Synthetic cannabinoids: an integrative theoretical review

Cannabinoides sintéticos: una revisión teórica integradora

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Abstract

Synthetic cannabinoids are agonists of cannabinoid receptors and produce similar effects to Δ^9-tetrahydrocannabinol, the main psychoactive phytocannabinoid of Cannabis Sativa. Synthetic cannabinoids are classified as "new psychoactive substances" (NPS), and are the most numerous type of substance in this group with over 200 types. The effects of synthetic cannabinoids, although similar to those produced by THC, are of the order of 2 to 800 times more potent, as they are total agonists of the receptors. Among the most reported effects are anxiety, nausea, paranoia, and tachycardia, although there is a strong relationship between psychotic disorders and synthetic cannabinoid use. Although the prevalence of the use of these substances is relatively low for the general population, there are different subpopulations such as people who are incarcerated or polyconsumers whose consumption is significantly higher due to different motivations of use, among which the difficulty of tracing them in drug analyses stands out.

Keywords

Cannabinoids; synthetic; THC; potency; NPS.

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Resumen

Los cannabinoides sintéticos son agonistas de los receptores cannabinoides, y producen efectos similares al Δ^9 – tetrahidrocannabinol, principal fitocannabinoide psicoactivo del Cannabis Sativa. Los cannabinoides sintéticos son drogas catalogadas como "nuevas sustancias psicoactivas" (NPS), siendo además el tipo de sustancia más numerosa de este grupo con más de 200 tipos. Los efectos de los cannabinoides sintéticos, aunque son similares a los producidos por el THC, son del orden de 2 a 800 más potentes, pues son agonistas totales de los receptores. Entre los efectos adversos más reportados destacan la ansiedad, las náuseas, las paranoias y la taquicardia, aunque existe una fuerte relación entre los trastornos psicóticos y el consumo de cannabinoides sintéticos. A pesar de que la prevalencia de consumo de estas sustancias es relativamente baja para la población general, existen diferentes subpoblaciones como las personas privadas de libertad o las personas policonsumidoras cuyo consumo es significativamente mayor debido a distintas motivaciones de uso entre las que destaca la dificultad de rastrearlos en los análisis de drogas.

Palabras clave

Cannabinoides; sintéticos; THC; potencia; NPS.

INTRODUCTION

Synthetic cannabinoids are substances that produce effects similar to Δ9-tetrahydrocannabinol (hereinafter THC), the main psychoactive component of the Cannabis Sativa plant. Additionally, in our nervous system, they act as agonists of the same receptors, primarily CB1, although they also interact with the CB2 receptor of the endocannabinoid system (European Monitoring Centre for Drugs and Drug Addiction, 2021). However, synthetic cannabinoids are not simply synthetically created cannabis and have clinically different effects compared to the cannabinoids present in organic cannabis, as they are generally more potent and toxic. In fact, some authors emphasize the need to stop using the term "synthetic cannabis," which can cause confusion, and instead refer to these substances as "synthetic cannabinoid receptor agonists" (SCRAs) (Darke et al., 2021). However, in this paper, the term "synthetic cannabinoids" will be used. In colloquial terms, these substances are known as "Spice," or "hardcore" (Isorna & Arias, 2022).

The first synthetic THC analogue was Nabilone, synthesized by Mechoulam and Carlini in 1978 (Mechoulam & Carlini, 1978). Like Nabilone, the earliest synthetic cannabinoids were synthesized within the context of scientific research on the endocannabinoid system. Following the production of a synthetic compound derived from cannabis, numerous studies focused on the search for new synthetic cannabinoids that could be useful as pharmaceuticals. It was

recognized that some cannabinoids from the Cannabis Sativa plant could be used in medicine, suggesting that synthetic cannabinoids might be developed into drugs that do not produce the psychotropic effects caused by cannabinoids extracted from the plant (EMCDDA, 2021).

