15] and only 15% in 1999-2002 [19]. In the US, a recent report found that the increased THC levels in cannabis over the last two decades was due to a shift towards high-potency (sinsemilla) as opposed to regularly (outdoor) grown cannabis [18]. Cannabis resin can be a more potent form of cannabis and has been found to reach potencies of over 60% THC (per weight) in the Netherlands [17], while in the UK resin (aka. hash) has low potency with equal quantities of THC (4%) and CBD (4%) [15]. More recently, new extraction techniques are being used to produce extremely high-potency concentrates (e.g. Butane Hash Oil) up to 75% THC [20]. Even more concerning are synthetic cannabinoids (e.g. "Spice") which typically act as full cannabinoid receptor agonists (THC is a partial agonist) and have been linked to severe adverse reactions including death [21].

The significance of CBD

The main possible adverse effects associated with cannabis use are dependence, cognitive and educational impairment and psychosis [22]. Crucially, evidence suggests that the incidence of adverse consequences of cannabis use is associated with the amount of THC and CBD it contains. Encouragingly, it appears that increasing the CBD dose does not influence the pleasurable effects of THC. A recent study found that CBD given orally up to 800mg did not influence the pleasurable, reinforcing or intoxicating effects of a smoked cannabis cigarette (~4.4mg THC) [23]. Two studies of inhaled cannabis vapour, with combinations including 8mg THC, 8mg THC + 10mg CBD and 8mg THC + 16mg CBD, found no differences in ratings of 'stoned' [24,25]. Lastly, a study where participants smoked their own cannabis found no difference in 'stoned' ratings when comparing low to high CBD:THC ratio strains of cannabis [26]. Although research to date has found no impact of CBD on the pleasurable effects of THC, more research is warranted to confirm this.

Dependence

Approximately one in eleven people who try cannabis will become dependent in their lifetime [27], although this risk is almost doubled if use starts in adolescence [28] and between 25-50% among daily users [29]. However, not all varieties of cannabis have the same liability towards dependence. An online survey study of over 2514 cannabis users found that high-potency (high THC, low CBD) cannabis use was associated with a greater severity of cannabis dependence along with self-reported memory problems and paranoia, compared with use of lower potency cannabis [30]. However, high-potency cannabis was rated as the preferred type and the type producing the best "high". This is potentially important, as interventions aiming at switching users to a less potent variety may fail if the alternative lacks the pleasurable effects of high-potency cannabis.

A few case reports have found that CBD can reduce the symptoms associated with withdrawal from cannabis [31,32], and two studies have found Sativex (CBD:THC ratio 1:1) to do the same [33,34] although it is not clear whether these effects were attributable to CBD, THC, or their interactive effects. Lastly, in an attentional bias task, cannabis containing

higher levels of CBD was found to reverse the heightened salience of cannabis and food cues compared to cannabis without CBD [26]. Therefore, varieties of cannabis with greater CBD content may reduce the likelihood of users developing dependence, whilst preserving the effects that users seek from cannabis.

Psychosis

High potency cannabis also carries a higher risk of psychosis as well as an earlier onset of the illness than low THC forms [35,36]. A recent case-control study of patients with first episode of psychosis found that daily use of high-THC, low CBD cannabis was associated with a 5-fold increase in the odds of psychosis but found no such increase among users of low potency hash (resin) [37].

In a Dutch population study of 1,877 participants, those who used cannabis higher in CBD had experienced fewer lifetime psychotic-like experiences compared to those who preferred varieties with less CBD [38]. Some neuroimaging studies have also suggested that the MRI correlates of cannabis use may vary with exposure to CBD. One study found that regular use of high-potency cannabis was associated with alterations in the corpus callosum, an effect that was absent in hash users [39]. Two other MRI studies have reported that cannabis users had smaller hippocampal volumes than non-users, but that this was not evident in cannabis users with hair samples that were positive for CBD [40,41]. However, the extent to which cannabis use is associated with neuroanatomical changes remains controversial: studies that have matched participants on alcohol use, or have accounted for heritable and genetic risk, have failed to find an association between cannabis use and brain structure [42–44].

