Informative document on the effects and uses of cannabis



Report presented by the Fédération Médicale Étudiante du Québec

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Table of Contents

Presentation by FMEQ and IFMSA-Québec	1
Introduction	2
Effects on health	Error! Bookmark not defined.
History and biochemistry	Error! Bookmark not defined.
Effets on mental health	Error! Bookmark not defined.
Cognitive impairment	Error! Bookmark not defined.
Psychotic disorders	Error! Bookmark not defined.
Suicidal risk	Error! Bookmark not defined.
Bipolar disorders, anxiety, depression	
Cannabis use disorder	Error! Bookmark not defined.
What is cannabis addiction?	7
Use of cannabis and other drugs, a gateway effect?	Error! Bookmark not defined.
Genetics of cannabis use disorder	Error! Bookmark not defined.
Effets on physical health	Error! Bookmark not defined.
Pregnancy and cannabis	Error! Bookmark not defined.
Public health	
Medical use	Error! Bookmark not defined.
Chemotherapy-induced nausea and vomiting (CINV)	
Neuropathic pain	
Contraindications	Error! Bookmark not defined.
Acute pain	Error! Bookmark not defined.
Patient care	
Intoxicated patients	
Definition of intoxication	
Signs and symptoms of acute cannabis intoxiation	
Diagnosis of acute cannabis intoxication	
Dose of severe or lethal intoxication	Error! Bookmark not defined.
Management of acute intoxication in adolescents and adults	Error! Bookmark not defined.
Management of acute intoxication in children	
Dependence and withdrawal	Error! Bookmark not defined.
Vulnerable populations	
Conclusion	
Appendix I	24
Bibliography	



Presentation by FMEQ and IFMSA-Québec

The *Fédération médicale étudiante du Québec* (FMEQ) was founded in 1974 by the four medical student associations of Quebec : AGÉÉMUS of University of Sherbrooke, MSS of McGill University, RÉMUL of Laval University, and AEEMUM of University of Montreal. The FMEQ represents the 4000 medical students of Quebec.

The FMEQ's primary goal is to represent Quebec's four medical associations with a single, united voice. It also works to defend and to promote the collective interests of Quebec medical students, notably in regards to pedagogical, political and social issues. For example, the FMEQ communicated with the *Commission de la Santé et des Services Sociaux* during the hearing of Bill 20 in spring of 2015. The FMEQ promotes communication and collaboration between its member associations and their individual members, and establishes partnerships to offer services to its members.

In 2002, IFMSA-Québec was founded as an international and community division of the FEMQ in order to promote the social implication of its members. IFMSA-Québec's mission is to raise awareness and to rally Quebec's medical students in regards to social, community and global health issues. Present in the six medical campuses in the province, IFMSA-Québec offers a wide range of training programs and health congresses; organises over 150 international exchanges annually; coordinates six peer educational projects in Quebec; positions itself in regards to current social issues; and forges external partnerships, all with the goal of training young medical professionals for whom the stethoscope is a lever for change.

In August of 2015, FMEQ partnered with IFMSA-Québec to present a document regarding Bill 44, a law seeking to reinforce the struggle against tobacco. We believe that this present document on cannabis enables us to continue promoting the health of all Canadians, of our patients, and of our society.



Introduction

Following the October 2015 elections, the Trudeau Iustin government has communicated its intent on legalizing recreational marijuana. This follows in the stead of Uruguay and certain American states, such as Colorado, Washington, and more recently, California. The government has appointed a Task Force to elaborate a series of recommendations to serve as the basis of the bill. A report was published by the committee last December.

Cannabis is the most frequently used illicit substance in Canada. Just over a third of Canadians over 15 years of age (33.7%) report having used cannabis at least once during their lives. Youth between 15 to 24 years of age represent approximately half of active users. In Quebec, 15.2% of people over 15 years old report having used cannabis during the past 12 months. Of this number, 52% use cannabis at least once per month and 11%, every day. [1].

The government's promptness in undertaking this project has raised concern among many, especially within the medical field. It is currently possible to obtain cannabis for medical use in order to treat chronic pain, as well as chemotherapy-induced nausea and vomiting. Nonetheless, this usage has not yet been recognized by Health Canada, and many physicians prescribe cannabis even in instances not indicated by the literature. Furthermore, many attribute benefits to cannabis that are unfounded.

This document does not serve to discuss the benefits or harm of cannabis, but rather to

objectively showcase its effects on health based on conclusive scientific evidence. Furthermore, there will be an enumeration of the medical uses of cannabis and its derivatives. Finally, for the goal of informing future health professionals, there will be a section regarding the care of patients with acute cannabis intoxication or cannabis use disorder, particularly among the populations deemed most vulnerable.



Effects on health

History and biochemistry

With the eminent legalization of marijuana around the globe, discussions of its effects on the body and brain are of utmost importance. The use of cannabis plant for manufacturing, clothing and other personal uses date back thousands of years [2], whereas euphoric uses of the marijuana plant can be traced to the temples of ancient Zoroaster priests[3]. The first instance of modern research on the cannabis plant is attributed to Dr. William Brooke O'Shaughnessy, who began research on the medical effects of cannabis in the 19th century. [4] His seminal work revealed the therapeutic benefits of cannabis in a wide range of disorders including cholera, rheumatic diseases, delirium tremens and infantile epilepsy [4]; [5]. More than a century later, its main psychoactive ingredient, Δ^9 -tetrahydrocannabinol (THC), was identified and synthesized by Mechoulam and Gaoni [6]. Between 1988 and 1993, two specific binding sites of THC, cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2), were discovered [7]; [8]; [9].

Since then, endogenous ligands of these receptors, such as anandamide and 2arachidonoylglycerol, and related enzymes responsible for synthesis and degradation been identified, allowing have the development of a research field dedicated to the understanding of the endogenous cannabinoid system (endocannabinoid system). CB1, a G-protein coupled receptor, is widely expressed throughout the brain and body. Meanwhile, CB2 is expressed primarily by immune cells and glial cells throughout the body and brain, and is thought to take part in a general neuronal "protective system" [10]. More specifically, CB1 is expressed in regions that are known to be involved in reward, addiction and cognitive function, including the amygdala, cingulate cortex, prefrontal cortex (PFC), ventral pallidum, caudate putamen, nucleus accumbens (NAc), ventral tegmental area (VTA) and lateral hypothalamus [11]; [12].

There exist three main species of marijuana plant, Cannabis sativa, Cannabis indica and Cannabis ruderalis. Over 110 different cannabinoid or cannabinoid-like molecules have been identified in the Cannabis Sativa plant [13], of which the best studied are THC and cannabidiol (CBD). THC exists in a nonpsychoactive form within the plant, and becomes active upon decarboxylation, a process catalyzed by heating [2]. Both THC and CBD are agonists of the eCB receptors, THC being the stronger agonist of the two[14]. Their action mimics that of the endogenous agonist, by binding to and activating the G protein coupled receptor (GPCR) function of CB1 and CB2. CBD, in its own right, has a complex relationship with the eCB system. Although CBD has low affinity for CB1, it can also act as a CB1 antagonist [14].