Years later, in the mid-2000s, alternative products to organic cannabis began to emerge under the name "Spice," taking advantage of a 'legal' status as they were not registered as drugs by any official body. In 2004, the first products were identified as a legal blend of herbs, the consumption of which produced effects similar to organic cannabis, and they were marketed as safe and legal alternatives to it. In 2008, it was analytically confirmed that the products circulating as legal alternatives to cannabis were, in fact, synthetic cannabinoids (Darke et al., 2021). These products are typically dissolved and sprayed onto non-psychoactive and pharmacologically inactive herbs to mimic organic cannabis, allowing the substance to be smoked in the form of "joints". However, the pure compound is generally a crystalline powder, ranging in color from white, grayish, yellowish, to brown, depending on its purity. While their solubility in water is usually low, they are highly lipophilic, meaning they dissolve well in solvents such as methanol, ethanol, or acetone (Tettey et al., 2021).

Over time, the illegal market for these types of drugs has become more sophisticated, and the product has been adapted for consumption through other routes of administration. As a result, new products have emerged, such as liquids for electronic cigarettes, powders, candies, blotter paper soaked in synthetic cannabinoids, or fake hashish, which are sold as meditation materials or incense. However, the most common form of presentation for synthetic cannabinoids remains herbal blends, typically sold in packages with eye-catching designs and colors, containing between 0.3–3 grams of dried plant material to which one or more types of synthetic cannabinoids are added. These products are usually produced in clandestine laboratories or companies, typically based in Asian countries, and are then shipped to Europe and other parts of the world by mail, either in powder form or mixed with other products (Craft et al., 2021; Ford et al., 2017).

Some synthetic cannabinoids are sold, despite prohibition, in retail stores and online, where they are labeled as "not for human consumption," "for laboratory use," or "for technical use" (Cooper, 2016; Papaseit et al., 2018). Synthetic cannabinoids have also been detected in products where the consumer was unaware, including cannabidiol (CBD)-based products, THC-based liquids for electronic cigarettes, opioids, and even products like cannabis herb or resin with low THC concentrations. The latter is an increasingly observed trend, where low-THC cannabis herb or resin is sprayed with synthetic cannabinoids to enhance the psychoactive effects. The adulteration of these products poses significant risks, as they are difficult to distinguish by smell or taste, and consumers are at high risk of poisoning and experiencing adverse effects. Confiscated samples of synthetic cannabinoids have been found to contain synthetic opioids such as desmetramadol, adrenergic receptor agonists like clenbuterol, hallucinogens like Salvia Divinorum, and also kratom, nicotine, benzodiazepines, vitamin E, and caffeine,

among others. Another risk is the presence of "hot spots" within batches, where the material is unevenly distributed, leading to areas with high concentrations of synthetic cannabinoids, increasing the risk of overdose (Darke et al., 2021; EMCDDA, 2021; Hobbs et al., 2018; Spaderna et al., 2013; Van Amsterdam et al., 2015). Consumers of these substances seek to experience the same effects as those produced by organic cannabis, but with greater potency. They also use them to alleviate pain, reduce organic cannabis consumption, or avoid detection in drug tests (Le Boisselier et al., 2017).

SYNTHETIC CANNABINOIDS AS NEW PSYCHOACTIVE SUBSTANCES (NPS)

New Psychoactive Substances (NPS) are a large, heterogeneous group of artificially synthesized psychoactive substances that began to be identified in the mid-2000s (Shafi et al., 2020). They tend to be analogues of controlled drugs and/or pharmaceuticals, emulating their actions and effects. Colloquially, they are known as "legal highs," as they are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, and thus are not regulated by any official body, enjoying a legal gray area until they are identified, monitored, and regulated (United Nations Office on Drugs and Crime, 2013).

New psychoactive substances can be classified into four major groups based on the illicit substances they aim to imitate: synthetic psychostimulants, synthetic hallucinogens, synthetic depressants, and synthetic cannabinoids, which form a distinct group due to their great heterogeneity (Shafi et al., 2020) and because they account for 46% of all new psychoactive substance seizures carried out in the Member States of the European Union, Norway, and Turkey. In 2017 alone, there were 32.605 seizures of synthetic cannabinoids reported in the European Union, Norway, and Turkey (Observatorio Europeo de las Drogas y las Toxicomanías, 2021).