Cannabis use is particularly harmful for patients already suffering from a psychotic illness. A recent meta-analysis found that patients who continue to use cannabis are more likely to relapse than their non-using counterparts [45]. Moreover, continued use of high potency cannabis appears to be more harmful to patients with psychosis than use of cannabis with lower THC and a relatively high proportion of CBD [46]. Sadly, clinical interventions to reduce cannabis use in patients with psychosis have been largely unsuccessful [47]. A recent study in patients with a first episode of psychosis found that patients experience both the positive and negative effect of cannabis more intensely compared to healthy controls [48]. This may

explain their unwillingness to stop using in spite of the negative effect the drug has on them and the failure of interventions in this population. Another potential factor is that reducing substance use usually depend on the subject having motivation and insight, both of which are impaired in patients with psychotic disorders [49].

Cognition and intelligence

There has been considerable debate regarding whether the use of cannabis may have lasting negative effects on memory functioning, intelligence and other aspects of cognition in the normal population [22]. A recent study across three large samples found that cannabis use before the age of 17 was related to lower rates of high-school completion and degree attainment [50]. Similarly, a 1-year follow-up study of 1155 adolescents found that weekly cannabis use was related to poorer performance in GCSE Maths and English at age 16 (albeit less than tobacco), after controlling for confounders [51]. However, a large twin study found that early school leaving was explained by shared environmental risk factors which increases the likelihood for both cannabis use and early school leaving [52]. These findings suggest that although there is a link between cannabis use and poorer educational outcomes, these effects may be explained by other factors.

As for general intelligence, a 38-year follow-up study of 874 individuals found that those who had been dependent on cannabis for up to 20 years had experienced a drop in IQ of an average of 6 points [53]. However, this study was limited in terms of controlling for confounds and a relatively small number of the total study population in the affected group. Two recent large scale follow-up studies have found that cannabis use is not associated with reduced IQ when controlling for additional confounders and genetic factors [54,55]. These latter studies only followed participants up to the ages of 15 and 20 years and do not exclude the possibility that IQ might be affected if cannabis use and/or dependence is maintained for longer.

Although there remains a debate on whether or not cannabis use leads to long term cognitive impairments or educational problems following abstinence, it is however clear that ongoing regular cannabis use impairs cognition. A recent meta-analysis found that cannabis users perform significantly worse on memory tasks than non-users, with the greatest impairments being in prospective memory, visual recognition, immediate and

delayed recall [56]. The authors reported that regular use (defined as using between 4 to 20 times/month) or more was related to worse performance while no effect was seen in light users (4 times/month or less). However, no significant difference is seen in users compared to controls following 4 weeks of abstinence [57]. This is in line with PET imaging studies showing that downregulation of CB1 receptor densities can be reversed within 4 weeks of abstinence or earlier [58,59].

Insights from cannabinoid experiments

While being fundamental to understand the population impact of a behaviour or exposure, epidemiological studies come with some clear limitations. When exploring different outcomes between cannabis users and non-users, one can never be certain that the observed effects (e.g. impaired cognition) are due to use itself or confounding variables. Hence, experimental studies such as randomised controlled trials (RCTs) are highly informative as the same person gets exposed to both experimental conditions or has a 50% chance of ending up in either condition. Unlike epidemiology, RCTs allow us to infer causality but with the caveat that it only allows conclusions relating to the acute effects of the drug and not from long-term exposure.

