Can we make cannabis safer?

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Cannabis use and related problems are on the rise globally alongside an increase in the potency of cannabis sold on both black and legal markets. Additionally, there haps been a shift towards abandoning prohibition for a less punitive and more permissive legal stance on cannabis, such as decriminalisation and legalisation. It is therefore crucial that we explore new and innovative ways to reduce harm. Research has found cannabis with high concentrations of its main active ingredient, δ-9-tetrahydrocannabinol (THC), to be more harmful (in terms of causing the main risks associated with cannabis use, such as addiction, psychosis, and cognitive impairment) than cannabis with lower concentrations of THC. By contrast, cannabidiol, which is a non-intoxicating and potentially therapeutic component of cannabis, has been found to reduce the negative effects of cannabis use. Here, we briefly review findings from studies investigating various types of cannabis and discuss how future research can help to better understand and reduce the risks of cannabis use.

Lancet Psychiatry 2017; 4: 643–48

Published Online March 1, 2017

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Introduction

The cannabis landscape is rapidly changing. Following the Single Convention on Narcotic Drugs in 1961, possession, distribution, and use of cannabis were criminalised and cannabis-related arrests increased substantially in Europe and North America, particularly among young and ethnic-minority populations.[1] In the decades following the convention, there has been an overall trend towards greater cannabis use in most parts of the world.[2] This trend might be due to prohibitive measures (eg, banning substances or law enforcement) having little or no effect on the harms related to the use or abuse of cannabis, as suggested by a systematic review.[3] In the UK, demand for the treatment of cannabis-related problems increased by 56% in adults and 51% in those younger than 18 years between 2005–06 and 2013–14.[4] Increased treatment seeking for problems related to cannabis use has also been evident in the USA,[5] and cannabis has become the primary illicit drug responsible for first-time entry to drug treatment in Europe, although one-quarter of first-time entries in Europe are thought to be referrals from the criminal justice system.[6]

Certain US states, including California, Oregon, Alaska, Maine, Massachusetts, Washington, Nevada, and Colorado, and Uruguay have decided to allow cannabis to be sold for recreational purposes.[7] Canada is set to legalise recreational use of cannabis in 2017, and several European countries have lessened or abolished criminal sanctions on cannabis possession and use.[8] Although it is likely that such moves will decrease crime-related financial costs to the state, the effects that they will have on cannabis consumption and the prevalence of cannabis-associated harms are unclear.

In any event, moves toward legalisation of medicinal or recreational cannabis are unlikely to decrease the number of people who use cannabis. However, these moves could facilitate measures to reduce population levels of harm—for example, by regulating cannabis potency and promoting safer (eg, non-tobacco) routes of administration.[9] Therefore, those concerned about cannabis-related harms should consider other means by which the use of cannabis might be made safer.

Increasing potency of cannabis

Cannabis sativa L. contains at least 144 different compounds known as cannabinoids, which are specific to the cannabis plant, and more than 1100 other compounds, such as terpenoids and flavonoids.[10] The most abundant of the cannabinoids are δ-9-tetrahydrocannabinol (THC) and cannabidiol (often known as CBD), which the plant produces in different ratios from the same precursor cannabigerol.[11] Hence, increased THC content in cannabis will be at the cost of cannabidiol content. Furthermore, prevention of pollination of the female plant leads to a more potent product because the plant converts its energy to the production of cannabinoids rather than seeds.[12] 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 four decades, cannabis potency (the percentage of THC) has on average doubled worldwide,[13] and cannabidiol concentrations have remained low or absent in most cannabis preparations.[14–17] Systematic crossbreeding of cannabis plants by growers on the black market has led to a market dominance of plants containing high concentrations of THC. By 2008, roughly 80% of cannabis sold on the UK black market was high-potency cannabis,[15] which was an increase from 55% in 2004–05[14] and 15% in 1999–2002.[18] In the USA, a report[17] showed that the increase in THC concentrations in cannabis over the past two decades was due to a shift towards high-potency cannabis (sinsemilla), as opposed to regularly (outdoor) grown cannabis.[17] Cannabis resin (so-called hash) can be a more potent form of cannabis, and it has been reported to reach potencies of more than 60% THC (per weight) in the Netherlands.[16] Conversely, resin usually has a low potency in the UK, where it consists of equal quantities of THC (4%) and cannabidiol (4%).[14] Additionally, new extraction techniques produce concentrates of an extremely high potency (eg, Butane Hash Oil), which contain up to 75% THC.[19] Of more concern are synthetic cannabinoids (eg, so-called Spice), which typically act as full agonists of cannabinoid receptors (THC is a partial

agonist) and have been associated with severe adverse reactions, including death.[20]

