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Cannabis and Mental Health

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Cannabis is currently the most widely consumed illegal drug in both Europe and the United States. Cannabis dependence criteria are defined by the principal diagnostic manuals (DSM-IV and ICD-10), but not cannabis withdrawal syndrome, although cannabis withdrawal produces certain significant symptoms that are beginning to be typified by research. While not all cannabis users present mental health problems, recent reviews point to a greater risk of various mental disorders in cannabis users. The risks are associated with younger age at first use, greater frequency of use or certain personal predispositions. Research has revealed not only alterations in both the psychotic and affective spectra, but also cognitive deterioration and associations between cannabis use and antisocial behavior, use of other illegal drugs and other health risks. Although contaminating factors and the difficulty of accurately assessing the extent and history of cannabis use represent considerable obstacles to progress in this research field, studies carried out in recent years have contributed conclusive findings on the potential risks of cannabis use. The present article reviews the main scientific findings and conclusions with respect to the association between cannabis use and mental health.

Key words:
 Cannabis, mental health, psychosis, affective disorders.

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Cannabis y Salud Mental

El Cannabis es actualmente la droga ilegal más consumida tanto en Europa como en Estados Unidos. Sus criterios de dependencia están definidos por los principales manuales diagnósticos (DSM-IV y CIE-10) y aunque no ocurre así con el síndrome de abstinencia, éste presenta ciertos síntomas significativos que la investigación co-

mienza a concretar. Si bien no todos los consumidores de esta droga presentan problemas de salud mental, las revisiones de los últimos años apuntan a un mayor riesgo de diversos trastornos mentales entre los usuarios de cannabis. Riesgos que están asociados a la menor edad de inicio del consumo, la mayor frecuencia del mismo o a ciertas predisposiciones personales. La investigación no sólo ha desvelado alteraciones que van del espectro psicótico al afectivo, sino también deterioros cognitivos o su relación con la conducta antisocial, el consumo de otras drogas ilegales o con otros riesgos para la salud. Aunque los factores contaminantes y las dificultades de una evaluación precisa del grado e historia de consumo son un gran obstáculo para los avances en este campo, las investigaciones realizadas en los últimos años han proporcionado resultados concluyentes sobre los posibles riesgos del uso de esta droga. El presente artículo revisa los principales hallazgos científicos y conclusiones sobre la asociación entre el uso de cannabis y la salud mental.

Palabras clave:
 Cannabis, salud mental, psicosis, trastornos afectivos.

INTRODUCTION

According to data of the National Institute on Drug Abuse,¹ at least 94 million people in the U.S. (14% of those over 12 years) and 70 million people in the E.U. (22% of the adult population) have consumed cannabis some time in life.² In Spain, more than 8.6 million people (28.6% of the population aged 15 to 64 years) have consumed marijuana or marijuana products on some occasion.³ Although the ratio of people with conditional cannabis dependence is lower than that produced by substances like alcohol (15%) or tobacco (32%), around 9% of the persons who use cannabis become dependent.⁴ The debate on the legal status of cannabis remains alive due to the heterogeneity of regulations and legislation around the world, which includes legalized cannabis use (Holland) as well as jail sentences,

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life imprisonment or capital punishment for trafficking in countries like Indonesia, the United Arab Emirates or Saudi Arabia. This legislative diversity is the result of a complex historical evolution consisting of cultural, scientific and political movements that debate the benefits and harm of regular cannabis use. In recent decades, research is striving to understand the relation between cannabis use and mental health.

Cannabis has been an object of disparate fear and praise throughout the centuries in relation to the predominant culture and policy. The Inquisition, an institution that developed its activity in a European culture with a tradition of alcohol use, in the 12th and 13th centuries opposed a drug associated with witchcraft rituals and Eastern religions. For religious motives as well as commercial pretensions, Napoleon prohibited hemp at the beginning of the 19th century, which is proof that diverse species of this plant were farmed⁵ in the newly founded American nation. While the Eastern cultures of Hindustan used cannabis as a source of happiness (*vijohia*) and life (*ananda*), the buddhas used *bangha* as an instrument for meditation, and in Babylon and Egypt hemp was recognized as either a medicine or a pleasure-giving substance, in the modern world culture, the attitude toward cannabis use is epitomized by a relatively homogeneous position that has become known as the "War on Drugs." The present situation affects cannabis and is the result of a prohibitionist attitude that developed throughout the 20th century and contrasts with more tolerant 19th century views on this drug. For example, the British Commission "*Indian Hemp Drugs*" of 1894 did not consider moderate cannabis use harmful enough for mental health to take measures to restrict its use in its Indian colonies. At this time, not only was cannabis resorted to as a muse of the arts, it was a fundamental component of the Western pharmacopeia. The lack of clarity about the effects of cannabis and the variability of active substance concentrations were responsible for the substitution of cannabis by synthetic products with better therapeutic results.