Experimental studies in healthy volunteers have shown that administration of high-dose THC can induce a range of psychological changes including transient psychotic symptoms [60–62]. They have also consistently found impairments in memory functioning in a dose response manner [60,63]. However, studies that have combined THC with CBD have found very different results. Co-administration of CBD significantly reduces THC-induced time estimation errors and psychological reactions [64] while a subsequent study found 1mg/kg CBD significantly reduced the anxiogenic effects of 0.5mg/kg THC in healthy volunteers [65]. In a recent study of 140 cannabis users, those who tested positive for both THC and CBD in hair-samples experienced significantly fewer psychotic-like effects compared to those testing positive for THC only [66]. These results were later replicated in a study of recreational cannabis users [67] The same group later administered inhaled THC (8mg) and CBD (16mg) to volunteers and found that CBD protected against the detrimental effects of THC on emotional processing [24]. Furthermore, there is evidence that CBD reverses THCs illusory effects on depth perception [68].

There is also evidence that CBD may reverse the negative impact of THC on cognitive performance. A naturalistic study of 134 cannabis users smoking their own cannabis found that participants using cannabis with higher CBD levels displayed no impairment on measures of immediate and delayed prose recall compared to when sober. By contrast, performance on these tasks was significantly impaired among those who used cannabis with equivalent THC but no CBD [69]. The same group explored memory functioning in 120 users while analysing hair-samples for presence of CBD. Participants who tested positive for CBD displayed significantly better performance [67].

In our own research we found that pre-treatment with 600mg oral CBD before the administration of 1.5mg intravenous THC significantly inhibited paranoia, the occurrence of psychotic symptom and impairments to delayed recall in 48 healthy volunteers [70]. These effects were not attributable to changes in THC plasma levels in the CBD group. Rather, they appear to reflect opposite effects of THC and CBD on the brain regions that mediate psychotic and anxiety symptoms, and support cognitive processes like memory, emotional processing and response inhibition [71,72].

Collectively, the available experimental evidence suggests that CBD, to a yet unknown extent, can mitigate the harmful effects of cannabis.

Making cannabis safer

It is vital, especially now that cannabis is becoming increasingly liberalised, that we explore alternative and innovative ways in which we can reduce and mitigate cannabis related harms.

Firstly, there should be more focus on the co-use of tobacco and cannabis and the additive harm this poses, especially since cannabis is frequently used together with tobacco, especially in Europe [73]. The use of other routes of administration such as smoke-free vaporisers have the potential of reducing the harmful effects the smoke poses to the user as well as reducing tobacco consumption [74]. This may be particularly important as tobacco increases the addictive potential of cannabis [75–77]. Furthermore, tobacco use may be an independent risk factor for psychosis [78], as well as modifying the risk from cannabis use [79]. Studies of the impact of cannabis use on cognition have also found the relationship

weakened after controlling for use of tobacco [51,54,80]. However, controlled experimental studies on the interaction between cannabis and tobacco are currently lacking [81]. Hence, it is vital that future studies address tobacco when evaluating the harms of cannabis.

Secondly, we need to better understand the harms posed by cannabis varieties with different THC potencies. Extremely potent cannabis concentrates (e.g. Butane Hash Oil) have gained popularity in the United States, where THC content is not currently regulated [82]. Policies proposed by both Uruguay and the Netherlands of a 15% THC-cap could be beneficial, but are not yet based on a scientific understanding of harms posed by potencies above this limit [83]. Alternative approaches include taxation based on THC content, although further research is needed their impact (including use of more harmful, synthetic cannabinoids). Only very recently have studies differentiated between different types of cannabis based on THC content [30,37–39], and most of these studies do not involve measures of THC and CBD content, but proxy measures of potency, such as analysis of police seizures or coffee shop cannabis, and a reliance on self-report measures. Although self-report measures are associated with THC and CBD content, these associations are modest and are weaker among infrequent users [84,85]. Future longitudinal studies may choose to collect cannabis cigarettes (joints) from their participants over the course of the study and collect information as to how often they would smoke such a cigarette. This will allow researchers to calculate a cumulative dose exposure of cannabinoids as well as tobacco – resulting in a far more accurate estimate of harm. This information could contribute to a cannabis use guideline, such as we currently have for alcohol.