From 1997 until the end of 2020, 830 drugs classified as new psychoactive substances were reported in the European Union, of which 90% were notified between 2008 and 2018. Synthetic cannabinoids were the most frequently reported substance, with 209 different varieties documented between January 2008 and December 31, 2020 (EMCDDAE, 2019; EMCDDA, 2021). The Spanish Early Warning System has reported 14 new cannabinoids detected for the first time in Spain (Observatorio Español de las Drogas y las Adicciones, 2021). Of the 18.700 seizures of new psychoactive substances carried out in the European Union, Turkey, and Norway in 2019, 6.500 were synthetic cannabinoids, and of the 900 kilograms of material seized in the same year, 200 kilograms were synthetic cannabinoids in any form (EMCDDAE, 2019; OEDT, 2021).

Despite policies aimed at restricting the availability of these substances, it is known that the illegal market continues to evolve to circumvent the laws, and synthetic cannabinoids remain prevalent due to their low cost, availability, and potent effects (EMCDDA, 2021).

MECHANISM OF ACTION OF SYNTHETIC CANNABINOIDS AND IMPLICATED NEUROTRANSMISSION SYSTEMS

The mechanism of action by which synthetic cannabinoids act in the central nervous system is primarily through the binding and activation of the CB1 and CB2 receptors of the endocannabinoid system, for which they show a high affinity, as they are full agonists, unlike the prototypical phytocannabinoid THC, which is a partial agonist. The differences in affinity for the CB1 and CB2 receptors between synthetic cannabinoids and THC are evident in the way they activate the G protein, being more effective in the case of synthetic cannabinoids, which more potently modulate signaling pathways, which may explain higher toxicity and more severe effects, ranging from 2 to 800 times more potent compared to THC (Ford et al., 2017). Although it is less common, there are some synthetic cannabinoids that act by inhibiting FAAH, the enzyme responsible for degrading anandamide, resulting in increased levels of anandamide in the synaptic space (EMCDDA, 2021).

Regarding neurotransmission systems, in addition to the endocannabinoid system, synthetic cannabinoids can act on other neurotransmission systems, making the effects generated in the central nervous system often unpredictable. Synthetic cannabinoids also act on the dopaminergic system, which may explain the range of doses of some synthetic cannabinoids that produce stimulating effects, and they also lead to the release of dopamine in the nucleus accumbens, increasing the firing rate of dopamine-expressing neurons, which is associated with substance addiction (Fantegrossi et al., 2018). In a study on the stimulant effects of the synthetic cannabinoids JWH-018 and AKB48 in mice, an increase in locomotor activity was observed, although to a lesser extent than with more well-known stimulants such as amphetamines and cocaine. The locomotor activity produced by these two types of synthetic cannabinoids was reversed using AM-251, a CB1 receptor antagonist (Ossato et al., 2017).

Additionally, it has been demonstrated that there is an interaction between synthetic cannabinoids and the serotonergic system. The modulation of the 5-HT2a serotonergic receptor, a target of psychedelic and empathogenic drugs, by synthetic cannabinoids may be a mechanism related to the onset of psychosis, as the interaction of these receptors along with dopaminergic ones in the prefrontal cortex is consistently associated with schizophrenia (Fantegrossi et al., 2018).

While the main metabolite of THC is 11-hydroxy-THC, known to have potency comparable to THC, the metabolites formed by most synthetic cannabinoids are unknown, unique, and different, although it is understood that they are primarily mediated by cytochrome P450. The metabolites can be active and exhibit affinity for CB1 and CB2, generating toxicological and pharmacological effects. Excretion occurs primarily via the renal route (Le Boisselier et al., 2017).