Significance of cannabidiol

The main adverse effects associated with cannabis use are dependence, cognitive and educational impairment, and psychosis.[21] Crucially, evidence suggests that the incidence of adverse effects related to cannabis use is associated with the concentrations of THC and cannabidiol. Encouragingly, increasing the concentration of cannabidiol does not appear to alter the pleasurable effects of THC, such as the subjective feeling of "stoned". A recent study showed that cannabidiol given orally up to 800 mg did not alter the pleasurable, reinforcing, or intoxicating effects of a smoked cannabis cigarette (containing about 4·4 mg of THC).[22] Two studies[23,24] of inhaled cannabinoid vapour (with combinations of 8 mg THC, 8 mg THC plus 10 mg cannabidiol, and 8 mg THC plus 16 mg cannabidiol) found no differences between the combinations in terms of participant ratings of feeling stoned. Lastly, a study[25] of participants who smoked their own cannabis found no difference in so-called stoned ratings among low to high ratios of cannabidiol to THC. Although cannabidiol has not been reported to alter the pleasurable effects of THC, more research is warranted to confirm this absence of effect.

Dependence

Approximately one in 11 people who try cannabis will become dependent in their lifetime,[26] although this risk is almost doubled if use starts in adolescence[27] and is between 25% and 50% for people who use cannabis daily.[28] However, not all varieties of cannabis have the same liability towards dependence. An online survey[29] of more than 2514 cannabis users found that use of high-potency cannabis was associated with a greater severity of cannabis dependence, alongside self-reported memory problems and paranoia, compared with use of cannabis of a lower potency. However, high-potency cannabis was rated as the preferred type and the type that produced the best "high".[29] This preference for high-potency cannabis is potentially important because interventions aimed at switching users to a less potent variety might fail if the alternative lacks the pleasurable effects of high-potency cannabis.

A few case reports[30,31] have found that cannabidiol can reduce symptoms associated with withdrawal from cannabis, which was also reported for nabiximols (cannabidiol to THC ratio of 1:1),[32,33] although it was unclear whether these effects were caused by cannabidiol, THC, or their interactive effects. Additionally, in an attentional bias task,[25] cannabis containing a high ratio of cannabidiol to THC reversed the tendency of participants to automatically orient attention towards cannabis and food cues compared with cannabis containing a low ratio of cannabidiol to THC. Therefore, varieties of cannabis with greater concentrations of cannabidiol might reduce the likelihood of users developing dependence, while preserving the pleasurable effects of cannabis.

Psychosis

High-potency cannabis is also associated with a higher risk of psychosis, and an earlier onset of psychosis, than low-potency forms.[34,35] In a case-control study[36] of patients with first-episode psychosis, daily use of cannabis containing high concentrations of THC and low concentrations of cannabidiol was associated with a 5-fold increase in the risk of psychosis, although no such increase was found among users of low-potency resin.

In a Dutch population study of 1877 participants,[37] people who used cannabis with a higher cannabidiol concentration had experienced fewer psychotic-like events in their lifetime than did those who preferred varieties containing less cannabidiol. Neuroimaging studies have also suggested that the MRI correlates of cannabis use can vary with exposure to cannabidiol. One study[38] found that regular use of high-potency cannabis was associated with alterations in the corpus callosum, an effect that was absent in hash users (UK hash). Two other MRI studies[39,40] reported that cannabis users had smaller hippocampal volumes than did non-users, although this change was not evident in cannabis users with hair samples that were positive for cannabidiol. However, the extent to which cannabis use is associated with neuroanatomical changes remains controversial; studies[41–43] that have matched participants on alcohol use, or have accounted for heritable and genetic risk, have failed to identify an association between cannabis use and brain structure.

