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Case Report

HHC-induced psychosis: a case series of psychotic illness triggered by a widely available semisynthetic cannabinoid

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Abstract

Use of both cannabis and synthetic cannabinoids has been regularly linked to the development of psychotic illness. Thus, semisynthetic cannabinoids such as hexahydrocannabinol (HHC), which have a similar neurobiological profile to delta-9-THC, may also be expected to lead to psychotic illness. However, no such relationship has yet been reported in scientific literature. HHC is readily available online and in many vape shops in Ireland. Here, we present two cases of psychotic illness which appear to have been precipitated by use of legally purchased HHC and discuss its psychotogenic role and factors linked to its current widespread availability.

Keywords: Cannabinoids; designer drugs; legislation and jurisprudence; psychosis; substance abuse detection

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Introduction

The relationship between cannabis and the development of psychotic illness has been well established. Cannabis contains over 500 known compounds, of which 125 are cannabinoid compounds, that have varying and often opposing systemic and psychoactive effects (Radwan et al. 2021). The main psychoactive compound of cannabis is delta-9-tetrahydrocannabinol (Δ9-THC), whose partial agonism of the cannabinoid receptor CB1 leads to the 'high' of cannabis intoxication (Ashton, 2001). A meta-analysis of 18 studies and 66,816 individuals reported an odds ratio of 3.90 for the risk of psychosis-related outcomes among the heaviest cannabis users compared to the nonusers (Marconi et al. 2016). A subsequent multi-center case–control study indicated that this relationship is likely mediated by THC, with higher levels of THC strongly correlated ($r = 0.8$) with high rates of psychosis (Di Forti et al. 2019). An effect of cannabidiol (CBD) in preventing psychosis is reported but uncertain (Englund et al. 2023), and the increasing THC potency in cannabis in recent years is a worrying trend (Freeman et al. 2021)

Although cannabis has been legalized in many jurisdictions in recent years, its apparent detrimental effects on mental health and in particular its association with the development of psychotic illness has slowed its legalization on a widespread basis in Europe. One possible consequence of continuing illegality is that users in an unregulated environment are consuming high-potency or synthetic cannabinoids (Klein et al. 2022), which are more likely to lead to adverse effects, including psychosis (Murray et al. 2016). Synthetic cannabinoids were first noted in Europe in 2008 and represent the largest group of novel psychoactive substances now being monitored (Andrews et al. 2023). European data also suggest increasing rates of detection of novel synthetic cannabinoids and that national prevalence rates in young people pertaining to recent use range from 0.1 to 5.1% (European Monitoring Centre for Drugs and Drug Addiction Hexahydrocannabinol (HHC) and related substances., 2023).

Hexahydrocannabinol (HHC) is a semisynthetic cannabinoid derived from CBD which is similar in chemical structure to Δ9-THC. It is classified as semisynthetic, rather than synthetic, because it is synthesized from CBD, which in turn is often derived from low-THC cannabis (hemp). This differentiates it from fully synthetic cannabinoids which are synthesized de novo. HHC binds to CB1 and CB2 receptors. It was first described in the scientific literature in 1940 but was only first reported to the European Monitoring Centre for Drugs and Drug Addiction (European Monitoring Centre for Drugs and Drug Addiction Hexahydrocannabinol (HHC) and related substances., 2023) as a substance of concern in May 2022. As of March 2023, it has been reported in 70% of EU states, which likely represents an underestimate. No studies have been published in humans regarding physical or psychoactive effects of HHC; however, animal studies indicate that the effects of this substance are largely similar to Δ9-THC (Edery et al. 1984, Mechoulam et al. 1980), and it shows a similar receptor-binding profile to Δ9-THC (Nasrallah & Garg 2023).

HHC is marketed openly as a 'legal' alternative to cannabis products. It has been produced and marketed in various forms including sprayed onto low-THC cannabis flower and resin,

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vaping cartridges, and food products such as sweets. Retailers of CBD-related products including HHC are easily accessible online or via retail stores in most large urban centers. A nationally representative survey recently reported a 0.8% rate of usage of novel psychoactive substances in 18–64 year olds within the last year, versus 5.9% for cannabis (Mongan, Millar & Galvin, 2021).

