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EDITORIAL

From heavy cannabis use to psychosis: is it time to take action?

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Cannabis is one of the most widely used recreational drugs among people with clinical psychosis, after nicotine and alcohol. There has been a debate in psychiatry about whether or not we can infer a cause-and-effect relationship between the use of cannabis and psychotic disorders. In this editorial, we first present and critically discuss the evidence to date of the association between heavy cannabis use and psychosis. We argue that while the biological mechanisms underlying individual susceptibility to develop a psychotic disorder following heavy cannabis use are still unknown, heavy cannabis use remains the most modifiable risk factor for the onset of psychotic disorders and for its clinical and functional outcome. This demands a clear move towards both primary and secondary prevention intervention to reduce the impact of heavy cannabis use on the incidence and prevalence of psychotic disorders.

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Psychosis

Epidemiology

Psychotic disorders are prevalent in 0.7% of the UK population (Department of Health, 2016). A multi-site incidence rate (IR) study investigating six countries and a total of 17 catchment areas of people with first-episode psychosis found that IRs for psychotic disorders vary widely across Europe, with, for example, an eightfold variation of IRs found between Santiago in Spain and Paris in France (Jongsma *et al*., 2018).

A wide range of genetic and environmental risk factors for psychotic disorders have been documented. Early-life risk factors include obstetric complications at birth and child abuse, and later-life risk factors include migration, childhood adversity, social disadvantage and urban living (Stilo *et al*., 2011). Cannabis use is the most consistently replicated environmental risk factor for psychotic disorders (Marconi *et al*., 2016).

Schizophrenia and psychotic disorders are highly heritable (Hilker *et al*., 2018), and genome-wide association studies (GWAS) have found a number of genetic risk variants for psychosis (Ripke *et al*., 2014). The genetic risk variants associated to psychosis can be summarised into polygenic risk scores (PRS) (Murray *et al*., 2021) which are believed to mediate the effects of environmental risk factors (Murray *et al*., 2017).

Cannabis-associated psychosis

Scepticism

One argument is that people experiencing early symptoms of psychosis self-medicate with cannabis as they experience negative symptoms of schizophrenia spectrum disorders such as anhedonia, and that cannabis use is indeed a prodromal or precursory sign of psychosis, a theory disputed by Murray *et al*. (2017). Indeed, similar reasons for using cannabis have been described by people with and without first-episode psychosis (Bianconi *et al*., 2016; Santacana & Pérez-Sola, 2014; Green *et al*., 2004).

More recently, and consistently, GWAS have indicated a positive and strong correlation between both cannabis use initiation and cannabis use disorder (CUD) with schizophrenia (Johnson *et al*., 2020). This has led to question whether the association between cannabis use and psychotic disorders described by epidemiological studies might be confounded by genetic effects and indeed reverse causation.

Mendelian randomization (MR) studies have used the available genetic data from both schizophrenia and cannabis initiation GWAS, to test for a) a genetic

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causal association between cannabis use and schizophrenia and b) its direction: whether it is from cannabis use initiation to schizophrenia or vice versa. While MR findings have been mixed and the jury is still out, as discussed by Johnson *et al.* (2020), genetic factors are likely to play an important role in the association between cannabis use and psychotic disorder (Giordano *et al.*, 2015).

In contrast, data from the EU-GEI multisite case–control study, a European collaboration study including 10 sites plus one from Brazil, reported that frequent use of high-potency cannabis was associated with a fivefold increase in the risk for psychotic disorders, compared to never having used cannabis, independent of the genetic load for schizophrenia measured as PRS (Di Forti *et al.*, 2019a).

