

Acute and Long-Term Effects of Cannabis Use: A Review

Laurent Karila^{1*}, Perrine Roux², Benjamin Rolland³, Amine Benyamina⁴, Michel Reynaud⁴, Henri-Jean Aubin⁴ and Christophe Lançon⁵

¹Addiction Research and Treatment Center, Paul Brousse Hospital, Paris Sud-11 University, AP-HP, INSERM-CEA U1000, Villejuif, France; ²INSERM U912 (SESSTIM), Université Aix Marseille, IRD, UMR-S912, ORS PACA, Observatoire Régional de la Santé Provence Alpes Côte d'Azur, Marseille, France; ³Department of Addiction Medicine, CHU Lille; EA1046, Univ Lille Nord de France, Lille, France; ⁴Addiction Research and Treatment Center, Paul Brousse Hospital, Paris Sud-11 University, AP-HP, Villejuif, France; ⁵Psychiatry and Addictology Department, AP-HM, Marseille, France

Abstract: Cannabis remains the most commonly used and trafficked illicit drug in the world. Its use is largely concentrated among young people (15- to 34-year-olds). There is a variety of cannabis use patterns, ranging from experimental use to dependent use. Men are more likely than women to report both early initiation and frequent use of cannabis. Due to the high prevalence of cannabis use, the impact of cannabis on public health may be significant. A range of acute and chronic health problems associated with cannabis use has been identified.

Cannabis can frequently have negative effects in its users, which may be amplified by certain demographic and/or psychosocial factors. Acute adverse effects include hyperemesis syndrome, impaired coordination and performance, anxiety, suicidal ideations/tendencies, and psychotic symptoms. Acute cannabis consumption is also associated with an increased risk of motor vehicle crashes, especially fatal collisions. Evidence indicates that frequent and prolonged use of cannabis can be detrimental to both mental and physical health. Chronic effects of cannabis use include mood disorders, exacerbation of psychotic disorders in vulnerable people, cannabis use disorders, withdrawal syndrome, neurocognitive impairments, cardiovascular and respiratory and other diseases.

Keywords: Cannabis, marijuana, cannabinoids, dependence, addiction, THC, acute effects, long-term effects, and cannabis use disorders.

I. INTRODUCTION

Cannabis is the most frequently used illegal substance in the world [1] [2]. Its use increased during the 1990s and the early part of the first decade of the twenty-first century in most European countries. Cannabis has been used at least once by approximately 80.5 million Europeans (15-64 years of age). The lifetime prevalence estimates of cannabis use are in the range of 10-30% of the adult population [2]. In the United States, more than 97.5 million Americans above age 12 have used this drug. In 2010, the Substance Abuse and Mental Health Services Administration (SAMHSA) estimated a lifetime prevalence of cannabis use of 52.1% [3]. Cannabis is widely used among young Europeans (15-34 years of age). Data have shown that 12.4% of this population has used cannabis in the last year and 6.6% have used it in the last month. The prevalence is higher among 15- to 24-year-olds. Data from Australia, Canada, and the United States on cannabis use among young adults in the previous year and the previous month are all above the European averages [2].

Estimates from two nationwide surveys, the Monitoring the Future Surveys and the National Survey on Drug Use and Health, have indicated that the prevalence of cannabis use among adolescents is exceeded only by the prevalences of alcohol and tobacco use [4, 5]. The European School Survey Project on Alcohol and other Drugs (ESPAD) provides regular data on levels of drug use, trends, and attitudes among 15- to 16-year-old students across Europe [6]. The highest levels of lifetime use of cannabis among students were reported by the Czech Republic (42%) and France (39%). The reported use of cannabis in the previous month ranged from 24% in France to 2% in Romania and Norway. Boys are more likely than girls to report both early initiation (initiating cannabis

use at age 13 years or younger) and frequent use of cannabis [6]. Early initiation of cannabis use is associated with the subsequent development of more intensive and problematic drug consumption [7].

