Adverse effects of heavy cannabis use: even plants can harm the brain

Lucia Sideli[a], Giulia Trotta[a], Edoardo Spinazzola[a,b], Caterina La Cascia[c], Marta Di Forti[d,e,f,*]

1. Introduction

The spread of laws legalising cannabis for medicinal or recreational use has been accompanied by more relaxed attitudes towards cannabis. Data from the United States show that in states that have legalised cannabis, prevalence of daily, weekly, and monthly cannabis use was 11.3%, 18.3%, and 25.0% respectively, whereas in countries where it is still illegal, it was lower (7.4%, 11.6%, and 16.8% respectively).[46] Evidence indicates a trend of increase among adolescents,[58] a particular vulnerable category for the initiation of substance use.[114] In parallel, we have seen the concentration of THC (Δ-9-tetrahydrocannabinol) in the cannabis sold both in the United States and in Europe rising and those types of cannabis with high THC,[35] and a corresponding decrease of cannabidiol (CBD) content,[17,35,95] becoming more widely available. Most commonly, cannabis is used for its enjoyable effects, the "high" feeling.[69] In addition, in those countries where its use has been legalised, many people smoke cannabis for medical use, anxiety, depression, and pain relief,[71] with those suffering from chronic pain being at higher risk of developing cannabis use disorder (CUD).[57]

This review aims to challenge the widespread view that cannabis being a "plant" does not carry adverse effects, and review the evidence concerning the effects of cannabis use on mental health and cognition.

2. Understanding cannabis

The plant *Cannabis sativa* contains more than 100 different psychoactive ingredients,[33,53,74] but the most widely studied are THC (Δ-9-tetrahydrocannabinol) and CBD (cannabidiol),[36,74,84] synthesised from the same precursor, cannabigerol. Therefore, types of cannabis with high concentrations of THC produce low CBD and vice versa.[23]

THC is a partial agonist at both the cannabinoid receptors (CB) $CB_2 R$ and $CB_1 R$, the latter highly abundant in the brain.[64, 83, 97] THC is responsible for most of the enjoyable and adverse effects that commonly arise after acute and regular cannabis use.[8,24,116] Conversely, CBD is a negative allosteric modulator at the CB_1R,[76] whose effects are distinct and, in many cases, opposite of those observed with THC. CBD does not induce euphoria but may exert anxiolytic, antiepileptic, anti-inflammatory, and analgesic properties **Figure 1**.[9,10,22,91,99,100,108]

3. Cannabis intoxication and dependence

3.1. Acute adverse effects

Cannabis use can lead to intoxication, defined as a series of "clinically significant problematic behavioural or psychological changes (eg, impaired motor coordination, euphoria, anxiety, sensation of slowed time, impaired judgment, and social withdrawal) that develop during, or shortly after, cannabis use."[2] The experience of feeling "high" after cannabis use is variable and subjective,[48] depending on the dose, the environment, and previous experience and expectations of the drug user.[101] The most common acute adverse effects are panic attacks and other forms of anxiety, mostly reported by naive users.[50,51] Because cannabis impairs psychomotor skills, reaction time, and motor coordination, its use leads to increased risk of motor vehicle accidents.[6,98] Current cannabis users have higher rates of hospitalization for injury from all causes than former cannabis users or nonusers.[41]

3.2. Cannabis use disorders

DSM-5 CUDs is now a single diagnostic entity including abuse and dependence[3]; it is prevalent (2.54% 12-month prevalence among U.S. adults), associated with comorbidity and disability, and largely untreated.[56] Moreover, CUD often presents comorbidly with psychotic disorders.[59] Preclinical studies support the evidence that exposure to THC leads to dependence.[1,16,19] Cannabis can induce tolerance in humans[60,65] and dependence.[16] Because cannabis is eliminated slowly from the body, withdrawal symptoms are generally mild. Nevertheless, discontinuation of long-term frequent cannabis use can induce anger, decreased appetite, irritability, nervousness, restlessness, and sleep difficulties,[13,79] suggesting that the alleviation of abstinence symptoms contributes to the maintenance of daily
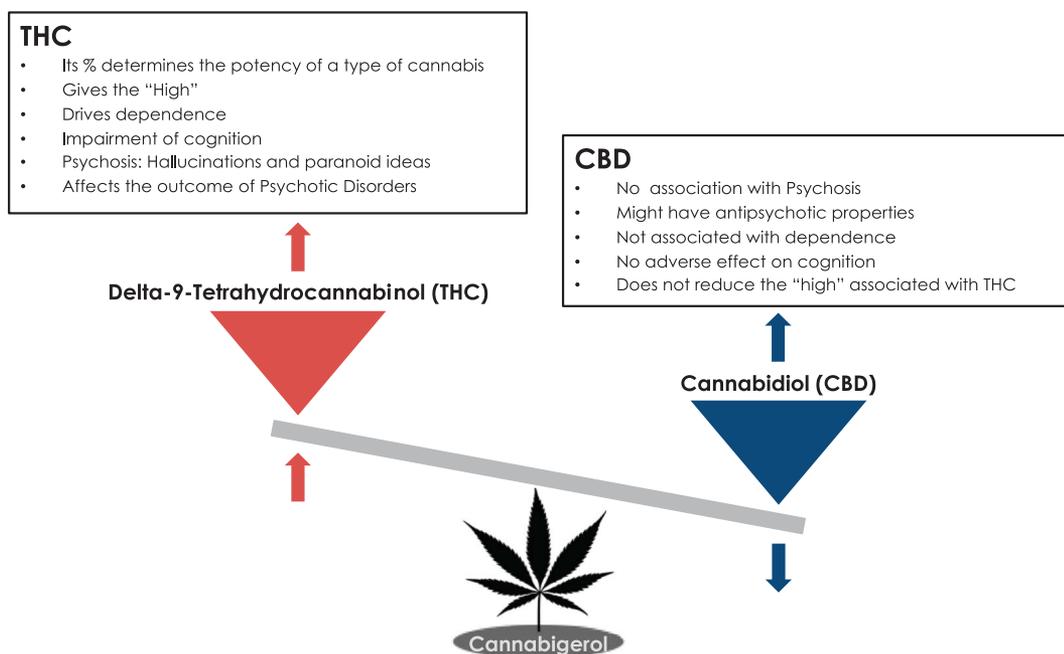
Figure 1. This diagram graphically illustrated first, the differential and in fact opposite psychiatric and cognitive effects of THC and of CBD, and second, how both compounds derive from the same precursor. Therefore if, for instance, a *Cannabis sativa* plant is genetically driven to the production of high quantity of THC, it will only be capable to synthesise small quantities of CBD.[10]

cannabis use.[52] Recent evidence, from the Netherlands, has shown an association between changes over time in average THC content in the type of cannabis available and rates of admission to specialist cannabis treatment units.[37]