Lastly, and perhaps most importantly, more knowledge is needed regarding the ratio between THC and CBD which reduces harm. As reviewed above, the available evidence suggests that CBD protects against many of the harms associated with THC; what is not known is the relative dose of CBD that is required to offset the negative effects of a given dose of THC. Experimental studies to date have been unable to establish this. Some have relied on the presence/absence of CBD in hair samples of participants [66,67]. Others have given CBD orally while administering inhaled or intravenous THC [23,70]. Cannabinoids are absorbed very differently orally as opposed to inhaled/intravenous (and result in differential metabolite profiles) and hence this does not allow an extrapolation of relative CBD:THC ratio [86]. Future experimental studies should therefore explore various CBD:THC ratios,

administered using the same route of administration, and using standardised measures of cognitive performance, psychopathology and liability for addiction. Once a "safer" CBD:THC ratio has been found, this may potentially be used as a harm-reduction strategy, where users (some also with a psychotic illness) experiencing negative effects from use of 'skunk'-type cannabis can be encouraged to switch to the less harmful one. Encouragingly, studies to date have not found CBD to influence the rewarding or pleasurable effects of THC [23–25]. This is crucial as any attempt to reduce the harms of cannabis would likely be ineffective if it also reduced the rewarding effects of cannabis.

Conclusion

In a rapidly changing political climate surrounding cannabis, the demand for effectively reducing cannabis related harms has never been greater, and more research (both experimental and observational) is urgently needed to inform policy decisions. Reducing the THC content of cannabis, smoke-free alternatives (vaporisers), and concurrent use of tobacco, may be effective harm reduction measures. However, increasing the content CBD may be especially promising as it can offset several harms of cannabis without compromising its rewarding effects.

Contributors

The article was conceptualised by AE and PM, and was written by AE. PM, RM and TF made additional comments, additional content recommendations and reviewed and corrected the manuscript

Declaration of interest

We declare no competing interests.

Search strategy and selection criteria

This was a narrative, critical review and was not carried out using standard search criteria and methods as for a systematic review. The articles used in producing this review obtained by means of searches through PubMed and Google Scholar, Google Scholar alerts for key terms ('cannabis', 'marijuana', 'cannabidiol') up to 07/10/16, reference lists in existing reviews and papers, and conference presentations.

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References

1 Room R, Fisher B, Hall W, Lenton S, Reuter P. Cannabis policy: moving beyond stalemate. Oxford University Press, 2010.

2 UNDOC. World Drug Report 2015. *United Nations Publ* 2015.

3 Stockings E, Hall WD, Lynskey M, *et al.* Prevention, early intervention, harm reduction, and treatment of substance use in young people. *The Lancet Psychiatry* 2016; **3**: 280–96.

4 Public Health England. Young people's statistics from the National Drug Treatment Monitoring System (NDTMS). 2015; : 1–37.

5 UNODC. World Drug Report 2014. 2014 DOI:10.1007/s12117-997-1166-0.

6 EMCDDA. European Drug Report 2015. 2015.

7 Room R. Legalizing a market for cannabis for pleasure: Colorado, Washington, Uruguay and beyond. *Addiction* 2014; **109**: 345–51.

8 Rosmarin A, Eastwood N. A Quiet Revolution: Drug decriminalisation policies in practice across the globe. 2012 http://www.release.org.uk/publications/quiet-revolution-drug-decriminalisation-policies-practice-across-globe.

9 Lynskey MT, Hindocha C, Freeman TP. Legal regulated markets have the potential to reduce population levels of harm associated with cannabis use. *Addiction* 2016; published online May 3. DOI:10.1111/add.13390.

10 Radwan MM, ElSohly MA, El-Alfy AT, *et al.* Isolation and Pharmacological Evaluation of Minor Cannabinoids from High-Potency Cannabis sativa. *J Nat Prod* 2015; **78**: 1271–6.