Cannabis is cultivated in 172 countries [8]. Between 13300 and 66100 tons of herbal cannabis and between 2200 and 9900 tons of cannabis resin were produced in 2008. An estimated 6251 tons of herbal cannabis and 1136 tons of cannabis resin were seized worldwide in 2010 [2]. The cannabis plant contains more than 421 chemicals, 61 of which are cannabinoids [9]. More than 2000 compounds are produced by pyrolysis during the smoking of cannabis [10]. Different classes of chemicals, including nitrogenous compounds, amino acids, hydrocarbons, sugar, terpenes, and simple fatty acids, together contribute to the unique pharmacological and toxicological properties of cannabis [11]. Delta-9-tetrahydrocannabinol (Δ -9-THC) and Cannabidiol [CBD], the two main ingredients of the cannabis sativa plant, have distinct symptomatic and behavioral effects [11]. These compounds may have opposite effects on regional brain function [12] [13]. Δ -9-THC is the primary psychoactive constituent of the cannabis sativa plant and is believed to be primarily responsible for its resulting cognitive effects, psychotic symptoms, and anxiety, as well as the addictive potential of smoked cannabis [14] [15]. The content of Δ -9-THC varies widely between and within countries, different cannabis products, and genetic varieties. In 2010, the reported mean Δ -9-THC content of cannabis ranged from 1-12% for cannabis resin and from 1-16.5% for herbal cannabis [2]. CBD can prevent the acute psychotic symptoms induced by Delta-9-THC [16] and has anxiolytic properties [15].

Endocannabinoids act as synaptic circuit breakers and regulate multiple physiological and pathological conditions (e.g., regulation of food intake, analgesia, cancer, and addiction) [17]. They share the same molecular target as Δ -9-THC [14]. Cannabinoid receptors are present at supraspinal, spinal, and peripheral levels. Cannabinoids suppress behavioral responses to noxious stimulation and

*Address correspondence to this author at the Addiction Research and Treatment Center, Paul Brousse Hospital, 12 avenue Paul Vaillant Couturier, Villejuif 94800, France; Tel: + 33 145 596 513; Fax: +33 145 593 862; E-mail: Laurent.karila@pbr.aphp.fr

suppress nociceptive processing through the activation of cannabinoid CB(1) and CB(2) receptor subtypes. CB1 receptors are located primarily in the pre-synaptic neurons of the central nervous system and are responsible for the acute psychological and cardiovascular effects of cannabis. CB2 receptors are located largely in the periphery and modulate immune function and the inflammatory response [13] [18] [19] [20].

Cannabis use, particularly among adolescents [21] [22] [23], is recognized as a significant public health problem, with evidence indicating that its use produces significant neurobiological, psychosocial, and health consequences [11] [24] [25]. This review aims to provide clinicians with a detailed description of the clinical aspects and the acute and long-term effects of cannabis use disorders. Literature searches were conducted for the period from January 1983-May 2013 using PubMed, EMBASE, PsycInfo, and Google Scholar. We used the following keywords, either alone or in combination: cannabis, marijuana, dependence, addiction, THC, acute effects, long-term effects, and cannabis use disorders.

II. ACUTE EFFECTS OF CANNABIS USE

Cannabis is generally smoked in a joint (the size of a cigarette) or in a water pipe. Tobacco may be added to assist burning. Cannabis can also be eaten (very rare, delayed psychoactive effects), but smoking it is the easiest way to achieve the desired psychoactive effects [1]. The concentration of Δ^9 -THC in the different presentations of cannabis (marijuana, hashish, skunk, bong, and oil) is proportional to the intensity of its toxic effects [26]. Effects may develop over a period of approximately 2 hours after the use of the drug, corresponding to the plasmatic peak of Δ^9 -THC [14].

II.1. Psychopharmacological Effects

Acute cannabis use is associated with subjective symptoms of euphoria, continuous laughter and talkativeness, sedation, lethargy, intensification of ordinary sensory experiences, perceptual distortion, and social withdrawal [27]. Physical signs of conjunctival hyperemia, increased appetite, food consumption, dry mouth, increased blood pressure and tachycardia, and acute bronchodilator effects have been reported. Heart rate increases by 20-50% within a few minutes to a quarter of an hour have also been reported; this effect lasts up to 3 hours [1].

II.2. Psychiatric Effects

First-time use, the dose of cannabis, personality traits, and pre-existing vulnerability are among the main factors related to acute psychiatric disorders derived from cannabis use [28].

In healthy volunteers, relative to placebo, the administration of THC was associated with anxiety, dysphoria, and positive psychotic symptoms [29]. Anxiety and panic reactions are common reasons for the discontinuation of cannabis use [28].