Although a link between synthetic cannabinoids and psychotic illness is established, no such literature has yet specifically referred to HHC. Here, we present two cases of HHC-induced psychosis and discuss the implications of the apparent link with regard to aetiopathogenesis and public policy.

Case 1

This was the first presentation of a 20-year-old man to psychiatry services. He presented to the emergency department complaining of distressing psychotic symptoms, including delusions of guilt and persecution with derogatory second person auditory hallucinations. He feared that he would be sent to prison and that he may have killed one of his friends. He had superficially burnt himself with a cigarette in the context of guilty cognitions toward himself. He reported total insomnia for three days. He reported apparent dissociative symptoms and stated he felt as if he was 'in a game". On mental state examination, he was agitated and distressed, thought disordered, with second person derogatory auditory hallucinations.

He reported that he was a habitual cannabis user for three years preceding his admission, smoking on average half a gramme of cannabis herb per day, with no recent change or increase in his cannabis use or type. However, he had begun utilizing a HHC vape in the two months prior to admission. He vaped daily and was unable to quantify his intake accurately but reported that a single vape would provide approximately five to seven days usage. A brand he used has packaging stating it contains 300 puffs (1 milliliter) of 95% HHC distillate with 5% terpenes, is derived from hemp, and was manufactured in the Netherlands. He reported occasional HHC consumption via edible products but predominantly ingested via vaping. He denied any other significant substance use in the months prior to admission.

He had no prior psychiatric or medical diagnoses. He was a single male student with no dependents and lived with housemates of a similar age. His family were located elsewhere in the country, but he remained close to them. He reported a history of psychotic illness in a maternal grandmother and a history of alcohol addiction in a maternal uncle. He reported some infrequent use of various substances, including benzodiazepines, codeine, and 3,4-methylenedioxymethamphetamine (MDMA) but denied using these substances in the weeks prior to his presentation. He reported occasional social alcohol intake and denied any history of alcohol or substance dependence. Routine physical examination and screening bloods were normal. A urine drug screen returned a positive result for cannabis only. He accepted recommendation of a voluntary admission to the adult psychiatry unit.

During admission, he initially presented as fearful and persecuted with prominent delusions of guilt and persecution associated with thoughts of self-harm. He spent prolonged periods praying with a Bible or rosary beads. He felt there was 'a devil inside of him'. The patient responded well to a combination of olanzapine and clonazepam, with a significant reduction in delusional beliefs and distress associated with same and quickly recovered insight into his presentation.

After a period of two weeks, he was discharged from the inpatient unit. His plan on discharge included a prescription for olanzapine 10 mg and follow-up by the community mental health team (CMHT). There was no further evidence of any psychotic symptoms on follow-up appointments with his CMHT. He returned to full social and occupational functioning. He reported abstinence from all substances, including cannabis and HHC. He had good insight into the nature of his illness and likely precipitants and was able to reflect well upon these. He weaned off olanzapine over a five-month period, resulting in rebound insomnia but no reoccurrence of psychotic symptoms.

Case 2

This man experienced his second episode of psychosis in his late-30s, having had one previous episode of cannabis-induced psychosis 28 months previously. Prior to his second admission, he presented for an urgent outpatient review with his partner. His partner stated that in the preceding two nights, he had not slept and had been talking to himself throughout the day. He repeatedly said 'sorry' to the assessing clinician, asked if what he was experiencing was reality, and continuously wrote in a copybook, but was unable to articulate why he was doing so. Two weeks prior to this presentation, he had purchased a vape from a CBD shop. This patient used the same branded vape as described in our first case (95% HHC distillate with 5% terpenes). He said that one vape lasted him roughly one week and that he began to use it to lessen his anxiety. He denied using any cannabis or other illicit substances in the last two years.