EFFECTS OF SYNTHETIC CANNABINOIDS ON THE BODY

Understanding the effects of synthetic cannabinoids on the body has been an area of research in recent years. Although they act on the CB1 and CB2 receptors of the endocannabinoid system, the heterogeneity of this group of substances and their constant emergence in the drug market complicate the creation of a solid list of the effects of synthetic cannabinoids. Some synthetic cannabinoids bind to other receptors in neurotransmission systems beyond the endocannabinoid system, leading to physiological and behavioral consequences that may differ from those typically described in the literature. When we also consider the unpredictable action of the metabolites of various synthetic cannabinoids, whether active or not, and with varying affinities for CB1 and CB2, we find a wide range of diverse effects (Cooper, 2016).

Nonetheless, the scientific literature has reported numerous effects resulting from acute intoxication with synthetic cannabinoids, as well as long-term effects. The most widely described effects of acute intoxication include tachycardia, anxiety, agitation, hypertension, paranoia, nausea, and vomiting (Jackson et al., 2021; Le Boisselier et al., 2017). Although most effects of synthetic cannabinoids on the body during acute use are not potentially fatal, they can lead to significant adverse consequences, including severe intoxication episodes, hospitalization, and up to 30 times higher likelihood of requiring emergency medical treatment compared to the use of organic cannabis (Sutherland et al., 2016; Tournebize et al., 2017). While it has been shown that synthetic cannabinoids interact with other neurotransmission systems, cannabinoid receptor antagonists, specifically CB1 antagonists such as rimonabant or AM-251, are used to reverse the acute symptoms of cannabinoid effects in animals. However, these two antagonists are not used in humans as an antidote for acute cannabinoid overdose, despite blocking effects in preclinical studies due to the occurrence of adverse psychiatric consequences. Therefore, the treatment for acute toxicity is supportive and symptom-oriented, with benzodiazepines, antipsychotics, or a combination of both potentially being used (Ford et al., 2017; Hobbs et al., 2018).

In chronic users of synthetic cannabinoids, cognitive deficits and affective disturbances have been reported due to changes in emotional and cognitive brain regions. The associated neuronal damage from chronic use of synthetic cannabinoids is alarming, as these neurotoxic effects have even more complications when consumed by adolescents and young adults (Cohen et al., 2020). In a global drug use survey (Winstock et al., 2021), users of various types of drugs were asked whether they had required emergency medical treatment in the past 12 months due to drug use. The results of this study indicate that, in 2020, synthetic cannabinoid users were the third group most in need of emergency medical treatment for their consumption (3.2%), only behind methamphetamine users (4.1%) and heroin users (12.7%), highlighting the danger of this substance.

The psychiatric effects of synthetic cannabinoids are more severe than those produced by organic cannabis consumption, which may be due to their high affinity for cannabinoid receptors. Furthermore, synthetic cannabinoids, unlike organic cannabis, do not

contain CBD, a phytocannabinoid found in the Cannabis Sativa L. plant that counteracts the psychoactive effects of THC, leading to greater psychiatric complications, especially in the risk of developing psychosis and schizophrenia (Van Amsterdam et al., 2015). The relationship between organic cannabis uses and the onset of psychosis is well-documented in the scientific literature (Di Forti et al., 2012), and there is a correlation between the increased potency of cannabis (THC percentage) and the development of this psychiatric disorder. In this case, the relationship between synthetic cannabinoids and the development of psychosis goes further, as the potency of these recreational substances is stronger than that of any organic cannabis (Hobbs et al., 2018).

Among the psychiatric effects of synthetic cannabinoids, there is also evidence of possible onset of hallucinations, severe anxiety, paranoia, amnesia, unconsciousness, depression, and suicidal ideation (Le Boisselier et al., 2017). Of the psychiatric effects, psychosis is one of the most frequently reported, along with anxiety (Gunderson et al., 2012). The consumption of synthetic cannabinoids, therefore, triggers psychotic episodes in predisposed individuals and can exacerbate pre-existing psychotic symptoms in an individual. There have also been reported cases of individuals experiencing psychotic episodes for the first time after a single use of synthetic cannabinoids, with the duration of symptoms varying widely (Van Amsterdam et al., 2015).