In high doses, cannabis can produce a toxic psychosis in people without a history of mental illness. Cannabis use can lead to many short-term symptoms, such as depersonalization, derealization, dream-like euphoria, disorientation, delusions, hallucinations, paranoid ideas, impaired memory, reduced attention spans, disordered thinking with a labile effect, psychomotor agitation, irrational panic, and emotional lability [28]. These symptoms may resolve within a week, followed by full recovery [26].

Heavy cannabis use may lead to an acute functional psychosis, similar to an acute schizophreniform disorder and lacking the organic features of a toxic psychosis. Cannabis-induced psychotic episodes may persist, in some cases, for a substantial period of time after acute intoxication [28] [30]. Cannabis use significantly increases the risk of developing psychotic illnesses in a dose-dependent manner in vulnerable individuals [31].

II.3. Cognitive Disorders

Cannabis users exhibit deficits in prospective memory and executive functions, which persist beyond acute intoxication [32]. Impaired short-term memory and attention, performance of complex mental processes, judgment, motor skills, and reaction time have been reported [1] [33] [34] [35, 36].

II.4. Driving Under the Influence of Cannabis

Cannabis impairs individuals' performance on the cognitive and motor tasks necessary for safe driving, which, according to studies of injured and fatally injured drivers, increases the risk of collision [37]. Rates of driving under the influence of cannabis have surpassed rates of drinking in young people. Acute cannabis use nearly doubles the risk of a collision resulting in serious injury or death. The influence of cannabis use on the risk of minor collisions remains unclear [38, 39].

III. LONG-TERM EFFECTS OF CANNABIS USE

III.1. Cannabis Use Disorders (CUDs)

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) replaced the DSM-4 TR in May 2013. The changes in diagnostic criteria have important implications for the clinical care of patients with substance use disorders [40]. The word "dependence" is now limited to physiological dependence, which is a normal response to repeated doses of many medications, including beta-blockers, antidepressants, opioids, anti-anxiety agents, and other drugs. The presence of tolerance and withdrawal symptoms is not considered part of the diagnosis of substance use disorder when they occur in the context of appropriate medical treatment with prescribed medications [40].

Cannabis addiction occurs with heavy chronic use in individuals who report problems controlling their use and who continue to use the drug despite experiencing adverse personal consequences [7, 41]. Furthermore, the use of tobacco with cannabis contributes to the development of cannabis dependence symptoms [42].

The DSM-5 work group has recommended that cannabis abuse/dependence be subsumed into a new disorder, namely cannabis use disorder (www.dsm5.org, accessed on March 15 2012). The clinical criteria, published in the DSM-5, are as follows in Table 1 [43]:

Table 1. Clinical criteria of cannabis use disorders

A. A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:
1. Cannabis is often taken in larger amounts or over a longer period than was intended
2. There is a persistent desire or unsuccessful efforts to cut down or control cannabis use failure to fulfill major role obligations
3. A great deal of time is spent in activities necessary to obtain cannabis, use cannabis or recover from its effects
4. Craving or a strong desire or urge to use cannabis.
5. Recurrent cannabis use resulting in a failure to fulfill major role obligations at work, school or home
6. Continued cannabis use despite having persistent social or interpersonal problems caused or exacerbated by the effects of cannabis
7. Important social, occupational, or recreational activities are given up or reduced because of cannabis use
8. Recurrent cannabis use in situations in which it is physically hazard-

ous
9. Cannabis use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis
10. Tolerance
11. Withdrawal
<i>Severity specifiers:</i> Mild: 2-3 criteria positive; Moderate : 4-5 criteria positive; Severe: 6 or more criteria positive

III.2. Cannabis Withdrawal Syndrome (CWS)

Cannabis withdrawal occurs in frequent users who quit without seeking treatment [44]. The diagnostic criteria for withdrawal are irritability, anger, or aggression; nervousness or anxiety; sleep difficulty (insomnia); decreased appetite or weight loss; restlessness; depressed mood; and physical symptoms causing significant discomfort, such as stomach pain, shakiness/tremors, sweating, fever, chills, and headache [45]. Cannabis withdrawal is clinically significant because it is associated with elevated functional impairment of normal daily activities [46]. The onset and time course of these symptoms appear similar to those of other substance withdrawal syndromes [47]. The more severe the withdrawal is, the more severe the functional impairment is. Higher levels of cannabis addiction predict greater functional impairment from cannabis withdrawal [48]. Cannabis withdrawal has been included in the DSM-5 [40]. The proposed diagnostic criteria for CWS had good concurrent and predictive validity in a sample of 384 adult, non-treatment-seeking, lifetime cannabis smokers. However, some aspects of the criteria, such as items in the symptom list, the number of required symptoms, and the handling of physical symptoms, require further studies [46].