Cannabis use is particularly harmful for patients with an existing psychotic illness. A meta-analysis[44] found that patients with schizophrenia (ie, psychotic illness) who continued to use cannabis were more likely to relapse than non-users. In another study,[45] continued use of high-potency cannabis was more harmful to patients with psychosis than use of cannabis containing lower THC concentrations and a relatively high concentration of cannabidiol. Clinical interventions to reduce cannabis use in patients with psychosis have been largely unsuccessful.[46] A study[47] of patients with first-episode psychosis found that these patients experience both the positive and negative effects of cannabis more intensely than do healthy controls, which might explain their unwillingness to stop using cannabis despite the negative effects of the drug, and also explain the failure of interventions in this population. Reducing substance use usually depends on the user having insight and motivation; both can be severely impaired in patients with psychotic disorders, which might also contribute to intervention failure.[48]

Cognition and intelligence

Whether the use of cannabis has lasting negative effects on memory functioning, intelligence, and other aspects

of cognition in the normal population has been extensively debated.[21] A study[49] of three large samples found that cannabis use before the age of 17 years was related to decreased rates of high school completion and degree attainment. Similarly, a 1-year follow-up study[50] of 1155 adolescents found that weekly cannabis use was related to a poorer performance (albeit less than tobacco) in maths and English when participants were aged 16 years after controlling for confounders. However, in a large twin study,[51] early school-leaving was explained by shared environmental risk factors. Therefore, although there is an association between cannabis use and poorer educational outcomes, these effects might be explained by other factors.

As for general intelligence, a 38-year follow-up study[52] 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. However, this study was limited in terms of controlling for confounding variables and the relatively small number of participants from the total study population in the affected group. Two large-scale, follow-up studies[53,54] found that cannabis use was not associated with a reduced IQ when additional confounders and genetic factors were controlled for. These studies only followed up participants up to the ages of 15 or 20 years and did not exclude the possibility that IQ might be affected if cannabis use or dependence are maintained beyond these ages.

Although there remains a debate about whether cannabis use leads to long-term cognitive impairments or educational problems following abstinence, it is clear that ongoing regular cannabis use impairs cognition. A meta-analysis[55] found that cannabis users performed significantly worse in memory tasks than non-users, with the greatest impairments in prospective memory, visual recognition, and immediate and delayed recall. The authors reported that more than regular or regular use (defined as using between four and 20 times per month) was related to worsened performance, whereas no change in performance was seen in light users (defined as four times per month or less). However, no significant difference in neurocognitive performance was seen between users and controls after 4 weeks of abstinence.[56] This observation is in line with PET imaging studies,[57,58] which showed that decreased cannabinoid receptor 1 densities can be reversed within 4 weeks of abstinence.

Insights from cannabinoid experiments

Although epidemiological studies are fundamental to understand the population effect of a behaviour or exposure, they come with some clear limitations. For example, when exploring the different outcomes for cannabis users and non-users, it is often unclear whether the observed effects (eg, impaired cognition) are due to cannabis use itself or confounding variables. Experimental studies, such as randomised trials, allow inference of causality, although with the caveat of only allowing conclusions relating to the acute effects of a drug and not to long-term exposure. As with all pharmaceutical randomised trials, safety and ethical considerations are of utmost importance. However, decades of experimental research with cannabinoids have shown them to be very safe when given in controlled settings to participants who have been screened for potential risk factors.[59] Furthermore, the toxicological risks of THC are extremely low.[60]

Randomised trials[61–63] in healthy volunteers have shown that administration of high-dose THC can induce several psychological changes, including transient psychotic symptoms. Experimental studies[61,64] have also consistently found that THC can induce impairments in memory functioning in a dose-response manner. However, studies that have combined THC with cannabidiol have found very different results: co-administration of cannabidiol and THC significantly reduced time estimation errors and psychological reactions caused by THC,[65] and 1 mg/kg cannabidiol significantly reduced the anxiogenic effects of 0·5 mg/kg THC in healthy volunteers.[66] In a study of 140 cannabis users,[67] people who tested positive for both THC and cannabidiol in hair samples had significantly fewer psychotic-like effects than did those who only tested positive for THC. These results were replicated in a study of recreational cannabis users,[68] and the same group found that cannabidiol protected against the detrimental effects of THC on emotional processing after administering inhaled THC (8 mg) and cannabidiol (16 mg) to volunteers.[23] Furthermore, cannabidiol reversed the illusory effects of THC on depth perception in another study.[69]