4. Cannabis and psychosis

4.1. Epidemiological evidence

Cross-sectional and prospective studies demonstrate a causal link between cannabis use and psychotic disorder, with greater risk for cannabis users, compared to nonusers.[73,85,88,89] The most recent meta-analysis reported a pooled odds ratio (OR) = 3.90 (95% confidence interval [CI] 2.84-5.34) and shows a dose–response association between cannabis use and psychosis outcomes.[82] Furthermore, findings from general population studies indicate, even after statistical adjustment for other known psychosis risk factors, a strong association between cannabis use and psychotic symptoms, and especially paranoia, beyond the clinical disorder.[34,92,95,102]

4.2. Harmful patterns of cannabis use

Data from South London showed that use of high-potency cannabis (skunk-type average THC% = 14%), compared to never use, was associated with a 3-fold risk (OR = 2.92, 95% CI 1.52-3.45), which increased to 5-fold when the use was daily (OR = 5.4, 95% CI 2.81-11.31), of developing psychotic disorders; hash-like cannabis use carried no additional risk compared to never use—likely because of ratio of THC: CBD = 1 ratio in most of the London hash available at the time of the study.[28,29] Consistently, survey data from general population samples suggest that use of cannabis with high CBD content is associated with fewer psychotic experiences.[10,87] Morgan and Curran[87] showed that healthy volunteers with hair traces of THC and cannabidiol reported less schizophrenia-like symptoms than those with only THC in their hair traces of THC.[87]

More recently, data from the EUGEI study, a large multicentre European collaboration,[40] confirmed that those who use daily types of cannabis with THC content = >10% are 5 times (OR = 4.8; 95% CI 2.5-6.3) more likely to suffer from psychotic disorder than never users[30]; a risk that was greater OR = 9.43 (95% CI 6.2-19.6) in Amsterdam where popular types of cannabis such as Nederhasj and Nederwiet have THC contents that can reach 67% and 22%, respectively.[30,90] Moreover, first episode psychosis patients (FEP), who used high-potency cannabis daily experienced, at their illness onset, more prominent positive symptoms (eg, delusions and hallucinations) and, in particular, paranoia.[96]

4.3. Cannabis use and age of onset of psychotic disorders

A meta-analysis by Large et al.[77] reported that subjects who used cannabis experienced, on average, their illness onset 3 years earlier compared to never users, a significantly higher effect than for use of other drugs including alcohol. Another study showed that if subjects had used high-potency cannabis daily, their illness onset was, on average, 6 years earlier[31] compared to never users.

4.4. Heavy cannabis use and rates of psychotic disorders

Boydell et al.[11] claimed that cannabis consumption could impact on the incidence of schizophrenia in those areas where the prevalence of cannabis use is high. The first, clear evidence of the impact of cannabis use on rates of psychotic disorder comes from the EUGEI study. Across 11 European sites, the incident rates for psychotic disorder—adjusted for age, sex, and ethnicity—were positively correlated with the prevalence of use of high-potency cannabis ($r = 0.7$; $P = 0.0286$) and, independently, with the prevalence of daily use ($r = 0.8$; $P = 0.0109$) among the controls representative of the local populations.[30] These findings suggest that where daily cannabis use and use of high-potency cannabis is prevalent in the general population, there are more new cases of psychotic disorders.

Indeed, the study shows that 12% of patients with FEP across Europe can be attributed to high-potency cannabis use, rising to 30% in London and 50% in Amsterdam.[30] If high-potency cannabis were no longer available, incidence in London would drop from 46 × 100,000 to 32 × 100,000 person-years, even after taking into account age, sex, and migration. Further independent evidence comes from Portugal that has registered a steady increase in the rate of hospital admissions for psychotic disorders with comorbid CUD.[45] Similar data were reported in Denmark.[59] Both countries have seen a rise in the potency of available cannabis over the same period.[35,111]

4.5. Reverse causality and self-medication hypotheses

The self-medication hypothesis suggests that patients with psychotic disorders use cannabis to seek relief from their symptoms.[4,43,106] The Christchurch Health & Development birth cohort study showed that although cannabis use was associated with increasing psychotic symptoms, the experience of psychotic symptoms inhibits rather than encourages subsequent cannabis use.[25,26] Moreover, findings from the Dunedin birth cohort indicated a specific temporal link between cannabis use and onset of psychosis outcomes. Cannabis use at 15 years of age was associated with a 4-fold increase in risk for schizophreniform psychosis at 26 years of age (OR = 4.50, 95% CI 1.11-18.21), compared to never use. This association remained present (OR = 3.12; 95% CI 0.73-13.29) after excluding those participants who at 11 years of age had reported psychotic symptoms, although failed to reach significance because of reduced power.[5]

More recently, Mendelian randomization investigated the relationship between cannabis use and randomly assorted genetic variants that are associated with psychosis, which were used as proxy for psychosis itself. Mendelian randomization studies have suggested that cannabis use initiation is partly explained by common genetic variants associated with risk of schizophrenia, thus proposing a direction of causality from schizophrenia genes to cannabis use (ie, reverse causality) rather than from cannabis use to schizophrenia and other psychosis.[39,93,115] By contrast, findings

Table 1

Summary of meta-analyses reporting adverse effects associated with cannabis use.

Adverse effect	Participants	Studies	Main findings	Estimate
Psychosis				
Marconi et al.[18]	66,816 individuals from 10 studies	Random-effects meta-analysis on risk of psychosis	High levels of cannabis use increase the risk of psychotic outcomes with a dose–response relationship	OR = 3.9, 95% CI [2.84-5.34]
Large et al.[77]	8167 substance using patients from 83 studies	Random-effects meta-analysis on age at onset of psychosis	Relationship between cannabis use and earlier onset of psychotic illness	ES = −2.70, 95% CI [−0.53 to −0.30]
Schoeler et al.[103]	16,565 individuals from 24 studies	Random-effects meta-analysis on clinical outcomes of psychosis	Continued cannabis use after onset of psychosis predicts adverse outcome than for nonusers	d = 0.31, 95% CI [0.04-0.57]
Bipolar				
Gibbs et al.[42]	2391 individuals from 6 studies	Random-effects meta-analysis	Association between cannabis use and both the exacerbation of manic symptoms in those with previously diagnosed bipolar disorder and new-onset manic symptoms	OR = 2.97, 95% CI [1.8-4.9]
Depression				
Gobbi et al.[44]	22,317 individuals from 11 studies	Random-effects meta-analysis	Cannabis consumption in adolescence is associated with increased risk of developing depression in young adulthood	OR = 1.37, 95% CI [1.16-1.62]
Lev-Ran et al.[78]	76,058 individuals from 14 studies	Random-effects meta-analysis	Heavy cannabis use may be associated with an increased risk for developing depressive disorders	OR = 1.62, 95% CI [1.21-2.16]
Anxiety				
Gobbi et al.[44]	22,317 individuals from 11 studies	Random-effects meta-analysis	No evidence of an association with anxiety	OR = 1.18, 95% CI [0.84-1.67]
Twomey et al.[113]	58,538 individuals from 10 studies	Random-effects meta-analysis	Cannabis use is no more than a minor risk factor for the development of elevated anxiety symptoms in the general population	aOR = 1.08, 95% CI [0.94-1.23]
Cognition				
Grant et al.[47]	623 cannabis users and 409 minimal or non-cannabis users from 11 studies	Fixed-effects meta-analysis	There might be decrements in the ability to learn and remember new information in chronic users, whereas other cognitive abilities are unaffected	Learning ES = −0.21, 99% CI [−0.39 to 0.02] Forgetting/retrieval ES = −0.27, 99% CI [−0.49 to −0.04]
Schreiner et al.[107]	1010 current or former cannabis users and 837 controls with no or limited cannabis use from 33 studies	Random-effects meta-analysis	A small negative residual effect of cannabis use on overall cognitive performance, no evidence of lasting residual effect	Overall cognitive performance ES = −0.29, 95% CI [−0.46 to −0.12] Lasting residual effect ES = −0.12, 95% CI [−0.32 to 0.07]