III.3. Amotivational Syndrome

According to Tennant and Groesbeck in 1972, heavy chronic cannabis users may experience an amotivational syndrome, described as a reduced motivation and capacity for the usual activities required for everyday life, loss of energy and drive to work, and personality deterioration. The validity of this diagnosis remains uncertain [1]. It may reflect a change in cognitive style emerging as a result of cannabis's ability to facilitate a unique attentional state [49], or it may be nothing more than ongoing intoxication in frequent cannabis users [50].

III.4. Cannabis-induced Depersonalization

There is an association between cannabis use and depersonalization disorder [51]. Depersonalization disorder is an alteration in the subjective experience of reality. It is characterized by persistent or recurrent experiences of feeling detached from, and as if one is an outside observer of, one's mental processes or body; alterations in body image; feeling like an automaton; time disturbances; feeling as if one's body or environment is dreamlike; and visual distortions [52]. During the depersonalization experience, reality testing remains intact. The depersonalization experience causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. There are a few case reports in which cannabis use has led to depersonalization [53] [54]; however, the mechanism of cannabis-induced depersonalization remains unclear. The two main hypotheses for this mechanism are residual neurotoxicity of cannabis or related effects due to the long elimination half-life of cannabinoid metabolites.

III.5. Cannabis and other Psychiatric Disorders

Cannabis use is associated with a wide range of psychiatric disorders [55] [56] [57]. Importantly, the co-occurrence of these

disorders appears to result in greater impairment and distress than that caused by either disorder alone [57].

Individuals with externalizing behaviors during childhood and adolescence have a significantly increased risk of a CUD in young adulthood [58]. In longitudinal analyses, non-cannabis substance use disorders and mood and anxiety disorders were associated with an increased risk of cannabis use and CUDs [59].

There is a clear relationship between cannabis use and psychosis [60] [61] [62]. There are common neurobiological and neuro-anatomical changes, as well as common cognitive dysfunction, between cannabis users and patients with schizophrenia [63]. Cannabis use is a risk factor for the development of incident psychotic symptoms. Continued cannabis use may increase the risk of developing a psychotic disorder by affecting the persistence of symptoms [64, 65]. The results of a meta-analysis provide evidence of a relationship between cannabis use and earlier onset of psychotic illness and support the hypothesis that cannabis use plays a causal role in the development of psychosis in some patients [66]. In another meta-analysis, one in four schizophrenic patients had a diagnosis of CUD. This diagnosis was especially common in younger and first-episode patient samples, as well as in samples with a high proportion of males [67].

Various hypotheses have been proposed for the association between CUD and psychosis. There is limited evidence of psychosis occurring exclusively with cannabis use, but there is strong evidence that cannabis use may precipitate schizophrenia or exacerbate its symptoms [68] [69]. Cannabis use also exacerbates the symptoms of psychosis [24].

Lifetime use of cannabis increases the risk of depression [70] and leads to greater suicidal ideation [71]. Additionally, cannabis use is a relevant risk factor associated with both suicidal attempts and behaviors in psychotic and non-psychotic samples [72].

There is a strong association between cannabis use and concurrent anxiety disorders [73]. Social anxiety disorder may be a risk factor for cannabis dependence [74]. Buckner *et al.* reported that the odds of cannabis dependence among individuals with social anxiety disorder were almost five times higher than those among individuals without social anxiety disorder [75].

Cannabis use and CUD were particularly associated with bipolar disorder [76], other substance use disorders, and specific (anti-social, dependent, and histrionic) personality disorders [57]. Co-occurring CUD is associated with significant co-morbidities and a more severe course of illness among individuals with bipolar disorder [57].