Epidemiological evidence

The first longitudinal case–control study investigating the association between cannabis use and psychosis was conducted on 45 570 Swedish military conscripts over 15 years (Andréasson *et al.*, 1987) following concerns of psychiatrists in Sweden about cannabis use in their patients with psychosis (Hamilton, 2017). Frequent use of cannabis was defined as having consumed it more than 50 times in a lifetime. They found an adjusted odds ratio of 2.41 (95% confidence interval = 1.72–3.30) of schizophrenia among frequent users of cannabis at follow-up compared to non-users. Interestingly, 7% of conscripts refused to disclose their cannabis consumption, which may have been due to stigma associated to cannabis use and could have been a limiting factor in this study (Hamilton, 2017).

A systematic review and meta-analysis of 11 cohort and case–control studies conducted in 2005 (Semple *et al.*, 2005) found an odds ratio of 2.9 (95% confidence interval = 2.4–3.6) of schizophrenia or schizophrenia-like psychotic illness associated with cannabis use. The dose–response relationship was found in some included studies that, similarly to the Swedish conscript study, had dichotomous categories for high and low use of cannabis (e.g., past and current use) and abuse and dependence as defined by the DSM-IV. A review published in 2007 of seven studies found similar results (Moore *et al.*, 2007), with all studies included showing a dose–response effect of duration of use and frequency. A limitation of these meta-analyses is that they used only both extreme categories (e.g., highest level of use compared to no use of cannabis) to measure the overall effect sizes (Marconi *et al.*, 2016).

A 2016 review of 18 studies and meta-analysis of 10 studies showed a dose–response effect of frequency of cannabis use and long-lasting psychotic disorders, with a 3.90 (95% confidence interval = 2.84 to 5.34) increase in risk for the heaviest users compared to non-users and a twofold increase in risk between the average cannabis-users and non-users (Marconi *et al.*, 2016). An important strength of this study was that it re-examined raw data from studies included in order to use an exposure continuum of cannabis use as opposed to binary categories of cannabis use to measure the magnitude of effect. This revealed that the magnitude of effect was higher than that documented in previous meta-analyses that had only compared two extreme categories. In addition, studies that included participants suffering from psychosis symptoms at baseline were excluded, which the authors argue means that results are unlikely to be explained by psychosis symptoms leading to cannabis use. These data support a causal role of cannabis use on psychosis, whereby consuming higher amounts of cannabis leads to a higher risk of psychosis.

While this meta-analysis provides insights into the role of cannabis exposure, the role of the potency of the cannabis used was not accounted for. The potency of a type of cannabis here refers to its levels of delta-9-tetrahydrocannabinol (THC), to which the psychosis-inducing effects are attributed (Di Forti *et al.*, 2009).

Clear evidence has shown that daily use of high-potency cannabis carries a fivefold increased risk for psychotic disorders (Di Forti *et al.*, 2015, 2019b); a risk that reached a ninefold increase in Amsterdam, where types of cannabis highly concentrated in THC are widely available (Di Forti *et al.*, 2019b). Furthermore, findings from the EUGEI study indicated that the prevalence of use of high potency cannabis (THC ≥10%) and separately of daily use of cannabis among the population controls, representative of each site catchment area, contributed to explain the reported significant variations in rates of psychotic disorders across the study sites, even after controlling for age, gender and migration (Di Forti *et al.*, 2019b). Moreover, this study calculated that 30% of the first-episode psychosis cases presenting to the South London site Mental Health services and 50% of those presenting to services in Amsterdam could have been prevented if high-potency forms of cannabis, such as 'skunk' had not been available to consumers. These findings support the view that for this significant proportion of people, who are likely to carry many other risk factors for psychosis, the use of high-potency cannabis represented the final risk factor that tipped them over the threshold into frank clinical psychosis.

Further evidence from this multisite study shows that patients in their first episode of psychosis who report having used high-potency cannabis daily presented with more positive symptoms compared to those who never used cannabis or used low-potency types (Quattrone *et al.*, 2020).