In addition to these psychiatric effects, repeated use of synthetic cannabinoids leads to tolerance, dependence, and a severe withdrawal syndrome similar in effects to that of organic cannabis, as well as cross-tolerance between the two substances (Ford et al., 2017; Tournebize et al., 2017). In the self-administration paradigm, used to measure the reinforcing efficacy of drugs, no cases have been reported in which there is maintenance of self-administration with THC. However, maintenance of self-administration has been reported with the synthetic cannabinoid WIN-55,212-2, although it has not been demonstrated with other types of cannabinoids (Fattore et al., 2001). While dependence and withdrawal syndrome occur as a result of continuous use, it is known that synthetic cannabinoids generally produce these effects more severely, more quickly, and with greater risk compared to organic cannabis. In a study on the withdrawal symptoms of synthetic cannabinoids involving over 20 countries (Craft et al., 2021), sleep difficulties, irritability, and low mood were reported as the most common withdrawal symptoms. In this regard, the amount of grams used in each session and the frequency of use establish a directly proportional relationship with the severity of these symptoms. To a lesser extent, symptoms such as palpitations, cravings, nausea, agitation, and sweating were reported. Some withdrawal symptoms even require hospitalization, and avoiding the more severe symptoms is one of the main reasons cited by users for the continued use of these substances (Cooper, 2016).

The cardiovascular effects generated by the consumption of organic cannabis are becoming increasingly noticeable due to the trend of a progressive increase in potency in recent years. With the emergence of synthetic cannabinoids for recreational use, this relationship between high potency cannabinoids and adverse cardiovascular events

has been solidified. A review by Pacher et al., (2018) on the cardiovascular effects of these substances indicates cases of myocardial infarction and cardiac arrest even in individuals without prior pathologies after a single use of JWH-018 and JWH-073. Cases of hypoxemic respiratory failure due to congestive heart failure, tachycardia, bradycardia, hypertension, and T-wave inversion on electrocardiograms have also been reported. According to the same review, these cardiovascular effects, along with alterations in the central nervous system, represent the greatest risk of experiencing serious adverse consequences, including death.

Neurological and neuromuscular effects from the use of synthetic cannabinoids may include seizures, hemorrhagic stroke, ischemic stroke, agitation, dizziness, paresthesia, aggression, and rhabdomyolysis (Tournebize et al., 2017). There is evidence of acute cerebral infarction in individuals without prior pathologies after a single use of XLR-11, a synthetic cannabinoid sold under the brand name "WTF" (Takematsu et al., 2014).

Among the causes of mortality associated with the use of synthetic cannabinoids, the following have been recorded: sudden cardiac arrhythmias, seizures, liver failure, renal failure, respiratory depression, and indirectly reported cases of death due to hypothermia, hyperthermia, suicides, and fatal self-harm (Giorgetti et al., 2020; Tait et al., 2016). In this regard, a retrospective study on deaths related to the use of synthetic cannabinoids in Australia between 2000 and 2017 (Darke et al., 2020) indicates that deaths primarily occurred due to the combination of substance toxicity and cardiovascular disease.

SYNTHETIC CANNABINOIDS EPIDEMIOLOGY

Although knowledge of the prevalence of synthetic cannabinoid use is limited and scarce, there is a noticeable trend of increasing consumption of these substances. Typically, studies on the prevalence of synthetic cannabinoids focus on populations and subpopulations where the use of these substances is concentrated, as the prevalence in the general population is approximately below 1% (EMCDDA, 2021). In the 2020 Global Drug Survey, a worldwide drug survey (Winstock et al., 2020), the prevalence of synthetic cannabinoid use is reported at 1.5%. However, while the consumption rates in the general population are low, there are subpopulations where prevalence is higher, such as among polysubstance users or people who are incarcerated. Among individuals who regularly use psychostimulants and/or consume drugs via injection, the prevalence of synthetic cannabinoid use in the last 12 months ranges from 3% to 10% (Darke et al., 2021).