III.6. Cognitive Disorders

Despite the large number of related studies, there are conflicting opinions regarding the association between cannabis use and cognitive disorders [77] [78-80] [81]. Cognitive deficits seem to be linked with the early onset of cannabis use [82]. There are associations between chronic cannabis use and dysfunction across a range of functions, including aspects of memory, attention, and executive functions [35, 36] [83] [84] [85] [86]. A recent study showed cognitive deficits in young cannabis users (18-29 years old) even in the absence of axis-I disorders and a history of other illicit drug use [87]. These neurocognitive deficits persisted for a few days following the cessation of cannabis intake [78], although other investigators have suggested that these deficits may persist for a month or longer [81] [88]. Cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset cannabis users [82]. The results of two meta-analyses demonstrated that any negative residual effects on neurocognitive performance attributable to either cannabis residue or withdrawal symptoms are limited to the first 25 days of abstinence; there is a limited evidence for long-term negative effects of cannabis use [89]. Further studies are needed.

III.7. Somatic Disorders

III.7.1. Oral Consequences

Chronic cannabis use may result in gingival enlargement, with clinical characteristics similar to those of phenytoin-induced enlargement. Uvulitis and nicotinic stomatitis appear to be the two most common of the several oral manifestations of cannabis use [90].

III.7.2. Digestive Consequences

Daily cannabis smoking has been identified as a novel independent predictor of steatosis severity in chronic hepatitis C. Specifically, one study strongly argued for a steatogenic role of the cannabinoid system [90]. Daily cannabis smoking is also significantly associated with fibrosis progression in chronic hepatitis C [91].

Coinciding with the increasing rates of cannabis abuse is the recognition of a new clinical condition known as Cannabinoid Hyperemesis Syndrome [CHS] [92]. This syndrome is characterized by chronic cannabis use, cyclic episodes of nausea and vomiting, and the learned behavior of hot bathing [93]. Patients with CHS usually remain misdiagnosed for a long time period [94].

III.7.3. Respiratory Consequences

Smoking cannabis may lead to respiratory symptoms (cough, increased sputum production, and wheezing) [95]. It is also associated with dyspnea, pharyngitis, hoarsening of the voice [95], and the exacerbation of asthma [96]. Both cannabis and tobacco smoking cause significant bronchial damage. There is an increased risk of developing airflow obstruction in smokers of both cannabis and tobacco compared with nonsmokers, suggesting a synergistic effect of tobacco smoking and cannabis in the development of chronic obstructive pulmonary disease (COPD) [97]. However, tobacco or cannabis alone may be involved. Further studies are needed. Cannabis causes central airway resistance to airflow associated with prominent symptoms of bronchitis and hyperinflation [98] [99]. The existing data are unable to confirm a definite link between cannabis and bullous emphysema [95]. Cannabis contains many carcinogenic substances, but it remains unclear whether it is a cause of lung cancer [100] [101, 102]. Therefore, further studies are needed.

III.7.4. Cardiovascular Consequences

Cannabis has been linked, in a dose-dependent manner, to elevated rates of myocardial infarction and cardiac arrhythmias [70]. The mechanisms of action on the cardiovascular system are complex, and different actions exist [103]. The cannabinoid system opposes the autonomic nervous system, causing paradoxical vasoconstriction, a decrease in cardiac output and hypoxia and an increase in carboxyhemoglobin, an increased risk of infarction in coronary patients, an arrhythmogenic effect, and orthostatic hypotension [104]. A causal association between cannabis exposure and ischemic stroke was suggested by a case series [105]. Cannabis is one of the most frequent causes of arteriopathy in young adults. Δ -9-THC seems to have a direct toxic effect on blood vessels. Cannabis seems to be a promoting factor for the arteritis disease process, perhaps in synergy with tobacco, although apparently it is not the only triggering factor. Although the main etiology of arteritis in young adults is atherosclerosis, adverse effects of cannabis account for 10% of patients who smoke less tobacco and have more distal disease and whose upper limbs are more often affected [106].

III.7.5. Cutaneous and Mucous Consequences

Conjunctivitis is the most frequent adverse effect due to the congestion of blood vessels in the conjunctiva. Cannabis can cause a very specific reaction of the uvula as well as of the postero-superior part of the palate. Acute angioedema, most likely due to toxic mechanisms, has been reported. Cases of contact urticaria, generalized pruritus, and even excoriated prurigo and type I allergy (asthma and even anaphylaxis) have been reported [107].

III.7.6. Metabolic Consequences

In a cross-sectional, case-control study, chronic cannabis use was associated with visceral adiposity and adipose tissue insulin resistance, but it was not associated with hepatic steatosis, insulin insensitivity, impaired pancreatic β -cell function, or glucose intolerance [108]. Chronic cannabis use had no relevant influence on thyroid function (TSH, total T3, and free T4) in humans [109].

III.7.7. Gynecologic and Obstetrical Complications

Chronic cannabis use impairs human reproductive potential by disrupting the menstrual cycle, suppressing oogenesis, and impairing embryo implantation and development in women and by increasing ejaculation problems, reducing sperm count and motility, and generating a loss of libido and impotence in men [110].

Cannabis use during pregnancy is associated with an increased risk of adverse birth outcomes [111]. Prenatal cannabis exposure influences brain development and may have long-lasting effects on cognitive functions [112]. Cannabis use during pregnancy is related to diverse neurobehavioral and cognitive outcomes, including symptoms of inattention, impulsivity, deficits in learning and memory, and deficiencies in aspects of executive functions [113]. It seems difficult to identify complications, such as lower birth weight, that are attributable only to cannabis as opposed to the multiple perinatal complications associated with tobacco smoking. Prenatal cannabis exposure is associated with fetal growth reduction [114, 115], and meconium testing primarily identifies prenatal cannabis exposure occurring in the third trimester of gestation [115].

III.7.8. Cancer

Cannabis use significantly increased the risk of nasopharyngeal carcinoma independently of cigarette smoking in western North Africa, suggesting dissimilar carcinogenic mechanisms between cannabis and tobacco [116]. It may be a risk factor for lung cancer [117]. However, tobacco smoking or other potential confounders may explain part of the increased risk [118] [119]. In a case-control study, cannabis use did not increase the risk of head and neck cancer; however, because of the limited power and duration of cannabis use studied, a small or longer term effect cannot be excluded [120].

III.7.9. Mortality

There is insufficient evidence, particularly because of the small number of studies, to assess whether the all-cause mortality rate is elevated among cannabis users in the general population. Case-control studies suggest that some adverse health outcomes may be elevated among heavy cannabis users (e.g., fatal motor vehicle accidents and possibly respiratory cancers). The evidence remains unclear as to whether regular cannabis use increases the risk of suicide [121].

IV. CONCLUSION

Cannabis is widely used among young adults. Due to the high prevalence of its use, the impact of cannabis on public health may be significant. A range of acute and chronic health problems associated with cannabis use has been identified. First-time use, the dose of cannabis, personality traits, and pre-existing vulnerability are among the main factors related to acute psychiatric disorders derived from cannabis use. Its use significantly increases the risk of developing psychotic illnesses in a dose-dependent manner in vulnerable individuals. Acute cannabis use nearly doubles the risk of a collision resulting in serious injury or death. Evidence indicates that frequent and prolonged use of cannabis can be detrimental to both mental and physical health. Chronic effects of cannabis use include mood disorders, exacerbation of psychotic disorders in vulnerable people, neurocognitive impairments and somatic disorders. Cannabis addiction occurs with heavy chronic use in individuals who report problems controlling their use and who continue to use the

drug despite experiencing adverse personal consequences. The DSM-5 work group has recommended that cannabis abuse/dependence be subsumed into a new disorder, namely cannabis use disorder. Cannabis withdrawal has also been included in the DSM-5. Coinciding with the increasing rates of cannabis abuse is the recognition of a new clinical condition known as Cannabinoid Hyperemesis Syndrome. Smoking cannabis may lead to acute and chronic respiratory diseases. Cannabis has been linked, in a dose-dependent manner, to elevated rates of myocardial infarction, cardiac arrhythmias and arteriopathy. Cannabis contains many carcinogenic substances, but it remains unclear whether it is a cause of cancer. Tobacco smoking or other potential confounders may explain part of the increased risk. Further studies are needed.

Health advice for cannabis users have to be given by medical practitioners about the most probable acute and chronic effects of cannabis use.

CONFLICT OF INTEREST STATEMENT

Dr. Laurent Karila has received consulting fees from Sanofi Aventis, BMS Otsuka, Lundbeck, Gilead, Shering Plough, Euthérapie, Merck/Serono, Astra Zeneca, Bouchara Recordati, and Reckitt Bentsick Pharmaceuticals.

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