Editorial

Hexahydrocannabinol (HHC): a new challenge in psychoactive substance control and public health

Hexahidroxicannabinol (HHC): un nuevo desafío en el control de sustancias psicoactivas y salud pública

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The link between cannabis use and the development of psychotic disorders is well-documented in scientific literature. Cannabis, a plant containing more than 500 known compounds, includes at least 125 cannabinoids that can have significant psychoactive and systemic effects, often triggering psychotic episodes in users (Radwan et al., 2021). Among these, delta-9-tetrahydrocannabinol (9-THC) is the primary psychoactive component, whose action as a partial agonist of CB1 receptors in the brain is responsible for the euphoric state associated with cannabis intoxication (Ashton, 2001).

Despite the increasing legalization of cannabis in several European countries, the adverse mental health effects, particularly its link to psychotic illnesses, have hindered its adoption across Europe. The continued illegality of cannabis in certain contexts has led some users to seek alternatives in unregulated markets, exposing them to high-potency synthetic cannabinoids, which more frequently result in severe adverse effects, including psychosis (Murray et al., 2016). These synthetic cannabinoids, first identified in Europe in 2008, constitute the largest group of new psychoactive substances currently monitored in Europe and Spain (Andrews et al., 2023).

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Recently, a new semi-synthetic cannabinoid called hexahydrocannabinol (HHC) has gained attention. This compound, though present in cannabis in very small amounts (Watanabe et al., 2007), is semi-synthetically derived from cannabidiol (CBD) or 9-THC. HHC is chemically very similar to 9-THC, differing only in the loss of one double bond, and has been marketed as a "legal" substitute for cannabis and 9-THC products, with reports suggesting it has psychoactive effects similar to those of 9-THC (EMCDDA, 2022a). HHC was first identified in Europe in May 2022. By March 2023, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) had received reports of HHC's presence in products marketed in 20 European Union (EU) member states through the EU Early Warning System (EMCDDA, 2023).

Unlike 9-THC, HHC is not currently controlled under the international drug framework or in most EU countries. Information on this substance in Europe remains limited, but its first detection in the region occurred in May 2022, in a product marketed as a tincture under the label "CBN night." This product, advertised as a sleep aid, was seized and analyzed by Danish police. Laboratory tests revealed the presence of HHC and cannabinol, although HHC was not listed on the packaging (EMCDDA, 2022b).

Since then, an increase in products containing HHC has been observed across Europe in various formats. According to EMCDDA reports, a wide range of products exists, including cannabis herbs and resins with low 9-THC content sprayed with HHC, disposable vape pens, cartridges and liquids for e-cigarettes, edible products (mainly gummies), and oils with high HHC content (EMCDDA, 2022a). These products are often presented with attractive designs and bright colors, making them more appealing to consumers, especially young people. Moreover, they are commonly sold online and in stores such as herbal shops, under brand names like Afghan Kush, Amnesia, BubbleGum Kush, Strawberry Kush, Pineapple Express, and Purple Haze (EMCDDA, 2022c).

Recently, clinical cases documenting severe psychotic episodes related to HHC consumption have been reported, requiring hospitalization and psychiatric treatment (O'Mahony, B. et al., 2024). Clinical symptoms observed included behavioral disorganization, delusions of guilt and persecution, and auditory hallucinations. Although human studies are scarce, it is unsurprising that HHC has psychogenic potential. CB1 receptor agonism, which underlies the effects of 9-THC, leads to dopamine release in key brain areas such as the nucleus accumbens and the ventral tegmental area (Gunasekera, Diederen & Bhattacharyya, 2022). HHC, through its R-epimer (Reggio et al., 1989), shows a similar CB1 receptor binding profile compared to 9-THC, although it is less potent in binding to these receptors, suggesting it could induce similar dopaminergic stimulation and trigger a psychotic episode.

HHC's appeal lies in its novelty and the lack of specific regulation in many countries, enabling its marketing as a "legal" alternative to 9-THC. However, this situation raises serious concerns. The lack of comprehensive studies on HHC leaves its long-term effects on physical and mental health largely unknown. Early reports indicate that HHC might have a psychoactive impact comparable to 9-THC, potentially increasing the risk of dependence and addiction.

Given this scenario, healthcare professionals must be prepared to address a possible rise in cases related to HHC use, including psychotic disorders, behavioral disturbances, addictions, and other severe side effects. As this substance gains popularity, it is crucial for public health services to develop strategies to raise awareness about the associated risks and for professionals to be trained to recognize and address issues stemming from its use.