11 Ahmed SA, Ross SA, Slade D, Radwan MM, Khan IA, ElSohly MA. Minor oxygenated

cannabinoids from high potency Cannabis sativa L. *Phytochemistry* 2015; **117**: 194–9.

12 Small E. Evolution and Classification of Cannabis sativa (Marijuana, Hemp) in Relation to Human Utilization. *Bot Rev* 2015; **81**: 189–294.

13 Potter DJ. A review of the cultivation and processing of cannabis (Cannabis sativa L.) for production of prescription medicines in the UK. *Drug Test Anal* 2013; **6**: 31–8.

14 Cascini F, Aiello C, Di Tanna G. Increasing delta-9-tetrahydrocannabinol (Δ-9-THC) content in herbal cannabis over time: systematic review and meta-analysis. *Curr Drug Abuse Rev* 2012; **5**: 32–40.

15 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. *J Forensic Sci* 2008; **53**: 90–4.

16 Hardwick S, King L. HOME OFFICE CANNABIS POTENCY STUDY. 2008 http://www.dldocs.stir.ac.uk/documents/potency.pdf.

17 Niesink RJM, Rigter S, Koeter MW, Brunt TM. Potency trends of Δ(9) -tetrahydrocannabinol, cannabidiol and cannabinol in cannabis in the Netherlands: 2005-15. *Addiction* 2015; **110**: 1941–50.

18 ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC. Changes in cannabis potency over the last two decades (1995-2014) - Analysis of current data in the united states. *Biol Psychiatry* 2016; **79**: 613–9.

19 King L, Carpentier C, Griffiths P. An overview of cannabis potency in Europe. 2004 http://www.emcdda.europa.eu/publications/insights/cannabis-potency.

20 Raber JC, Elzinga S, Kaplan C. Understanding dabs: contamination concerns of cannabis concentrates and cannabinoid transfer during the act of dabbing. *J Toxicol Sci* 2015; **40**: 797–803.

21 Trecki J, Gerona RR, Schwartz MD. Synthetic Cannabinoid-Related Illnesses and Deaths. *N Engl J Med* 2015; **373**: 103–7.

22 Curran HV, Freeman TP, Mokrysz C, Lewis DA, Morgan CJA, Parsons LH. Keep off the

grass? Cannabis, cognition and addiction. *Nat Rev Neurosci* 2016; **17**: 293–306.

23 Haney M, Malcolm RJ, Babalonis S, *et al.* Oral Cannabidiol does not Alter the Subjective, Reinforcing or Cardiovascular Effects of Smoked Cannabis. *Neuropsychopharmacology* 2015; **41**: 1974–82.

24 Hindocha C, Freeman TP, Schafer G, *et al.* Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: A randomised, double-blind, placebo-controlled study in cannabis users. *Eur Neuropsychopharmacol* 2015; **25**: 325–34.

25 Lawn W, Freeman TP, Pope RA, *et al.* Acute and chronic effects of cannabinoids on effort-related decision-making and reward learning: an evaluation of the cannabis 'amotivational' hypotheses. *Psychopharmacology (Berl)* 2016; **233**: 3537–52.

26 Morgan CJA, Freeman TP, Schafer GL, Curran HV. Cannabidiol attenuates the appetitive effects of Delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis. *Neuropsychopharmacology* 2010; **35**: 1879–85.

27 Lopez-Quintero C, Pérez de los Cobos J, Hasin DS, *et al.* Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug Alcohol Depend* 2011; **115**: 120–30.

28 Anthony JC. The epidemiology of cannabis dependence. In: Roffman R., Roffman R., eds. Cannabis Dependence: Its nature, consequences and treatment. Cambridge: Cambridge University Press, 2006: 58–105.

29 Hall W. The adverse health effects of cannabis use: what are they, and what are their implications for policy? *Int J Drug Policy* 2009; **20**: 458–66.

30 Freeman TP, Winstock AR. Examining the profile of high-potency cannabis and its association with severity of cannabis dependence. *Psychol Med* 2015; **45**: 3181–9.