There is also evidence that cannabidiol can reverse the negative effect of THC on cognitive performance. A naturalistic study of the acute effects of cannabis,[70] involving 134 cannabis users who were smoking their own cannabis, found that participants who used cannabis containing higher concentrations of cannabidiol showed no impairment in immediate and delayed prose recall compared with the same participants when they had not used cannabis. By contrast, performance of these tasks was significantly impaired among those who used cannabis containing equivalent THC concentrations, but no cannabidiol. The same group explored the memory function of 120 users while analysing hair samples for the presence of cannabidiol; participants who tested positive for cannabidiol had significantly better performances than did those who tested negative for cannabidiol.[68]

We found[71] that pretreatment with 600 mg oral cannabidiol before administration of 1·5 mg intravenous THC significantly inhibited paranoia, psychotic symptoms, and impairments to delayed recall in 48 healthy volunteers. These effects were not caused by changes to plasma concentrations of THC in the group pretreated with cannabidiol. Rather, these effects appeared to reflect the opposite effects of THC and cannabidiol on the regions of the brain that mediate psychotic and anxiety

symptoms and support cognitive processes, such as memory, emotional processing, and response inhibition.[72,73]

Making cannabis safer

It is vital, especially now that cannabis is becoming increasingly liberalised, that researchers, clinicians, and policy makers explore alternative and innovative ways by which we can reduce and mitigate cannabis-related harms.

First, more focus on the co-use of tobacco and cannabis and the additive harm it poses is needed, especially since cannabis is frequently used together with tobacco, particularly in Europe.[74] Use of other routes of administration, such as smoke-free vapourisers, has the potential to reduce tobacco consumption and the harmful effects that smoke poses to the user.[75] Reduced tobacco consumption might be particularly important because tobacco increases the addictive potential of cannabis.[76–78] Furthermore, tobacco use might be an independent risk factor for psychosis[79] and modify the risk of psychosis from cannabis use.[80] Studies[50,53,81] of the effect of cannabis use on cognition have also found that the association between cannabis use and cognition weakened after controlling for tobacco use. However, few controlled experimental studies have investigated the interaction between cannabis and tobacco.[82] Hence, future studies should address tobacco when investigating the harmful effects of cannabis.

Second, we need to better understand the harms posed by cannabis varieties with different THC potencies. Extremely potent cannabis concentrates (eg, Butane Hash Oil) have gained popularity in the USA, where THC content is not regulated.[83] Policies of a 15% THC cap proposed by Uruguay and the Netherlands could be beneficial, but they are not yet based on a scientific understanding of harms posed by potencies above this limit.[84] Taxation based on THC content is an alternative approach to reduce use of more potent forms of cannabis, although further research is needed to assess its effect (these measures would also have to minimise use of synthetic cannabinoids, since they pose a greater health risk than cannabis). Only since 2009 have studies[29,34–38] differentiated between types of cannabis based on their THC content. However, most of these studies have not measured THC and cannabidiol content directly but have used indirect measures of potency, such as strengths reported in studies of cannabis from police seizures or coffee shops, and have relied on self-report measures. Although self-report measures are associated with THC and cannabidiol content, these associations are modest and weaker among infrequent users.[85,86] Future longitudinal studies might collect cannabis cigarettes (joints) from their participants over the course of the study and obtain information about how often they would smoke such a cigarette. This information will allow researchers to calculate cumulative dose exposures for cannabinoids and tobacco, which will result in a far more accurate estimate of harm. Furthermore, this information could contribute to cannabis use guidelines, such as we have for alcohol.