This table illustrates the findings from meta-analyses that report an association between several mental health outcomes, cognition, and cannabis use.
CI, confidence interval; ES, effect size; OR, odds ratio.

from the EUGEI study showed that (1) genetic summary score for schizophrenia (polygenic risk score [PRS]) did not predict the propensity to initiate cannabis use, (2) how frequently someone uses it, and (3) the potency of the cannabis used. On the contrary, heavy cannabis use increased the risk for psychotic disorders independent of the individual's schizophrenia PRS. For instance, daily users of high-potency cannabis (THC = >10%) had a 5-fold increase (OR = 5.4; 95% CI 3.21-10.63) in their risk for psychotic disorders, even after controlling for the schizophrenia PRS.[32]

4.6. Course and outcome of psychosis

A meta-analysis indicates that patients with a psychotic disorder who continue to use cannabis after their illness onset experience a worse clinical and functional outcome than those who stop.[103] Data from a 2-year follow-up study showed that FEP who used high-potency cannabis daily over the follow-up period were 3 times more likely to relapse (OR = 3.28; 95% CI 1.22-9.18), experienced more relapses (incidence rate ratio 1.77; 95% CI 0.96-3.25), and received more intense psychiatric care (OR 3.16; 95% CI 1.26-8.09), compared to those who stopped.[18,104,105]

Some evidence begin to suggest that individuals at ultra-high risk for psychosis have higher rates of CUDs[14] and, conversely, patients with CUDs are more likely to transition to psychosis.[72]

4.7. Self-reported measures of cannabis use

All the above epidemiological studies rely on self-reported current and/or lifetime information on cannabis use, not validated by biological measures (eg, urine, blood, and hair samples). This is often considered a limitation. Nevertheless, although biological measures can provide valid and reliable measures of current use, they cannot provide data on use over time. Indeed, studies that analysed both self-reported information and laboratory data indicated that cannabis users are reliable in reporting how frequently they use and the type they used.[21,36]

4.8. Human experimental studies

Administration of cannabis and THC has shown to precipitate, with a dose–response relationship, the onset of transient positive psychotic symptoms (eg, ideas of reference, paranoid delusions, hallucinations, depersonalization, or derealization) and, to a less extent, negative symptoms (eg, blunted affect) in healthy volunteers and to temporary exacerbated psychotic symptoms in schizophrenia patients.[88,110] Furthermore, in healthy volunteers, administration of CBD before the THC was found to ameliorate the psychotogenic effects of THC.[88,110]

Table 2

Summary of the mental health and cognitive acute and persistent adverse effects associated with cannabis use.

Adverse effects	Acute	Persistent	Pattern of cannabis use	Vulnerable individuals
Onset of psychotic symptoms	+++	+++	1. Dose–response relationship (% THC) 2. CBD ameliorates THC effects	1. Family history of psychosis 2. High polygenic risk score for schizophrenia 3. Adolescents (age at first use = <15 y)
Worsening of psychotic symptoms	+++	+++	1. Daily use of high-potency cannabis	NAD
Onset of mania	++−	++−	1. Dose–response relationship with frequency of use	NAD
Worsening of manic symptoms	++−	++−	1. Cannabis use disorder	NAD
Depression	+−−	+−−	1. Dose–response relationship with frequency of use	NAD
Anxiety	++−	+−−	1. Dose–response relationship with frequency of use	NAD
Suicidal ideation	+−−	+−−	NAD	Adolescents (age at first use = <15 y)
Dependence (CUD)	NA	+++	1. Dose–response relationship with THC content (high-potency cannabis and daily use) 2. CBD ameliorates THC effects	NAD
Withdrawal symptoms	NA	+++	Long-term frequent use	NAD
Psychomotor skills, reaction time, and motor coordination	+++	NAD	1. Dose–response relationship (% THC)	Cannabis-naive individuals
Verbal learning and memory	+++	+−−	1. Dose–response relationship (% THC) 2. CBD ameliorates THC effects	
Working memory	++−	+−−	1. Dose–response relationship (% THC) 2. CBD ameliorates THC effects	
Spatial working memory	++−	+−	1. Dose–response relationship (% THC)	Adolescents
Attention	+++	++−	1. Dose–response relationship (% THC) 2. CBD ameliorates THC effects	Adolescents
Executive function domains	++−	+−−	NAD	Adolescents

+++, strong consistent evidence; ++−, modest evidence; +−−, weak or inconsistent evidence; CBD, cannabidiol; CUD, cannabis use disorder; NAD, not available data and/or not investigated; NA, not applicable; THC, delta 9-tetrahydrocannabinol.
This table lists (1) the acute (2) and/or persistent effects that have been reported after cannabis use and the strength of the related evidence, (3) the patterns of cannabis use mostly associated with each adverse effects, and (4) the individuals reported to be the most vulnerable to experience them.

4.9. Vulnerable groups

The Dunedin study was the first to indicate adolescents as a group particularly vulnerable to the psychotogenic effect of cannabis use.[5] Since then, other studies have reported an association between early cannabis initiation and greater risk for psychosis.[15] It remains unclear if this association reflects (1) a longer duration of exposure (eg, earlier start, longer use) or (2) the vulnerability of a developing brain.[88, 117]

Subjects with a family history of psychotic disorders have a greater sensitivity to the psychotogenic effect of cannabis[66] and if they develop a cannabis-induced psychotic disorder, they are more likely to transition to schizophrenia.[68] Furthermore, individuals who have a high schizophrenia PRS and use cannabis heavily are at higher risk for psychosis than those who either carry a high schizophrenia PRS or smoke cannabis heavily.[32] A recent study described an additive interaction between schizophrenia PRS and cannabis use,[32,49] with no evidence that genetic liability increases the risk for cannabis use.

