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

Lucia Sidel, Giulia Trotta, Edoardo Spinazzola, Caterina La Cascia, Marta Di Forti

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 18.6% respectively). Evidence indicates a trend of increase among adolescents, a particular vulnerable category for the initiation of substance use. 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, and a corresponding decrease of cannabidiol (CBD) content, becoming more widely available. Most commonly, cannabis is used for its enjoyable effects, the “high” feeling. In addition, in those countries where its use has been legalised, many people smoke cannabis for medical use, anxiety, depression, and pain relief, with those suffering from chronic pain being at higher risk of developing cannabis use disorder (CUD).

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, but the most widely studied are THC (Δ-9-tetrahydrocannabinol) and CBD (cannabidiol) synthesised from the same precursor, cannabinol. Therefore, types of cannabis with high concentrations of THC produce low CBD and vice versa. THC is a partial agonist at both the cannabinoid receptors (CB) CB2 R and CB1 R, the latter highly abundant in the brain. Conversely, CBD is a negative allosteric modulator at the CB1 R, whose effects are distinct and, in many cases, opposite of those observed with THC. CBD does not induce euphoria but may exert anxiolytic, anti-epileptic, anti-inflammatory, and anagasic properties.

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 (e.g., impaired motor coordination, euphoria, anxiety, sensation of slowed time, impaired judgment, and social withdrawal) that develop during, or shortly after, cannabis use.” The experience of feeling “high” after cannabis use is variable and subjective, depending on the dose, the environment, and previous experience and expectations of the drug user. The most common acute adverse effects are panic attacks and other forms of anxiety, mostly reported by naive users. Because cannabis impairs psychomotor skills, reaction time, and motor coordination, its use leads to increased risk of motor vehicle accidents. Current cannabis users have higher rates of hospitalization for injury from all causes than former cannabis users or nonusers.

3.2. Cannabis use disorders

DSM-5 CUDs is now a single diagnostic entity including abuse and dependence; it is prevalent (2.54% 12-month prevalence among U.S. adults), associated with comorbidity and disability, and largely untreated. Moreover, CUD often presents comorbidly with psychotic disorders. Preclinical studies support the evidence that exposure to THC leads to dependence, and cannabis can induce tolerance in humans and dependenc. 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, suggesting that the alleviation of abstinence symptoms contributes to the maintenance of daily use.
cannabis use. 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.

### 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. 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. 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.

#### 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. Consistently, survey data from general population samples suggest that use of cannabis with high CBD content is associated with fewer psychotic experiences. More recently, data from the EUGEI study, a large multicentre European collaboration, 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; 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. 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.

#### 4.3. Cannabis use and age of onset of psychotic disorders

A meta-analysis by Large et al. 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 compared to never users.

#### 4.4. Heavy cannabis use and rates of psychotic disorders

Boydell et al. 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. 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.

---

**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. 

---

**THC**
- Its % determines the potency of a type of cannabis
- Gives the "High"
- Drives dependence
- Impairment of cognition
- Psychosis: Hallucinations and paranoid ideas
- Affects the outcome of Psychiatric Disorders

**CBD**
- No association with Psychosis
- Might have antipsychotic properties
- Not associated with dependence
- No adverse effect on cognition
- Does not reduce the "High" associated with THC
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. 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. Similar data were reported in Denmark. Both countries have seen a rise in the potency of available cannabis over the same period.

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. 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. 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 schizophreniaiform 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. 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. 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] |
| Scheiner 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] |

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 CUDs14 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

| 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 | NAD |
| Working memory | + - | + - | 1. Dose–response relationship (% THC) 2. CBD ameliorates THC effects | NAD |
| 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 |

+++ strongly 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.86, 117

Subjects with a family history of psychotic disorders have a greater sensitivity to the psychotogenic effect of cannabis46 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-analyses47,107 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 reasoning12,38,118 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.113 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.42,80,94 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,78,114 to examine the role of self-medication.30,119

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.

Acknowledgments

Medical Research Council MRC.

Article history:

Received 6 March 2020
Received in revised form 8 June 2020
Accepted 12 June 2020
13 August 2020

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, Stasulis 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: 183–9.
[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, Gabayet F, Laouamri H, Lancon C, Le Strat Y, Tronche AM, Fond G, Gabayet F, Laouamri H, Lancon C, Le Strat Y, Tronche AM, Misrahi D, Roy R, Passerieux C, Schandrin A, Urbach M, Vidalhret P, Llorca PM, Schurhoff F. Differential effects of childhood trauma and cannabis use disorders 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-Browne T, Nosarti C, O’Carroll CM, Seal M, Allen...
Di Forti M, Morgan C, Dazzan P, Mondelli V, Marconi A, La Barbera D, Ferraro L, La Cascia C, Murray RM, Powell J, Murray RM. High-potency cannabis and the risk of psychosis. Br J Psychiatry 2009;195:488–91.