The conclusions of the *Hemp Drugs Commission* are relevant and coincide with the opinion expressed by the father of Chinese medicine, *Shen Nung*, in 2737 b.c., reported in the *Pen Tsao Ching* (first century a.c.), who associated regular cannabis use with mental health problems. This legendary figure warned that "[hemp] consumed in excess makes one see monsters, and if used for a long time can make one communicate with the spirits and lose weight."⁶ Almost five thousand years later, this Commission advised that excessive hemp use apparently stimulates mental instability and, in the case of a hereditary disposition or weakness, can induce dementia.

A variety of value judgments exist about whether the present prohibition is a result of the development of more effective solutions by the pharmaceutical industry,

prohibitionist or moralistic trends, or scientific discoveries. After World War I, the United States took the first steps toward prohibition, which it defended in the Geneva Conventions of 1931 and 1936 and with the *Marijuana Tax Act* of 1937, following the attempts of the frustrated "Dry Law." This position limited the medical use of cannabis and scientific research with the substance, leading within years to the absence of any scientific advances in the study of this substance. Although reports like that of LaGuardia in 1944 did not choose to side with prohibition, prohibition gradually became the international standard for attitudes towards drugs, leading to the illegalization of cannabis even in countries where it has been traditionally used. As part of the psychedelic revolution of the 1960s, marijuana again came into use and cannabis use, particularly by young people (NIDA,⁶), increased. However, despite the recommendations of the *National Commission on Marijuana and Drug Abuse* of 1972, which indicated that it did not produce sufficiently serious damage to justify criminalization, the Nixon government implemented the necessary laws. As a consequence, the inheritance of the "aborted rebellion," as it was called by Escobedo⁵, was an even more prohibitionist situation.

In contrast, the 1960s provided a scientific basis for future research in the field of cannabis. In 1964, Gaoni & Mechoulam isolated Δ^9 -tetrahydrocannabinol (THC), the primary active substance in marijuana, which opened up the possibility for in-depth analysis of its characteristics and effects. This discovery is complemented by the research of Devane et al.⁷ and Gerard et al.,⁸ who identified and cloned (respectively) the target of this substance, the CB1 receptor of the endocannabinoid system, and of Munro et al. of 1993,⁹ who characterized the second CB2 receptor. The CB1 receptor is found mainly in nerve cell terminations, the reproductive system and some glandular systems, whereas the CB2 receptor is found in lymphoid organs (mainly B lymphocytes) and in other cells such as microglia.¹⁰ The addition of better knowledge of the endocannabinoid system¹¹ to these discoveries provided the basis for better understanding the effects of cannabis, and offered the first opportunity to begin to exactly study the psychoactive effects and possible harm and pharmacologic benefits produced by cannabis. This article reviews in depth the conclusions regarding the risks of cannabis use for mental health, together with other risks of cognitive and psychosocial nature, beginning with certain key aspects for understanding how cannabis functions as a substance of abuse.

RISK FACTORS FOR CANNABIS USE AND RELATED DISORDERS

Despite the high prevalence of cannabis use in Europe¹² and the United States,⁶ especially among the young people,

not all cannabis users have problems.¹³ Some known risk factors for abusive or problematic cannabis use, factors that identify the population most susceptible to experiencing negative mental health consequences, are reviewed below.