Another potentially vulnerable population might be represented by individuals exposed to childhood adversity, which may enhance the psychotogenic effect of cannabis, through sensitization. Several studies observed that the joined effect of early trauma and cannabis use on psychosis was greater than their independent effect,[54,62,63,70] but the findings were not fully consistent.[7,86,112]

5. Cannabis and cognitive impairment

Two meta-analyses[47,107] described a modest residual cannabis-related impairment in measures of both overall and specific cognitive functions after 12 hours to 25 days of abstinence, with no residual cognitive impairment after 25 days of abstinence.[107] Another meta-analysis including samples of adolescent and young adults found a modest overall negative effect (d = −0.25; 95% CI −0.32 to −0.17) of cannabis use on cognition and no residual effect (d = −0.08; 95% CI −0.22 to 0.07).[109]

In young adults, chronic cannabis use most commonly affects immediate recall and verbal reasoning[12,38,118] but not spatial working memory; however, the latter is affected in adolescents,[55] suggestive of a differential effect on the developing brain. Both in adolescents and adult users, attention is impaired during cannabis intoxication and persists for several weeks.[61] Executive function domains (eg, inhibition, problem solving) are differently affected by acute or chronic cannabis use, and it is not clear how likely impairments are to persist after abstinence.[27,75]

6. Cannabis and bipolar disorder

Regular cannabis use is associated to about a 3-fold risk (OR = 2.97, 95% CI 1.8-4.9) of developing a manic episode, with some evidence of dose–response relationship between frequency of use and risk for mania.[42,81,94] Furthermore, continued cannabis use and CUDs increases the severity of manic and psychotic symptoms and facilitates a rapid-cycling course of bipolar disorder.[42,80]

7. Cannabis, depression, and anxiety

Regular cannabis use is associated with lack of motivation for naturally rewarding activities, which is a core feature of depressive disorders.[117] Systematic reviews indicate that cannabis use leads to a modest increase in the risk for depression (OR = 1.49, 95% CI 1.15-1.94),[85] which becomes slightly greater (OR = 1.62, 95% CI 1.21-2.16)[78] for frequent cannabis use. Furthermore,

those who start using cannabis at age = <15 years are at greater risk for suicidal ideation (OR = 1.50, 95% CI 1.11-2.03) and suicidal behaviours (OR = 3.46, 95% CI 1.53-7.84) both in general population and clinical samples.[44]

Evidence for a weaker association between cannabis use and anxiety disorders comes from a meta-analysis, estimating ORs from 1.15 (95% CI 1.03-1.29)[113] to 1.24 (95% CI 1.06-1.45).[67] Nevertheless, more longitudinal studies are needed to clarify the direction of the association between cannabis use depression and anxiety,[78,113] to examine the role of self-medication.[20,119]

8. Conclusions

All prescribed and recreational drugs have adverse effects, even those coming from plants, fruits, and flowers as we have learnt from the use of tobacco, alcohol, and opium. Cannabis is not an exception (**Tables 1 and 2**). Therefore, at a time of changes in the laws concerning cannabis use, it is of clinical and public health importance to provide evidence-based and clear information on what we know concerning (1) the acute and persistent adverse effects and (2) how to screen for those individuals more susceptible to experience them when cannabis is used recreationally or medicinally.

Conflict of interest statement

M. Di Forti reports personal fees from Janssen, outside the submitted work. The remaining authors have no conflict of interest to declare.

References

[1] Aceto MD, Scates SM, Lowe JA, Martin BR. Dependence on delta-9-Tetrahydrocannabinol: studies on precipitated and abrupt withdrawal. J Pharmacol Exp Ther 1996:1290–95.

[2] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: APA, 2013.

[3] American Psychiatric Association. Highlights of changes from DSM-IV to DSM-5. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association, 2013. doi:10.1176/appi.books.9780890425596.changes.

[4] Archie S, Boydell KM, Stasiulis E, Volpe T, Gladstone BM. Reflections of young people who have had a first episode of psychosis: what attracted them to use alcohol and illicit drugs? Early Interv Psychiatry 2013;7:193–9.

[5] 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 Br Med J 2002;325:1212–3.

[6] Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. BMJ 2012;344:1–9.

[7] Baudin G, Godin O, Lajnef M, Aouizerate B, Berna F, Brunel L, Capdevielle D, Chereau I, Dorey JM, Dubertret C, Dubreucq J, Faget C, Fond G, Gabayet F, Laouamri H, Lancon C, Le Strat Y, Tronche AM, Misdrahi D, Rey R, Passerieux C, Schandrin A, Urbach M, Vidalhet P, Llorca PM, Schürhoff F. Differential effects of childhood trauma and cannabis use in patients suffering from schizophrenia. Schizophr Res 2016;175:161–7.

[8] Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, Nosarti C, O'Carroll CM, Seal M, Allen

P, Mehta MA, Stone JM, Tunstall N, Giampietro V, Kapur S, Murray RM, Zuardi AW, Crippa JA, Atakan Z, McGuire PK. Opposite effects of δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology 2010;35:764–74.

[9] Black N, Stockings E, Campbell G, Tran LT, Zagic D, Hall WD, Farrell M, Degenhardt L. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. Lancet Psychiatry 2019;6:995–1010.

[10] Bonn-Miller MO, ElSohly MA, Loflin MJE, Chandra S, Vandrey R. Cannabis and cannabinoid drug development: evaluating botanical versus single molecule approaches. Int Rev Psychiatry 2018;30: 277–84.

[11] Boydell J, Van Os J, Caspi A, Kennedy N, Giouroukou P, Fearon P, Farrell M, Murray RM. Trends in cannabis use prior to first presentation with schizophrenia, in South-East London between 1965 and 1999. Psychol Med 2006;36:1441–6.

[12] Broyd SJ, Van Hell HH, Beale C, Yücel M, Solowij N. Acute and chronic effects of cannabinoids on human cognition—a systematic review. Biol Psychiatry 2016;79:557–67.

[13] Budney AJ, Hughes JR, Moore BA, Vandrey R. Review of the validity and significance of cannabis withdrawal syndrome. Am J Psychiatry 2004; 161:1967–77.

[14] Carney R, Cotter J, Firth J, Bradshaw T, Yung AR. Cannabis use and symptom severity in individuals at ultra high risk for psychosis: a meta-analysis. Acta Psychiatr Scand 2017;136:5–15.

[15] Casadio P, Fernandes C, Murray RM, Di Forti M. Cannabis use in young people: the risk for schizophrenia. Neurosci Biobehav Rev 2011;35: 1779–87.