According to a study analyzing the prevalence of synthetic cannabinoid use in certain countries among the general non-clinical population (Loeffler et al., 2016), the results vary significantly across different countries and populations, with a lifetime prevalence estimated to be between 0.2% and 4% globally. The study indicates that adolescence is the period with the highest consumption rates, with the sole exception of our country, where the age group with the highest prevalence of use is between 25 and 34 years. Regarding gender differences, the findings suggest that men have a consumption rate that is up to three times higher than that of women.

Focusing on our country, the Spanish Observatory on Drugs and Addictions, under the National Drug Plan, conducts a report on alcohol and other drug use among individuals aged 15 to 64 every two years. In the last two reports, EDADES 2020 and EDADES 2022, there is limited information on the use of synthetic cannabinoids; however, it indicates that among the new psychoactive substances (which include ketamine, synthetic cannabinoids, mephedrone, ayahuasca, pink cocaine, flakka, and nitrous oxide), only 0.5% of the Spanish population has used synthetic cannabinoids at least once in their lifetime, just behind the prevalence of ketamine use (0.9%) and with the same prevalence as pink cocaine. When broken down by sex, 0.8% of men have used synthetic cannabinoids compared to 0.3% of women, although this difference is consistent across all new psychoactive substances. By age group, synthetic cannabinoids surpass ketamine in the 15-24 age range (0.9% vs. 0.7%), and in the 25-34 age group, the prevalence rises to 1.2%, reaching 1.8% among men in this age group (OEDA, 2022; OEDA, 2020).

Similarly to the EDADES survey, the ESTUDES survey conducted in 2021 assesses drug use among secondary school students aged 14 to 18 in Spain. For synthetic cannabinoids, there is a downward trend observed in recent years, as the lifetime prevalence of these substances has decreased from 1.4% in 2012 to 0.6% in 2021. Nevertheless, they remain the second most commonly used new psychoactive substance among young people aged 14 to 18, just behind ketamine. When looking at the use of synthetic cannabinoids in the past 12 months within this age group, their prevalence is higher than that of ketamine, standing at 0.5%, although this is still half of what it was in 2012 (1%). Regarding the perception of risk, 75% of students aged 14 to 18 believe that even a single use of these substances can lead to problems, and 51.5% of these young individuals indicate that synthetic cannabinoids are highly accessible and easy to obtain. This percentage has decreased after the COVID-19 pandemic, as the perception of availability had been on the rise in the years leading up to the pandemic (OEDA, 2021).

Outside of Spain, focusing on different populations, a study by Wohlfarth et al. (2015) analyzed the urine of over 20,000 U.S. military personnel and used biomarkers to identify 29 distinct types of synthetic cannabinoids. They found that 1.4% of the military personnel tested positive for synthetic cannabinoid use, indicating recent consumption. However, each synthetic cannabinoid has different pharmacokinetic characteristics, making it difficult to determine when and how frequently these military personnel consume synthetic cannabinoids.

In almost all epidemiological studies and reviews on synthetic cannabinoids, men consume more than women, and adolescents and young adults are the primary users of these substances, although there is significant variation among studies, samples, and methodologies (Van Amsterdam et al., 2015). In this context, according to the global drug use survey by Winstock and Barrat (2013), which involved 14,966 participants online, 2,513 (16.8%) reported having consumed synthetic cannabinoids at some point in their lives, of which 40.6% indicated they had used them in the past 12 months. Among these users, 79.6% were male, with an average age of 25.3 years. The average age of first use was 21 years. Additionally, 60.6% of those who

had used synthetic cannabinoids in the past 12 months had not consumed them in the last month, and only 4.8% of those who had used in the past month reported daily use.