In addition to open attitudes towards drugs, social pressure and certain personal factors, cannabis use at early ages and high frequency use are associated with a greater risk of problems, which are more serious when smoking or previous mental health problems are added.^{14, 15} Likewise, school difficulties, a low socioeconomic setting or a negative family atmosphere characterize risk situations.¹⁶

The analysis of cannabis users in subgroups with different profiles and patterns reveals different consequences. The youngest users (11–12 years) are characterized as having less resistance to group pressure and lower scores on academic factors, poorer self-esteem and family relations, as well as more arrests compared to those who do not use cannabis. Those who start using cannabis later (14–15 years) present results on these variables that are intermediate between younger and older groups.¹⁷ This suggests an association between early use and the level of psychological functioning, age of onset being a good predictor of later disorders and a mediating factor for psychological damage. In effect, as regards mental health, cannabis use at earlier ages can advance the appearance of the first psychotic episode by 3 to 7 years, as also occurs with more frequent cannabis use.¹⁸

Experimental cannabis use and regular early use, more frequent use, longer duration of the period of use, mental disorders and a lower level of psycho-social resources are all risk factors for problematic cannabis use.¹⁵ The reasons that lead individuals to use cannabis also influence consequences, so that persons for whom cannabis use is a coping strategy have worse mental health, more psychopathology, and worse psycho-social adaptation than persons who use cannabis within the context of socialization for reasons of cohesion or social conformity, with the aim of integration.¹⁹ The latter group also has social support contexts that act as a protective factor against many risks and they are not less psychologically well-adjusted than the group of nonusers.

Certain individual predispositions, including personality traits, can lead to relations, contexts or situations in which the risk of substance use is greater, and other external factors may mediate that cause these traits to lead to abuse.^{20, 21} Heavy cannabis use usually occurs in people with marked novelty seeking traits, associated with poor behavioral control, impulsivity, anger, or a sensation-seeking trait as well as greater exposure to risk. According to Flory et al.,²² the characteristics of the marijuana user, which in conjunction account for up to 10% of the explicative variance, are summarized by low scores on amiability, responsibility and extraversion on the NEO-PI-R as opposed

to a high degree of willingness to experiment; the latter two remain prevalent even after controlling for comorbidity.²²

DEPENDENCE AND WITHDRAWAL SYNDROME

A point that has been extensively debated is related to the capacity of cannabis to produce withdrawal symptoms. The main diagnostic manuals, DSM-IV²³ and ICD-10,²⁴ list cannabis dependence as a disorder. Although some authors question the relevance of relatively mild symptoms of dependence,²⁵ all the dependence criteria are met to a greater or lesser degree in heavy, long-term users;²⁶ about one in ten cannabis users eventually becomes dependent.^{4, 27} It is common for users who have repeatedly tried to reduce or stop using cannabis to seek treatment voluntarily, claiming psycho-social and psychiatric problems and signs of dependence.^{28, 29} The demand for treatment in Europe has grown in recent years.³⁰

While the diagnostic manuals recognize cannabis dependence, they do not list cannabis withdrawal syndrome because it does not have a clear clinical significance²³ or well defined symptoms.²⁴ Recently, however, Budney et al. have found a withdrawal syndrome that occurs in heavy users after long periods of cannabis use and in most adults who seek treatment for abuse or dependence.²⁶ The syndrome produces irritability, nervousness, depressed mood, restlessness, sleep difficulties and anger,³¹ which make it difficult to stop using the substance. The symptoms appear after about two days without cannabis use and extend over 7–14 days,³² producing primarily emotional and behavioral symptoms as compared to the classic medical or physical symptoms of other drugs like opioids.^{31, 32}

MENTAL DISORDERS DERIVED FROM CANNABIS USE

In the area of mental health, recent research has analyzed the relation between cannabis and psychotic disorders and their course, which is the aspect that has attracted most interest, and has tried to control for the diverse contaminating factors that mediate the relation between cannabis use and affective disorders. In addition, the effects of cannabis on cognitive deterioration or antisocial behavior, classically associated with cannabis users, have been analyzed. Research has also been conducted into the well-known "amotivational syndrome," although it has received less attention and fewer conclusions have been reached.

Psychotic disorders

Research in recent years in the field of cannabis and mental disorders has evolved to the point where it has been

concluded that cannabis use and psychotic disorders are somehow related, although not causally.^{27, 33-35} Ever since *The Lancet* published in 1995³⁶ an editorial ruling that cannabis use, even long-term cannabis use, is not harmful for health, the growing body of research has evolved in divergent directions. Although no clear causal nature has been found, there is agreement that a warning should be given advising of the negative effects of cannabis use on mental health, which is supported by the *The Lancet*.³⁷

As for what type of relation exists between cannabis use and psychotic disorders, several hypotheses have been offered based on the research, including:

- Cannabis use begins as a way of coping with and relieving psychotic symptoms ("self-medication hypothesis").
- Cannabis use occurs with the use of other illegal substances that, in conjunction, are responsible for mental health problems.
- Cannabis use and the development of schizophrenia share etiological factors.
- Cannabis use is a risk factor that accelerates and aggravates schizophrenia in vulnerable people and affects its course.
- Cannabis use contributes in a unique way to increasing the risk of suffering a psychotic disorder, whether specific or nonspecific.