[16] Castle D, Murray RM, D'Souza DC. Marijuana and madness. Cambridge, United Kingdom: Cambridge University Press, 2011.

[17] Chandra S, Radwan MM, Majumdar CG, Church JC, Freeman TP, ElSohly MA. New trends in cannabis potency in USA and Europe during the last decade (2008–2017). Eur Arch Psychiatry Clin Neurosci 2019; 269:5–15.

[18] Colizzi M, Carra E, Fraietta S, Lally J, Quattrone D, Bonaccorso S, Mondelli V, Ajnakina O, Dazzan P, Trotta A, Sideli L, Kolliakou A, Gaughran F, Khondoker M, David AS, Murray RM, MacCabe JH, Di Forti M. Substance use, medication adherence and outcome one year following a first episode of psychosis. Schizophr Res 2016;170:311–17.

[19] Cooper ZD, Haney M. Actions of delta-9-tetrahydrocannabinol in cannabis: relation to use, abuse, dependence. Int Rev Psychiatry 2009;21:104–12.

[20] Crippa JA, Zuardi AW, Martín-Santos R, Bhattacharyya S, Atakan Z, McGuire P, Fusar-Poli P. Cannabis and anxiety: a critical review of the evidence. Hum Psychopharmacol 2009;24:515–23.

[21] Curran HV, Hindocha C, Morgan CJA, Shaban N, Das RK, Freeman TP. Which biological and self-report measures of cannabis use predict cannabis dependency and acute psychotic-like effects? Psychol Med 2019;49:1574–80.

[22] van de Donk T, Niesters M, Kowal MA, Olofsen E, Dahan A, van Velzen M. An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. PAIN 2019;160:860–9.

[23] Englund A, Freeman TP, Murray RM, McGuire P. Can we make cannabis safer? Lancet Psychiatry 2017;4:643–8.

[24] Englund A, Morrison PD, Nottage J, Hague D, Kane F, Bonaccorso S, Stone JM, Reichenberg A, Brenneisen R, Holt D, Feilding A, Walker L, Murray RM, Kapur S. Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. J Psychopharmacol 2013;27:19–27.

[25] Fergusson DM, Horwood LJ, Ridder EM. Tests of causal linkages between cannabis use and psychotic symptoms. Addiction 2005;100: 354–66.

[26] Fergusson DM, Horwood LJ, Swain-Campbell NR. Cannabis dependence and psychotic symptoms in young people. Psychol Med 2003;33:15–21.

[27] Fontes MA, Bolla KI, Cunha PJ, Almeida PP, Jungerman F, Laranjeira RR, Bressan RA, Lacerda ALT. Cannabis use before age 15 and subsequent executive functioning. Br J Psychiatry 2011;198:442–7.

[28] Di Forti M, Marconi A, Carra E, Fraietta S, Trotta A, Bonomo M, Bianconi F, Gardner-Sood P, O'Connor J, Russo M, Stilo SA, Marques TR, Mondelli V, Dazzan P, Pariante C, David AS, Gaughran F, Atakan Z, Iyegbe C, Powell J, Morgan C, Lynskey M, Murray RM. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. Lancet Psychiatry 2015; 2:233–8.

[29] Di Forti M, Morgan C, Dazzan P, Pariante C, Mondelli V, Marques TR, Handley R, Luzi S, Russo M, Paparelli A, Butt A, Stilo SA, Wiffen B,

Powell J, Murray RM. High-potency cannabis and the risk of psychosis. Br J Psychiatry 2009;195:488–91.

[30] Di Forti M, Quattrone D, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H, Rodriguez V, Jongsma HE, Ferraro L, La Cascia C, La Barbera D, Tarricone I, Berardi D, Szöke A, Arango C, Tortelli A, Velthorst E, Bernardo M, Del-Ben CM, Menezes PR, Selten JP, Jones PB, Kirkbride JB, Rutten BP, de Haan L, Sham PC, van Os J, Lewis CM, Lynskey M, Morgan C, Murray RM, Amoretti S, Arrojo M, Baudin G, Beards S, Bernardo M, Bobes J, Bonetto C, Cabrera B, Carracedo A, Charpeaud T, Costas J, Cristofalo D, Cuadrado P, Díaz-Caneja CM, Ferchiou A, Franke N, Frijda F, García Bernardo E, Garcia-Portilla P, González E, Hubbard K, Jamain S, Jiménez-López E, Leboyer M, López Montoya G, Lorente-Rovira E, Marcelino Loureiro C, Marrazzo G, Martínez C, Matteis M, Messchaart E, Moltó MD, Nacher J, Olmeda MS, Parellada M, González Peñas J, Pignon B, Rapado M, Richard JR, Rodríguez Solano JJ, Roldán Díaz L, Ruggeri M, Sáiz PA, Sánchez E, Sanjuán J, Sartorio C, Schürhoff F, Seminerio F, Shuhama R, Sideli L, Stilo SA, Termorshuizen F, Tosato S, Tronche A-M, van Dam D, van der Ven E. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. Lancet Psychiatry 2019;6:427–36.

[31] Di Forti M, Sallis H, Allegri F, Trotta A, Ferraro L, Stilo SA, Marconi A, La Cascia C, Marques TR, Pariante C, Dazzan P, Mondelli V, Paparelli A, Kolliakou A, Prata D, Gaughran F, David AS, Morgan C, Stahl D, Khondoker M, MacCabe JH, Murray RM. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. Schizophr Bull 2014;40:1509–17.

[32] Di Forti M, Wu-Choi B, Quattrone D, Richards AL, Freeman TP, Tripoli G, Gayer-Anderson C, Rodriguez V, Jongsma H, Ferraro L, Cascia CLa, Tosato S, Tarricone I, Berardi D, Szoke A, Arango C, Bobes J, Sanjuan J, Santos JL, Arrojo M, Velthorst E, Bernardo M, Ben CMD, Selten JP, Jones PB, Kirkbride JB, Rutten BN, Haan Lde, Os Jvan, Lynskey M, Morgan C, Vassos E, O'Donovan M, Lewis C, Sham PC, Murray RM; Group EGW. The independent and combined influence of schizophrenia polygenic risk score and heavy cannabis use on risk for psychotic disorder: a case-control analysis from the EUGEI study. bioRxiv 2019:844803.

[33] Freeman AM, Petrilli K, Lees R, Hindocha C, Mokrysz C, Curran HV, Saunders R, Freeman TP. How does cannabidiol (CBD) influence the acute effects of delta-9-tetrahydrocannabinol (THC) in humans? A systematic review. Neurosci Biobehav Rev 2019;107:696–712.

[34] Freeman D, Garety PA, Bebbington PE, Smith B, Rollinson R, Fowler D, Kuipers E, Ray K, Dunn G. Psychological investigation of the structure of paranoia in a non-clinical population. Br J Psychiatry 2005;186:427–35.