RISK FACTORS FOR SYNTHETIC CANNABINOID USE

The use of synthetic cannabinoids, like any type of drug use, presents risk factors that we understand as variables that increase the likelihood of consuming drugs. Risk factors, as well as protective factors, should be understood in probabilistic terms rather than causal terms; that is, the more risk factors present, the higher the probability of use (Buelga et al., 2006).

In a study on psychological risk factors for synthetic cannabinoid use (Cohen et al., 2020), it was highlighted that schizotypal personality is more closely related to individuals who use synthetic cannabinoids compared to those who consume organic cannabis. In the same study, synthetic cannabinoid users scored higher in neuroticism and lower in agreeableness. Additionally, synthetic cannabinoid users exhibited symptoms of depression, anxiety, and antisocial behavior. Another notable difference between synthetic cannabinoid users and organic cannabis users is that the former scored significantly lower in extraversion (being more introverted), while the latter had higher scores in this regard. Thus, schizotypal personality constitutes a risk factor for synthetic cannabinoid users, making them more vulnerable to adverse effects, particularly in developing psychosis.

According to the Global Drug Survey 2020, a worldwide survey collecting data on drug use and published by Winstock et al., (2021), synthetic cannabinoid users indicated that avoiding pain was the most important motivation for their consumption, as well as for avoiding withdrawal syndrome. Another item regarding motivations for using major drugs was the desire to experience maximum pleasure, in which synthetic cannabinoids scored the lowest. In another item concerning how the drug helps users have fun with others, synthetic cannabinoids again scored very low, being the least enjoyable drug for social interactions, surpassed only by heroin.

In this regard, the literature on synthetic cannabinoids extensively documents the motivations for use, which can help explain the increase in consumption and the reasons for using synthetic cannabinoids. One of the most frequently reported attractions by consumers is the difficulty of detecting metabolites of this range of substances, whether to avoid legal consequences for drug use among people who are incarcerated, those on probation, or military personnel, among others. Similarly, users also indicate that synthetic cannabinoids allow for driving under their influence without detection in tests, unlike organic cannabis. On the other hand, it is important to note that while most consumers prefer organic varieties to synthetic ones, some individuals report using synthetic cannabinoids because they believe they have positive effects, as they find them relaxing, out of curiosity, as an alternative to organic cannabis, as a means to reduce their organic cannabis use, due to perceived stronger subjective effects, and, to a lesser extent, due to availability and cost (Alves et al., 2020; Jackson et al., 2021; Winstock & Barrat, 2013).

Another study that collected data on the consumption of new psychoactive substances in Portugal, Germany, Hungary, the Netherlands, Ireland, and Poland indicates that a group labeled as socially marginalized individuals, recruited from social care centers, homeless shelters, or supervised consumption rooms, reported daily use of synthetic cannabinoids in up to 17.9% of cases, significantly higher than other population subgroups (Van Hout et al., 2018). A study on the consumption of new psychoactive substances in Australia found that users of synthetic cannabinoids in the past six months had higher rates of daily tobacco use, organic cannabis consumption, and greater involvement in criminal activities (Sutherland et al., 2016).

Regarding the profile of synthetic cannabinoid consumers, a shift has been observed before and after their prohibition in various countries. Prior to the ban, the profile typically consisted of young men with high employment rates who were also consumers of organic cannabis, alcohol, and tobacco. However, the change in legislation and the consequences of consumption have led to a shift towards individuals with high rates of criminality, homelessness, mental illnesses, and poly-drug use (Jackson et al., 2021). In a study comparing usage patterns among regular synthetic cannabinoid users (Mensen et al., 2019), it was found that these consumers had higher prevalence rates of use in the past 12 months and the last two weeks for drugs such as amphetamines, cocaine (both base and powder), tranquilizers, MDMA, hallucinogens (LSD, mushrooms, Salvia Divinorum, ketamine), and GHB. This reinforces the idea that poly-drug use is a strong predictor of synthetic cannabinoid consumption.