He was admitted to the psychiatric unit on a voluntary basis. On admission, the patient was noted to be pacing around the ward, insisted on keeping office doors open, and sat in a doorway. He displayed a perplexed appearance and was alogic. He denied feeling paranoid, but his speech was bizarre in content. His physical examination and routine blood tests were unremarkable. He declined to give a urine drug sample. He was commenced on aripiprazole 10 mg OD. Three days into his admission, his mental state was noted to have improved dramatically. He was discharged for follow-up with the first-episode psychosis team after ten days of admission.

Following his discharge, he had a successful phased return to work and there was no evidence of psychotic or affective symptoms in the following months. At review nine months post-admission, the patient was prescribed aripiprazole 10 mg and had returned to his baseline level of functioning.

His prior episode of cannabis-induced psychosis had followed a period of total insomnia for two days, during which time the patient was grossly thought disordered again with prominent alogia. During this admission, he had also experienced delusions of reference, was admitted involuntarily for a brief period, and was treated with olanzapine 10 mg and discharged after nine days. He recovered well with the support of the first-episode psychosis team, successfully returned to work, and completed a course of psychotherapy. His medication was switched to aripiprazole 15 mg OD which was stopped 14 months post-admission with no further psychotic symptoms.

He had never previously received treatment in primary or secondary care for any mental health concerns. There was no family history of any psychiatric disorder or substance misuse. The patient had been a regular cannabis smoker since his twenties and had increased his intake to two joints per day (roughly one gram of cannabis) in the six months prior to his

first admission. He denied any other illicit substance use before this admission.

Discussion

Here, we present two cases of psychotic illness which appear to be precipitated by use of HHC. In both cases, the patients were regular cannabis users, but the episodes of psychotic illness only developed when they began vaping HHC. Both were diagnosed with synthetic cannabinoid-induced psychotic disorder (ICD11 code 6C42.6). As with cannabis-induced psychosis, the presentations were heterogenous in phenomenology (Padhi, Shukla & Chaudhury, 2021). One patient presented with delusions of guilt and persecution, as well as auditory hallucinations. The other patient presented with prominent thought disorder, notably alogia, as well as disordered subjective time.

To our knowledge, this is the first description specifically of HHC-induced psychosis. As a semisynthetic cannabinoid, it is unsurprising that HHC appears to be a psychotogenic substance. Agonism of the CB1 receptor, which underlies Δ9-THC's effects, leads to dopamine release in the nucleus accumbens and ventral tegmental area (Gunasekera, Diederen & Bhattacharyya, 2022). Acute d-9THC ingestion leads to increased dopamine release and neuronal activity, and long-term use is associated with blunting of the dopamine system (Bloomfield et al. 2016, Solinas et al. 2006, Bloomfield et al. 2014). HHC, through its R epimer (Reggio, Greer & Cox, 1989), has a similar binding profile to the CB1 receptor compared with Δ9-THC, it is therefore likely to produce similar stimulation of dopamine release in these areas. Notably, patient 1 was using both cannabis (containing Δ9-THC) and a HHC vape prior to his admission with a psychotic episode. It may be that the combined effect of these two substances on the CB1 receptor may have contributed to his development of psychosis after years of consistent cannabis use.

In relation to diagnosis, ICD-11 includes entries for cannabis-induced psychotic disorder (6C41.6) and synthetic cannabinoid-induced psychotic disorder (6C42.6). HHC is classed technically as a semisynthetic cannabinoid and thus does not fit neatly into either criterion, but we opted for the latter due to the synthetic phase of its production. Of note, Rossheim et al recommended use of the term 'derived psychoactive cannabis products', as it is encapsulates all related products while being specific enough to exclude other substances (Rossheim et al. 2023).

Both patients legally purchased these HHC products in commercial stores in city centers. HHC, as a semisynthetic cannabinoid, is banned in several EU countries (European Monitoring Centre for Drugs and Drug Addiction Hexahydrocannabinol (HHC) and related substances., 2023). However, in Ireland, it is not rendered illegal by the Misuse of Drugs Acts 1977, which specifically cites only 'tetrahydro derivatives of cannabinol' (Department of Justice and Law Reform Misuse of Drugs Act, 1977). Of note, Δ9-THC has been shown to be present in unregulated hemp-derived CBD products (Johnson, Kilgore & Babalonis, 2022) and there have been reports of HHC products containing Δ8-THC, Δ9-THC, and Δ6a,10a-THC but no HHC (European Monitoring Centre for Drugs and Drug Addiction Hexahydrocannabinol (HHC) and related substances., 2023). Thus, the possibility of unregulated HHC products in Ireland containing THC cannot be ruled out.