[35] Freeman TP, Groshkova T, Cunningham A, Sedefov R, Griffiths P, Lynskey MT. Increasing potency and price of cannabis in Europe, 2006–16. Addiction 2018;114:1015–23.

[36] Freeman TP, Morgan CJA, 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.

[37] Freeman TP, Van Der Pol P, Kuijpers W, Wisselink J, Das RK, Rigter S, Van Laar M, Griffiths P, Swift W, Niesink R, Lynskey MT. Changes in cannabis potency and first-time admissions to drug treatment: a 16-year study in The Netherlands. Psychol Med 2018;48:2346–52.

[38] Fried PA, Watkinson B, Gray R. Neurocognitive consequences of marihuana—a comparison with pre-drug performance. Neurotoxicol Teratol 2005;27:231–9.

[39] Gage SH, Jones HJ, Burgess S, Bowden J, Davey Smith G, Zammit S, Munafò MR. Assessing causality in associations between cannabis use and schizophrenia risk: a two-sample Mendelian randomization study. Psychol Med 2017;47:971–80.

[40] Gayer-Anderson C, Jongsma HE, Di Forti M, Quattrone D, Velthorst E, de Haan L, Selten J-P, Szöke A, Llorca PM, Tortelli A, Arango C, Bobes J, Bernardo M, Sanjuán J, Santos JL, Arrojo M, Parellada M, Tarricone I, Berardi D, Ruggeri M, Lasalvia A, Ferraro L, La Cascia C, La Barbera D, Menezes PR, Del-Ben CM, Rutten BP, van Os J, Jones PB, Murray RM, Kirkbride JB, Morgan C. The EUropean network of national schizophrenia networks studying gene–environment interactions (EU-GEI): incidence and first-episode case–control programme. Soc Psychiatry Psychiatr Epidemiol 2020;55:645–57.

[41] Gerberich SG, Sidney S, Braun BL, Tekawa IS, Tolan KK, Quesenberry CP. Marijuana use and injury events resulting in hospitalization. Ann Epidemiol 2003;13:230–7.

[42] Gibbs M, Winsper C, Marwaha S, Gilbert E, Broome M, Singh SP. Cannabis use and mania symptoms: a systematic review and meta-analysis. J Affect Disord 2014;171:39–47.

[43] Gill KE, Poe L, Azimov N, Ben-David S, Vadhan NP, Girgis R, Moore H, Cressman V, Corcoran CM. Reasons for cannabis use among youths at ultra high risk for psychosis. Early Interv Psychiatry 2015;9:207–10.

[44] Gobbi G, Atkin T, Zytynski T, Wang S, Askari S, Boruff J, Ware M, Marmorstein N, Cipriani A, Dendukuri N, Mayo N. Association of cannabis use in adolescence and risk of depression, anxiety, and suicidality in young adulthood: a systematic review and meta-analysis. JAMA Psychiatry 2019;76:426–34.

[45] Gonçalves-Pinho M, Bragança M, Freitas A. Psychotic disorders hospitalizations associated with cannabis abuse or dependence: a nationwide big data analysis. Int J Methods Psychiatr Res 2019;29: e1813.

[46] Goodman S, Wadsworth E, Leos-Toro C, Hammond D. Prevalence and forms of cannabis use in legal vs. illegal recreational cannabis markets. Int J Drug Pol 2020;76:102658.

[47] Grant I, Gonzalez R, Carey CL, Natarajan L, Wolfson T. Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study. J Int Neuropsychol Soc 2003;9:679–89.

[48] Green B, Kavanagh D, Young R. Being stoned: a review of self-reported cannabis effects. Drug Alcohol Rev 2003;22:453–60.

[49] Guloksuz S, Pries L, Delespaul P, Kenis G, Luykx JJ, Lin BD, Richards AL, Akdede B, Binbay T, Altınyazar V, Yalınçetin B, Gümüş-Akay G, Cihan B, Soygür H, Ulaş H, Cankurtaran E, Kaymak SU, Mihaljevic MM, Petrovic SA, Mirjanic T, Bernardo M, Cabrera B, Bobes J, Saiz PA, García-Portilla MP, Sanjuan J, Aguilar EJ, Santos JL, Jiménez-López E, Arrojo M, Carracedo A, López G, González-Peñas J, Parellada M, Maric NP, Atbaşoğˇlu C, Ucok A, Alptekin K, Saka MC, Arango C, O'Donovan M, Rutten BPF, van Os J, Alizadeh BZ, van Amelsvoort T, van Beveren NJ, Bruggeman R, Cahn W, de Haan L, Delespaul P, Luykx JJ, Myin-Germeys I, van Winkel R, van Os J. Examining the independent and joint effects of molecular genetic liability and environmental exposures in schizophrenia: results from the EUGEI study. World Psychiatry 2019;18: 173–82.

[50] Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. Lancet 2009;374:1383–91.

[51] Hall W, Pacula RL. Cannabis use and dependence : public health and public policy. Cambridge, United Kingdom: Cambridge University Press, 2003.

[52] Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following oral THC administration to humans. Psychopharmacology (Berl) 1999;141:385–94.

[53] Hanuš LO, Meyer SM, Muñoz E, Taglialatela-Scafati O, Appendino G. Phytocannabinoids: a unified critical inventory. Nat Prod Rep 2016;33: 1357–92.

[54] Harley M, Kelleher I, Clarke M, Lynch F, Arseneault L, Connor D, Fitzpatrick C, Cannon M. Cannabis use and childhood trauma interact additively to increase the risk of psychotic symptoms in adolescence. Psychol Med 2010;40:1627–34.

[55] Harvey MA, Sellman JD, Porter RJ, Frampton CM. The relationship between non-acute adolescent cannabis use and cognition. Drug Alcohol Rev 2007;26:309–19.

[56] Hasin DS, Kerridge BT, Saha TD, Huang B, Pickering R, Smith SM, Jung J, Zhang H, Grant BF. Prevalence and correlates of DSM-5 cannabis use disorder, 2012-2013: findings from the national epidemiologic survey on alcohol and related conditions-III. Am J Psychiatry 2016;173:588–99.

[57] Hasin DS, Shmulewitz D, Cerdá M, Keyes KM, Olfson M, Sarvet AL, Wall MMUS. Adults with pain, a group increasingly vulnerable to nonmedical cannabis use and cannabis use disorder: 2001–2002 and 2012–2013. Am J Psychiatry 2020;177:611–18.

[58] Hasin DS, Wall M, Keyes KM, Cerdá M, Schulenberg J, O'Malley PM, Galea S, Pacula R, Feng T. Medical marijuana laws and adolescent marijuana use in the USA from 1991 to 2014: results from annual, repeated cross-sectional surveys. Lancet Psychiatry 2015;2:601–8.