Di Forti M, Quattrone D, Freeman TP, Tripoli G, Gayer-Anderson C, Quigley H, Rodriguez V, Jongisma HE, Ferrara L, La Cascia C, Barbera D, Tamccone I, Berardi D, Szoke A, Arango C, Tortelli A, Velthorst E, Bernardo M, Del-Ben CM, Menezes PR, Selten JP, Jones PB, Kirkbride JB, Rutten BP, de Haan LM, van Os J, Lewis CM, Lyons K, 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, Diaz-Caneja CM, Fierchou A, Franke N, Frijda F, Garcia Bernardo M, Garcia-Portilla P, Gonzalez E, Hubbard K, Janmaan S, Jimenez-Lopez E, Leboyer M, Lopez Monciga G, Lorente-Rovira E, Marcelino Loureiro C, Marrazzo G, Martinez C, Matteis M, Meschant E, Molto MD, Nacher J, Olmeda MS, Pallarede M, Gonzalez Peñas J, Pignon B, Rapado M, Richard JR, Rodriguez Solano JJ, Roldán Daz L, Ruggeri M, Salat PA, Sánchez E, Sanjuán J, Sartorico C, Schiöffur H, Seminero F, Shuhama R, Siddell L, Sisto SL, Termonshuizen F, Tosato S, Tronche A-M, Van Darn 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.

Di Forti M, Salis H, Allegrini F, Trotta A, Ferrara L, Stilo MA, Saravanan D, Leong TA, Haddad L, de Haan LM, Selten JP, Jones PB, Kirkbride JB, Rutten BP, van Os J, Lewis CM, Lyons K. Assessing causality in associations between cannabis use and schizophrenia risk: a two-sample Mendelian randomization study. Eur Arch Psychiatry Clin Neurosci 2019;269:5–15.

ElSohly MA. New trends in cannabis potency in USA and Europe during the last decade (2008–2017). Eur Arch Psychiatry Clin Neurosci 2019;161:6967–77.

Ence H, Cotter J, Firth J, Bradshaw T, Yung AR. Cannabis use and mania symptoms: a systematic review and meta-analysis. Psychiatry Res 2014;171:661–77.

Englund A, Moore BA, Hughes JR, Vandrey R. Review of the validity and evidence for acute effects of cannabinoids on human cognition—a systematic review. Biol Psychiatry 2016;79:557–67.

Englund A, Moore BA, Hughes JR, Vandrey R. Review of the validity and evidence for acute effects of cannabinoids on human cognition—a systematic review. Biol Psychiatry 2016;79:557–67.

Epenetos AA, Yuricki V, Kwiatkowski P, Mehta MA, Stone JM, Tunstall N, Giampietro V, Kapur S, Murray RM, 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.

Fried PA, Watkinson B, Gray R. Neurocognitive consequences of cannabis: relation to use, abuse, dependence. Int Rev Psychiatry 2006;18:427–35.

Fullmer NW, Rice DC, Greenfield SF, Nutt DJ. Cannabis potencies and first-time admissions to drug treatment: a 16-year control analysis from the EUGEI study. PLoS One 2014;11:e0159447.

Gayer-Anderson C, Jongsma HE, Di Forti M, Quattrone D, Velthorst E, de Haan L, Selten JP, Jones PB, Rutten BP, van Os J, Lewis CM, Lyons K, 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, Diaz-Caneja CM, Fierchou A, Franke N, Frijda F, Garcia Bernardo M, Garcia-Portilla P, Gonzalez E, Hubbard K, Janmaan S, Jimenez-Lopez E, Leboyer M, Lopez Monciga G, Lorente-Rovira E, Marcelino Loureiro C, Marrazzo G, Martinez C, Matteis M, Meschant E, Molto MD, Nacher J, Olmeda MS, Pallarede M, Gonzalez Peñas J, Pignon B, Rapado M, Richard JR, Rodriguez Solano JJ, Roldán Daz L, Ruggeri M, Salat PA, Sánchez E, Sanjuán J, Sartorico C, Schiöffur H, Seminero F, Shuhama R, Siddell L, Sisto SL, Termonshuizen F, Tosato S, Tronche A-M, Van Darn 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.

Gibbs J, Winpiser C, Warwaha S, Gilbert E, Broome M, Singh SP. Cannabis use and mania symptoms: a systematic review and meta-analysis. J Affect Disord 2018;217:93–106.

Gil 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.
Huestis MA, Gorelick DA, Heishman SJ, Preston KL, Nelson RA, Mammen G, Rueda S, Roerecke M, Bonato S, Lev-Ran S, Rehm J. Cannabis effects. Drug Alcohol Rev 2003;22:453–60.

Harley M, Kelleher I, Clarke M, Lynch F, Arsenault 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.

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.

Hasin DS, Kendle BJ, Saha TD, Huang B, Pickering R, Smith SM, Jung J, Zhang H, Grant BF. Prevalence and correlates of OSM-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.

Hasin DS, Shumlevitz D, Cerdà M, Keyses KM, Olsson M, Savet 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.

Haan L, 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 2019;16:467–82.

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

Lev-Ran S, Roeckele 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.

Lichtman AH, Martin BR. Cannabinoid tolerance and dependence. Cannabinoids. In: Pertwee RG (ed). Handbook of Experimental Pharmacology. Heidelberg: Springer-Verlag. 2005;172:4790–805.

Mammen G, Rueda S, Roeckele 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;79:111839.

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.

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

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

Mecozzi S, Pelosi S. Cannabinoids: a neglected pharmacological treasure trove. Br J Pharmaco 2005;146:913–15.

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.

Morgan CJA, Curran HV. Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. Br J Psychiatry 2019;192:306–7.