Cannabinoids and endocannabinoid ligand activation of CB1 and CB2 are associated with plastic changes in the brain. Phytocannabinoids (such as THC) and endocannabinoids have been associated with short- term depression (STD) [15]; [16] longterm depression (LTD) [17]; [18]; [19] and even long-term potentiation (LTP) [20]. Moreover, these effects are found at both excitatory and inhibitory synapses



throughout the brain, demonstrating the wide effect of THC and other eCB agonists. Following synthesis, endocannabinoids enter cells through diffusion or facilitated transport and are metabolized by enzymes such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) [21];[22];[23]; [24].

Effects on mental health

In recent years, a number of studies have attempted to demonstrate the effects of cannabis and its active constituents on the mental health of its users. The consequences discussed include cognitive impairment, psychotic disorders, suicide, anxiety, and short-term as well as long-term depressive symptoms.

Cognitive impairment

Although research is limited, recent studies have demonstrated significant evidence that cannabis affects cognitive function. Normally, during adolescence, the quantity of gray matter in the brain diminishes while the quantity of white matter increases, a process attributed to synaptic pruning [25];[26]. Filbey et al. have demonstrated that, among adults who use cannabis, those who began before the age of 16 present with increased cortical thickness as a function of the amount consumed, whereas those who began after the age of 16 exhibit the opposite effect. These structural changes take place in the prefrontal cortex, an area of the brain in charge of multiple cognitive and executive functions [27]. Other studies have shown similar effects [28];[29];[30], based on the

hypothesis that cannabis use in adolescence reduces synaptic pruning, thus impacting the cognitive function of its users (especially those who are young). As a result, adolescents are particularly vulnerable to the effects of cannabis on cognitive function, given the active development of their nervous system. This development, believed to be partially regulated by the endocannabinoid system of thought to the human brain, is be dysregulated bv the flooding of exocannabinoid substances due to marijuana use [31].

Cognitive impairment associated with shortterm and long-term cannabis use has been the subject of many studies. Prolonged cannabis use appears to negatively impact memory, attention, psychomotor functions, executive functions, and both short and longterm decision making. Some effects may persist despite a prolonged period of abstinence. However, it is unclear whether the consequences of cannabis use on cognitive functions are attributable to active effects, to residual effects from chronic use, or to the effects of cumulative exposition to THC throughout an individual's lifespan [32].

Some studies have shown that verbal memory (measured by the memorization of lists of words) is particularly affected by marijuana use in the time interval following consumption [33];[31]. Chronic users also present with a persistent deficit in verbal memory. It is less clear, however, whether these deficits remain after a period of abstinence, as studies are divided on this subject [33]. Furthermore, the influence of cannabis on working memory, as defined by the capacity to mentally retain elements during the execution of a complex task, remains uncertain. A few studies show no



impact, whereas others demonstrate dosedependent effects which appear to reverse after a few weeks of abstinence [33].

Cannabis intoxication also causes reduction in attention in a dose-dependent manner. The chronic use of cannabis is associated with attention loss, particularly in regular users and in those who began using in adolescence. Some deficits persist after a few weeks of abstinence, but gradually regress, likely due to the long clearance time of cannabinoids. Psychomotor functions are also affected by cannabis use. Multiple studies have shown that marijuana intoxication affects scores on an array of tests, including reaction time and fine motor control, in a dose-related manner. Chronic effects are less clearly defined, as only a few studies have shown reduced test performance that persists for weeks. Executive functions such as planning, reasoning, problem solving and inhibition are particularly affected during acute intoxication as well as following chronic exposition. On the other hand, moderate users appear to regain such functions after cessation. However, regular and prolonged cannabis use has indeed been linked to reduced executive function despite prolonged abstinence [33].

One study has shown that chronic cannabis users lose on average 8 IQ points compared to non-users, and the effect is more pronounced in those who began use in adolescence. The effect also persisted after adjusting for confounding factors. Following a period of abstinence, users who began in adulthood regained all of their cognitive functions, whereas users who started in adolescence retained certain losses [32]. However, any such changes in cognitive function appear to be subtle and noticeable only in regular, chronic users (weekly use over 10 years or more)[34].

The multiplicity of tests and markers of cognitive function renders evaluating the effects of cannabis use a complex task. The nature of the tests themselves, furthermore, limits the applicability of the results obtained. Nonetheless, it appears that cannabis use exerts acute, dose-dependent repercussions on multiple markers of cognitive function. It is, however, difficult to pinpoint whether these consequences result from residual effects of acute or subacute intoxications, from accumulated anterior expositions, or if from adverse effects that truly persist in time. Many studies seem to demonstrate that such harmful effects of cannabis are reversible with time. However, persistent deficits may be incurred in heavy users who have consumed cannabis regularly for over more than 10 years, as well as in users who started in adolescence. Such sequelae, however, remain minimal for the majority of users.

Psychotic disorders

Cannabis may be the leading modifiable risk factor responsible in the induction of psychotic disorders, including schizophrenia. According to a meta-analysis conducted on a number of observational studies (including longitudinal, transversal and case-control), the scientific literature appears in favor of a causal link between cannabis use and after psychosis, even adjusting for confounding variables [35]. Indeed, it has been clinically demonstrated that cannabis use induces fleeting and minor psychotic symptoms. In regards to chronic, long-term effects, a systematic review of longitudinal studies has demonstrated an increased incidence of psychosis in subjects who have



been exposed to cannabis (OR : 1.41, CI 95%=1,20-1,65). Furthermore, a doseresponse relationship is observed, given that psychotic effects are more pronounced in subjects who consume larger quantities [36]. It has also been shown that cannabis use is associated with the presentation of psychotic symptoms three years earlier than would be expected [37]. In the case of schizophrenia, the causal link remains uncertain. One hypothesis is that cannabis promotes the development of schizophrenia in certain genetically predisposed individuals [38]. However, cannabis use does not appear to influence the prevalence of schizophrenia in the population. For example, in 1995, a study demonstrates that the prevalence of schizophrenia remained stable and even showed a slight decline, despite an increase in cannabis use over the last few decades [39].

Suicidal risk

Currently, there is a tendency in the literature supporting the claim that chronic cannabis use is a risk factor for suicidality, defined in one study as suicidal ideation, suicide attempts, and death related to suicide. However, literature on this subject is still in development, and results appear heterogeneous and may be affected by publication bias. Suicidal ideation in the context of acute cannabis use is an understudied subjects, and results are not very conclusive. According to a meta-analysis [40], only a single study has shown an association between the acute use of this drug and suicidal ideation, whereas another study has shown, on the contrary, a reduction of such risks. As a general rule, studies appear to show either a null or statistically insignificant relationship between cannabis exposure and the risk of suicidal ideation. However,

intensive cannabis use has indeed correlated with an increased incidence of suicidal ideation and suicide attempts [40].