[59] Hjorthøj C, Larsen MO, Starzer MSK, Nordentoft M. Annual incidence of cannabis-induced psychosis, other substance-induced psychoses and dually diagnosed schizophrenia and cannabis use disorder in Denmark from 1994 to 2016. Psychol Med 2019. doi: 10.1017/ S0033291719003532 [Epub ahead of print].

[60] Hollister LE. Health aspects of cannabis. Pharmacol Rev 1986;38:1–20.

[61] Hooper SR, Woolley D, De Bellis MD. Intellectual, neurocognitive, and academic achievement in abstinent adolescents with cannabis use disorder. Psychopharmacology (Berl) 2014;231:1467–77.

[62] Houston JE, Murphy J, Adamson G, Stringer M, Shevlin M. Childhood sexual abuse, early cannabis use, and psychosis: testing an interaction model based on the national comorbidity survey. Schizophr Bull 2008; 34:580–5.

[63] Houston JE, Murphy J, Shevlin M, Adamson G. Cannabis use and psychosis: re-visiting the role of childhood trauma. Psychol Med 2011; 41:2339–48.

[64] Huestis MA, Gorelick DA, Heishman SJ, Preston KL, Nelson RA, Moolchan ET, Frank RA, Dsouza DC, Kosten TR. Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. Arch Gen Psychiatry 2001;58:322–8.

[65] Jones RT. Marihuana: Human effects. In: Iversen LL, Iversen SD, Snyder SH (eds) Handbook of Psychopharmacology. Drugs of Abuse. New York, NY: Plenum Press, 1978. pp. 373–412.

[66] Kahn RS, Linszen DH, Van Os J, Wiersma D, Bruggeman R, Cahn W, De Haan L, Krabbendam L, Myin-Germeys I. Evidence that familial liability for psychosis is expressed as differential sensitivity to cannabis: an analysis of patient-sibling and sibling-control pairs. Arch Gen Psychiatry 2011;68:138–47.

[67] 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.

[68] Kendler KS, Ohlsson H, Sundquist J, Sundquist K. Prediction of onset of substance-induced psychotic disorder and its progression to schizophrenia in a Swedish national sample. Am J Psychiatry 2019; 176:711–19.

[69] Kolliakou A, Joseph C, Ismail K, Atakan Z, Murray RM. Why do patients with psychosis use cannabis and are they ready to change their use ? Int J Dev Neurosci 2011;29:335–46.

[70] Konings M, Stefanis N, Kuepper R, de Graaf R, Have MT, van Os J, Bakoula C, Henquet C. Replication in two independent population-based samples that childhood maltreatment and cannabis use synergistically impact on psychosis risk. Psychol Med 2011;42: 149–59.

[71] Kosiba JD, Maisto SA, Ditre JW. Patient-reported use of medical cannabis for pain, anxiety, and depression symptoms: systematic review and meta-analysis. Soc Sci Med 2019;233:181–92.

[72] Kraan T, Velthorst E, Koenders L, Zwaart K, Ising HK, Van Den Berg D, De Haan L, Van Der Gaag M. Cannabis use and transition to psychosis in individuals at ultra-high risk: review and meta-analysis. Psychol Med 2016;46:673–81.

[73] Kuepper R, Morrison PD, van Os J, Murray RM, Kenis G, Henquet C. Does dopamine mediate the psychosis-inducing effects of cannabis? A review and integration of findings across disciplines. Schizophr Res 2010;121:107–17.

[74] Lafaye G, Karila L, Blecha L, Benyamina A. Cannabis, cannabinoids, and health. Dialogues Clin Neurosci 2017;19:309–16.

[75] Lane SD, Cherek DR, Tcheremissine OV, Steinberg JL, Sharon JL. Response perseveration and adaptation in heavy marijuana-smoking adolescents. Addict Behav 2007;32:977–90.

[76] Laprairie RB, Bagher AM, Kelly MEM, Denovan-Wright EM. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. Br J Pharmacol 2015;172:4790–805.

[77] Large M, Sharma S, Compton MT, Slade T, Nielssen O. Cannabis use and earlier onset of psychosis: a systematic meta-analysis. Arch Gen Psychiatry 2011;68:555–61.

[78] Lev-Ran S, Roerecke M, Le Foll B, George TP, McKenzie K, Rehm J. The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. Psychol Med 2014;44: 797–810.

[79] Lichtman AH, Martin BR. Cannabinoid tolerance and dependence Cannabinoids. In: Pertwee RG (ed). Handbook of Experimental Pharmacology. Heidelberg: Springer-Verlag. 2005;168:691–717.

[80] Mammen G, Rueda S, Roerecke M, Bonato S, Lev-Ran S, Rehm J. Association of cannabis with long-term clinical symptoms in anxiety and mood disorders: a systematic review of prospective studies. J Clin Psychiatry 2018;79:17r11839.

[81] Marangoni C, Hernandez M, Faedda GL. The role of environmental exposures as risk factors for bipolar disorder: a systematic review of longitudinal studies. J Affect Disord 2016;193:165–74.

[82] Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. Meta-Analysis of the association between the level of cannabis use and risk of psychosis. Schizophr Bull 2016;42:1262–9.

[83] Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 1990;346:561–4.

[84] Mechoulam R. Plant cannabinoids: a neglected pharmacological treasure trove. Br J Pharmacol 2005;146:913–15.

[85] Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 2007;370:319–28.

[86] Morgan C, Reininghaus U, Reichenberg A, Frissa S, Hotopf M, Hatch SL. Adversity, cannabis use and psychotic experiences: evidence of cumulative and synergistic effects. Br J Psychiatry 2014;204:346–53.

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

[88] Murray RM, Englund A, Abi-Dargham A, Lewis DA, Di Forti M, Davies C, Sherif M, McGuire P, D'Souza DC. Cannabis-associated psychosis: neural substrate and clinical impact. Neuropharmacology 2017;124:89–104.

[89] Murray RM, Quigley H, Quattrone D, Englund A, Di Forti M. Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. World Psychiatry 2016;15:195–204.

[90] Niesink RJM, Rigter S. THC-concentrations in wiet, nederwiet en hasj in Nederlandse coffeeshops (2012–2013). Utrecht, The Netherlands: Trimbos-instituut, 2013.

[91] Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, Sansom C. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 "N of 1" studies. Anaesthesia 2004;59:440–52.

[92] Van Os J, Bak M, Hanssen M, Bijl RV, De Graaf R, Verdoux H. Cannabis use and psychosis: a longitudinal population-based study. Am J Epidemiol 2002;156:319–27.

