Cannabis, cannabinoids, and health

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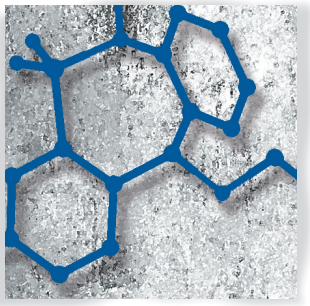

Cannabis (also known as marijuana) is the most frequently used illicit psychoactive substance in the world. Though it was long considered to be a "soft" drug, studies have proven the harmful psychiatric and addictive effects associated with its use. A number of elements are responsible for the increased complications of cannabis use, including the increase in the potency of cannabis and an evolution in the ratio between the two primary components, Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (toward a higher proportion of Δ^9-THC). Synthetic cannabinoid (SC) use has rapidly progressed over the last few years, primarily among frequent cannabis users, because SCs provide similar psychoactive effects to cannabis. However, their composition and pharmacological properties make them dangerous substances. Cannabis does have therapeutic properties for certain indications. These therapeutic applications pertain only to certain cannabinoids and their synthetic derivatives. The objective of this article is to summarize current developments concerning cannabis and the spread of SCs. Future studies must further explore the benefit-risk profile of medical cannabis use.

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Introduction

Cannabis (also known as marijuana) is a psychoactive plant that contains more than 500 components, of which 104 cannabinoids have presently been identified.[1] Two of these have been the subject of scientific investigation into their pharmacological properties: Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD). Cannabis potency is primarily evaluated according to a sample's THC concentration. This is the primary psychoactive cannabinoid in cannabis. The adverse effects after acute or regular cannabis use are in direct relation to THC concentrations in the product.[2]

Over the last few years, many studies have shown that CBD levels may also have an important impact. CBD may have a protective effect against certain negative psychological effects from THC. It may also be capable of antagonizing at least some of the adverse effects related to THC.[3]

Various cannabis preparations are available on the illicit drug market: hashish, herbal cannabis (leaves and flowers), and oils. Real-time monitoring of confiscated cannabis preparations has enabled scientists to measure the potency of currently used products. Changes can then be compared with the prevalence of negative health consequences in users. Certain authors speculate that an increase in cannabis potency and in the ratio of

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the psychoactive component (^{9}-THC) to CBD may be the reason behind increases in harmful effects associated with cannabis use.

Furthermore, the last few years have seen a substantial rise in the use of synthetic cannabinoids (SCs), especially in frequent cannabis users. The attraction of SCs may be that whereas they provide psychoactive effects that are similar to cannabis and are also easily obtained, they are undetected through usual screenings. However, their composition and pharmacological properties make them potentially dangerous substances.

Here, we summarize current developments concerning cannabis and the spread of SCs. Despite increasing detrimental issues arising from cannabis use, studies have shown that this drug and some SCs may have a number of therapeutic effects, depending on the specific posology.

Cannabis today

Evolution of THC:CBD ratios

Recent reports indicate that cannabis production is increasing and that cannabinoid formulations have been changing over the last two decades, especially with regard to their THC and CBD concentrations. This trend has been observed not only in the United States, but also in several European countries, such as the Netherlands and Italy.[4-6] Results are comparable since they use a similar validated methodology: samples seized by law enforcement officials are analyzed using gas chromatography with a flame ionization detector.

In a study by ElSohly et al,[4] 38 681 samples seized in the United States between January 1, 1995 and December 31, 2014 were analyzed. The results showed an 8% increase in average THC levels during that period. In parallel, CBD concentration decreased from 0.5% to less than 0.2%. The resulting THC:CBD ratios increased from 14 in 1995 to 80 in 2014.[4] Elsewhere, Zamengo et al[5] analyzed 4962 cannabis products seized in the Venice area (Italy) from 2010 to 2013. Median THC content showed a significant increasing trend from about 6.0% to 9.5%, especially between 2012 and 2013, with the total median THC content showing an increase of about 16.7%. This increase pertained particularly to herbal materials (+25%), whereas resin materials increased by about +9.7%. Interestingly, the average and median THC content of handmade cigarettes, which was determined by calculating the percentage of THC in the whole tobacco-cannabis mixture, and which can be a relevant indicator when studying patterns of cannabis use, also showed significant increases in 2013: +28% and +45%, respectively.