The incarcerated population is one of the subpopulations most frequently reported as consumers of synthetic cannabinoids. A study on the consumption of these substances in English prisons found that use increased from 6% to 10% before and after entering prison. Specifically, one-third (33%) of surveyed people who are incarcerated reported having used synthetic cannabinoids in the past month, which represents significantly higher rates compared to the general population, as the motivation for consumption often revolves around avoiding detection in drug tests. Moreover, these substances were the most commonly used in prison, surpassing heroin substitutes (14%), organic cannabis (14%), and heroin, which was reported by 8% of the surveyed incarcerated individuals. The consumption of these substances in prisons leads to various associated problems, such as debts, intimidation, violence, self-harm, mental health issues, overdoses, suicides, and deaths. In the same survey, people who are incarcerated in English prisons indicated that, although they generally prefer organic cannabis, synthetic cannabinoids are easier to obtain and are consumed due to a lack of alternative drugs (Grace et al., 2020).

Several studies report urine analyses conducted on U.S. military personnel to detect potential drug use. Following an increase in synthetic cannabinoid consumption among service members to avoid detection, these substances have been included in the routine drug testing protocols of the United States military. The primary motivation for using this drug was that, initially, it was not detectable in standard tests, leading to a prevalence of synthetic cannabinoid use that sometimes exceeded that of organic cannabis (Castaneto et al., 2014).

CONCLUSIONS

Recent studies shed more light on these substances, as it has been less than 20 years since they were first identified as recreational drugs, and their proliferation has been continuous. Therefore, we are not talking about a single substance but rather a group comprising over 200 different varieties. Although all of these are agonists of cannabinoid receptors, they differ in structural and pharmacological characteristics. The prevailing misinformation surrounding synthetic cannabinoids further enhances their danger, as they were initially marketed as safe and legal alternatives to organic cannabis.

The high potency of synthetic cannabinoids has a more severe impact on our bodies, largely due to these substances' ability to bind more effectively to cannabinoid receptors. This suggests a directly proportional relationship between the capacity to activate cannabinoid receptors and the severity of adverse effects. Studies have documented severe intoxications and even deaths resulting from the use of these substances, supported by data from emergency services, forensic analyses, and calls to poison control centers. These reports indicate that intoxications from synthetic cannabinoids can be more severe than many substances typically regarded as dangerous, which often have a higher perceived risk than synthetic cannabinoids. For these reasons, the consumption of these substances is concerning not only to the scientific community but also to regulatory drug agencies, which foresee that the situation surrounding synthetic cannabinoids could complicate in the future.

The prevalence of synthetic cannabinoid use in the global general population is not high, with epidemiological studies indicating it is no more than 2% for lifetime use. While there is an increasing focus on these substances, there are still national drug surveys that either do not include synthetic cannabinoids or group them with new psychoactive substances, making it difficult to compare consumption rates across countries. Furthermore, epidemiological studies vary in methodology and sample size, complicating the establishment of solid data. However, the reality is that these substances are consumed by various subpopulations, with a higher prevalence among men than women. The motivations for use uniquely affect these individuals, meaning that synthetic cannabinoids should not be regarded as substances with minimal impact on society. Additionally, they are often used by adolescents and young adults, similar to trends observed with new psychoactive substances.

Finally, this study suggests that we are currently in a period where these substances are still relatively novel. The true impact of synthetic cannabinoids may become apparent in the coming years, or the rapid proliferation of these substances may simply be an indication that they are a trendy drug. What is certain is that there is still much to learn about synthetic cannabinoids.

Limitations

The relative novelty of these substances as drugs of abuse is the reason for the limited number of scientific articles on synthetic cannabinoids. Therefore, this scarcity of studies may limit this paper, especially in the epidemiological section, as few organizations include questions about synthetic cannabinoids in their surveys, making it difficult to understand

the consumption of these substances. In the future, more studies will emerge that will further refine the understanding of their effects on the body, epidemiology, and risk factors associated with the use of these substances.

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