[93] Pasman JA, Verweij KJH, Gerring Z, Stringer S, Sanchez-Roige S, Treur JL, Abdellaoui A, Nivard MG, Baselmans BML, Ong JS, Ip HF, van der Zee MD, Bartels M, Day FR, Fontanillas P, Elson SL, de Wit H, Davis LK, MacKillop J, Derringer JL, Branje SJT, Hartman CA, Heath AC, van Lier PAC, Madden PAF, Mägi R, Meeus W, Montgomery GW, Oldehinkel AJ, Pausova Z, Ramos-Quiroga JA, Paus T, Ribases M, Kaprio J, Boks MPM, Bell JT, Spector TD, Gelernter J, Boomsma DI, Martin NG, MacGregor S, Perry JRB, Palmer AA, Posthuma D, Munafò MR, Gillespie NA, Derks EM, Vink JM. The 23andMe Research T, the Substance Use Disorders Working Group of the Psychiatric Genomics C, International Cannabis C. GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. Nat Neurosci 2018;21:1161–70.

[94] Pinto JV, Medeiros LS, Santana da Rosa G, Santana de Oliveira CE, Crippa JAdeS, Passos IC, Kauer-Sant'Anna M. The prevalence and clinical correlates of cannabis use and cannabis use disorder among patients with bipolar disorder: a systematic review with meta-analysis and meta-regression. Neurosci Biobehav Rev 2019;101:78–84.

[95] Potter DJ, Hammond K, Tuffnell S, Walker C, Di Forti M. Potency of Δ9–tetrahydrocannabinol and other cannabinoids in cannabis in England in 2016: implications for public health and pharmacology. Drug Test Anal 2018;10:628–35.

[96] Quattrone D, Ferraro L, Tripoli G, Cascia ELa, Quigley H, group E-G, Gayer-Anderson C, Jones PB, Kirkbride JB, Barbera DLa, Tarricone I, Lynskey MT, Freeman TP, Sham PC, Cardno A, Vassos E, Os Jvan, Morgan C, Reininghaus U, Lewis CM, Murray RM, Di Forti M. Cannabis-associated symptom profiles in patients with first episode psychosis and population controls. bioRxiv 2019;577932. doi:10.1101/577932.

[97] Radhakrishnan R, Wilkinson ST, D'Souza DC. Gone to pot-a review of the association between cannabis and psychosis. Front Psychiatry 2014;5:1–24.

[98] Ramaekers JG, Berghaus G, Van Laar M, Drummer OH. Dose related risk of motor vehicle crashes after cannabis use. Drug Alcohol Depend 2004;73:109–19.

[99] Rong C, Lee Y, Carmona NE, Cha DS, Ragguett RM, Rosenblat JD, Mansur RB, Ho RC, McIntyre RS. Cannabidiol in medical marijuana: research vistas and potential opportunities. Pharmacol Res 2017;121:213–18.

[100] Russo EB, McPartland JM, ElSohly MA, Wachtel SR, Wit H. Cannabis is more than simply δ9-tetrahydrocannabinol [2] (multiple letters). Psychopharmacology (Berl) 2003;165:431–4.

[101] Saunders JB, Conigrave KM, Latt NC, Nutt DJ, Marshall EJ, Ling W, Higuchi S. Addiction Medicine. Oxford, United Kingdom: Oxford University Press, 2016.

[102] Schizophrenia Commission. The abandoned illness: a report by the Schizophrenia Commission. London, United Kingdom: Rethink Mental Illness, 2012.

[103] Schoeler T, Monk A, Sami MB, Klamerus E, Foglia E, Brown R, Camuri G, Altamura AC, Murray R, Bhattacharyya S. Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. Lancet Psychiatry 2016;3:215–25.

[104] Schoeler T, Petros N, Di Forti M, Klamerus E, Foglia E, Ajnakina O, Gayer-Anderson C, Colizzi M, Quattrone D, Behlke I, Shetty S, McGuire P, David AS, Murray R, Bhattacharyya S. Effects of continuation, frequency, and type of cannabis use on relapse in the first 2 years after onset of psychosis: an observational study. Lancet Psychiatry 2016;3:947–53.

[105] Schoeler T, Petros N, Di Forti M, Klamerus E, Foglia E, Murray R, Bhattacharyya S. Poor medication adherence and risk of relapse associated with continued cannabis use in patients with first-episode psychosis: a prospective analysis. Lancet Psychiatry 2017;4:627–33.

[106] Schofield D, Tennant C, Nash L, Degenhardt L, Cornish A, Hobbs C, Brennan G. Reasons for cannabis use in psychosis. Aust New Zeal J Psychiatry 2006;40:570–4.

[107] 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.

[108] 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.

[109] Scott JC, Slomiak ST, Jones JD, Rosen AFG, Moore TM, Gur RC. Association of cannabis with cognitive functioning in adolescents and young adults A systematic review and meta-analysis. JAMA Psychiatry 2018;75:585–95.

[110] Sherif M, Radhakrishnan R, D'Souza DC, Ranganathan M. Human laboratory studies on cannabinoids and psychosis. Biol Psychiatry 2016;79:526–38.

[111] SICAD A Situação do País em Matéria de Drogas e Toxicodependências. Lisboa: Serviço de Intervenção nos Comportamentos Aditivos e nas Dependências, 2014.

[112] Sideli L, Fisher HL, Murray RM, Sallis H, Russo M, Stilo SA, Paparelli A, Wiffen BDR, O'Connor JA, Pintore S, Ferraro L, La Cascia C, La Barbera D, Morgan C, Di Forti M. Interaction between cannabis consumption and childhood abuse in psychotic disorders: preliminary findings on the role of different patterns of cannabis use. Early Interv Psychiatry 2018;12:135–42.

[113] Twomey CD. Association of cannabis use with the development of elevated anxiety symptoms in the general population: a meta-analysis. J Epidemiol Community Health 2017;71:811–16.

[114] UNODC. World drug report 2018. Drugs and age; Drugs and associated issues among young people and older people. Vienna, Austria: United Nations, 2018.

[115] Vaucher J, Keating BJ, Lasserre AM, Gan W, Lyall DM, Ward J, Smith DJ, Pell JP, Sattar N, Paré G, Holmes MV. Cannabis use and risk of schizophrenia: a Mendelian randomization study. Mol Psychiatry 2018;23:1287–92.

[116] Volkow N, Compton W, Weiss S. Adverse health effects of marijuana use. N Engl J Med 2014;371:879.

[117] Volkow ND, Swanson JM, Evins AE, DeLisi LE, Meier MH, Gonzalez R, Bloomfield MAP, Curran HV, Baler R. Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review. JAMA Psychiatry 2016;73:292–7.

[118] Wadsworth EJK, Moss SC, Simpson SA, Smith AP. Cannabis use, cognitive performance and mood in a sample of workers. J Psychopharmacol 2006;20:14–23.

[119] Wycoff AM, Metrik J, Trull TJ. Affect and cannabis use in daily life: a review and recommendations for future research. Drug Alcohol Depend 2018;191:223–33.