Bipolar disorders, anxiety, depression

In regards to manic symptoms, a metaanalysis has shown a significant relationship between exacerbations and cannabis use. Indeed, cannabis may aggravate the progression of bipolar disorder, due to an increase in the severity and frequency of manic symptoms. Furthermore, results from the study indicate a threefold risk of developing manic symptoms in cannabis users as compared to the general population. The duration of cannabis use appears to be correlated with the duration of manic phases [41]. In regards to anxiety, a meta-analysis has established a positive correlation between cannabis use and anxiety, regardless of dose. The relationship is weak, but persists despite an adjustment for confounding variables. The risk of developing cannabis dependency disorders that require treatment is higher in patients who have been diagnosed with anxiety-related disorders (*OR* = 1.68, 95% *CI*: 1.23-2.31). Cannabis use may also exacerbate symptoms of anxiety already present. The first few times that a subject consumes cannabis, temporary clinical symptoms of anxiety may be induced (but will be insufficient to lead to the diagnosis of anxiety disorders). Furthermore, patients with cannabis use disorder may also present with symptoms of anxiety during withdrawal [42]. Finally, in regards to depression, a meta-analysis by Moore et al. [36] has demonstrated a positive relationship between cannabis use and depression (OR =1.49, 95% CI: 1.15, 1.94), albeit less significant than the association demonstrated between cannabis and psychosis.



It is, however, important to note that the illegality of marijuana prevents a complete review of its impacts on health, and impedes on a clear comparison between cannabis and alcohol, tobacco, and other psychoactive substances [1].

Mental health – summary:

- Cannabis causes acute, dose-dependent effects on many markers of cognitive function.
 - However, these harmful effects tend to reverse with time.
 - Some deficiencies may persist in heavy users who consume regularly for over 10 years, and also in users who first began using in adolescence.
- Cannabis users are at greater risk for developing psychotic episodes, and the probability is proportional to the quantity of cannabis consumed.
- Risks of suicidal ideation and suicide attempts appear to be increased by intensive cannabis use.
- Cannabis use appears to increase the risk of developing manic symptoms, as well as exacerbating the severity of bipolar disorder.
- There appears to be a positive relationship between cannabis use and the development of anxiety.
- The risk of depressive episodes appears to be increased after cannabis use.

Cannabis addiction

Before undertaking the discussion on cannabis addiction, we must first define addiction itself. We shall use a definition proposed by the latest review on cannabis addiction by Curran and colleagues, published in Nature Neuroscience reviews in 2016 [43]:

[A]n acquired, chronic, relapsing disorder that is characterized by a powerful motivation to continually engage in an activity despite persistent negative consequences. Addictive drugs can all cause similar changes to brain circuits underpinning reward, salience, impulsivity, compulsivity, learning and memory, although these changes differ according to class of drug (including cannabis).

What is cannabis addiction?

In the DSM-V, cannabis abuse and cannabis dependence have been grouped together to define the criteria for cannabis use disorder (CUD) [49]. According to DSM V, CUD is "A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least two [psychosomatic symptoms], occurring within a 12-month period." Contrary to popular belief, cannabis addiction is a common phenomenon; a specific cannabis withdrawal syndrome is a recognized clinical entity, affecting up to 50% of users upon cessation of use [43];[50]. Symptoms include craving, sleep problems, nightmares, anger, irritability, dysphoria and nausea [51]. During withdrawal of THC, there is an associated increase of corticotropin-releasing factor (CRF) in the amygdala. A similar increase in CRF is equally observed in the withdrawal of other drugs of abuse such as alcohol, nicotine, psychostimulants and opiates [52];[53]; [54].



Cannabis use and other drugs, a gateway effect?

THC produces a "high" and users report desiring more after use [55]. In addition, cannabis high in THC, which has become increasingly common, may increase susceptibility to the development of addiction. This may explain the currently increased demand for treatment of cannabis use disorder [56] [57]. CBD may also play a role in cannabis addiction; although CBD does not influence the cannabis "high" [58]; [59];[60], research has suggested that CBD may, in fact, protect against addiction [58];[61].

Many animal studies have been conducted to model the development of cannabis addiction. Similarly to humans, experiments in rats have shown that the reward effect of THC is dosedependent; this effect, however, follows an inverted U-shaped curve [43]. Lower doses of THC administration increase response in the intracranial self-stimulation paradigm [62], whereas very high doses decrease this response [63]; [64]. This pattern of reward is seen in humans who prefer potent cannabis to other products that are extremely potent (such as synthetic CB1 agonists) [43];[65];[66]. On the other hand, CB1 antagonism produces the opposite effect, blocking the rewarding effects of low dose agonists and preventing the aversive effects of a high CB1 agonist dose [43]. Moreover, chronic cannabis use can dysregulate the eCB system. CB1 is downregulated in chronic users, explaining tolerance to THC. However, this downregulation is reversed after several weeks of abstinence [67];[68]. It has also been shown that THC exposure can block eCB-mediated plasticity in the nucleus accumbens and hippocampus [69];[70];[71],

which can affect the reward pathway. Moreover, chronic cannabis users have lower levels of endocannabinoids (AEA) in their cerebrospinal fluid [72] and chronic use in rodents has been shown to lead to increased AEA clearance by eCB enzymes [73];[74];[75]. Due to eCB system's major role in modulating neurotransmission in the reward areas of the brain, an imbalance in the eCB system likely plays a role in the development of addiction.

Of the different models of addiction, the dopamine hypothesis is still the most prominent. According to this model, the development of addiction is mediated by a change in dopamine signalling affecting the mesolimbic reward circuitry [76];[77]. Studies have shown that the eCB system plays a role in modulating dopamine signalling. Moreover, nuclear imagery (PET) studies in humans have shown that THC increases dopamine concentration in the striatum [78]. It has also been shown that CB1 agonists (including THC) increase the firing rate of VTA DA neurons, in rodents, with an increase of DA release in mesolimbic areas such as the nucleus accumbens [79];[80];[81]. However, chronic cannabis use in humans seems to cause only modest long-term DA associated abnormalities, and more research is required to explain the mechanisms of cannabis addiction [82];[43].

Genetics of cannabis addiction

Due to the complex nature of the development of addiction, it has been difficult to pinpoint the genes involved in CUD. Moreover, twin studies suggest "that genetic influence account for 55% of the vulnerability cannabis addiction. with shared to non-shared environmental factors and environmental factors accounting for much



lower proportions (17.5% and 27.5%, respectively)" [83];[43]. Studies have identified multiple possible candidate genes that may be involved in CUD, such as CNR1 (CB1 receptor gene), CNR2 (CB2 gene), FAAH, MAGL and novel cannabinoid receptor genes such as TRPV1 and GPR55 [84]. Taken together, these results suggest a complex polygenetic and environmental influence on the development of cannabis addiction.