A gray area of legislation was previously exploited in the Republic of Ireland by so-called 'head shops', allowing production and sale of several legal psychoactive substances, including mephedrone, methylone, and methylenedioxypyrovalerone (MDPV) that were not specifically banned by the 1977 act. Notably, synthetic cannabinoids were reported to be the most common 'legal' psychoactive substances involved in psychiatric presentations (Lally et al. 2013). At their most widespread, there were over 100 such stores active in the country. In response to this, the government enacted a catch-all banning of novel psychoactive substances through of the Criminal Justice (Psychoactive Substances) Act, 2010. This was done as naming of specific substances in legislation led to 'head shops' replacing sales of these named substances with unnamed novel psychoactive substances, for example, a ban on the sale of mephedrone leading to the sale of flourotropococaine (Smyth et al. 2020).

The introduction of this act led to these 'head shops' closing, and a reversal in the upward trend of drug-related psychiatric admissions which had occurred in Ireland (Smyth et al. 2020). This act prohibited the sale of any 'psychoactive substance', which was defined as a 'substance, product, preparation, plant, fungus or natural organism which has, when consumed by a person, the capacity to produce stimulation or depression of the central nervous system of the person, resulting in hallucinations or a significant disturbance in, or significant change to, motor function, thinking, behaviour, perception, awareness or mood' (Department of Justice and Law Reform Criminal Justice (Psychoactive Substances) Act 2010).

Thus, the current legal status of HHC would appear to be based on it being classified as non-'psychoactive substance' under the Criminal Justice (Psychoactive Substances) Act. Although there is a lack of scientific literature HHC's acute effects on humans (Graziano et al. 2023), we contend that this is a misclassification. Many online accounts, and accounts communicated to the author, outline its psychoactive effects, and indeed stores themselves often advertise the product as intoxicating.

Patient 2 described the high from HHC as being similar to that of conventional cannabis, but said that he felt 'more heavy and drowsy' than when he smoked conventional cannabis. He said his two episodes of psychoses were similar in phenomenology, but that his HHC-induced episode came on more rapidly. He also described discussing HHC use with other patients who described a 'weird, less long-lasting high' from its ingestion, and who also believed that their HHC use contributed to their psychotic episode. Notably, he described patients as smoking HHC vapes on the psychiatric inpatient unit, and how their odorless use allowed discrete inhalation of HHC in public places. The ease of such HHC products with psychotogenic risk entering psychiatric wards clearly generates substantial risk for other patients with a predisposition to psychotic illness being exposed to further precipitants.

The Criminal Justice (Psychoactive Substances) Act was introduced to prevent intoxicating, harmful substances being sold in an unregulated manner. Meanwhile, HHC appears to cause intoxication and our case series suggests that HHC does indeed contribute to induction of psychotic illness. A wide variability in potency of available HHC products (Nasrallah & Garg 2023), coupled with increasing rates of ingestion of synthetic cannabinoids via 'edibles', has created public health concerns around potential poisoning events or accidental ingestion by children of high-potency synthetic cannabinoids (European Monitoring Centre for Drugs and Drug Addiction Hexahydrocannabinol (HHC) and related substances, 2023). The most recently available data indicate that the presence of HHC in Ireland may not yet be reported to the EMCDDA early warning system for monitoring novel psychoactive substances (Ujváry, 2024).

Conclusion

We present two cases of psychotic illness likely precipitated by use of HHC, a semisynthetic cannabinoid which is currently widely sold as a legal product in Ireland. Given the widespread and increasing use of vaping and the ready access to this compound, clinicians and policymakers should be aware of its psychotogenic potential to protect potentially vulnerable patients from its deleterious effects through psychoeducation and legislative restriction.

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Ethical standard. 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.

Consent. Written informed consent was obtained by both patients for publication of this report.

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