Regulating HHC presents a significant challenge. As a relatively new substance, many legal frameworks have yet to establish a consensus on how to classify and control it. This legal loophole facilitates its availability and use, especially among young and vulnerable individuals. It is essential for health authorities and lawmakers to work together to develop policies that adequately regulate HHC's sale and distribution, thus protecting society from its potential harms.

In summary, the emergence of HHC in the market underscores the need for a proactive approach in understanding and studying this new substance. We cannot allow the lack of information and regulation to turn this new substance into the next public health crisis. In this regard, it is essential for the scientific community, healthcare professionals, and authorities to collaborate closely to better understand this substance, educate the public, and prevent the potential harms associated with its use.

REFERENCES

Andrews, R, Jorge, R, Christie, R, Gallegos, A (2023). From JWH-018 to OXIZIDS: structural evolution of synthetic cannabinoids in the European Union from 2008 to present day. *Drug Testing and Analysis,* 15, 378-387.

Ashton, CH (2001). Pharmacology and effects of cannabis: a brief review. *The British Journal of Psychiatry,* 178, 101-106.

EMCDDA (2022a). EMCDDA technical expert meeting on hexahydrocannabinol (HHC) and related cannabinoids, EMCDDA, Lisbon, 19 December 2022. https://www.emcdda.europa.eu/news/2022/emcdda-technical-expert-meeting-hexahydrocannabinol-hhc-and-related-cannabinoids_en

EMCDDA (2022b). Formal notification of 6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-3-pentyl-6H[1]dibenzo[b,d]pyran-1-ol (hexahydrocannabinol; HHC) by Denmark as a new psychoactive substance under the terms of Regulation (EC) No 1920/2006 and Council Framework Decision 2004/757/JHA. EU-EWS-RCS-FN-2022-0031, EMCDDA, Lisbon, 21 October 2022.

EMCDDA (2022c). Formal notification of (6,6,9-trimethyl-3-pentyl-6a,7,8,9,10,10a-hexahydrobenzo[c]chromen-1-yl) acetate (hexahydrocannabinol acetate; HHC acetate) by Hungary as a new psychoactive substance under the terms of Regulation (EC) No 1920/2006 and Council Framework Decision 2004/757/JHA. EU-EWS-RCS-FN-2022-0035, EMCDDA Lisbon, 5 December 2022

EMCDDA (2023). Formal notification of 3-heptyl-6a,7,8,9,10,10a-hexahydro-6,6,9-trimethyl-6H- dibenzo[b,d]pyran-1-ol (hexahydrocannabiphorol; HHC-P) by Slovenia as a new psychoactive substance under the terms of Regulation (EC) No 1920/2006 and Council Framework Decision 2004/757/JHA. EU-EWS-RCS-FN-2023-0001, EMCDDA, Lisbon, 6 January 2023

Gunasekera, B., Diederen, K., & Bhattacharyya, S. (2022). Cannabinoids, reward processing, and psychosis. *Psychopharmacology,* 239, 1157-1177.

Klein, T.A., Dilley, J.A., Graves, J.M., & Liebelt, E.L. (2022). Synthetic cannabinoid poisonings and access to the legal cannabis market: findings from US national poison centre data 2016–2019. *Clinical Toxicology,* 60, 1024-1028.

Murray, R.M., Quigley, H., Quattrone, D., Englund, A., & Di Forti, M. (2016). Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. *World Psychiatry,* 15, 195-204.

O'Mahony, B., O'Malley, A., Kerrigan, O., & McDonald, C. (2024). HHC-induced psychosis: a case series of psychotic illness triggered by a widely available semisynthetic cannabinoid. *Irish Journal of Psychological Medicine*, *41*(3), 405-408. https://doi.org/10.1017/ipm.2024.3

Radwan, M.M., Chandra, S., Gul, S., & ElSohly, M.A. (2021). Cannabinoids, phenolics, terpenes and alkaloids of cannabis. *Molecules,* 26, 2774.

Reggio, P.H., Greer, K.V., & Cox, S.M. (1989). The importance of the orientation of the C9 substituent to cannabinoid activity. *Journal of Medicinal Chemistry,* 32, 1630-1635.

Watanabe, K., Itokawa, Y., Yamaori, S., Funahashi, T., Kimura, T., & Kaji, T. (2007). "In vitro metabolism of cannabichromene, a major component of fiber-type cannabis, by human hepatic microsomes and recombinant cytochrome P450 enzymes." *Life Sciences*, *80*(15), 1415-1423.