Cannabis and addiction – summary

- Contrary to popular belief, cannabis addiction is a common phenomenon; a specific cannabis withdrawal syndrome is recognized and affects up to 50% of users upon cessation.
- Research suggests that both THC and CBD play a role in cannabis addiction, the former being linked to addiction development and the latter playing a possible protective role.
- Chronic cannabis use appears to dysregulate the eCB system and synaptic plasticity.
- Twin studies have shown that genetic influence accounts for 55% of vulnerability to cannabis addiction, with shared environmental factors and nonshared environmental factors accounting for a much lower proportion (17.5% and 27.5%, respectively).

Effects on physical health

In 2012, diseases attributable to cannabis use caused the loss of more than 66000 disability-adjusted life years in Canada [85]. Although the magnitude of this impact is less than that of other substances, it is still important to consider when establishing cannabis-related policies. This loss in life years is notably related to lung cancer that may be caused by marijuana smoking [86];[87]. The composition of the smoke inhaled appears to contain carcinogens similar to cigarette smoke [88]. Some studies do not show an increase in airway cancers in marijuana users, but one study reports a twofold risk in ENT carcinomas in cannabis users (OR=2) :

A Tunisian case-control study of 110 cases of hospital-diagnosed lung cancer and 110 community controls indicated an association of lung cancer with cannabis use (OR 8.2) that persisted after adjustment for cigarette smoking [...] cannabis use can increase the risk of myocardial infarction 4.8 times in the hour after use. [34]

Other years lost are in part attributable to road accidents incurred under the influence of cannabis. Although there is controversy regarding the impact of cannabis on driving, combined use with alcohol consumption causes a sixfold increase in the risk of motor vehicle accidents [89].

The risk of motor vehicle accidents (relative risk 1.96) persisted after statistical adjustment in men. [...] Individuals with blood THC concentrations greater than 5 μ g/mL had a higher accident risk (OR 6.6) than those without THC. [34].

The exact serum concentration of THC that predisposes to an increase in accidents remains to be determined. Further studies must be conducted on the subject.



Otherwise, direct physical effects can be noted with cannabis use. The effects of smoked cannabis take around 30 minutes to manifest, and generally persist over 2 to 4 hours following consumption. Individuals may present with the following symptoms: dry mouth, red eyes, agitation and tachycardia. Individuals using oral cannabis may present with other symptoms, such as hypotension, hypothermia, and a multiplicity of other psychiatric symptoms [90]. Given that cannabis use influences cardiac output as well as arterial blood pressure, individuals suffering from cardiovascular disease are advised to avoid cannabis use.

Cannabis and pregnancy

Women who consume marijuana are more likely to use other drugs and alcohol during pregnancy. The combined use of recreational drugs and alcohol during gestation increases the risk of congenital malformations, in addition to more severe embryonic and fetal development disorders compared to use of cannabis alone. It is important to consider that, although organogenesis takes place during the embryonic stage (the 8 first weeks of gestation), the brain continues to develop throughout pregnancy. Any use of drugs, including cannabis and alcohol, may thus affect the neurological development of the embryo.

Two mechanisms appear to explain the use of cannabis during pregnancy. First of all, the majority of women experience nausea and vomiting during pregnancy. Some women report using cannabis as an effective means to relieve these symptoms. In addition, many women simply continue the same level of recreational use of cannabis as before their pregnancy, without modifying their habits. Although cannabis is not recognized as a teratogenic substance, its other effects on *in utero* child development have sometimes been downplayed.

Multiple studies have sought to elucidate the potential negative impact of cannabis use during pregnancy, both on the mother and child. First of all, studies using animal models have demonstrated that THC can enter the placenta and thus enter fetal circulation, albeit at lower concentrations than those found in maternal serum. Furthermore, it has been shown that the fetal brain expresses cannabinoid receptors, which may explain some of the effects of cannabis on the neurological development of the neonate [91].

A recent meta-analysis [92] has revealed harmful effects of this "soft drug." Results of this study show that women who consume cannabis during pregnancy have an increased risk of anemia compared to pregnant nonuser women (OR = 1.36 : CI 95% : 1.10-1.69). Furthermore, it has been noted that weight at birth is decreased in neonates whose mothers consumed cannabis during gestation (OR = 1.77 : CI 95% 1.04- 3.01; weighted mean difference (WMD) for weight at birth = 109,42 g : 38.72-180.12) compared to neonates not exposed to cannabis *in utero*.

According to one study [93], the use of cannabis during pregnancy results in certain risks for the neurological development of the child, both in the development and growth of the brain in gestation, as well as during its maturation of in adolescence. Infants exposed to cannabis *in utero* have an increased risk of neuropsychiatric and behavioral disorders, and are more likely to suffer from problems of executive function.



A recent study [94] shows other noteworthy effects in regards to the impact of cannabis on infants:

- Reduction of height at birth (0.5 cm shorter; 21.26cm)
- Reduction of the duration of pregnancy (27.78 weeks)
- Reduction of head circumference
- Subtle alterations in sleep waves
- Slight delays as measured by the Brazelton neonatal behavioral assessment scale
- Delays in the visual system

However, the study remains inconclusive in other aspects. Despite the relatively widespread use of cannabis by pregnant women, current data only provides general information on its effects on the pediatric brain. Little information is available on the effects of cannabis use during breastfeeding. Thus, use of cannabis during pregnancy should be strongly discouraged in women who are pregnant or who wish to be.

Public health

The psychosocial impact of cannabis use is particularly important in the adolescent. A meta-analysis has shown that the age of initiation of cannabis use is associated with a reduced likelihood of completing secondary and university studies. This relationship appears to be gender-specific, as effects are more pronounced in males [95]. It has also been shown in a review of the literature that cannabis use is associated with lower educational performance, that is, lower marks, a higher rate of absenteeism, a negative attitude towards school, and reduced school performance. Possible explanations for this relationship include: an increased risk of difficulties in school already present in users; amotivational syndrome; a reduction in cognitive function; and the social context associated with marijuana use, including affiliation with peers who reject schooling and adopt precocious adult behavior such as quitting school and becoming pregnant at an early age [96].

Medical use

To this day, cannabis is not recognized by either Health Canada or the Royal College of Physicians and Surgeons of Canada as a medication with clearly defined guidelines of use. There is a great paucity of research regarding the therapeutic dosage and potential drug interactions of cannabis. The situation is further complicated by the erratic bioavailable quantity of the active compounds in cannabis, which varies with the route of administration as well as the particularities of the individual. Nonetheless, certain synthetic cannabinoids (dronabinol, nabilone, *nabiximol*), whose bioavailability and toxicity profile have been explored in greater detail, have currently been accepted for certain medical use. Furthermore, cannabis has been authorized as a prescription at the physician's discretion.