According to the first hypothesis, cannabis use is understood to occur as a self-medication mechanism to reduce the negative symptoms of schizophrenia in prodromal patients. In recent years, this hypothesis has lost support and has been generally rejected.^{27, 38-40} After controlling for the subclinical psychotic symptoms preceding cannabis use, the risk of suffering schizophrenia continues to be greater after cannabis use, indicating that cannabis use is not secondary to a pre-existing psychosis.⁴¹ It does not depend on other types of psychopathology⁴² or on the use of other illegal substances. Cannabis seems to have an effect on the course of psychotic disorders in an individual⁴³ and, after controlling for multiple known contaminating factors, the probability of suffering psychotic symptomatology continues to increase significantly.^{35, 44} The role of contaminating factors sometimes allows the risk of presenting affective disorders as a result of cannabis use to be ruled out, as will be discussed below.

The hypothesis that cannabis use and schizophrenia share common etiological factors is still open to debate.⁴³ Both events might be the product of the same causal factor and be ultimately related to neurobiological bases shared by both phenomena. This common mechanism could be based on the endocannabinoid system and its relation with dopaminergic activity.^{11, 18, 45} This hypothetical common etiology has still not been studied sufficiently, but it could

indicate a predisposition to suffer both phenomena, with the consequent overlap between cannabis use and the mental disorder.

The present investigation centers fundamentally on the two remaining hypotheses, according to which cannabis use is a risk factor for the development of psychotic symptomatology. Cannabis use could be an additional risk factor in the Diathesis-Stress Model of Schizophrenia of Nuechterlein and Dawson,⁴⁶ contributing to the development of the disorder in vulnerable people.^{18, 47} The alternative is that cannabis use *per se* can cause psychotic disorders in subjects who otherwise would not have experienced them. The classical study by Chopra and Smith⁴⁸ found that among individuals who presented psychotic symptomatology after consuming large amounts of cannabis, two groups are observed based on the duration of the symptoms associated with their clinical history. Thirty-four percent of the group without clinical history recovered within a few days and had a complete final recovery, whereas the group with a history of schizophrenia or personality disorders presented symptoms during a more prolonged period of time. This study offers a scheme for understanding the current perspective of the problem.

Cannabis users present transitory psychotic reactions that derive from the direct effects of THC, with hallucinations, delusions, confusion, amnesia, paranoia, hypomania or mood changes, which can occur in subjects without any previous clinical history after using large amounts of cannabis and remit in a few days.⁴⁹ This cannabis-induced psychosis is not easily distinguishable from schizophrenic symptomatology,⁵⁰ although it has been characterized by more bizarre behavior, violence, panic, more hypomanic symptoms and agitation, and fewer hallucinations and less blunting of affect, incoherent speech and hysteria.⁵¹ Despite the fact that up to 15% of cannabis users report psychotic symptoms after cannabis use,⁵² the variety of associated psychopathological symptoms does not indicate that the use of this drug produces a "cannabic psychosis" as its own nosologic entity.^{34, 51, 53} Leweke et al.⁵¹ propose the term "cannabis-associated psychosis," which emphasizes the potential nature of the role of cannabis use in the genesis of psychotic states. Arendt et al.⁵⁴ consider that this cannabis-induced psychosis is an early expression of schizophrenia in vulnerable individuals rather than part of the differential diagnosis, and that it can later result in the development of the disease.