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These findings have public health implications because the potency of cannabis has increased in the UK and beyond in the last 40 years, from 5% THC or less in the 1970s to levels averaging 16–20% reported in by Freeman *et al.* (2020). Recent evidence report that in Denmark the incidence of dual diagnoses of schizophrenia and CUD rose in conjunction with the rise in cannabis use and of its THC content between 1994 and 2006 (Hjorthøj *et al.*, 2019). Furthermore, forms of street cannabis containing cannabidiol (CBD) are becoming increasingly rare, while CBD-only products are now popular on the shelves of many UK health shops, advertised for their anxiolytic effects but without any evidence about the efficacy and safety (Chesney *et al.*, 2020). The fact that potency is not measured in most of the epidemiological literature is an important research gap, and future studies need to measure potency as well as frequency of cannabis use.

Experimental studies

Cannabis contains more than 500 components, of which around 100 cannabinoids have been identified, the two most studied being THC and CBD (Pertwee, 2014). These act on the endocannabinoid system of which the most important cannabinoid receptors are CB-1 and CB-2 (Lu and MacKie, 2016). Human laboratory studies have demonstrated that the administration of THC induces psychotic-like symptoms such as paranoia and cognitive impairment, which is mediated by action on the CB1 receptor (D'Souza *et al.*, 2005), while CBD counters this effect (Englund *et al.*, 2013). Indeed functional magnetic resonance imaging data show that THC and CBD have opposite effects on regional brain function (Bhattacharyya *et al.*, 2010). The strength of laboratory studies is that they allow for causal inference to be made about the effect of different cannabinoids on psychotic symptoms in a controlled environment. However, while these studies demonstrate acute short-term effects of cannabinoids, they cannot explain the association between cannabis use and lasting psychosis. Neuroimaging evidence on this topic is mixed (Murray *et al.*, 2017), and more evidence is needed in order to make any claims about how cannabis may induce long-lasting psychosis.

It is important to note that new evidence from animal and human studies suggests that the CBD to THC ratio in cannabis plays an important role in its psychoactive properties, as CBD has been found to potentiate the effects of THC in certain doses (Freeman *et al.*, 2019). Future studies should aim to clarify the exact impact of different CBD doses on the effects of THC.

Adverse outcomes associated with continued cannabis use in people with psychosis

A meta-analysis found that patients who continue to use cannabis, and in particular those who use daily high potency cannabis after their first episode of psychosis, show a longer time spent in hospital, have higher rates of psychosis relapse and show more severe psychotic symptoms (Schoeler *et al.*, 2016). A 10-year follow-up study conducted in Spain found that patients who stop using cannabis after their first psychosis episode had similar remission rates to people who had never consumed cannabis (Setién-Suero *et al.*, 2019). These data show the importance of interventions reducing cannabis use in patients presenting with first-episode psychosis in order to improve their prognosis.

Cannabis withdrawal syndrome and cannabis dependence

Substance use disorders are characterised by dependence, which occurs when an individual experiences craving for the substance, withdrawal when they stop consuming it and show failed attempts to reduce consumption (American Psychiatric Association, 2013). Cannabis withdrawal symptoms include anxiety, disturbed sleep and decreases in appetite (Bonnet & Preuss, 2017). A review found that cannabis withdrawal syndrome (CWS) is prevalent in the majority of daily users of cannabis upon abrupt cessation (Budney *et al.*, 2004). One study conducted in the United States found that 94.2% of 120 chronic cannabis users with schizophrenia reported withdrawal symptoms (Boggs *et al.*, 2013).

On top of an association between cannabis potency and psychosis risk, there is evidence of an association between the potency of cannabis and cannabis dependence severity. A 16-year observational study in the Netherlands found a positive association between increases in cannabis potency and first-time cannabis admissions to specialist drug treatment (Freeman *et al.*, 2018). Furthermore, a study of 410 participants found that THC exposure was associated with cannabis dependence measured via self-report and clinician ratings of dependency (Curran *et al.*, 2019).