Chemotherapy-induced vomiting nausea and vomiting (CINV)

The main side effect of many chemotherapy regimens include nausea and vomiting, which remain a major problem in the care of cancer



patients despite significant progress in antiemetic therapies.

First described in the late 1970s, synthetic cannabinoids have been demonstrated as having effects that are superior [97] to dopamine antagonists in the treatment of CINV. However, few studies comparing such compounds to 5-HT3 antagonists (ondansetron, granisetron, etc.) have yet to be produced. A randomized trial [98] comparing nabilone with ondansetron, when used in combination with dexomehasone, did not demonstrate a significant difference between the two or the combination of the two. In addition, no study has yet to compare the use of cannabinoids with first-line therapies for severe CINV, including the use of a NK1 receptor inhibitor (aprepitant, fosaprepitant, etc.), and no controlled study has been conducted comparing cannabis to antiemetics in the context of CINV. One study [99] comparing cannabis with ondansetron for nausea induced in healthy individuals demonstrated a significant effect on nausea control, but which remained inferior to that of ondansetron. Furthermore, the main concerns of cannabinoid and cannabis use relate to the undesirable side effects compatible with cannabis intoxication (drowsiness, euphoria, loss of balance, etc.).

Current recommendations do not include the use of cannabinoids in CINV [100], or otherwise place them as third-line agents [101] following failure of tritherapy (5-HT3 antagonist, corticosteroids, and NK1 inhibitor) with the addition of a fourth medication. The prescription of cannabis remains at the discretion of the physician, for cases of refractory nausea only once the prescription of synthetic cannabinoids has been considered [102]. Furthermore, in chronic [103] cannabis users, a hyperemesis syndrome [104] has been described as a late secondary effect of cannabis consumption. This syndrome [105], characterized by brief and cyclical episodes of abdominal pain in addition to frequent vomiting that are relieved by showers or hot baths, is poorly understood. However, the phenomenon may be linked to the bioaccumulation [106] of toxic metabolites of cannabis in chronic users.

The therapeutic use of cannabis should therefore be reserved for patients who do not respond to or who are intolerant to existing therapies.

Neuropathic pain

Among the most interesting avenues for research on cannabis and cannabinoids is their potential effect as an analgesic. In animal models, cannabinoids have shown an antinociceptive effect similar to that of opiates, but whose pathway is independent of that of endogenous opiates. This analgesic effect is, however, difficult to reproduce in humans. Nonetheless, cannabis remains an interesting avenue for chronic neuropathic pain, according to the handful of randomized trials that have been conducted to this day.

A randomized, double-blind study [107] comprised of 38 participants non-naïve to cannabis showed a statistically significant reduction in central and peripheral neuropathic pain after the inhalation of cannabis. The patients enrolled in the study suffered from etiologically diverse causes of neuropathic pain, including central causes such as multiple sclerosis and sectioning of



the spinal cord, as well as peripheral causes such as diabetes and neuronal transection. Patients continued to take their usual analgesic medication during this study, which, depending on the case, may have included opioids, anticonvulsants, and nonsteroid anti-inflammatory medication. In addition to elucidating the potential analgesic effect of inhaled cannabis, the study showed a plateau effect of the analgesia produced after a certain cannabinoid concentration was attained; after this threshold, the subsequent increase in the dose of cannabis no longer decreased pain. On the other hand, harmful side effects, including confusion and sedation, were clearly shown to be dose-dependent. A randomized. double-blind studv with crossover [108] conducted by the same team, but this time using vaporized cannabis instead of smoked cannabis, demonstrated that 3.2 patients would have to be treated by low-dose, vaporized cannabis to reduce the pain of one participant by 30% (number needed to treat, NNT). Such an NNT is comparable to that of traditionally used analgesics for neuropathic pain, while keeping in mind that non-intoxicating doses of cannabis may still offer an adequate analgesic effect.

In regards to its compatibility with other analgesics, a study [109] conducted on participants following regiment а of morphine or oxycodone for analgesia has shown that the addition of inhaled cannabis induced a 27% decrease in pain in these patients. This addition did not affect plasma concentrations of opioids, which translates into the absence of interaction between these two analgesic compounds. In short, cannabis did not increase the risk of opioid overdose, but managed to decrease pain in these patients. Cannabis may therefore possibly be

considered as a safe supplement to opioids in the treatment of pain.

Therefore, cannabis remains a promising therapeutic substance in the clinical setting as an analgesic, due to its capacity to reduce the intensity of chronic pain refractory to other treatments; its ability to be safely coupled with opioids; and its potential to reduce the dose of opioids required to attain acceptable analgesia. Furthermore. despite the pronounced neurocognitive side effects resulting from higher doses of cannabis, it has been shown that a dose below the threshold of undesirable effects was sufficient to relieve pain, and that an increased dose of cannabis did not decrease the intensity of pain. This characteristic distinguishes cannabis from traditional neuropathic analgesics, making it a promising therapeutic avenue.

Contraindications

Acute pain

Despite encouraging results from animal studies [110], very few studies have been conducted on the analgesic effects of cannabis for acute pain in humans, and the available disappointing. data is Despite its demonstrated effects on certain types of chronic pain, such a benefit has yet to be shown for acute pain. Studies conducted on humans appear to show a negligible analgesic effect for cannabinoids when used alone; there is a potential synergetic effect [111] when combined with opiates, but the results are far from those observed in animals. However, one study [112] conducted on inhaled cannabis has shown a somewhat more significant dose-dependent response for the use of cannabis alone. Nonetheless, the antinociceptive effect of cannabis remains poorer than that of currently available



therapies, and any such effects are short-lived.

Furthermore, it appears that, in certain cases, cannabis can exert a hyperalgesic effect on other types of pain. However, this result has not been consistently described in all studies. It remains to be seen whether future studies shall corroborate this phenomenon.

Finally, as in the case of chronic pain, the critical issue encountered in the use of cannabis as an analgesic is the frequency and intensity of its undesirable effects, which are all the more significant given that they persist longer than the analgesic effect itself. All this considered, the use of cannabinoids or cannabis as medication for acute pain is not recommended, whether as a monotherapy or as a co-analgesic with an opiate.

Patient care

As health professionals, it is our responsibility to respond to illnesses or disorders resulting from cannabis use, including amotivational syndrome, anxiety disorders, potential violence, depressive disorders, psychotic disorders, progression to multiple drug abuse (especially transition to heroin), and physical as well as psychological dependence. Cannabis intoxication and dependence will be discussed in the following sections on the management of cannabis users.

Intoxicated patients

Definition of intoxication

According to the DSM-V [49], cannabis intoxication is diagnosed according to the following criteria:

A. Recent use of cannabis.

B. Clinically significant problematic behavioral or psychological changes (e.g., impaired motor coordination, euphoria, anxiety, sensation of slowed time, impaired judgment, social withdrawal) that developed during, or shortly after, cannabis use.

