Title: Are we any closer to identifying a causal relationship between cannabis and psychosis?

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Highlights

- The increasing availability of high potency cannabis increases the risk of developing cannabis psychosis, as a dose response relationship has been established as a risk factor.
- Defining and standardizing terms and measurement of cannabis products and use could usefully transform research and practice for cannabis psychosis.
- Evidence based interventions for patients with cannabis psychosis are limited and those that show promise are symptom-specific rather than treating all symptoms.
- Liberalisation of cannabis policy in some countries may support studies designed to better understand the impact of cannabis on mental health

Keywords: Cannabis, cannabis psychosis, schizophrenia, medicinal cannabis, public health.

Abstract

This review provides the reader with an update on developments in research relating to cannabis psychosis. For over four decades researchers and clinicians have focused on the relationship between exposure to cannabis and the emergence of psychotic symptoms. This has proved to be a complicated topic to investigate but research has provided some valuable insights as to the nature of this relationship while also identifying the limits of our understanding.

There are significant gaps in understanding of almost every aspect of the journey that people who have cannabis psychosis experience. Not only are treatment options limited, but we still have little evidence to help reliably predict who is at risk of developing cannabis psychosis. This would provide an opportunity to intervene early to reduce the number of people who experience this type of problem, although it is unrealistic to think it would be eliminated completely.

Introduction

Researchers and clinicians have been concerned about the relationship between cannabis and psychosis for four decades, although the pace of investigation has increased in recent years. Exploring the relationship between these two issues has proved to be challenging not least due to cannabis being a controlled drug, and a variety of cofounding variables such as individuals using more than one psychoactive drug which might also account for observed psychotic symptoms or those reported in research [1,2,3]. However, improved methods have been developed which have partly taken into account these cofounding variables, and this has helped provide a clearer idea of the relationship between cannabis and psychosis.

This review will guide the reader through the latest evidence in this field and includes discussion of prevalence through to treatment interventions. We conclude by identifying important research gaps and priorities.

Prevalence and incidence of cannabis psychosis

Knowing how many people have cannabis psychosis clearly matters, as does observing trends in incidence and prevalence over time. However, there are already weaknesses in epidemiological estimates of psychotic disorders including those that are cannabis-induced [4]. Whilst estimates of cannabis use prevalence, use disorders, and disease burden are improving there are no global estimates of the incidence of cannabis psychosis. It has been estimated that only 0.04% of the disability-adjusted life years (DALYs) associated with schizophrenia can be attributed to heavy (weekly) cannabis use, with highest levels reported for high income territories such as North America [5]. However, confidence in these estimates is weakened by the poor quality of much epidemiological research in many countries.

Even if overall population prevalence of cannabis remains stable this doesn't mean that rates of cannabis psychosis will follow this trend. As potency of cannabis has increased lower potency cannabis has become more difficult to source. This limiting of availability of lower potency cannabis could increase the risk of psychosis and schizophrenia in these populations (Chandara et al 2019).

Measuring the impact of exposure to cannabis on rates of cannabis psychosis will be subject to a time lag if anything more than acute symptomatology is assessed. Individual manifestation of symptoms could take a few months to a few years, and one recent metanalysis reported a pooled estimate of the interval between initiation of cannabis and onset of psychosis of 6.3 years [6].

Unlike other areas of medicine such as diabetes or cancer, defining and estimating incidence and prevalence of cannabis psychosis has proved to be difficult. DSM and ICD definitions of substance-induced psychotic disorder differ, even across editions, and may relate to presence of any symptoms after recent exposure, or a severity that is in excess of what would normally be expected during intoxication. One of the clearest differences for researchers and clinicians in using the DSM and ICD definitions are the differing thresholds to meet the criteria for a substance-induced disorder, including cannabis-induced psychosis [7]. For DSM-V the patient only needs to exhibit a symptom of psychosis after recent exposure to a substance, whereas for ICD-11 the symptoms must be in excess of what would be expected from substance intoxication or withdrawal. Even for a skilled and experienced clinician this distinction can prove challenging.

Genetics

There may be a bi-directional association between cannabis use and psychosis, with some shared

genetic aetiology between psychosis risk and propensity to use cannabis [8]. For example, using a twin registry sample drawn from the Netherlands, Verweij and colleagues used self-reported questionnaires to determine the overlap between use of cannabis and psychosis [9]. Using genotyping of the sample they were able to establish polygenic risk scores, these scores were significantly correlated with five out eight types of cannabis use, including lifetime use, regular use and quantity of use. This indicated that individuals who had a genetic predisposition to schizophrenia were also significantly more likely to use cannabis. As usual there are caveats not least the reliance on self-reports which are subject to recall bias.