Psychotic disorders have a prevalence in the general population of about 5 new cases per 10,000 inhabitants a year, but mild and transitory subclinical psychotic symptoms are a common phenomenon in the nonclinical population, where up to one out of every four subjects responds positively to items related with psychotic experiences.⁵⁵ This evolutionary expression of nonclinical psychotic symptomatology can persist abnormally as a consequence of exposure to diverse factors

that act additively, one of them being cannabis use, particularly early cannabis use.^{56, 57} Cannabis use would prolong persistence in subjects that otherwise would not become clinical cases according to an interactive evolutionary model of psychosis. The risk of developing psychosis after cannabis use is greater in subjects with prodromal symptoms (12.5%) than in subjects without prodromal symptoms (3.1%).⁵⁸

The most important reviews have found greater probabilities of suffering psychotic symptoms or disorders in subjects who use cannabis as opposed to nonusers. In one of the most complete follow-up studies,⁴⁰ the adjusted probability ratio of developing schizophrenia at any time after cannabis use was 6.7 (95%CI: 2.1 - 21.7) for subjects who had used cannabis more than 50 times as compared to cannabis nonusers, which reflected a dose-response effect. Moore³⁵ came to a similar conclusion after a review, reporting a 40% higher risk of psychosis in subjects who occasionally used cannabis and a probability 50% to 200% higher in regular cannabis users.

Cannabis use is very common in the population of persons with schizophrenia, which reinforces the association between the two phenomena but makes it difficult to draw conclusions about the causality relation. Around 43% of patients with schizophrenia use cannabis, and although the self-medication hypothesis apparently does not account for a causal association between cannabis use and psychosis, this does not invalidate the hypothesis that patients with schizophrenia may resort to cannabis to cope with the disease.⁴³ Cannabis use greatly alters the onset, course, phenomenology, results and relapses in schizophrenia^{51, 59} and presumably accelerates the development of schizophrenia in vulnerable subjects,⁶⁰ producing a decrease in negative symptomatology in some cases.^{61, 62}

Although the differences in the psychopathology of schizophrenic subjects who are cannabis users/non-users are not very large,⁵⁹ patients with cannabis dependence present less negative symptomatology than non-dependents.⁶¹ This might be the product of the effect of cannabis on dopaminergic activity, which is related to schizophrenic symptomatology. Other alternative explanations suggest that the presence of less negative symptomatology might constitute a greater risk of exposure to substance abuse.⁶³

Despite the evidence offered by research, the association between cannabis and psychotic disorders cannot be defined as causal in nature.⁶⁴ However, cannabis use involves certain risks of an increase in the appearance of latent psychotic disorders, particularly in the vulnerable population, heavy users and early-onset users. Although most users do not develop these psychotic problems, the population at risk may be considerable and certain authors,^{35, 65} and writers of editorials,³⁷ have already decided to advise of a probable relation between cannabis use and psychotic disorders.

Affective disorders

Whereas in recent years a lot of information on the possible association between cannabis use and psychotic disorders has been collected, investigations in the setting of affective disorders have not been as numerous or conclusive. Aside from the "amotivational syndrome," the consequences that have been most examined until now in the affective setting include affective disorder, mood and bipolar disorders, or unspecified affective disorders, depression, suicidal thoughts or attempts, anxiety, neurosis and mania.³⁵

The complexity of this study topic means that contaminating factors greatly influence the possible relation between cannabis use and affective disorders. This section includes sociodemographic factors, other mental disorders, intellectual capacity or personality traits, as well as the use of other substances. All these variables affect the prevalence of affective disorders, making it difficult to draw conclusions about the relation between cannabis and these disorders. Contaminating factors explain 10% to 100% of the observed association.^{35, 66}

Depression and depressive syndromes

As occurs with other psychotic disorders, the study attempts to discover the direction of the relation between cannabis use and depression, and whether there is anything causal in this relation.

According to cross-sectional studies, a history of depression seems to explain cannabis use, but longitudinal studies free of the bias of a possible retrospective reconstruction indicate that cannabis use increases or aggravates depressive symptoms (OR: 4) whereas individuals with depressive alterations are no more likely to use cannabis during follow-up.⁶⁷ After controlling for diverse contaminating factors, the studies reveal a small association between cannabis use and depression, with an adjusted probability ratio of 1.4 or somewhat greater among the most frequent users, which is consistent with a dose-response effect.^{35, 68, 69} In addition, the risk of suicidal ideation and behavior is greater among cannabis users,^{35, 70} although some studies conclude that this association is not significant after eliminating third variables.⁷¹ Therefore, there seems to be a modest association that still must be interpreted with caution.