31 Crippa JAS, Hallak JEC, Machado-de-Sousa JP, *et al.* Cannabidiol for the treatment of cannabis withdrawal syndrome: a case report. *J Clin Pharm Ther* 2013; **38**: 162–4.

32 Shannon S, Opila-Lehman J. Cannabidiol Oil for Decreasing Addictive Use of Marijuana: A Case Report. *Integr Med (Encinitas)* 2015; **14**: 31–5.

33 Trigo JM, Lagzdins D, Rehm J, *et al.* Effects of fixed or self-titrated dosages of Sativex on cannabis withdrawal and cravings. *Drug Alcohol Depend* 2016; **161**: 298–306.

34 Allsop DJ, Copeland J, Lintzeris N, *et al.* Nabiximols as an Agonist Replacement Therapy During Cannabis Withdrawal: A Randomized Clinical Trial. *JAMA psychiatry* 2014; **71**: 1–11.

35 Di Forti M, Morgan C, Dazzan P, *et al.* High-potency cannabis and the risk of psychosis. *Br J Psychiatry* 2009; **195**: 488–91.

36 Di Forti M, Sallis H, Allegri F, *et al.* Daily Use, Especially of High-Potency Cannabis, Drives the Earlier Onset of Psychosis in Cannabis Users. *Schizophr Bull* 2013; : 1–9.

37 Di Forti M, Marconi A, Carra E, *et al.* Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. *The Lancet Psychiatry* 2015; **2**: 233–8.

38 Schubart CD, Sommer IEC, van Gastel W a, Goetgebuer RL, Kahn RS, Boks MPM. Cannabis with high cannabidiol content is associated with fewer psychotic experiences. *Schizophr Res* 2011; **130**: 216–21.

39 Rigucci S, Marques TR, Di Forti M, *et al.* Effect of high-potency cannabis on corpus callosum microstructure. *Psychol Med* 2016; **46**: 841–54.

40 Demirakca T, Sartorius A, Ende G, *et al.* Diminished gray matter in the hippocampus of cannabis users : Possible protective effects of cannabidiol. *Drug Alcohol Depend* 2011; **114**: 242–5.

41 Yücel M, Lorenzetti V, Suo C, *et al.* Hippocampal harms, protection and recovery following regular cannabis use. *Transl Psychiatry* 2016; **6**: e710.

42 Weiland BJ, Thayer RE, Depue BE, Sabbineni A, Bryan AD, Hutchison KE. Daily Marijuana Use Is Not Associated with Brain Morphometric Measures in Adolescents or Adults. *J Neurosci* 2015; **35**: 1505–12.

43 Pagliaccio D, Barch DM, Bogdan R, *et al.* Shared Predisposition in the Association Between Cannabis Use and Subcortical Brain Structure. *JAMA psychiatry* 2015; **72**: 994–1001.

44 French L, Gray C, Leonard G, *et al.* Early Cannabis Use, Polygenic Risk Score for Schizophrenia and Brain Maturation in Adolescence. *JAMA Psychiatry* 2015; **72**: 1002–11.

45 Schoeler, Monk A, Sami MB, *et al.* Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. *The Lancet Psychiatry* 2016; **3**: 215–25.

46 Schoeler, Petros N, Di Forti M, *et al.* Effects of continuation, frequency and type of cannabis use on relapse in the first two years following onset of psychosis - an observational study. *Lancet Psychiatry* 2016; **3**: 947–53.

47 Cooper K, Chatters R, Kaltenthaler E, Wong R. Psychological and psychosocial interventions for cannabis cessation in adults: a systematic review short report. *Health Technol Assess* 2015; **19**: 1–130.

48 Bianconi F, Bonomo M, Marconi A, *et al.* Differences in cannabis-related experiences between patients with a first episode of psychosis and controls. *Psychol Med* 2016; **46**: 995–1003.