C. Two (or more) of the following signs or symptoms developing within 2 hours of cannabis use:

- 1. Conjunctival injection.
- 2. Increased appetite.
- 3. Dry mouth.
- 4. Tachycardia.

D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance.

Specify if :

With perceptual disturbances Hallucinations with intact reality testing or auditory, visual, or tactile illusions occur in the absence of a delirium.

Signs and symptoms of acute cannabis intoxication

It is rare for an adolescent or adult patient to present with cannabis intoxication as the chief complaint, given that such effects are usually sought voluntarily. Nevertheless, some patients will consult for behavioral or psychological problems (panic attack,



psychosis, agitation, etc.) or for hyperemesis associated with cannabis use [113]. Patients may also consult for consequences related to the method of administration, including bronchospasm, associated pneumothorax, and more rarely, angina pectoris [114]. In the adult population, sympathicomimetic symptoms such as tachycardia and arterial hypertension predominate. Behavioral symptoms such as euphoria, paranoia, agitation and anxiety may also be observed [114] [115].

In the pediatric population, cannabis intoxication may in itself be the motive for consultation, often resulting from the accidental ingestion of foods containing high doses of THC. Neurological symptoms often predominate in children, notably ataxia, drowsiness, hyperkinesia, coma and respiratory distress [114].

Diagnosis of acute cannabis intoxication

Cannabis intoxication is a primarily clinical diagnosis, based on signs, symptoms and particularly, patient history. In children, it is sometimes more difficult to obtain a clear history (from either the child or the accompanying adult). Considering the relatively nonspecific symptoms of cannabis intoxication, it is sometimes necessary to prescribe a urinary test for THC carboxylase. [114]

Dose of severe or lethal intoxication

Among the adult population, severe reactions such as orthostatic hypotension, delirium, panic attacks and myoclonus may occur at doses of > 7.5 mg/m^2 of THC, whereas psychosis more often occurs at doses that are even higher. It is to note, however, that severe intoxication is rare and the possibility of cointoxication must be considered, thus requiring the screening for other street drugs [114]. One study estimated that 30 mg/kg constitutes the lethal dose of THC in humans, when administered intravenously. However, in Canada, no case of lethal cannabis intoxication has yet to be reported to this day [113].

A small cohort study on the care of pediatric patients, which followed a group of fifty children, has shown that a dose of < 3,2 mg/kg of THC only required observation or minimal interventions, whereas doses up to 13 mg/kg may lead to admission to intensive care [114] due to symptoms such as apnea, bradycardia, cyanosis and hypotonia [115].

Management of acute intoxication in adolescents and adults

The majority of symptoms of acute cannabis intoxication are resolved in a few hours, and do not require hospital admission.

The first step in the management of intoxicated patients is reassurance. Some techniques may favor the resolution of unpleasant symptoms: adopting a comfortable position, going outside, taking a warm shower, drinking, and eating. When a patient presents with panic attack or a psychotic state, it is of utmost importance to address the patient in a calm voice, to bring them to a quiet place, and to employ respiratory techniques by coaching them to follow a slow breathing rhythm [116].



The next step is to evaluate and to treat the severe acute consequences of cannabis intoxication as individual clinical entities [114]. For example, angina induced by marijuana, albeit rare, requires habitual management protocols for acute coronary syndrome. Meanwhile, the administration of oxygen and needle thoracotomy, if necessary, are suggested for the management of pneumothorax. The exacerbation of asthma resulting from the inhalation of cannabis smoke requires the administration of inhaled beta-2 agonists. Hyperemesis syndrome associated with cannabis is often caused by chronic use, and symptoms typically regress after a hot shower. It is not advised to administer activated carbon as a means to decontaminate the gastrointestinal tract following cannabis ingestion. [114]

Delirium, anxiety or prolonged agitation may sometimes require hospitalization and/or the administration of short-acting benzodiazepines or antipsychotics. Patients who experience psychotic symptoms must immediately cease cannabis or cannabinoid use, and consult a physician or psychiatrist as soon as possible [113]. It is important to show concern for the well-being and the mental state of patients, in order to screen for a substance use disorder or a mood disorder, as drug abuse may constitute a cry for help.

Management of acute intoxication in children

Acute intoxication in the pediatric population warrants special concern, and requires a stricter control of symptomatology. It is suggested to begin by consulting an antipoison centre. In the pediatric patient who is asymptomatic, or who presents few symptoms of low intensity, a "watch and wait" approach for 4-6 hours after ingestion may prove sufficient. However, if severe neurological symptoms (as already mentioned) are present, intra-hospital admission becomes necessary. Central nervous system depression caused by cannabis consumption may, in severe cases, result in lethargy, and possibly coma. If such is the case, it becomes necessary to evaluate and to maintain airway patency. Cannabisinduced coma generally lasts between 1 and 3 days, and reverses completely. It is important to eliminate hypoglycemia by dosing serum glucose concentrations. Furthermore, if concomitant opiate intoxication is suspected, naloxone may be administered (note that naloxone cannot reverse intoxication caused by cannabis alone). In the case of cointoxication (ex. cocaine), the patient may present with convulsions, which must be treated with first-line benzodiazepines. This treatment is also used for severe dysphoria, a rare clinical consequence of acute cannabis intoxication. Of note: in children with marijuana intoxication, whether accidental or non-accidental, it is important to suspect abuse or negligence and to report to youth protection services as necessary [114].

Dependence and withdrawal

Cannabis dependence is identified in the DSM-V [49] as "Cannabis Use Disorder." This disorder is defined on the basis of four symptom categories. The first category relates to the intense desire to consume, resulting in the loss of control of cannabis use (whose mechanism implicates classical conditioning by the activation of reward circuits in the brain). Furthermore, social



function is altered, including incapacity to work or the abandoning of social activities in order to consume. Also, risky use continues despite the patient's understanding of the negative impacts on their life. Finally, pharmacologic criteria constitute the last category, including the notion of tolerance [49], to be discussed later. Note that it is not necessary for all categories to be present for a diagnosis to be made [117].

Dependence is a problem most likely encountered in adult users, but which is equally present in adolescents. In France, the prevalence of cannabis dependency is situated around 33% - 50% of its population of cannabis users [118].

In regards to the psychological aspect of dependence, the mechanism begins in the dopaminergic system, often called the reward circuit [118]. Use of the substance leads to pleasure, which motivates the user to consume more. With time, physical dependence manifests as the appearance of somatic withdrawal symptoms. These occur with the loss of THC's effects on CB1 receptors, following modifications in the adenylate cyclase signalling pathway in the cerebellum.

The first step in treatment and care of these patients is to encourage consultation when problems arise. A study conducted in 1999 demonstrated that the majority of youth do not believe in the benefits of psychological and medical aid, even after multiple failed attempts to cease cannabis use [119].