Amotivational syndrome

One of the consequences classically associated to cannabis use is amotivational syndrome. The symptoms range from lack of interest, apathy and affective indifference

to problems of concentration, fatigue and intolerance of frustration. However, despite the strong connection in the collective mind between the stereotype of the cannabis user and amotivational syndrome, the WHO⁷² does not recognize the clinical existence of this syndrome and does not seem to have reached any consensus regarding its nature as a clinical entity or symptom derived from cannabis use. It has been hypothesized as a possible subclinical symptom of anhedonia derived from cannabis use, a by-product of the presence of depressive disorder, a consequence of the alterations of cannabis intoxication or personality traits.^{67, 73, 74} Depressive symptomatology prior to cannabis use cannot be ruled out as an alternative explanation.⁷⁵ Therefore, no clear conclusions yet exist about this syndrome, but it seems that multiple sociocultural factors, psychological alterations or even personality factors may be involved in its development.

Other mental disorders

Bipolar disorder and panic disorder, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, personality disorders, and adjustment disorders have also been related to cannabis use with significant probability rates in cannabis users seeking treatment for dependence versus control subjects (Table 1).

In contrast with the general population, among subjects seeking treatment for cannabis dependence 40.7% have received psychiatric treatment for disorders not related to substance use, a figure eight times higher than in nonusers. In the study by Arendt et al.,⁷⁶ subjects who had received treatment for psychiatric disorder had a greater probability of re-admission for treatment for cannabis abuse than those who had not received treatment (23.4% vs. 20.6%). The age at first use also was significantly younger among subjects who had received psychiatric treatment for anxiety disorders, psychosis and personality disorders.⁷⁶

Cognitive deterioration

Another area of interest in relation to the consequences of cannabis use is related to the effects of cannabis on neuropsychological functioning and cognitive performance.⁷⁷ Certain cognitive functions are directly affected by cannabis use,^{1,78} resulting in attention disorders,⁷⁹ short-term memory,⁸⁰ processing speed,⁸¹ estimation of time,⁸² executive functions,⁸³ cognitive flexibility⁸⁴ and motor control.⁸⁵ Although some deficits might even persist for months after discontinuing cannabis use, normal levels generally recover after a prolonged period of abstinence, suggesting that they are product of intoxication and not clinically significant permanent damage.⁸⁶ It can be concluded that in this setting

Table 1

Probability ratios of various psychiatric disorders in persons with cannabis dependence compared to the non-dependent population, according to ICD-10 criteria. Adapted from Arendt et al.⁷⁶

Diagnostic Groups	Probability Ratio
Bipolar disorders	4.9
Other affective disorders	7.6
Agoraphobia / Panic Disorder	2.4
Social Phobia	10.0
Generalized Anxiety Disorder	5.0
Obsessive-Compulsive Disorder	6.6
Adjustment Disorder	8.2
Personality Disorder	17.3

major damage disappears upon discontinuing cannabis use, whereas learning deficits and new information recall may be somewhat more permanent but of limited clinical relevance. The main concern with respect to these alterations is related to regular users, especially younger users, who present diminished cognitive performance as a consequence of regular use during a critical stage for mental and academic development, such as adolescence, and whose personal consequences may not be so reversible. However, more investigation is needed on the possible long-term alterations that may result from long-term cannabis use, including at the neurological level.

OTHER EFFECTS

Cannabis and use of other substances

In addition to the possible damage derived from regular cannabis use analyzed so far, cannabis use has been hypothesized as a risk factor for the use of other substances in an evolutionary model^{87, 88} known as the *Gateway Hypothesis*. Cannabis use, abuse and dependence are powerful factors associated with the use of other substances and with problems derived from this substance use.^{66, 89, 90}

In the West, regular use of this substance is associated with as much as 59-fold higher probability for the use of other illegal substances and early onset of use is a predictor of the progression of this sequence.⁹¹ One idea is that a shared risk exists for the use and abuse of diverse substances due to an individual's tendency to experiment with substance use or to exhibit risk-taking behavior.⁹² The investigations suggest that cannabis use does not directly lead to the use

of other illegal substances, but that certain cultural factors are crucial to the order of use in this progression,⁹⁰ such as substance availability, perception of the risk of different substances, or contact with substance subcultures that increase the availability of and access to other illegal substances.

