Can we increase risk perception among medical cannabis users?

¿Es posible crear la adecuada sensación de riesgo entre los consumidores de cannabis medicinal?

José Antonio Ramos Atance*, Francisco Arias Horcajadas**.

* Instituto Universitario de Investigación en Neuroquímica. Universidad Complutense, Madrid.
** Programa de Alcohol y Patología Dual. Servicio de Psiquiatría, Hospital Doce de Octubre, Madrid.

Research regarding the possible therapeutic applications of cannabinoids continues to expand. Although the results obtained in some diseases are encouraging, developmental research is still in its initial stages. For some symptoms, the medicinal effectiveness of cannabinoids has been proven, but in many cases, adequate evidence is not yet available in this regard, nor are the existing data on the risks associated with the use of medicinal cannabis sufficient.

The lack of conclusive clinical research results does not stop social networks being flooded with messages proclaiming the efficacy of cannabis preparations for almost all diseases. Such propaganda does not usually indicate the potential appearance of side effects in this type of treatment. Perhaps the most insidious of all this biased information, however, is that the invitation to use it does not mention the need to consult with the true specialists in the treatment of diseases, namely, doctors.

When about to take any medicine, it is a matter of common sense to be aware of its potential risks as well as its benefits. Nevertheless, this rule is not followed by many of those currently using medical cannabis. The existence of risks associated with the recreational use of cannabis suggests such risks could also appear when used for therapeutic purposes.

It is therefore necessary that research on the therapeutic effects of cannabinoids be accompanied by the study of possible side effects linked to their medical use. The results obtained may serve to guide doctors in their proper clinical application and to warn those who decide to use them without proper medical control.

The aim is to discover the frequency with which the effects associated with cannabis use occur, such as addiction and dependence, myocardial infarction, stroke and schizophrenia, and other types of risk that, given their low incidence, would be difficult to identify in small clinical samples. Possible pharmacological interactions between cannabinoids and other drugs used by patients should also be identified (Bonn-Miller et al., 2019).

What is the state of the art regarding the medical use of cannabinoids?

Over time, many reviews have compiled information available on this matter. None of them, however, managed to reach the degree of systematization necessary to be able to adequately reflect the real situation. This aim was only achieved in 2017, after the appearance of several reports meeting this requirement.

Among these, three stand out, given the scale and rigour of the information contained:
- "The health effects of cannabis and cannabinoids", published in January 2017 by the Health and Medicine Division of the National Academy of Sciences, Engineering and Medicine of the United

States (National Academies of Sciences, Engineering, and Medicine, 2017).

- "Information for health care professionals. Cannabis (marihuana, marijuana) and the cannabinoids. Dried or fresh plant and oil administration by ingestion or other means", issued in October 2018 by the Canadian Ministry of Health (Health Canada, 2018).
- "Medical use of cannabis and cannabinoids. Questions and answers for policymaking", issued by the European Monitoring Center for Drugs and Drug Addiction (2018).

These reports concluded that in relation to cannabinoids there is:

- Substantial evidence of its therapeutic effects in chronic pain in adults, antiemesis in chemotherapy and spasticity symptoms in multiple sclerosis.
- Moderate evidence of improvements in sleep disturbances associated with apnea, fibromyalgia, chronic pain and multiple sclerosis.
- Knowledge that an appreciable amount of limited evidence exists regarding its effectiveness or ineffectiveness in other cases.

To these conclusions must be added its most recent use in the treatment of two infrequent forms of epilepsy: Lennox-Gastaut syndrome and Dravet syndrome.

The above reports also indicated the danger that in some patients, medical prescription of cannabinoids may be responsible for the appearance of some of the problems linked to recreational use.

In this regard, there is substantial evidence that cannabis can:

- Increase the risk of traffic accidents or accidents involving the handling of machinery.
- Reduce the weight of the newborn.
- Lead to overdose in children under 6 years of age after accidental consumption.
- Cause schizophrenia or other psychoses.
- Increase the risk of cardiovascular problems.
- Worsen respiratory symptoms when smoked, which would increase episodes of chronic bronchitis and, with less evidence, contribute to the appearance of some type of cancer associated with the respiratory tract, such as lung cancer.
- Contribute to the appearance of cannabis dependence.
- Increase the risk of cognitive disorders.

Age of onset and frequency of consumption were also indicated as risk factors for the appearance of problems related to its use.

In summary, the reports presented some conclusive results regarding the medical applications of cannabinoids in some diseases and opened the door to the treatment of others. Nevertheless, they also warned of the risks that may arise during treatment.

Problems associated with cannabis use

The existence of risks associated with cannabis use raises the need to define them and to understand in what situations they may appear, above all, in those pathologies that may be related to disorders of the endocannabinoid system or in those patients whose clinical condition makes them vulnerable to the administration of cannabinoids.