Another study performed in the Netherlands in 2015 confirmed these results with a different trend.[6] Indeed, from 1999 to 2004, the THC content increased from 8.5% to 20%. In the years 2005 to 2015, they found a small but statistically significant decline in THC concentration: a 0.22% decrease per year. Thus, in the Netherlands, the THC content has remained stable during the last 10 years. This study emphasized the fact that global increases in THC levels and decreases in CBD levels are largely linked to the spread of indoor cultivation practices. On average, cultivars from the Netherlands are twice as potent as imported products. The high THC concentrations obtained from the various cannabis varieties result from technical advances in production, such as genetic manipulations, cross-breeding, and improvements in indoor hydroponic cultivation. As advanced techniques and more potent seeds have become more widely available, this has contributed to the steadily increasing THC concentrations in cannabis.[4]

These changes may have significant real-world clinical consequences because the chances of detrimental psychological effects seem to increase when cannabis with high concentrations of THC is consumed.[7,8] CBD:THC ratio also appears to be an important factor.[7,9] Epidemiological studies have shown that cannabis use during adolescence is an important risk factor in the development of schizophrenia later in life.[4] These studies seem to show a risk of psychotic effects that is proportional to THC concentrations and inversely proportional to CBD concentrations. Some data also suggest that the CBD:THC ratio may play a role in the risk of addiction.[2,7-9]

Emerging market of synthetic drugs: synthetic cannabinoids

Synthetic cannabinoids (SCs) emerged in the 1970s when researchers were first exploring the endocannabinoid system and attempting to develop new treatments for cancer pain. Around the year 2000, SC appeared on the illicit drug market, where their prevalence had long been underestimated. Since then, their place in the market has steadily increased. More than 560 synthetic psy-

choactive substances have been identified on the illicit market. There has been a steep rise over the last 5 years with the appearance of 380 new synthetic drugs. Since 2008, more than 160 SCs have been identified in various products, 24 of which appeared in 2015.[10] Most SCs are manufactured by chemical companies located in Asia (China, South Korea). Today, intra-European production is closely monitored.[10,11] Current legislation is frequently defeated and outwitted by manufacturers who regularly modify their chemical formulations, resulting in rapid turnover of SCs. Indeed, each SC is replaced by newer analogs within a year or two.[12]

SC use varies a great deal between different countries and populations.[13] For example, in Spain in 2012, there was a low percentage (1.4%) of use of "Spice" and its derivatives among youth between 14 and 18 years of age. In 2013 in Germany, a survey conducted with students between 15 and 18 years of age showed that 5% of them had used herbal blends. In 2016, the European Monitoring Center for Drugs and Drug Addiction's (EMCDDA's) 2015 European School Survey Project on Alcohol and Other Drugs (ESPAD) report showed that approximately 4% of all youths between 15 and 16 years of age had used an SC at least once in their lifetime; few differences were noted between boys and girls.

Compared with other new drugs on the market, the increase in consumption of SCs was particularly remarkable.[13] Generally, these products are offered as herbal blends. They may also be sold as tablets, capsules, or powders.[14] Frequently, they are smoked by pipe or as a joint.[15] Recently, newer liquid formulations have appeared that can be vaped via electronic cigarette.[16]

SCs have different pharmacological properties than cannabis. These molecules are particularly lipophilic[15] and are full agonists of CBD receptor 1 (CB1) and CBD receptor 2 (CB2).[17] Their potential binding affinity for these receptors is also much stronger than that of THC, thus causing much more pronounced psychoactive effects. They also do not contain any CBD whatsoever, contrary to cannabis, where it is present in varying concentrations.[18]

Products of the same brand and sold under the same name have highly variable product compositions and concentrations.[19,20] SC effects depend on the type of product used and its dose. Similarly, the pharmacokinetics depends on the administration route. In some cases, the onset of psychoactive effects and physical symptoms begins a few minutes after smoking.[15] The effects are comparable to those observed after high doses of THC, and the high efficacy—as well as differences from batch to batch—results in the risk of accidental overdosing.[21] Anxiety is frequently reported. Some users have described feeling limited in their movements, whereas no motor deficits are objectively observed. On average, the effects last for about 6 hours, steadily decreasing until the next day.[15,21,22]

Herbal formulations containing SC that are smoked, known as Spice, imitate the psychoactive effects of THC.[19] Several studies have shown that a large majority of SC users are also frequent cannabis consumers,[23,24] especially among adolescents.[25] It is possible such use is influenced by the fact that whereas SCs provide similar psychoactive effects to cannabis, they are not detected during routine screening.[26] Some consumers may also use SC in order to decrease their cannabis use or to diminish symptoms of cannabis withdrawal.[26]

Certain serious complications

Evolution of THC:CBD ratios and psychosis risk

Almost 30 years ago, Andréasson et al showed an association between cannabis use and the later emergence of schizophrenia.[27] Since then, numerous prospective, longitudinal studies have been published. Despite confounding factors, sufficient proof currently exists showing that cannabis use increases the risk of psychotic disorders.[28]

Over the last 5 decades, increasing THC concentrations have been observed in products available in many countries. In the 1970s, the THC concentration in cannabis found in England and in the Netherlands was less than 3%. Current varieties contain on average 16% in England and 20% in the Netherlands. New cannabis preparation techniques have led to products containing THC levels of up to 40%. Traditional hashish (resin) contains THC and CBD in similar proportions. However, newer varieties and forms, such as sinsemilla, have high THC levels but contain almost no CBD.[29]

Some studies have indicated that CBD may have antipsychotic properties.[30,31] One recent case-control study revealed that the use of cannabis with high levels of THC may be associated with an increased risk of psychosis, especially when its CBD levels are low.[32] Certain recent epidemiological studies have shown an

increased incidence of schizophrenia in countries such as England and the Netherlands where highly THC-concentrated cannabis is regularly used versus in Italy where more traditional cannabis varieties with lower concentrations of THC are used.[29] High THC cannabis may increase the risk of earlier psychosis onset. One study has suggested an association between dose and response, showing that daily users of high-dose cannabis begin their first psychotic episode an average of 6 months earlier than those who had never used cannabis.[7] A recent meta-analysis has also shown that continued use may have a negative impact on schizophrenia outcome. Psychotic patients who continue to use cannabis had a significantly greater number of relapses than patients who had stopped using cannabis or had never used.[33]

Based on studies examining the evolution of THC levels in cannabis over the last few decades, one hypothesis is that previous studies may have underestimated the impact of cannabis on existing psychosis. In fact, ecological proof seems to argue in favor of greater psychosis risk among youths who have recently been exposed to high-dose cannabis than in former generations exposed to lower THC doses. Such an analysis, however, has yet to be performed.[34] Future research would need to show that different cannabis varieties are associated with different psychosis risks.

It is too soon to confirm this hypothesis. Current clinical data are insufficient to justify prevention measures concerning cannabis use or restriction of highly concentrated varieties. Estimates that integrate data from different countries have shown that between 8% and 24% of all psychotic disorders could be avoided if use of highly concentrated cannabis were prevented.[32]

Psychiatric, addictive, and physical consequences of SC use

Numerous complications have been observed in SC users.[35] Because of its pharmacological characteristics, SC may be the source of more serious adverse effects than those seen with cannabis.[15,17,18]

Anxious symptoms, such as ruminations, anxiety, and panic attacks, are often seen following SC use. Sleep disorders, hyperactivity, agitation, and irritability have also been reported. Acute intoxication may be associated with cognitive disorders such as short-term memory loss. There have also been cases of paranoia, flashbacks, and suicidal ideation.[36,37] In one case report, manic symptoms were noted to have followed a single use of SC.[38]

Although SCs have a similar mechanism of action to THC, the different pharmacological properties, such as higher affinity for CB1 and CB2 receptors, higher efficacy, as well as the absence of CBD, result in different physiological and toxicological effects, especially concerning its pro-psychotic effects. The psychotogenic effects of SC are increasingly alarming, with numerous reports of individuals who become psychotic after SC use.[39,40]

Delirious symptoms, acoustico-verbal hallucinations, and dissociative elements have all been described in individuals without a history of psychosis.[41,42] Two cases of catatonia after SC use have also been reported in patients with no history of psychosis.[43]SC may also worsen psychotic symptoms in patients who were previously stabilized or cause transitory psychotic episodes in healthy, but vulnerable individuals.[15]

SCs are potentially addictogenic because these substances can increase dopamine secretion within the nucleus accumbens and the ventral tegmental area.[18,19,44-46] Symptoms of tolerance and of withdrawal resulting from long-term use have also been described.[36,47,48] The symptoms associated with ceasing SC use are similar to cannabis-withdrawal syndrome: sleep disturbances, intense dreams, severe anxiety, nausea, restlessness or leg cramps, sweating, shaking, and loss of appetite.[49] Nacca et al observed that withdrawal symptoms lasted an average of 6 days after quitting. Intense and severe cravings have also been reported.[50]

An increasing number of nonfatal intoxications, as well as deaths, after presentation to the emergency room or in consultation have been reported, especially in young people.[51] SC use has been associated with the following physical complications: cardiac, pulmonary, neurological, digestive, renal, and even dermatological.[13] These consequences may be severe and potentially fatal, as reported in a number of cases in the literature.[52]

Therapeutic applications of cannabis and cannabinoids

THC is the psychoactive principle of cannabis, inducing the cannabis inebriation sought by many users. Its addictive potential and negative consequences are now well known.[53] The effects of CBD are distinct and, in many cases, the opposite of THC's effects. CBD seems

not to induce euphoria and seems to have antipsychotic, anxiolytic, antiepileptic, and anti-inflammatory properties.[54]

According to an evaluation (in 1999) by the Institute of Medicine in the United States on cannabis as a medication, the future of medical cannabis resides in isolating its cannabinoid components and their synthetic derivatives. The variable composition within the raw cannabis plant and especially the differing THC/CBD ratios make therapeutic applications of these products quite complex.[55]

Various forms of cannabis have been studied to ascertain the therapeutic properties of cannabis. Currently, three molecules have been approved by the US Food and Drug Administration (FDA); a single molecule in Canada and Europe.[56] Dronabinol, a synthetic THC, has been approved by the FDA in the treatment of anorexia in patients suffering from AIDS and as a second-line treatment in nausea and vomiting induced by cancer chemotherapies. Nabiximols, a combination of synthetic THC and CBD in equal proportions, is delivered in spray form. It has been approved in several countries (Canada, Europe), but not in the United States, as an adjunctive therapy in the treatment of spastic pain in patients with neurological disorders.[56]

A 2015 meta-analysis reviewed randomized clinical trials worldwide of medical cannabis and cannabinoids from 1974 through 2014.[57] This study analyzed the results from 79 clinical trials performed in various domains: chronic pain, nausea and vomiting induced by chemotherapy, spasticity in multiple sclerosis or in paraplegics, orexigenic effects in patients with human immunodeficiency virus (HIV) or AIDS, sleep disorders, Tourette syndrome, psychosis, anxiety disorders, intraocular pressure from glaucoma, and depression. The most frequently studied cannabinoid forms were medications produced by pharmaceutical companies: nabilone, nabiximols, and dronabinol. The other evaluated cannabinoids included THC, CBD, and a combination THC/CBD. This study included only two trials using plant-based cannabis (smoked and vaped).

The results of this meta-analysis revealed moderate-quality proofs in favor of nabiximols, nabilone, dronabinol, or THC/CBD in treating spasticity from multiple sclerosis. The same level of proof was shown for nabiximols or smoked THC in the treatment of chronic cancer pain and neuropathic pain. Proofs of lesser quality were found in favor of dronabinol or nabiximols in treating nausea and vomiting induced by chemotherapy and in weight gain in HIV/AIDS patients; for nabilone and nabiximols in treating sleep disorders; and for THC capsules in treating Tourette syndrome. This meta-analysis showed that CBD was not significantly more efficient in treating psychosis than a usual antipsychotic, such as amisulpiride, or depression compared with nabiximols. Finally, one very small crossover trial with six patients was not able to detect an effect of cannabinoids on intraocular pressure.[57]

A systematic review by the American Academy of Neurology examined publications from 1948 through November 2013 concerning the use of cannabinoids in the treatment of multiple sclerosis, movement disorders, and epilepsy.[58] Only oral cannabis extracts (combined THC/CBD or CBD alone) had a sufficient level of proof in treating spasticity from multiple sclerosis and central pain. The other formulations seemed to be effective in these indications, but with lower levels of proof. Proof was insufficient to conclude as to the efficacy of smoked cannabis. In other neurological indications, such as Huntington disease and Tourette syndrome, proofs were judged insufficient.

Cannabinoids would seem to have some therapeutic interest in the following indications: epilepsy, addictions, psychotic disorders, anxiety, and sleep disorders. However, there are currently insufficient levels of proof. Indeed, a Cochrane review from 2014, for example, concluded that there were insufficient levels of proof for cannabinoids in the treatment of epilepsy.[59] Nevertheless, cannabis-based treatments continue to elicit great interest. They remain the subject of preclinical and human research. In animal studies, CBD has shown significant antiepileptic activity, reducing seizure severity. Recent studies in young patients suffering from severe, treatment-resistant epilepsy have shown that CBD may have a specific indication in these forms.[60,61]

Due to its implications in the reward system, endocannabinoid signaling represents a potential therapeutic target in treating addictions. The results from randomized, controlled trials suggest that CB1 receptor agonists such as dronabinol and nabiximols may be effective in treating cannabis withdrawal. Dronabinol may also decrease opioid withdrawal symptoms. Rimonabant, an inverse agonist of CB1 receptors, has shown promising effects in tobacco cessation; it also causes adverse psychiatric effects. Few clinical trials have examined the effect of cannabinoids in treat-

ing alcohol-use disorder; those examining rimonabant have shown negative results.[62] A systematic review has examined the preclinical and clinical data on the impact of CBD on addictive behaviors. Fourteen studies were found, nine in animals and five in humans. Some preclinical studies suggest that CBD may have some therapeutic properties in treating opioid-, cocaine-, and psychostimulant-use disorders. Some preliminary data suggest that it could be advantageous in treating cannabis- and tobacco-use disorder in humans.[63,64]

One randomized, double-blind clinical trial compared the use of CBD versus amisulpride for 4 weeks in, respectively, 20 and 19 patients with psychosis. This study showed comparable efficacy between amisulpride and CBD (Positive and Negative Syndrome Scale [PANSS], Brief Psychiatric Rating Scale [BPRS]). A potential advantage for CBD is its milder side effects: fewer extrapyramidal symptoms, less weight gain, and no hyperprolactinemia.[65]

Contrary to the effects of THC, several preclinical studies have shown that CBD may have anxiolytic effects.[66,67] In individuals with social anxiety, CBD 400 mg considerably decreases anxiety measures versus placebo; measures were correlated with decreased activity within the limbic and paralimbic areas on functional magnetic resonance imaging (fMRI).[67] One clinical trial in healthy volunteers has shown that acute CBD administration (300-600 mg) seems to decrease experimentally induced anxiety without modifying baseline anxiety levels; it would also seem to decrease social phobias.[68]

The understanding of the relationship between sleep and cannabinoids has been obscured by significant methodological differences resulting in mitigated results. The results from the literature seem to favor a beneficial effect of acute cannabis intoxication on sleep. On the other hand, regular cannabis use seems to have a negative impact on sleep quality. Different cannabinoids seem to have a differential impact on sleep. One study has suggested a therapeutic potential for dronabinol and nabilone on sleep disorders and nightmares.[69] Studies specifically examining CBD have shown that when used at small doses, it may have some stimulant effects.[70] At medium-to-high doses, it seems to have a more sedative effect and thus may improve sleep quality.[71] When CBD is associated with THC, it seems to reduce slow-wave sleep.[72]

Thus, there is preclinical evidence and some clinical evidence for therapeutic properties regarding a number of diseases. However, larger controlled clinical trials are needed to show efficacy and safety for each disorder.