Cannabis and antisocial behavior

In Spain,³ 21.7% of medical emergencies directly related to substance use are due to cannabis as the primary substance, and a high percentage of individuals with delinquency problems are cannabis users. For that reason, in addition to the direct risks of cannabis for health, it is the main substance of abuse in reports on arrests, violence, emergency room and therapeutic admissions, and involuntary injuries.⁹³ According to the NIDA, in the U.S.A., 38% of young women and 53% of young men arrested test positive for marijuana.²⁷ Although this association may be due to the fact that cannabis use and antisocial behavior share common risk factors⁹² instead of a causal relation, it suggests that cannabis use is an indicator of risk in the early detection of antisocial behaviors and other substance use, as indicated.

LIMITATIONS

Despite abundant recent evidence about the association between cannabis use and some mental disorders, investigations still face certain methodologic and theoretical difficulties. Sufficient knowledge is lacking of the dynamics underlying these associations, although advances in knowledge of the role of the endocannabinoid system in the process of deterioration of cognitive and mental functions show promise.⁹⁴ Likewise, studies to date, whether retrospective or longitudinal, have certain methodologic limitations.

To date, it has not been possible to determine whether a causal relation exists between cannabis and mental disorders and not all users develop negative consequences. While retrospective studies suffer limitations inherent to the information recovery bias, which can be imprecise, longitudinal studies correct this deficiency. However, longitudinal and retrospective studies share the difficulties of imprecision in the measurements and evaluation of certain critical variables or in controlling for contaminating factors.

After reviewing the cumulative research, no clear consensus exists as to how the level of cannabis use should be measured, with the options ranging from the total number of times used or mean use per time period to

different degrees of use according to scales prepared *ad hoc*. Comparisons between studies are complicated if we take into account variations in the concentrations of THC and cannabidiol in marijuana and the derivatives used in recent years. For instance, in the U.S.A., the THC concentration of the samples seized increased by 3% to 5% in the last decade of the 20th century.⁹⁵ These levels range from 2% to 8% THC in some varieties up to 20% in home-grown *sinsemilla* hydroponic varieties or the *Netherwood* variety.^{60, 96} The effects on mental health may not be similar given equivalent degrees of use. Something similar occurs with the definition and evaluation of mental disorders or psychological and psychiatric symptoms, as the use of different instruments and clinical criteria make comparison between studies difficult. These obstacles are complicated to resolve given the present state of science because it is not simple to measure the amount of THC consumed objectively or to properly control for certain individual factors when evaluating the effects of THC. In addition, mental disorders like schizophrenia or depression and their symptomatology are too complex for simple causality analysis.

However, certain limitations can be overcome with the present technology, such as controlling for the influence of contaminating factors. The effects of intoxication *per se*, the use of other substances or the evaluation of prodromal symptomatology, among others, are variables that must necessarily be considered for the results to be conclusive. In addition, the examination must be continued in search of other possible contaminating factors not contemplated and their proper evaluation. Any possible errors due to recovery bias can be corrected by recurring to precise longitudinal studies that exhaustively follow-up psychopathology and levels of use, as has already been done.

CONCLUSIONS

In the midst of the political and social debate about marijuana and its recreational and medical uses, science is trying to clarify the risks of a substance subject to contrasting opinions. Although the investigation has not found a causality relation between use and long-term alterations, a risk for mental health seems to exist for regular users with a certain vulnerability or predisposition, in whom cannabis use significantly increases the risks of presenting mental disorders, particularly psychotic disorders. The younger the age of onset and the greater the amount of cannabis consumed, the greater the probability is that cannabis use will cause harm. On the other hand, disorders of the affective spectrum show only a weak relation with cannabis use that is susceptible to moderation by a variety of cultural and contextual variables. This, however, does not prevent cannabis use from facilitating or aggravating these disorders.

As for amotivational syndrome, to date there is no consensus about its existence as an independent clinical entity with its own identity; instead, amotivational syndrome tends to be characterized as a subclinical symptom of other affective disorders. If we add the cognitive alterations directly caused by regular cannabis use to these risks, it would seem necessary to emphasize the importance of prevention and early intervention, especially in young people, and to warn users against the risks of cannabis. In the meantime, science must continue its work to control individual and contextual contaminating factors, to develop consensus about how to control levels of use and the evaluation of mental disorders, and to increase understanding of how the endocannabinoid system and other brain structures work in order to know the mechanisms that underlie these detrimental effects.

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