To meet this objective, we may begin by consulting the data reported in those countries where medical treatment with cannabinoids is already approved and in operation.

Reviews published in this regard show that treatment had to be withdrawn in some patients. Others described the appearance of psychiatric, neurological, musculoskeletal or connective tissue disorders.

Adverse effects included: asthenia, loss of balance, dizziness, disorientation, diarrhoea, euphoria, drowsiness, headache, dry mouth, fatigue, euphoria, hallucinations, nausea and vomiting. Psychiatric symptoms included confusion, paranoia, psychosis, and substance dependence (EMCDDA, 2018; Mücke, Phillips, Radbruch, Petzke & Häuser, 2018; Whiting et al., 2015).

There is still not enough data to indicate the long-term effects produced by the medical use of cannabinoids. Knowledge of this would be interesting, since prolonged use can lead to negative consequences that do not necessarily appear in the initial stages.

Given the difficulties existing in Spain to implement this type of treatment, "verified" information on this subject is scarce. Nevertheless, this should not be an excuse for health professionals to ignore the necessary requirements for the proper treatment of patients and to identify and solve the problems associated with medical cannabis.

The guide issued by the College of Family Physicians of Canada for the prescription of medical cannabis can be very useful for advising those doctors who want to proceed with its use. The report provides recommendations for use in primary care, based on existing experience in the four clinical areas with the most evidence on cannabinoid treatment: pain, nausea and vomiting, spasticity, and adverse effects (Allan et al., 2018).

Although the Canadian guide is preferable, the information issued by the College of Pharmacists of Barcelona can also be consulted. This is aimed at those who self-administer certain types of cannabis preparations for the treatment of their illness. It is intended to warn of the risks associated with its use, given the lack of medical control and the variability in the active ingredients of the plant, which makes adequate dosage and appropriate monitoring of its use difficult (Borrás, 2019).

Effects of the legalization of medicinal cannabis on the perception of risk

Uruguay was the first country to legalize the use of cannabis for medicinal purposes; since then, a large number of countries, mainly European and American, have followed suit. It is interesting to assess how this legalization has managed to influence the perception of risk regarding cannabis.

The legalization of medicinal cannabis has involved an increase in THC content and, curiously, a decrease in CBD concentrations, which, a priori, is the one of greatest therapeutic interest and has fewer adverse psychoactive effects (Cash, Cunnane, Fan & Romero-Sandoval, 2020). At the same time, the consumption of new forms of cannabis has increased and the price has fallen, thus making it more accessible (Isorna, Pascual, Aso & Arias, 2022).

The legalization of medicinal cannabis is considered to have had little direct impact on recreational use among young people (Melchior et al., 2019). However, the marketing of cannabis products for therapeutic uses in some states may be influencing the perception of risk. A California study found that teens who had seen medical marijuana advertisements on billboards, in magazines or other media in the past three months were more likely to use cannabis and more likely to be using cannabis up to a year later (D'Amico, Miles & Tucker, 2015).

Conversely, in adults, the legalization of medical cannabis in the USA has involved an increase in recreational use and cannabis use disorder (CUD) (Cerdá et al., 2020). Using data from surveys carried out in the same country from 1991 to 2013 (NLAES and NESARC studies), Hassin et al. (2017) show that legal medicinal cannabis is accompanied by an increase in the prevalence of illegal consumption and CUD.

It has been observed that several years after the legalization of medicinal cannabis, the frequency of CUD has risen, especially in states where dispensaries and collective cultivation is permitted. The demand for treatment for CUD is increasing both globally and for young people (Smart & Pacula, 2019), and there is a link between higher density of medical cannabis dispensaries in California and CUD hospitalizations (Mair, Sumetsky, Kranich & Freisthler, 2021).

In addition to higher cannabis consumption, it has been observed that the sense of risk regarding cannabis use is lower and perception of its potential benefits for reducing pain or other medical or psychopathological problems is greater in states where medicinal cannabis is legal (Steigerwald et al., 2020).

Moreover, the legalization of medical cannabis can increase the concomitant use of cannabis and alcohol or tobacco, and there is no evidence that it has a positive role in reducing the use of prescription opioids (Isorna et al., 2022).

Regarding medical emergencies, after the liberalization of medical cannabis in Colorado, an increase in visits and calls to emergency departments due to cannabis use was observed (Wang et al., 2017; Wang, Davies, Halmo, Sass & Mistry, 2018).