Following 15 years of multidisciplinary research regarding the optimisation of intervention strategies [120], it has been suggested that accessibility to a variety of

different resources (school, youth centres, public, private and/or community resources) offers the most benefit to patients suffering from cannabis dependence. These resources may provide first-line interventions, including primary prevention, access to information and screening, as well as secondline interventions ranging from secondary to tertiary prevention. Indeed, according to Karine Bertrand, in the document "Intervenir *auprès des jeunes et de leur entourage dans les* Centres de réadaptation pour personnes alcooliques et toxicomanes: pratiques *qaqnantes et offre de service de base" (loose* translation: Intervening among youth and their entourage in rehabilitation centres for alcohol and drug addiction: winning practices and offering of basic services), the majority of patients followed for cannabis use disorder employ more than one resource. [121] Therefore, it is imperative to establish a network that encompasses all such services, and which employs a common language and common tools. Interdisciplinary collaboration remains the key to success in such interventions. Studies that evaluate the impact of "therapeutic communities" have shown statistically significant improvements in many areas of the user's life, including use of drugs other than alcohol, social and judicial situations, delinquency, and self-image. [122]

A number of therapies have proven beneficial to patients with cannabis use disorder, particularly motivational therapy and cognitive behavioral therapy, regardless whether on an individual or family basis. A study has shown that the rate of remission, that is, complete cessation of use after 9 months of follow-up, is comparable between therapies and varies at around 24% [123]. However, the authors have stated that, for a vulnerable clientele, such as patients who are



homeless, a motivational approach should be prioritized [124]. In other cases, the use of multiple combined strategies increases the effectiveness of care [125].

All throughout, the physician should equally examine the past experiences of the patient, and act on multiple levels (family, friends, community) in addition to continually reassessing the patient. The goal is to assure that follow-up is adequate, and that the program of intervention chosen corresponds to the patient's needs. [125]

Furthermore, it is important to address the possibility of pharmacological interventions that may help in reducing excessive cannabis use. *Buspirone*, an anxiolytic used to treat anxiety, has been shown to be useful in suppressing the sensation of irresistible need to consume, as well as in reducing irritability and depressive symptoms associated with withdrawal. It is the only medication to this day proven to be useful in the treatment of cannabis dependency [126].

Physical dependence on marijuana, although less important and less recurrent than physical dependence on other drugs such as opiates and cocaine, is a real phenomenon. Cannabis withdrawal is in itself a clinical entity that is surprisingly common. Among patients who report using cannabis regularly at one moment in their life, 33% have also reported symptoms of withdrawal. However, many such patients do not consult, because their symptoms are not severe enough for them to consider medical assistance.

According to the DSM-V [49], cannabis withdrawal is defined as the cessation of cannabis use that has been heavy and prolonged. The condition leads to at least three of the following groups of psychosomatic symptoms: irritability/anger/aggression;

nervousness/anxiety; sleep difficulty (e.g. insomnia, disturbing dreams); decreased appetite or weight loss; restlessness; depressed mood; and at least one of the following physical symptoms: abdominal pain, shakiness/tremors, sweating, fever, chills or headaches. These signs and symptoms must equally cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. Finally, differential diagnostics must be evaluated and excluded. In addition to these diagnostic symptoms, patients in cannabis withdrawal may report later-onset fatigue, yawning, difficulty in concentration, and periods of increased appetite as well as hypersomnia.

These symptoms usually begin in the 24-72h following the cessation of use, and peak after one week without use. This peak then lasts for about one to two weeks. Symptoms of withdrawal may be reduced by pharmacological or behavioral strategies. Of note, patients who make use of such strategies show an improved prognostic. The physician must therefore strive to offer these to the patient.

One study has concluded that the oral uptake of THC, coupled with the addition of an alphaadrenergic agonist such as *lofexidine*, or otherwise CB1 receptor agonist [126] (not yet available on the market), reduces symptoms of withdrawal. However, this treatment may hinder the goal of ultimately ceasing exaggerated cannabis use. Medication may also target specific symptoms of withdrawal [126]. It is also recommended to direct the patient to non-pharmacological therapies



such as those discussed above, such that the psychological aspect of dependence may also be addressed.

Management- summary:

In patients suffering from intoxication:

- Begin by reassuring the patient in a calm voice, and leading them to a quiet place.
- Acute consequences of intoxication (angina, bronchospasm, pneumothorax, etc.) must each be addressed as separate clinical entities.
- If the patient presents with delirium or agitation, short-acting benzodiazepines or antipsychotics are indicated.

In pediatric cases :

- If symptoms are moderate, simply observing for 4-6h may prove sufficient.
- In severe cases, such as coma, it becomes a priority to hospitalize the patient and to maintain airway patency.

In patients affected by dependency or withdrawal :

 Management of the dependent patient is multifactorial, and encompasses motivational and cognitive behavior therapy; pharmacological treatment (*Buspirone*); and the symptomatic treatment of withdrawal symptoms.

Vulnerable populations

The potentially deleterious effects of marijuana use appear most frequently in the context of high-risk practice (ex. frequent use, use of products containing high doses of THC, driving under influence) and among users at risk (ex. children and adolescents). Therefore, recommendations for vulnerable populations must be developed with these factors in mind, while also considering the impact of cannabis on social, educational, professional and financial spheres of patients' lives.

The decriminalization (i.e. legalization) of recreational marijuana use in other nations has been associated with an increase in accidental ingestion in children. For example, in Colorado, an increase of 34% in such cases has been reported. Furthermore, an increase in the number of children hospitalized for cannabis has also been noted, but the absolute number of cases remains low. [114]

Frequent and consistent use of marijuana beginning early in adolescence can progress into dependence in adult life. It has been said that 1 in 9 users will develop dependence, which increases to 17% if first use was in adolescence, and to 25-50% with daily use. [113]

A cohort study comprising more than 1000 children, followed from birth to the age of 26 years, has shown a threefold risk of psychotic disorders in those who have used cannabis. The implication, therefore, is that exposition to cannabis in psychologically vulnerable adolescents is strongly advised against. [113]

Management of such patients is therefore a crucial public health concern, and the legalization of cannabis must be adequately implemented such that the deleterious effects of cannabis use may be minimised in populations at risk. The following is a summary of some recommendations by the Canadian Government for this end:

1. Minimal age to purchase: scientific studies indicate that the brain continues to develop until around 25



years of age, which may serve as an adequate age limit for purchase. However, for practical purposes, it may be legally easier to coordinate if the minimal age to purchase matches that of alcohol and tobacco.