49 Salamone JD, Koychev I, Correa M, McGuire P. Neurobiological basis of motivational deficits in psychopathology. *Eur Neuropsychopharmacol* 2015; **25**: 1225–38.

50 Silins E, Horwood LJ, Patton GC, *et al.* Young adult sequelae of adolescent cannabis use: an integrative analysis. *The Lancet Psychiatry* 2014; **1**: 286–93.

51 Stiby AI, Hickman M, Munafò MR, Heron J, Yip VL, Macleod J. Adolescent Cannabis and Tobacco use and Educational Outcomes at Age 16: Birth Cohort Study. *Addiction* 2015; **110**: 658–68.

52 Verweij KJH, Huizink AC, Agrawal A, Martin NG, Lynskey MT. Is the relationship between early-onset cannabis use and educational attainment causal or due to

common liability? *Drug Alcohol Depend* 2013; **133**: 580–6.

53 Meier MH, Caspi A, Ambler A, *et al.* Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci U S A* 2012; **109**: E2657–64.

54 Mokrysz C, Landy R, Gage S, Munafo M, Roiser J, Curran H. Are IQ and educational outcomes in teenagers related to their cannabis use? A prospective cohort study. *J Psychopharmacol* 2016; **30**: 159–68.

55 Jackson NJ, Isen JD, Khoddam R, *et al.* Impact of adolescent marijuana use on intelligence: Results from two longitudinal twin studies. *Proc Natl Acad Sci U S A* 2016; **113**: e500–8.

56 Schoeler T, Kambeitz J, Behlke I, Murray R, Bhattacharyya S. The effects of cannabis on memory function in users with and without a psychotic disorder: findings from a combined meta-analysis. *Psychol Med* 2016; **46**: 177–88.

57 Schreiner AM, Dunn ME. Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: a meta-analysis. *Exp Clin Psychopharmacol* 2012; **20**: 420–9.

58 D'Souza DC, Cortes-Briones JA, Ranganathan M, *et al.* Rapid Changes in CB1 Receptor Availability in Cannabis Dependent Males after Abstinence from Cannabis. *Biol psychiatry Cogn Neurosci neuroimaging* 2016; **1**: 60–7.

59 Hirvonen J, Goodwin RS, Li C-T, *et al.* Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. *Mol Psychiatry* 2012; **17**: 642–9.

60 D'Souza DC, Perry E, MacDougall L, *et al.* The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology* 2004; **29**: 1558–72.

61 D'Souza DC, Ranganathan M, Braley G, *et al.* Blunted psychotomimetic and amnestic effects of delta-9-tetrahydrocannabinol in frequent users of cannabis.

Neuropsychopharmacology 2008; **33**: 2505–16.

62 Morrison PD, Zois V, McKeown D a, *et al.* The acute effects of synthetic intravenous Delta9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. *Psychol Med* 2009; **39**: 1607–16.

63 Curran HV, Brignell C, Fletcher S, Middleton P, Henry J. Cognitive and subjective dose-response effects of acute oral Delta 9-tetrahydrocannabinol (THC) in infrequent cannabis users. *Psychopharmacology (Berl)* 2002; **164**: 61–70.

64 Karniol IG, Shirakawa I, Kasinski N, Pfeferman A, Carlini EA. Cannabidiol interferes with the effects of delta 9 - tetrahydrocannabinol in man. *Eur J Pharmacol* 1974; **28**: 172–7.

65 Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology (Berl)* 1982; **76**: 245–50.

66 Morgan CJA, Curran HV. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *Br J Psychiatry* 2008; **192**: 306–7.

67 Morgan CJA, Gardener C, Schafer G, *et al.* Sub-chronic impact of cannabinoids in street cannabis on cognition, psychotic-like symptoms and psychological well-being. *Psychol Med* 2012; **42**: 391–400.

68 Leweke FM, Schneider U, Radwan M, Schmidt E, Emrich HM. Different effects of nabilone and cannabidiol on binocular depth inversion in Man. *Pharmacol Biochem Behav* 2000; **66**: 175–81.