Furthermore, in keeping with the findings of other studies, a recent meta-analysis of three large human genetic datasets using Mendelian randomization techniques found that genetic risk factors for cannabis use and schizophrenia were positively correlated [10]. There was strong evidence for a significant causal relationship for the influence of schizophrenia risk on cannabis use, whereas the opposite relationship was much weaker. One explanation given by the study authors for this finding is that individuals at risk of developing schizophrenia experience prodromal symptoms that make them more likely to start using cannabis to cope or self-medicate. However, it is important to note that this study only examined lifetime cannabis use. As frequency of cannabis use is strongly associated with increased likelihood of developing psychotic disorder, a different causal relationship may have emerged if frequency of consumption data had been used versus lifetime use [11].

More broadly, any investigation of a genetic link between cannabis and psychosis cannot establish a causal link between the two based purely on inherited genes as participants will be exposed to multiple environmental factors during their lifetimes which could influence both cannabis use and symptoms of psychosis [12]. It therefore continues to be difficult to isolate a conclusive relationship between cannabis and psychosis beyond the status of association.

Cannabis potency, frequency of use, and the nature of cannabis markets

Research into cannabis psychosis continues to support a dose response relationship as a significant risk of developing this problem [13]. More potent forms of cannabis and frequent exposure are linked to an elevated risk of developing psychosis and exacerbating symptoms for individuals with psychosis and schizophrenia [14]. One recent multi-centre case-controlled study conducted in 10 European and one Brazilian site concluded that 12% of cases of first episode psychosis could be prevented in Europe if high potency products (defined as cannabis containing 10% tetrahydrocannabinol (THC) or greater) were removed from the market [15]. THC is the primary psychoactive intoxicating constituent of cannabis but is associated with psychotic symptomatology. The risk of a range of adverse cannabis effects may be reduced in consumers of products with a balanced ratio of THC and cannabidiol (CBD) [16]. In Canada, 'lower risk' guidelines supported by the Ministry of Health were published to accompany national legislation which introduced a legally regulated cannabis market [17]. These recommend that people with a personal or family history of psychosis should avoid use altogether. The guidelines also highlighted that high THC products increase the risk of psychosis and that CBD can counteract these and other adverse effects. The review underpinning the guidelines concluded that there was substantial evidence based on several supportive findings from good-quality studies, with few opposing studies, to support this recommendation [17]. However, another review found inconsistencies in findings across human adult administration studies and suggested that this may have been because moderating effects of CBD were only apparent in individuals who experience more extreme, and clinically relevant psychotic-like effects [18]. Less research has been undertaken with adolescents and young cannabis users who face an elevated risk of psychosis compared to

their adult peers, but there is emerging evidence to suggest that CBD may also partially reduce this risk [19]. Recent research has suggested that frequent users of cannabis are less susceptible to health warnings about cannabis, therefore information and education campaigns may have limited utility in reducing psychosis risk [20]. Importantly, however, CBD does not reduce the subjective intoxication effects of cannabis, including desired effects [18]. In legal markets such as Canada, where cannabinoid content can be carefully regulated, provision of balanced THC: CBD products that are still appealing to consumers, could be a more effective means of reducing risk than education in those who decide to use cannabis.

The THC content of illicit cannabis products has increased in many countries in recent years, whilst CBD has remained stable [21]. This change in market profile has been argued to be a result of prohibition of cannabis, and traditional drug control legislation has proven ineffective at reducing harmful illicit market features [22]. Proponents of legal regulation cite this as one of the reasons for regulating its supply and distribution [23]. Limits on the maximum concentration of THC in legally supplied products could be imposed in a regulated market, or product price could be based on THC content to discourage purchase of higher concentration products. However, this assumes that a 'safe' level of THC can be identified, and that at-risk consumers have good understanding of product content and can change their use patterns accordingly [24]. Sales data suggests that consumers of legal cannabis seem to have a preference for higher THC products and whilst product regulations may control cannabis sold in legal markets, sizeable illicit markets may persist allowing consumers to circumvent product restrictions to purchase higher potency cannabis [25].

It is important to note that most of the data we have relating to cannabis potency is drawn from high income countries, and western Europe, North America, and Australia. This leaves us with little information about populations in Africa and Asia and the potency of cannabis they are exposed to. This appears to be a significant gap in understanding and given the size of these populations there would be benefits to their knowledge and policy if this information were available.

We still don't have an internationally agreed definition of terms like 'high potency' or 'strong cannabis', and assessments are complicated by the different types of cannabis product available (e.g. herbal, oils, THC vaping liquids). These inconsistencies make comparison between studies difficult and this limits the application of much research to practice. The ability to formally monitor cannabis sales, and availability of clearly labelled and standardized products in legal markets may make untangling the relationship between patterns of cannabis use and individual risk easier. Work is underway to develop a standardized THC unit in a similar manner to a unit of alcohol (e.g. 5mg THC cf 8g ethanol in the UK) [26]. Some authors have suggested that based on psychosis studies, cannabis containing more than 10% THC should be considered 'high strength' [27]. However, this is below the mean potency of herbal cannabis available in the USA and Europe so is not a useful cut off point and does not take into account the potential mitigating effects of a balanced THC:CBD ratio [22].