Treatments for cannabis use disorder in patients with psychotic disorders

While there are currently no recommended psychological interventions for cannabis use reduction and/or cessation and CWS in patients with co-morbid psychosis, some recent evidence suggests the possible effectiveness of cannabinoids agonists (Lintzeris *et al.*, 2019) or compounds able to modulate the endocannabinoid system (D'Souza *et al.*, 2019) in patients with CUD. Harm

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reduction measures for non-medicinal cannabis use have been published, notably in Canada (Fischer et al., 2011), encouraging, for example, people to opt for lower-potency cannabis forms and to reduce the frequency of consumption. However, for these guidelines to be effective, especially in a sample of people with psychosis and cannabis use who have been shown to struggle with engagement, they need to be turned into targeted interventions. Indeed, while we are able to offer several intervention strategies for tobacco smoking cessation, we still expect patients with psychotic disorders to stop their heavy cannabis use just because, we, psychiatrists and mental health professionals say so, ignoring their degree of dependence, as well as the withdrawal symptoms and craving that they are likely to experience.

The Circle Trial was the first to test whether combining contingency management with a psychoeducation package was more effective in the treatment of CUD in patients with first-episode psychosis than psychoeducation alone (Rains *et al.*, 2019). Although the overall findings failed to show an advantage of the new intervention, the latter led to better outcomes in those who engaged throughout the trial. This underlines the importance of developing interventions able to successfully engage patients with first-episode psychosis.

Recently, in south London, thanks to the funding of the Maudsley Charity (https://maudsleycharity.org/), a new clinical service was developed to deliver an intervention for cannabis use reduction/cessation to young adults suffering their first episode of psychosis. The Cannabis Clinic for patients with Psychosis (CCP) (https://maudsleycharity.org/case-studies/cannabis-clinic/) is the first service in UK that combines the expertise of Early Intervention (EI) services in engaging patients at their first episode of psychosis with established addiction models. These encompass motivational interviewing, contingency management, psychoeducation, nicotine replacement therapy for the frequent co-morbid tobacco smoking and medications reviews when appropriate. The CCP has also developed a Peer group, currently running online because of the COVID19 pandemic, where patients referred to the CCP can attend small educational talks on cannabis dependence, on the effects of cannabis on mental health and overall well-being and share their lived experience of both psychosis and cannabis dependence. The Peer group is co-run by peer mentors who have recovered from cannabis-induced psychosis and stopped their cannabis use. By sharing their experience, they play a central role in this service. While it is too early to make conclusions about the effectiveness of the CCP, preliminary observations are encouraging. Given the robust evidence that indicate cannabis use as the most modifiable risk factor for poor clinical and functional outcome in psychosis, the work of the CCP should prompt us mental health professionals to bring together the existing recourses and expertise to provide support to patients with psychosis who are smoking cannabis and wish to stop.

Conclusion and future directions

Epidemiological studies consistently support heavy cannabis use as a component cause for developing psychosis and provide convincing evidence that both frequency of use and potency play important roles in this association.

Challenging social norms and widespread misconceptions such as the notion that cannabis cannot be harmful or addictive will be a crucial step forwards. As people who start using cannabis from a young age are more likely to develop CUD (Leung et.al, 2020), which will make it harder for them to reduce their consumption if confronted with psychiatric illness, we need to address young people with the message that certain forms of cannabis can be harmful and cause dependence.

Therefore, while the underlying biological mechanisms of this association are still unclear and while we are still exploring the role of genetic variants in shaping individual susceptibility to the psychotogenic effects of heavy cannabis use, there is enough evidence to justify the development 1) of a public education campaign using engaging dissemination tools (e.g. social media platforms, school seminars, short movies) tailored to reach adolescents to inform them about the hazards of the frequent use of high potency cannabis on mental health and 2) of targeted interventions for people with first-episode psychosis who continue to use cannabis after the onset of their illness.

Conflict of interest

M Di Forti reports personal fees from Janssen, outside the submitted work.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008.

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