Lastly, and perhaps most importantly, more knowledge is needed about the ratio of THC to cannabidiol that reduces harm. The available evidence suggests that cannabidiol protects against many of the harmful effects of THC, although the relative dose of cannabidiol that is required to offset the negative effects of a given dose of THC is unknown. Experimental studies have been unable to establish this dose. Some studies[67,68] have relied on the presence or absence of cannabidiol in the hair samples of participants, whereas other studies[22,71] have given cannabidiol orally while administering inhaled or intravenous THC. Cannabinoids are absorbed differently when administered orally than when inhaled or administered intravenously (and produce different metabolite profiles), which prevents extrapolation of the relative cannabidiol to THC ratio.[87] Therefore, future experimental studies should explore various cannabidiol to THC ratios administered via the same route and assess standardised measures of cognitive performance, psychopathology, and liability for addiction. Establishment of a "safe" cannabidiol to THC ratio might be used as a harm reduction strategy, wherein cannabis users (particularly those with a psychotic illness) who are experiencing negative effects from the use of skunk-type cannabis can be encouraged to switch to a less harmful type. Encouragingly, cannabidiol has not been shown to alter the rewarding or pleasurable effects of THC,[22–24] which is important because any attempt to reduce the harmful effects of cannabis would most likely be ineffective if it also reduced the rewarding effects of cannabis.

With the rapidly changing political climate around cannabis, the demand to effectively reduce cannabis-related harms has never been greater, and more research (both experimental and observational) is urgently needed to inform policy decisions. A strategy based on increasing the content of cannabidiol in cannabis might be especially promising because cannabidiol can offset several harms associated with cannabis without compromising its rewarding effects.

Search strategy and selection criteria

This narrative, critical Personal View was not done using the standard search criteria and methods for a systematic review. The articles in this Personal View were obtained by searches of PubMed and Google Scholar, Google Scholar alerts for key terms ("cannabis", "marijuana", "cannabidiol") up to Oct 7, 2016, reference lists in existing reviews and papers, and conference presentations.

Contributors

The article was conceptualised by AE and PMcG, and was written by AE. PMcG, RMM, and TPF made additional comments and content recommendations, and reviewed and corrected the manuscript.

Declaration of interests
We declare no competing interests.

Acknowledgments
This work was supported by a grant from the UK Medical Research council (MR/P006841/1).