Complementing knowledge and understanding of the role that dose plays in cannabis psychosis is research into frequent use and dependence [28]. As with other potentially health harming goods such as alcohol, although they only account for a small proportion of the total number of users, people classed as frequent and daily users account for the majority of cannabis consumed, and likely carry the majority of the harm burden [29]. From a commercial perspective, if cannabis is anything like alcohol, then industry profits will rely on the heaviest consumers with the highest risk of psychosis, and marketing spend would be focused on recruiting younger consumers and retaining the heaviest [30].

Interventions for cannabis psychosis

Many users and healthcare professionals still view cannabis as relatively benign or think that individuals can't develop a physical or psychological dependency [31]. Globally an estimated 13 million people are dependent on the drug, accounting for two million disability adjusted life years, and the disorder is most prevalent in young people in higher income countries [30]. These research insights have a bearing on how and when interventions are offered when people develop cannabis psychosis. It is clearly an added complication and challenge if a patient is dependent on cannabis even if using this drug harms their mental health.

Overall, there is limited evidence in relation to clinical interventions for cannabis psychosis, and although some are in the development stage, these tend to be focused on a specific symptom of psychosis such as thoughts rather than targeting all aspects of the condition [32,33,34]. There are encouraging signs that a cognitive based model could be used to treat those who have developed a cannabis psychosis [35]. Rather than trying to treat all the symptoms associated with psychosis it appears that cognitive models that target specific symptoms such as paranoia may offer an advantage. Self-monitoring of cannabis use and the corresponding emotions is the focus of a mobile app being developed for young people who are at risk of developing cannabis psychosis [36]. Harnessing technology in this way is encouraging and may have greater acceptability in adolescents who are familiar with this type of technology. In the same way that self-recorded diaries have been used, these mobile apps could help users keep a record of cannabis use which would be a useful aid for clinicians assessing these young people.

Development of comprehensive intervention may be unrealistic given the range of symptoms involved and the fact that the condition involves an interaction between substance use and mental health. Future research which aims to mitigate specific symptoms or clusters of symptoms such as negative or positive symptoms of psychosis in addition to those that support the individual to reduce their exposure to cannabis may provide the optimum combination for this group.

Policy on the status of cannabis as a restricted or accessible drug also influences early intervention provided for young people who are at risk of using cannabis and developing psychosis and schizophrenia. In jurisdictions where cannabis is prohibited this can restrict the role public health can play in providing information and education to this at-risk group. Equally, prohibition may deter young people seeking help if they develop problems with cannabis such as psychotic-like experiences for fear of criminal sanctions and attracting a criminal record that would limit their employment prospects and other aspects of their lives.

Conclusion

There are several future research priorities that would lead to a better understanding of the impact of policy change on the risks of cannabis psychosis at a population level. These should include an internationally agreed set of terms which define cannabis types, strength, and patterns of use. This would not only allow cross study comparison it would improve the credibility of this specialist field, and its ability to serve policy and public health.

Exclusion criteria of much current research also limits application to clinical practice. Most trials of interventions for addiction exclude individuals with current or previous mental health problems, while trials in mental health reciprocate by excluding those with addiction. This clearly hampers innovation of treatment for people who have cannabis psychosis. This division is not aided by separate funding for research and treatment, budgets for these areas are siloed in mental health and addiction bodies. Integrating these or at least providing some jointly funded calls would improve research activity and inform treatment.

The exclusion criteria used in research trials is mirrored by many treatment providers. Patients with

cannabis psychosis are likely to be referred onto mental health services if they present to specialist drug treatment providers. Conversely should they present to mental health services there is a risk that they could be excluded and referred to specialist drug treatment to address their use of cannabis. Both examples of treatment exclusions leave patients having to navigate multiple services at a point in their life when they are likely to be experiencing acute symptoms and have limited cognitive functioning which reduces their working memory and ability to concentrate.

Commissioners and treatment providers should collaborate and work together to minimize the risk of patients being excluded from services and adopt an approach that ensures access to treatment is timely and sensitive to the patient's needs.

Whilst we clearly acknowledge the risks of cannabis-induced psychosis and the concerns of professionals, more liberal cannabis policies do not necessarily have to mean an increase in the burden of mental ill health. Although there are risks in establishing legally regulated cannabis markets, a public health led approach to policy development provides better opportunities and tools to militate against these than current criminal markets.

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* Denotes an article of interest & why

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Conflict of Interest

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: