



SCIREA Journal of Health

<http://www.scirea.org/journal/PMH>

November 13, 2023

Volume 7, Issue 2, April 2023

<https://doi.org/10.54647/pmh330309>

## **Tobacco and cannabis co-use : toxicity, dependence and cessation management.**

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### **Abstract.**

Objectives : Tobacco and cannabis are the most used inhaled drugs worldwide. This review looked at the effects of their combined use, the dependence induced, and the ways of helping people to quit.

Method. Medline was searched using the keywords « tobacco smoking » or « cannabis use » or « tobacco marijuana co-use » and « health effects » or « dependence » or " « smoking cessation intervention » with « Title/Abstract » limits and search period from 1980 to 2023. A selection of articles in English or in French was analyzed.

Results. Combustion smoke from tobacco and cannabis is more toxic than of tobacco or cannabis, induced dependence is more elevated, tobacco and cannabis cessation is more difficult than quitting tobacco or cannabis alone.

Conclusion. The marketing of cannabis with a high active ingredient content, the availability of synthetic forms and the increasing legalization of recreational use, against a backdrop of a slow decline in the prevalence of smoking, is leading to the danger of an increase in the combined use of tobacco and cannabis ; this risk should be a concern for all health authorities and professionals.

**Keywords** : Tobacco smoking ; Cannabis use ; Marijuana tobacco co-use ; Dependence ; Treatment.

## **I - Introduction.**

Smoking is responsible for the deaths of 8 million people worldwide every year. However, since 2000, when 32.7% of the world's population smoked, the prevalence of smoking has fallen ; the World Health Organization (WHO) aims to reduce it to 20.4% by 2025 [1]. Cannabis is the most widely consumed psychoactive substance in the world, after alcohol and tobacco. In 2017, according to the WHO, 188 million people aged 15 to 64 worldwide used cannabis at least once a year (3.8% of the global population), and the total number of annual users appears to have increased by 30% over the period 1998-2017 [2]. Mortality due to its use is unknown, but it is the cause of many morbid effects ; many users believe that smoking cannabis carries little health risk. Cannabis use often is associated with tobacco use, making it more difficult to stop [3,4]. The objective of this article is to review the data on Tobacco and cannabis co-use regarding toxicity, dependence as well as management of cessation

## **II - Tobacco and cannabis.**

### II -1. Tobacco.

Tobacco belongs to the *Solanaceae* family. The *Nicotiana* genus is grouped into three subgenera : *Nicotiana tabacum* is the main form used to prepare manufactured tobacco, *Nicotiana rustica* is used as a lower-quality smoking tobacco and snuff, and *Nicotiana*

*petuniae* is an ornamental plant. Tobacco alkaloids belong to three families : pyridil-pyrrolidines (nicotine, nornicotine, cotinine, myosmine), pyridil-piperidines (anabasine, anatabine) and betacarbolines (harmane, norharmane, which act as monoamine oxidase inhibitors [MAOIs]). [5].

## II -2. Cannabis.

Cannabis belongs to the *Cannabaceae* family, with two main varieties : *Cannabis sativa sativa* (textile hemp) and *Cannabis sativa indica* (Indian hemp). Indian hemp grows endemically in tropical and subtropical regions, producing a resin rich in active ingredients located in the inflorescences or flowering tops. The cannabinoids present in the resin and leaves are the psychoactive substances specific to cannabis. Among the more than sixty cannabinoids present in *Cannabis sativa indica* are Delta-9-trans-tetrahydrocannabinol ( $\Delta$ 9-THC), the main psychoactive substance in humans, Cannabidiol (CBD), Cannabinol (CBN), derived from the oxidation of THC, Cannabichromen (CBC), Cannabigerol (CBG), Tetra Hydro Cannabivarin (THCV) [6].

## III - Types of tobacco and/or cannabis use.

### III -1. Tobacco.

Tobacco is mainly smoked in the form of manufactured or rolled cigarettes, pipes or cigars ; in Scandinavian countries (Sweden or Norway) it is mostly used in smokeless form (snus) [7]. There are many culturally marked modes of use (narghile in the Middle East, « bidies » in India, « kretek » (tobacco blended with cloves) in Indonesia and Malaysia) [7].

### III -2. Cannabis

Cannabis is consumed in the form of cigarettes or cigars made from weed (marijuana) or resin mixed with tobacco (joints), or pipes, using a narghile (shisha or hookah : oriental pipes connected to a bottle of water flavored, which the smoke passes through before being inhaled) [6]. The « bong » is a home-made water pipe often made from a plastic bottle ; its use increases toxicity by mixing the smoke with products produced by heating the plastic. In New Zealand, cannabis is often smoked alone (marijuana), making it possible to identify its toxicity [8] and to correlate the respiratory consequences with cannabis inhalation. As most studies express cumulative tobacco consumption in pack-years (1 pack-year [PA] corresponds to 1 pack of cigarettes smoked per day for 1 year), cannabis consumption is expressed in

joint-years (1 joint-year [JA] corresponds to 1 joint smoked per day for 1 year). These methods of calculation are approximate, particularly for cannabis, as the quantity of substance used to make a joint and the depth of each puff inhaled are highly variable [3].

## **IV - Smoke from tobacco and cannabis combustion.**

### **IV-1. Smoke composition.**

Apart from nicotine and cannabinoids, which are specific to tobacco and cannabis, the smoke produced by combustion of both contains the same toxic substances (carbon dioxide, acrolein, benzene, toluene) and carcinogens (vinyl chloride, dimethylnitrosamine, methyl ethylnitrosamine, benzopyrene, benzanthracene) [3-5]. A study [9] has shown that cannabis smoke contained ammonia in concentrations 20 times higher than tobacco smoke, and hydrogen cyanide and nitric oxide concentrations 3 to 5 times higher.

### **IV-2. Mode of inhalation.**

Cannabis smokers have a different inhalation technique to tobacco smokers. The volume of puffs is greater, inhalation is faster and deeper, and lung retention time is longer (4 times longer), due to a pause in breathing of several seconds at the end of inhalation, which sometimes includes a Valsalva maneuver to improve cannabinoid absorption and the psychoactive effects induced [10]. A joint of cannabis is equivalent to 2.5 to 3 cigarettes of tobacco in terms of irritation and inflammation of the bronchial mucosa and on the lung function [8]. Smoking in this way increases particle impaction of particles in the mucosa of the large airways and penetrating the small airways and prolonging contact time with the bronchial mucosa, promoting irritation [11,12]. The serum carboxyhaemoglobin (HbCO) concentration and the quantity of inhaled tars are significantly greater when cannabis is inhaled compared with exclusive tobacco use ( $p < 0.001$ ) [13]. A study by Tashkin et al. [14] in regular cannabis smokers has shown that in subjects smoking a cigarette with 1.24% THC, increasing the duration of pulmonary smoke retention between smoking sessions resulted in a significant ( $p < 0.05$ ) increase in blood THC and HbCO concentrations, associated with an increase in pulmonary tar retention. In contrast, increasing puff volume did not induce these changes. The duration of pulmonary smoke retention, not puff volume, increased the harmfulness of cannabis smoke.

## **V - Tobacco and cannabis dependence.**

### V-1. Tobacco and alkaloids.

Nicotine is the main substance in tobacco dependence, reaching the brain from the pulmonary alveoli in a matter of seconds, with a plasma elimination half-life of around 2 hours. Its action is reinforced by betacarbolines (harmane, norharmane) contained in tobacco smoke, which have an MAOI action [5]. Nicotine binds to specific cholinergic receptors (AChN-Rs) located on dopaminergic, noradrenergic and serotonergic neurons, ultimately activating the brain's hedonic system (ventral tegmental area, nucleus accumbens, cerebral cortex) and triggering the release of dopamine. The peripheral sensory effects of tobacco appear to be mediated by AChN-Rs located on trigeminal afferent fibers [5]. Functional brain imaging studies have revealed regional differences in dopamine secretion as a function of craving for nicotine and other psychoactive drugs [15].

### V-2. Cannabis and $\Delta$ 9- THC

$\Delta$  9-THC is the main alkaloid in cannabis, with bioavailability ranging from 10 to 50%, depending on smoking style, and reaches a maximum blood concentration in 10 minutes. It is a lipophilic molecule with a half-life of 96 hours, eliminated in 10 to 30 days after smoking a joint [10]. The slow release of cannabinoids reduces the extent of craving [3,16]. Cannabinoids exert their psychoactive effects by binding to CB1 receptors (CB1-R) located in the central nervous system (hippocampus, cortex, substantia nigra, cerebellum), coupled to G proteins, stimulating the endogenous cannabinoid system and altering endocannabinoid levels, as well as inhibiting the release of neurotransmitters such as gamma-aminobutyric acid. (GABA) and glutamate and/or increasing dopamine release, decreasing acetylcholine and noradrenaline. Other CB2 receptors (CB2-R), located on the viscera, notably in immune cells, are responsible for the somatic effects of cannabis [3]. Synthetic cannabinoids [17] of heterogeneous chemical structure are marketed under various names (Spice, Dream...) and consumed with tobacco or incorporated into electronic-cigarette liquid. These CB1-R and CB2-R agonists bind more strongly than THC to receptors, and their effects are very marked.

### V – 3. Neurobiological consequences of interactions between these substances.

In the brain's reward system, CB1-R endocannabinoids are located on glutamatergic and gabaergic interneurons ; their activation suppresses gabaergic inhibition and glutamatergic stimulation of GABA neurons, preventing inhibition of dopaminergic neurons [5]. Therefore,

cannabis can sensitize the brain to the rewarding effects of nicotine and promote tobacco dependence; conversely, cannabinoid antagonists (rimonabant) reduce the desire to smoke [4].

#### V – 4. Reciprocal addictive power of tobacco and cannabis.

Dependence on cannabis alone is difficult to assess. Woody et al. [18] note that tobacco is much more addictive than cannabis, with 20% to 40% of regular tobacco smokers becoming dependent, compared with 5% to 10% of cannabis users. The DSM-5 [19] defines substance use disorders in an unambiguous way, making it possible to assess the severity of withdrawal syndromes for substance use. Irrespective of the combination of individual vulnerability factors and the frequency of daily consumption, the reciprocal reinforcement of dependence on each product generally leads to higher dependence and an earlier onset of withdrawal syndrome for tobacco than for cannabis [4-6]. Use of at least one joint a week increases the risk of tobacco dependence by a factor of 8, and tobacco may be used by some patients as a substitute for cannabis [17]. Tobacco has been considered a gateway to cannabis use, and in a population of adolescent regular smokers, compared with non-smokers, the risk of becoming cannabis users in late adolescence is higher (OR=4.9) [20]. In a cross-sectional survey by Okoli et al. [21], adolescent marijuana users were 5.9 times more likely to be tobacco smokers, with a higher level of perceived sensory dependence on tobacco than non-marijuana users (reverse gateway effects ?). Genome-wide association studies (GWAS) have shown that tobacco and cannabis use is partly attributable to variants (SNPs) located on genes coding for AChN-R subunits, in particular *CHRNA3* [22], which are thought to be involved in the mechanisms contributing to the emergence of addiction (product exposure, early, associated, regular use, high doses) [6].

## **VI - Toxicity of tobacco and cannabis use.**

Most cannabis smokers smoke tobacco alternatively or in combination. A study by Meier et al. [23] has shown higher levels of exposure biomarkers (volatile organic compounds, polycyclic aromatic hydrocarbons, etc.) in tobacco and cannabis users than in cigarette smokers, for the same number of cigarettes smoked. Therefore, it is virtually impossible to dissociate the effects of tobacco from those of cannabis when the substances are co-used.

#### VI -1. Pediatric toxicity.

Passive smoking is associated with severe viral or bacterial respiratory infections, bronchiolitis and bronchial obstruction in children [24]. During pregnancy, fetal exposure to tobacco and/or cannabis has been implicated in the occurrence of impaired cognitive functioning, attention deficit hyperactivity, impulsivity, and dependence disorders in childhood or adolescence [25]. The change in the legal status of cannabis in a growing number of States has led to an increase in cannabis exposure among children in the USA and admissions to paediatric emergency units for encephalopathy, coma or respiratory depression connected with voluntary or involuntary cannabis use [26]. A study carried out in France between 2004 and 2014 [27] in paediatric emergency departments revealed that, among 235 children aged under 6 years (71% aged under 18 months), the number of annual intoxications had increased by a factor of 13 over the study period ; there was a significant link between the increase in the frequency of intoxication cases and the increase in THC concentration in cannabis resin. Among the children, 86% had neurological symptoms, 30% had cardiovascular problems, 9.2% had respiratory problems (3.5% required ventilatory assistance).

#### VI -2. Carbon monoxide poisoning.

Hookah smokers and heavy consumers of cigarettes and cannabis can inhale very large quantities of carbon monoxide, causing symptoms of CO poisoning which may require referral to emergency services with normobaric and sometimes hyperbaric oxygen therapy [28, 29].

#### VI – 4. Respiratory toxicity.

The meta-analysis by Jayes et al. [40] has shown that active smokers are at greater risk of developing COPD (RR = 4.01), asthma (RR = 1.61) and lung cancer (RR = 10.92) than non-smokers. Compared with non-smokers, they present a higher risk correlated with the level of daily and cumulative consumption of bacterial infections (pneumococcal: RR=2.97, legionella: RR=3.75), tuberculosis (RR=3.75), as well as viral infections and influenza [41], severe COVID infection and epidemic progress [42]. Impaired mucociliary clearance, macrophagic function and deficient release of pro-inflammatory proteins (IL-1, IL-6, IL12, TN $\alpha$ , IFY) would be involved [43]. The role played by smoking in the occurrence of interstitial lung disease is debated [44] ; however, its responsibility in the onset of pulmonary langerhansian histiocytosis is probable, as over 90% of patients with the disease are smokers, and cessation

of smoking can lead to reversion of pulmonary lesions [45]. Smoking is a cause of pneumothorax [46], particularly in association with cannabis use (OR=8.74).

The effect of cannabis use on the occurrence of COPD has not been fully demonstrated ; however, the cumulative effect of cannabis and tobacco smoke inhalation on COPD is found in most studies [47]. Aldington et al. [8] were able to estimate from a study of subjects classified into four groups : cannabis-only smokers, mixed smokers, tobacco-only smokers and non-smokers that, in terms of bronchial obstruction, one joint had the effect of 2.5 to 5 cigarettes. They noted a positive association between cannabis use and the occurrence of asthma after the age of 16 years [8]. Consumption of cannabis alone does not induce more extensive emphysema areas on chest CT than the combination of tobacco and cannabis [48]. Cannabis smokers may present with intrathoracic gas effusions (pneumothorax, pneumomediastinum, pneumopericardium) ; these manifestations are more frequent in cases of combined tobacco and cannabis use [49]. The results of studies on the association between cannabis use and lung cancer are discordant, the combination of tobacco and cannabis use making it difficult to establish the specific responsibility of cannabis in the occurrence of cancer [50]. Nevertheless, a study conducted in New Zealand [51] has shown that cannabis smokers who did not smoke tobacco, aged at least 35 years with a cumulative marijuana consumption equal or greater than 10.5 joint-years, compared with subjects who had never smoked cannabis, had an excess risk of lung cancer (OR= 5.7; 95 % CI :1.5-21.6). Inhalation of cannabis smoke may cause fungal [52], bacterial [53] and eosinophilic [54] pneumonitis. Cases of diffuse alveolar haemorrhage have been described in cannabis smokers [55]. An epidemic of severe toxic pneumonitis following the use of electronic cigarettes (e-cig.) containing THC mixed with vitamin E acetate has been described [56].

#### IV - 5- Psychiatric toxicity.

##### - Tobacco and psychiatric disorders.

Tobacco consumption is strongly associated with various psychiatric disorders ; this may explain the higher prevalence of smoking in this population and the difficulty these people have in quitting. The mechanisms linking mental health problems and smoking are diverse (genetic and environmental factors, the action of nicotine on the brain, nicotinic receptor abnormalities, redox phenomena, emotional regulation disorders, etc.) [57].

Schizophrenic patients smoke in 80% of cases, and have a strong dependence on tobacco [58]. The co-occurrence of attention deficit hyperactivity disorder (ADHD) and nicotine



dependence is common ; people with ADHD are more likely to start smoking, become dependent on nicotine and have difficulty quitting than those without ADHD [59]. The prevalence of smoking among people with an anxiety disorder (social phobia, generalized anxiety disorder, post-traumatic stress disorder) or alcohol misuse [57,60] is significantly higher compared to those without disorders. It is estimated that 30% of patients suffering from depression in the USA smoke daily and smokers in smoking cessation clinic have a higher lifetime prevalence of major depression [61], The same would be true for 30% to 60% of people with bipolar disorder, the latter frequently use other substances and present a high suicidal behavior [62]. A meta-analysis of fifteen prospective cohort studies showed that current smokers, compared with non-smokers, have an increased risk of suicide (RR= 1.81 ; 95% CI : 1.50 - 2.19), with a 27% increase in risk for every additional 10 cigarettes smoked [63].

- Cannabis and psychiatric disorders.

The psychological effects of cannabis differ according to the quantity consumed, the level of cannabinoids delivered, the mode of consumption, the subject's tolerance, the underlying psychological state, whether it has been taken alone or combined with tobacco or other drug [3,6].

. Acute psychological effects.

Isolated use of cannabis may be the cause of psychological disorders [64] : changes in perception of time and distance, sensory disturbances (exacerbation of perception of sound and vision), reduction in vigilance, even to the point of falling asleep, impaired intellectual, motor and cognitive performance, mood and dissociative disorders with euphoria, aggressiveness, depersonalization, disinhibition or indifference to others, acute anxiety attacks or panic attacks, disturbances in immediate memory which may persist for several days or weeks after stopping consumption [65] and may require recourse to emergency care [66].

. Chronic psychological effects.

Regular and heavy cannabis use can lead to various psychological disorders. The amotivational syndrome is characterized by a loss of pleasure; the cannabis user, focused on the cannabis use, ignores the environment and loses interest in social relationships [64]. A meta-analysis [67] brought together 35 longitudinal and prospective studies to assess the risk linking cannabis use among adolescents under 18 years old to the development of anxiety disorders, depression or suicidal tendencies between the ages of 18 and 32. Cannabis use in

young people, compared with no use, was not significantly associated with the risk of developing anxiety, but with that of depression (OR = 1.37 ; 95% CI, 1.16-1.62) and suicide (OR = 3.46 ; 95% CI, 1.53-7.84). Psychotic-type thought disorganization syndromes can occur in subjects with no psychiatric history [68] and cannabis use appears to participate with other risk factors in the occurrence of schizophrenia [69] ; it is estimated that one in four schizophrenic patients has consumed cannabis, which would be an unfavourable factor in the course of the illness [70,71].

Alcohol and cannabis alter driving performance and drivers behavior [72]. A study carried out in Ontario (Canada) [73] between January 2010 and December 2021, before and after the legalization and retail marketing of cannabis, examined changes in the number of cannabis-related road traffic accidents resulting in emergency department visits among 16-year-olds. Visits for alcohol-related road traffic accidents increased by 9.4% ; in contrast, those related to cannabis use increased by 94% (RRa = 1.94 ; 95% CI : 1.37-2.75), which could indicate that the legalization of cannabis and cannabis-derived products would lead to an increase in road traffic accidents.

#### VI - 6. Other tobacco and cannabis toxicities.

##### - Stomatological toxicity.

Tobacco and cannabis smokers suffer more frequently from stomatological conditions than non-smokers ; THC-induced hypo-salivation increases the risk of dental caries, periodontal disease and fungal infections [74].

##### - Digestive toxicity.

Tobacco can cause esophagitis, gastritis, cancer of the stomach, pancreas or biliary tract, and promote the development of hyperplastic polyps of the distal colon or rectum and the early onset of colorectal cancer ; it contributes to the development of cirrhosis or liver cancer in excessive drinkers or those with B or C viral infections [75]. Cigarette smoking may be a cause of worsening Crohn's disease ; on the other hand, smoking cessation improves the course of this chronic inflammatory bowel disease [76]. Chronic cannabis use can cause abdominal pain and cannabich hyperhaemesis whose mechanism is poorly understood ; it combines nausea, vomiting, abdominal pain, asthenia, polydipsia, weight loss, hypothermia and can lead to hospitalization ; repeated hot showers or baths can improve the symptoms but recovery after cessation of consumption often occurs over several weeks [77].

##### - Endocrine toxicity.

Tobacco and cannabis are endocrine disruptors. Smoking is a risk factor for basedowian ophthalmopathy (RR=7.7) [75]. Both modify testosterone secretion and have an anti-oestrogenic action ; they reduce fertility and libido in men and women [78,79] ; they cause erectile dysfunction in men [80,81] and a risk of lactation difficulties and premature menopause in women [75].

## **VII - Is there a benefit to tobacco and/or cannabis use ?**

- Tobacco and alkaloids.

Promoting the benefits of smoking is the responsibility of the tobacco companies [82]. Snus is a product of the tobacco industry ; its use has contributed to the reduction in the prevalence of tobacco smoking in Scandinavia but it is not free from toxicity (cardiovascular, diabetes, pancreatic cancer) [83]. Research regarding the benefits of tobacco alkaloids on cognitive disorders [84] and Parkinson's disease has been carried out [85]. Nicotine is cause of various biological effects such as neoangiogenesis, cell proliferation and could affects neural and non-neural cells [86].

- Cannabis and cannabinoids.

The use of cannabis and cannabinoids for therapeutic purposes is growing ; the results of studies evaluating their indications and effects are heterogeneous [87]. A study including systematic reviews and meta-analyses [88] assessed the efficacy, safety and associated level of evidence, of cannabis use, cannabinoids and cannabis-based medicines. Cannabidiol improved seizure episodes (OR = 0.59 ; 95% CI : 0.38-0.92) with a high grade of evidence, at the cost of increased gastrointestinal adverse events (OR = 2.25; 95% CI :1.33-3.81) and drowsiness. For chronic pain, cannabis-based medicines or cannabinoids reduced pain by 40% (OR = 0.59 ; 95 CI : 0.37-0.93), notably in cases of spasticity in multiple sclerosis, with a high grade of evidence but increased the risk of dizziness, dry mouth, nausea and drowsiness. In inflammatory bowel disease, cannabinoids improved patients' quality of life (OR = 0.34 ; 95 % CI : 0.22-0.53) with high grade of evidence. Cannabidiol had no effect on sleep disturbance apart from cancer, but with gastrointestinal adverse effects. In the general population, cannabis worsened total psychiatric symptoms (OR = 7.49 ; 95 % CI :5.31-10.42) and positive psychotic symptoms (OR = 5.21 ; 95% CI : 3.36-8.01).

## **VIII - Smoking and cannabis co-use cessation management.**

Simultaneous cessation of tobacco and cannabis, which share the same route of administration, neurobiological interactivities and similar rituals, is a coherent proposal. However, a systematic review [89] and clinical practice have shown that users of cannabis and tobacco experienced greater difficulty quitting cannabis than cannabis users alone and preferred stopping tobacco before cannabis. Therefore, the respect for the patient's preferences is essential [4].

VIII -1. Inform patient about drug use, offer helping cessation.

The harmful effects and dependence linked to the use of tobacco and cannabis must be reminded to each user as well as the benefits of abstinence ; an offer to help quitting is made. The level of nicotine dependence can be assessed using the « Fagerström Test for Nicotine Dependence » (FTND) [90] and the difficulties caused by cannabis using the « Cannabis Abuse Screening Test » (CAST) [91]. Identification of psychiatric history, current anxiety or depressive disorders by the clinic and taking advantage of the « Hospital Anxiety and Depression scale » (HAD scale) [92] is made, as well as, of psychoactive drugs consumption, social precariousness and legal problems. Patients with multiple difficulties require specialized care [4].

VIII -2. Helping stopping tobacco and cannabis.

- Psychotherapeutic aspects.

Psychotherapeutic treatment can take a variety of forms (behavioral, cognitive, psychodynamic and family therapies), increasing the patient's motivation to quit and strengthening adherence to treatment, facilitating relapse prevention after cessation [4]. Remote support methods (internet, telephone) provide additional help [93].

- Pharmacological aspects.

Smoking cessation medications (nicotine replacement therapy, varenicline, bupropion, nortriptyline, etc.) and e-cig. are effective in smoking cessation [94]. The benefit of pharmacotherapies in cannabis cessation is uncertain ; some molecules (serotonin reuptake inhibitors, buspirone, atomoxetine, gabapentin, N-acetylcysteine) could limit withdrawal syndrome or craving [95]. Varenicline is at an experimental stage in this indication [96], while cannabinoid agonists (dronabinol) appear promising. The reference pharmacological treatment remains nicotine replacement therapy (NRT) [97], a study involving 148 patients

aged 17 to 40 years old showed that the use of NRT improved adherence to therapeutic follow-up [98]. The role of e-cig. to help people stopping cannabis is poorly understood ; severe toxic pneumonia following its use containing THC have been described [56]. Recently, it has been shown that a signaling-specific inhibitor of the cannabinoid receptor 1 (CB1-SSi) [98], electively inhibits a subset of intracellular effects resulting from  $\Delta^9$ -tetrahydrocannabinol (THC) binding without modifying behavior in mice and non-human primates. A phase 2a, placebo-controlled crossover trial was carried out in volunteers with cannabis use disorder (CUD) randomized into two cohorts. In the treated group the positive subjective effects of cannabis and cannabis self-administration were reduced ( $P < 0.05$ ) ; tolerance was good. These data suggest that it is a safe and potentially effective treatment for CUD.

- Changing behavior and habitus.

Psychoactive drugs use reflects an inappropriate strategy of adaptation to the environment. Consumption often begins at an early age, the repeated drug use leads to dependence. After stopping use, abstinence is more stable when it is part of a global change of habitus.

## **IX- Conclusion.**

Tobacco and cannabis are among the most widely used psychoactive drug in the world. Cannabis users often consume tobacco at the same time, reinforcing dependence on each substance. The smoke produced by their combustion is highly toxic, and stopping tobacco and cannabis co-use is more difficult than that of either substance. The increase in the active ingredient content of cannabis, the availability of synthetic cannabinoids and the legalization of their recreational use raise questions about the risk of increased combined use of tobacco and cannabis and how to overcome this risk.

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