Another relevant aspect is the impact that legalization may have among the pediatric population, since it increases the likelihood of minors being exposed to this substance. Thus, cases of accidental pediatric exposure to cannabis increased in Massachusetts after medical marijuana was legalized in 2012, despite the use of child-resistant packaging and warning labels (Whitehill et al., 2019). A review found an increase in pediatric patients with cyclic vomiting syndromes due to the intake of edible cannabis products. This is mainly attributed to the high concentrations of THC in the plants cultivated for medical cannabis and the greater appetite produced when incorporated into sweet foods, such as candies and baked goods, contributing to repeated visits to emergency departments (Wolf, Perhats, Clark, Frankenberger & Moon, 2020).

A further aspect of interest is that the legalization of medical cannabis does not imply that patients and clinicians know more about its therapeutic and adverse effects given the difficulty in distinguishing medical from recreational use (Lancaster, Seear & Ritter, 2017). Thus, among cancer patients in states with legal medicinal cannabis there was an increase in use, but despite wanting information about it, they did not obtain it (Pergam et al., 2017). One year after legalization in Thailand, a significant lack of information has also been noted for patients, with a significant percentage believing that it cured cancer, and for physicians, reporting frequent adverse effects (Zinboonyahgoon, Srisuma, Limsawart, Rice & Suthisisang, 2021).

How the problem should be tackled

The data from studies carried out on the possible risks linked to medical treatments with cannabis preparations allow us to conclude that there is evidence, especially at the level of short-term effects, of the appearance of side effects in some patients undergoing these types of treatments.

This means that medical cannabis users need to be aware that they cannot make the decision to medicate with cannabinoids on their own. It is the doctor who, in view of existing clinical data, has to advise on the possible benefits of the "new treatment".

Once the treatment has begun, the doctor must carry out a series of checks on the patient regarding the suitability of the cannabis preparations prescribed, and, in view of the results obtained, continue or abandon the treatment.

Patients must become used to understanding the existing data on possible complications that may accompany the

use of these preparations, in the same way as they would read the corresponding directions for use when taking other medications.

In addition, it should be taken into account whether the patient's previous or current use of cannabis can influence medication with cannabinoids. In both cases, a synergy may be generated in the occurrence of problems linked to uncontrolled cannabis use.

This argument should also be considered by those patients thinking about the possibility of taking up recreational use to reinforce the effects of treatment. This also applies to those who try to justify that the consumption of cannabis or any type of cannabis preparation can be used to prevent the appearance of diseases in which there is scientific evidence regarding the usefulness of cannabinoids.

Finally, it should be clear that therapeutic treatments with cannabinoids cannot serve as an argument in favour of their recreational use. It is necessary to learn to separate both types of consumption to avoid medical use serving as a justification for recreational use and the latter leading to the former.

References

Allan, G. M., Ramji, J., Perry, D., Ton, J., Beahm, N. P., Crisp, N.,… Lindblad, A. J. (2018). Simplified guideline for prescribing medical cannabinoids in primary care. *Canadian Family Physician, 64,* 111-120. PMID: 29449241.

Bonn-Miller, M. O., Pollack, C. V. Jr., Casarett, D., Dart, R., ElSohly, M., Good, L.,… Abrams, D. (2019). Priority considerations for medicinal cannabis-related research. *Cannabis and Cannabinoid Research, 4,* 139–157. doi:10.1089/can.2019.0045.

Borrás, R. (2019). *Prospecto del cannabis para uso terapéutico.* Colegio de Farmacéuticos de Barcelona. Retrieved at https://www.farmaceuticonline.com/es/cannabis/.

Cash, M. C., Cunnane, K., Fan, C. & Romero-Sandoval, E. A. (2020). Mapping cannabis potency in medical and recreational programs in the United States. *PloS One, 15.* doi:10.1371/journal.pone.0230167.

Cerdá, M., Mauro, C., Hamilton, A., Levy, N., Santaella-Tenorio, J., Hasin, D.,... Martins, S. (2020). Association between recreational marijuana legalization in the United States and changes in marijuana use and cannabis use disorder from 2008 to 2016. *JAMA Psychiatry, 77,* 165-171. doi:10.1001/jamapsychiatry.2019.3254.

D'Amico, E. J., Miles, J. N. & Tucker, J. S. (2015). Gateway to curiosity: Medical marijuana ads and intention and use during middle school. *Psychology of Addictive Behaviors, 29,* 613–619. doi:10.1037/adb0000094.

European Monitoring Centre for Drugs and Drug Addiction. (2018). *Medical use of cannabis and cannabinoids: Questions and answers for policymaking.* Luxemburgo: Publications Office of the European Union. doi:10.2810/979004.

Hasin, D. S., Sarvet, A. L., Cerdá, M., Keyes, K. M., Stohl, M., Galea, S. & Wall, M. M. (2017). US adult illicit cannabis use, cannabis use disorder, and medical marijuana laws: 1991-1992 to 2012-2013. *JAMA Psychiatry, 74,* 579-588. doi:10.1001/jamapsychiatry.2017.0724.