References

1 Room R, Fisher B, Hall W, Lenton S, Reuter P. Cannabis policy: moving beyond stalemate. Oxford, NY: Oxford University Press, 2010.
2 UNODC. World Drug Report 2015. 2015. https://www.unodc.org/documents/wdr2015/World_Drug_Report_2015.pdf (accessed Oct 15, 2015).
3 Stockings E, Hall WD, Lynskey M, et al. Prevention, early intervention, harm reduction, and treatment of substance use in young people. *Lancet Psychiatry* 2016; **3:** 280–96.
4 PHE. Young people's statistics from the National Drug Treatment Monitoring System (NDTMS): 1 April 2014 to 31 March 2015. London: Public Health England, 2015: 1–37.
5 UNODC. World Drug Report 2014. 2014. https://www.unodc.org/documents/wdr2014/World_Drug_Report_2014_web.pdf (accessed April 1, 2016).
6 EMCDDA. European Drug Report 2015. 2015. http://www.emcdda.europa.eu/edr2015 (accessed Oct 15, 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 (accessed May 29, 2013).
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; **111:** 2091–92.
10 Hanuš LO, Meyer SM, Muñoz E, Taglialatela-Scafati O, Appendino G. Phytocannabinoids: a unified critical inventory. *Nat Prod Rep* 2016; **33:** 1357–92.
11 Small E. Evolution and classification of *Cannabis sativa* (marijuana, hemp) in relation to human utilization. *Bot Rev* 2015; **81:** 189–294.
12 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:** 31–38.
13 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.
14 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:** 90–94.
15 Hardwick S, King L. Home Office cannabis potency study. 2008. http://www.dldocs.stir.ac.uk/documents/potency.pdf (accessed Nov 29, 2011).
16 Niesink RJM, Rigter S, Koeter MW, Brunt TM. Potency trends of Δ(9)-tetrahydrocannabinol, cannabidiol and cannabinol in cannabis in the Netherlands: 2005–2015. *Addiction* 2015; **110:** 1941–50.
17 ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC. Changes in cannabis potency over the last 2 decades (1995–2014): analysis of current data in the United States. *Biol Psychiatry* 2016; **79:** 613–19.
18 King L, Carpentier C, Griffiths P. An overview of cannabis potency in Europe. 2004. http://www.emcdda.europa.eu/publications/insights/cannabis-potency (accessed May 28, 2014).
19 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.
20 Trecki J, Gerona RR, Schwartz MD. Synthetic cannabinoid-related illnesses and deaths. *N Engl J Med* 2015; **373:** 103–07.
21 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.
22 Haney M, Malcolm RJ, Babalonis S, et al. Oral cannabidiol does not alter the subjective, reinforcing or cardiovascular effects of smoked cannabis. *Neuropsychopharmacology* 2016; **41:** 1974–82.
23 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.
24 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.
25 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.
26 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.
27 Anthony JC. The epidemiology of cannabis dependence. In: Roffman RA, Stephens RS, eds. Cannabis dependence: its nature, consequences and treatment. Cambridge: Cambridge University Press, 2006: 58–105.
28 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.
29 Freeman TP, Winstock AR. Examining the profile of high-potency cannabis and its association with severity of cannabis dependence. *Psychol Med* 2015; **45:** 3181–89.
30 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:** 162–64.
31 Shannon S, Opila-Lehman J. Cannabidiol oil for decreasing addictive use of marijuana: a case report. *Integr Med (Encinitas)* 2015; **14:** 31–35.
32 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.
33 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:** 281–91.
34 Di Forti M, Morgan C, Dazzan P, et al. High-potency cannabis and the risk of psychosis. *Br J Psychiatry* 2009; **195:** 488–91.
35 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; **40:** 1509–17.
36 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. *Lancet Psychiatry* 2015; **2:** 233–38.
37 Schubart CD, Sommer IEC, van Gastel WA, Goetgebuer RL, Kahn RS, Boks MPM. Cannabis with high cannabidiol content is associated with fewer psychotic experiences. *Schizophr Res* 2011; **130:** 216–21.
38 Rigucci S, Marques TR, Di Forti M, et al. Effect of high-potency cannabis on corpus callosum microstructure. *Psychol Med* 2016; **46:** 841–54.
39 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:** 242–45.
40 Yücel M, Lorenzetti V, Suo C, et al. Hippocampal harms, protection and recovery following regular cannabis use. *Transl Psychiatry* 2016; **6:** e710.
41 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.
42 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.
43 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.
44 Schoeler, Monk A, Sami MB, et al. Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. *Lancet Psychiatry* 2016; **3:** 215–25.

45 Schoeler T, 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.

46 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.

47 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.

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

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

50 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.

51 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:** 580–86.

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

53 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.

54 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 USA* 2016; **113:** e500–08.

55 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.

56 Schreiner AM, Dunn ME. Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: a meta-analysis. *Exp Clin Psychopharmacol* 2012; **20:** 420–29.

57 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:** 60–67.

58 Hirvonen J, Goodwin RS, Li CT, et al. Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. *Mol Psychiatry* 2012; **17:** 642–49.

59 Carbuto M, Sewell RA, Williams A, et al. The safety of studies with intravenous Δ9-tetrahydrocannabinol in humans, with case histories. *Psychopharmacology* 2012; **219:** 885–96.

60 Lachenmeier DW, Rehm J. Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach. *Sci Rep* 2015; **5:** 8126.

61 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.

62 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.

63 Morrison PD, Zois V, McKeown DA, et al. The acute effects of synthetic intravenous delta9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. *Psychol Med* 2009; **39:** 1607–16.

64 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.

65 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:** 172–77.

66 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.

67 Morgan CJA, Curran HV. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *Br J Psychiatry* 2008; **192:** 306–07.

68 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.

69 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.

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

71 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.

72 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.

73 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.

74 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.

75 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.

76 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.

77 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.

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

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

80 van Gastel WA, 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.

81 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.

82 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.

83 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.

84 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.

85 Freeman TP, Morgan CJ, 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.

86 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:** 1801–08.

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