Conclusion

Cannabis use and its negative consequences have increased over the last several years in parallel with increasing cannabis potencies. SCs seem to be particularly popular among cannabis users. This emerging market represents a specific public health problem in light of the severe complications in relation to their use. What the risks are of developing a psychotic disorder after SC administration remains a fundamental question.

This is an emerging area of research in which more robust epidemiological studies must be developed. These must provide detailed information concerning not only the quantity and the frequency of cannabis use, but also, and more importantly, the type of cannabis used. Longitudinal studies including precise THC and CBD measurements must be established in order to clarify the impact of THC/CBD ratios on psychosis risk. The use of SCs must also be more largely examined in light of the severe consequences associated with their use.

The legislative policies that have been established to reduce the risks in relation to cannabis have long represented an obstacle to research concerning medical cannabis use. Improved knowledge of the endocannabinoid system and of exocannabinoids has proven that cannabis may have significant therapeutic effects. Despite sparse research, certain countries, such as the United States, have authorized the use of plant-based medical cannabis.[73] Future studies must further explore the benefit-risk profile of medical cannabis use. ❑

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La cannabis, los cannabinoides y la salud

La sustancia psicoactiva ilícita que se emplea con mayor frecuencia en el mundo es la cannabis. Aunque se consideró por largo tiempo una droga "suave", los estudios han probado los efectos dañinos asociados con su empleo. Hay algunos elementos que son responsables del aumento de las complicaciones del empleo de cannabis, como el incremento en la potencia de ella y una evolución en la relación entre los dos componentes principales, el delta-9-tetrahidrocannabinol y el cannabidiol (con un porcentaje más importante de delta-9-tetrahidrocannabinol). El empleo de cannabinoides sintéticos (CS) ha tenido un rápido aumento en los últimos años, especialmente entre los usuarios frecuentes de cannabis, ya que tienen la ventaja de producir efectos psicoactivos similares a esta droga. La composición y las propiedades farmacológicas de los CS los hacen sustancias peligrosas. Para ciertas indicaciones la cannabis también tiene propiedades terapéuticas, pero esto se aplica sólo para ciertos cannabinoides y sus derivados sintéticos. El objetivo de este artículo es resumir el progreso actual relacionado con la cannabis y la difusión de los CS. Se requieren futuros estudios que promuevan la exploración del perfil de riesgo-beneficio del empleo medicinal de la marihuana.

Cannabis, cannabinoïdes et santé

Le cannabis (connu aussi sous le nom de marijuana) est la substance psychoactive la plus fréquemment utilisée dans le monde. Longtemps considérée comme une drogue « douce », des études ont prouvé les effets addictifs et psychiatriques nocifs associés à son utilisation. Un certain nombre d'éléments sont responsables de l'augmentation des complications liées à l'utilisation du cannabis, comme l'augmentation de sa puissance et une évolution du rapport entre les deux principaux composants, le ∆9-tétrahydrocannabinol (∆9-THC) et le cannabidiol (avec une proportion plus importante de ∆9-THC). L'utilisation des cannabinoïdes synthétiques (CS) a rapidement progressé ces dernières années, principalement parmi les utilisateurs fréquents de cannabis, les CS apportant des effets psychoactifs similaires à ceux du cannabis. Cependant, leur composition et leurs propriétés pharmacologiques en font des substances dangereuses. Le cannabis a bien des propriétés thérapeutiques pour certaines indications. Ces applications thérapeutiques concernent seulement certains cannabinoïdes et leurs dérivés synthétiques. L'objectif de cet article est de résumer les développements actuels concernant le cannabis et la progression de l'utilisation des CS. Il faut entreprendre de nouvelles études pour mieux étudier le profil bénéfice-risque de l'usage médical du cannabis.