Health Canada. (2018). *Information for health care professionals. Cannabis (marihuana, marijuana) and the cannabinoids. Dried or fresh plant and oil administration by ingestion or other means.* Otawa: Canadian Ministry of Health. Government of Canada. Retrieved at https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-medication/cannabis/information-medical-practitioners/information-health-care-professionals-cannabis-cannabinoids-eng.pdf.

Isorna, M., Pascual, F., Aso, E. & Arias, F. (2022). Impacto de la legalización del consumo recreativo del cannabis. *Adicciones.* Advance publication online. doi:10.20882/adicciones.1694.

Lancaster, K., Seear, K. & Ritter, A. (2017). Making medicine; producing pleasure: A critical examination of medicinal cannabis policy and law in Victoria, Australia. *International Journal of Drug Policy, 49,* 117-125. doi:10.1016/j.drugpo.2017.07.020.

Mair, C., Sumetsky, N., Kranich, C. & Freisthler, B. (2021). Availability of medical cannabis dispensaries and cannabis abuse/dependence-related hospitalizations in California. *Addiction, 116,* 1908-1913. doi:10.1111/add.15420.

Melchior, M., Nakamura, A., Bolze, C., Hausfater, F., El Khoury, F., Mary-Krause, M. & Da Silva, M. A. (2019). Does liberalisation of cannabis policy influence levels of use in adolescents and young adults? A systematic review and meta-analysis. *BMJ Open, 9.* doi:10.1136/bmjopen-2018-025880.

Mücke, M., Phillips, T., Radbruch, L., Petzke, F. & Häuser, W. (2018). Cannabis-based medicines for chronic neuropathic pain in adults. *Cochrane Database Syst Rev, 3.* CD012182. doi:10.1002/14651858.CD012182.pub2.

National Academies of Sciences, Engineering, and Medicine. (2017). *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research.* Washington, DC: The National Academies Press. doi:10.17226/24625.

Pergam, S. A., Woodfield, M. C., Lee, C. M., Cheng, G. S., Baker, K. K., Marquis, S. R. & Fann, J. R. (2017). Cannabis use among patients at a comprehensive cancer center in a state with legalized medicinal and recreational use. *Cancer, 123,* 4488-4497. doi:10.1002/cncr.30879.

Smart, R. & Pacula, R. L. (2019). Early evidence of the impact of cannabis legalization on cannabis use, cannabis use disorder, and the use of other substances: Findings from state policy evaluations. *The American*

Journal of Drug and Alcohol Abuse, 45, 644-663. doi:10.108 0/00952990.2019.1669626.

Steigerwald, S., Cohen, B. E., Vali, M., Hasin, D., Cerda, M. & Keyhani, S. (2020). Differences in opinions about marijuana use and prevalence of use by state legalization status. *Journal of Addiction Medicine, 14*, 337. doi:10.1097/ ADM.0000000000000593.

Wang, G. S., Hall, K., Vigil, D., Banerji, S., Monte, A. & VanDyke, M. (2017). Marijuana and acute health care contacts in Colorado. *Preventive Medicine, 104*, 24-30. doi:10.1016/j.ypmed.2017.03.022.

Wang, G., Davies, S., Halmo, L., Sass, A. & Mistry, R. (2018). Impact of marijuana legalization in Colorado on adolescent emergency and urgent care visits. *Journal of Adolescent Health, 63*, 239-241. doi:10.1016/j. jadohealth.2017.12.010.

Whitehill, J. M., Harrington, C., Lang, C. J., Chary, M., Bhutta, W. A. & Burns, M. M. (2019). Incidence of pediatric cannabis exposure among children and teenagers aged 0 to 19 years before and after medical marijuana legalization in Massachusetts. *JAMA Network Open, 2.* doi:10.1001/jamanetworkopen.2019.9456.

Whiting, P. F., Wolff, R. F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A. V.,… Kleijnen, J. (2015). Cannabinoids for medical use: A systematic review and meta-analysis. *Journal of American Medical Association, 313,* 2456–2473. doi:10.1001/ jama.2015.6358.

Wolf, L. A., Perhats, C., Clark, P. R., Frankenberger, W. D. & Moon, M. D. (2020). The perceived impact of legalized cannabis on nursing workload in adult and pediatric emergency department visits: A qualitative exploratory study. *Public Health Nursing, 37,* 5-15. doi:10.1111/ phn.12653.

Zinboonyahgoon, N., Srisuma, S., Limsawart, W., Rice, A. S. C. & Suthisisang, C. (2021). Medicinal cannabis in Thailand: 1-year experience after legalization. *Pain, 162 (Suppl. 1),* 105-109. doi:10.1097/j. pain.0000000000001936.