69 Morgan CJA, Schafer G, Freeman TP, Curran HV. Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study: naturalistic study [corrected]. *Br J Psychiatry* 2010; **197**: 285–90.

70 Englund A, Morrison PD, Nottage J, *et al.* Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. *J Psychopharmacol* 2013; **27**: 19–27.

71 Bhattacharyya S, Morrison PD, Fusar-Poli P, *et al.* Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology* 2010; **35**: 764–74.

72 Fusar-Poli P, Allen P, Bhattacharyya S, *et al.* Modulation of effective connectivity during emotional processing by Delta 9-tetrahydrocannabinol and cannabidiol. *Int J Neuropsychopharmacol* 2010; **13**: 421–32.

73 Hindocha C, Freeman TP, Ferris JA, Lynskey MT, Winstock AR. No Smoke without tobacco: A global overview of cannabis and tobacco routes of administration and their association with intention to quit. *Front Psychiatry* 2016; **7**: 104.

74 Hindocha C, Freeman TP, Winstock AR, Lynskey MT. Vaping cannabis (marijuana) has the potential to reduce tobacco smoking in cannabis users. *Addiction* 2016; **111**: 375.

75 Hindocha C, Shaban NDC, Freeman TP, *et al.* Associations between cigarette smoking and cannabis dependence: a longitudinal study of young cannabis users in the United Kingdom. *Drug Alcohol Depend* 2015; **148**: 165–71.

76 Ream GL, Benoit E, Johnson BD, Dunlap E. Smoking tobacco along with marijuana increases symptoms of cannabis dependence. *Drug Alcohol Depend* 2008; **95**: 199–208.

77 Valjent E, Mitchell JM, Besson M-J, Caboche J, Maldonado R. Behavioural and biochemical evidence for interactions between Delta 9-tetrahydrocannabinol and nicotine. *Br J Pharmacol* 2002; **135**: 564–78.

78 Gurillo P, Jauhar S, Murray RM, *et al.* Does tobacco use cause psychosis? Systematic review and meta-analysis. *The Lancet Psychiatry* 2015; **2**: 718–25.

79 van Gastel W a, Maccabe JH, Schubart CD, *et al.* Cigarette smoking and cannabis use are equally strongly associated with psychotic-like experiences: a cross-sectional study in 1929 young adults. *Psychol Med* 2013; **43**: 2393–401.

80 Meier MH, Hill ML, Small PJ, Luthar SS. Associations of adolescent cannabis use with academic performance and mental health: A longitudinal study of upper middle class

youth. *Drug Alcohol Depend* 2015; **156**: 207–12.

81 Schauer GL, Rosenberry ZR, Peters EN. Marijuana and tobacco co-administration in blunts, spliffs, and mulled cigarettes: A systematic literature review. *Addict Behav* 2017; **64**: 200–11.

82 Daniulaityte R, Nahhas RW, Wijeratne S, *et al.* 'Time for dabs': Analyzing Twitter data on marijuana concentrates across the U.S. *Drug Alcohol Depend* 2015; **155**: 307–11.

83 Van Laar M, Van Der Pol P, Niesink R. Limitations to the Dutch cannabis toleration policy Assumptions underlying the reclassification of cannabis above 15% THC. *Int J Drug Policy* 2016; **34**: 58–64.

84 Freeman TP, Morgan CJ a, Hindocha C, Schafer G, Das RK, Curran HV. Just say 'know': how do cannabinoid concentrations influence users' estimates of cannabis potency and the amount they roll in joints? *Addiction* 2014; **109**: 1686–94.

85 van der Pol P, Liebregts N, de Graaf R, Korf DJ, van den Brink W, van Laar M. Validation of self-reported cannabis dose and potency: an ecological study. *Addiction* 2013; **108**: 1801–8.

86 Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 2003; **42**: 327–60.