- 2. Advertising restrictions: suppliers are to be required to add a health warning on products, as already practiced for the tobacco industry.
- 3. Pricing and taxation: products derived from cannabis must be priced and taxed at an adequate rate in order to deter use among the population, while remaining acceptably low so as to dissuade the development of a black market.
- 4. Product restrictions: it is important to establish a limit for the acceptable quantity of THC to be found in cannabis-derived products, and to prohibit products whose THC content exceeds that limit.
- 5. Restrictions on derived products (ex. comestibles, candies, creams)
- 6. Limits on the quantity allowed in personal possession
- 7. Limits on sale points
- 8. Restriction on sites of use
- 9. Prohibition of use while driving



Conclusion

In conclusion, cannabis is a drug whose effects may indeed be implemented for beneficial uses, notably in regards to the treatment of chronic pain as well as chemotherapy-induced nausea and vomiting. Nonetheless, cannabis remains a drug that also has deleterious effects on health, notably by affecting the development of the brain and by increasing the risk of associated psychosis. Furthermore, smoke from inhaled cannabis constitutes respiratory health risks (chronic bronchitis, COPD).

Given the imminent legalisation of cannabis, concern has been voiced regarding the risk of increasing cannabis use in the general population. However, examples from other nations, such as the Netherlands, appear to suggest that decriminalizing the use of "soft drugs" does not cause an increase in consumption per capita *(see document by counsel-committee)*.

The legalisation of cannabis must take place in the best interests of public health, and a notable aspect of the project is to reinvest the revenue generated (anticipated to be around 3 to 5 billion annually) [127] for research, rehabilitation programs and care of patients suffering from the problematic use of cannabis and other drugs. The document containing the Task Force's recommendations regarding the legalisation of cannabis is promising, because it highlights the importance of protecting populations at risk. However, to us, some recommendations appear insufficient or lacking in precision. In the near future, the FMEQ will publish a series of its own recommendations in response to those of the Task Force, to be presented to the federal government in order to assure that the health of Canadians remains at the forefront of the project.

The present document is not intended to be exhaustive, nor to serve as a reference on the subject. Instead, its goal is to provide a summary for medical students, in regards to the various effects of cannabis on health, its medical uses, and the management of patients who have consumed it. For more information, we invite you to consult the *Framework for the Legalization and Regulation of Cannabis in Canada*, as well as the report by the *National Academies of Sciences, Engineering and Medicine* [128] on the effects of cannabis on health, in addition to the report conclusions presented in the appendix.



The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research

THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS

Report Conclusions⁵

Chapter 4 Conclusions—Therapeutic Effects

There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults (cannabis) (4-1)
- As anti-emetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)

There is moderate evidence that cannabis or cannabinoids are effective for:

• Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols) (4-19)

There is limited evidence that cannabis or cannabinoids are effective for:

- Increasing appetite and decreasing weight loss associated with HIV/AIDS (cannabis and oral cannabinoids) (4-4a)
- Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)
- Improving symptoms of Tourette syndrome (THC capsules) (4-8)
- Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (cannabidiol) (4-17)
 Improving symptoms of posttraumatic stress disorder (nabilone; one single, small fair-quality trial) (4-20)

There is limited evidence of a statistical association between cannabinoids and:

• Better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage (4-15)

There is limited evidence that cannabis or cannabinoids are *ineffective* for:

- Improving symptoms associated with dementia (cannabinoids) (4-13)
- Improving intraocular pressure associated with glaucoma (cannabinoids) (4-14) Reducing depressive symptoms in individuals with chronic pain or multiple sclerosis (nabiximols, dronabinol, and nabilone) (4-18)

There is no or insufficient evidence to support or refute the conclusion that cannabis or cannabinoids are an effective treatment for:

- Cancers, including glioma (cannabinoids) (4-2)
- Cancer-associated anorexia cachexia syndrome and anorexia nervosa (cannabinoids) (4-

⁵ Numbers in parentheses correspond to chapter conclusion numbers.



The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Researc SUMMARY

4b)

- Symptoms of irritable bowel syndrome (dronabinol) (4-5)
- Epilepsy (cannabinoids) (4-6)
- Spasticity in patients with paralysis due to spinal cord injury (cannabinoids) (4-7b)
- Symptoms associated with amyotrophic lateral sclerosis (cannabinoids) (4-9)
- Chorea and certain neuropsychiatric symptoms associated with Huntington's disease (oral cannabinoids) (4-10)
- Motor system symptoms associated with Parkinson's disease or the levodopainduced dyskinesia (cannabinoids) (4-11)
- Dystonia (nabilone and dronabinol) (4-12)
- Achieving abstinence in the use of addictive substances (cannabinoids) (4-16)
- Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis (cannabidiol) (4-21)

Chapter 5 Conclusions—Cancer

There is moderate evidence of *no* statistical association between cannabis use and:

- Incidence of lung cancer (cannabis smoking) (5-1)
- Incidence of head and neck cancers (5-2)

There is limited evidence of a statistical association between cannabis smoking and:

• Non-seminoma-type testicular germ cell tumors (current, frequent, or chronic cannabis smoking) (5-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- Incidence of esophageal cancer (cannabis smoking) (5-4)
- Incidence of prostate cancer, cervical cancer, malignant gliomas, non-Hodgkin lymphoma, penile cancer, anal cancer, Kaposi's sarcoma, or bladder cancer (5-5)
- Subsequent risk of developing acute myeloid leukemia/acute non-lymphoblastic leukemia, acute lymphoblastic leukemia, rhabdomyosarcoma, astrocytoma, or neuroblastoma in offspring (parental cannabis use) (5-6)

Chapter 6 Conclusions—Cardiometabolic Risk

There is limited evidence of a statistical association between cannabis use and:

- The triggering of acute myocardial infarction (cannabis smoking) (6-1a)
- Ischemic stroke or subarachnoid hemorrhage (6-2)
- Decreased risk of metabolic syndrome and diabetes (6-3a)
- Increased risk of prediabetes (6-3b)

There is no evidence to support or refute a statistical association between *chronic effects* of cannabis use and:

• The increased risk of acute myocardial infarction (6-1b)



S-12

THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS

Chapter 7 Conclusions—Respiratory Disease

There is substantial evidence of a statistical association between cannabis smoking and:

• Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term cannabis smoking) (7-3a)

There is moderate evidence of a statistical association between cannabis smoking and:

- Improved airway dynamics with acute use, but not with chronic use (7-1a)
- Higher forced vital capacity (FVC) (7-1b)

There is moderate evidence of a statistical association between *the cessation* of cannabis smoking and:

• Improvements in respiratory symptoms (7-3b)

There is limited evidence of a statistical association between cannabis smoking and:

• An increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use (occasional cannabis smoking) (7-2a)

There is no or insufficient evidence to support or refute a statistical association between cannabis smoking and:

- Hospital admissions for COPD (7-2b)
- Asthma development or asthma exacerbation (7-4)

Chapter 8 Conclusions—Immunity

There is limited evidence of a statistical association between cannabis smoking and:

• A decrease in the production of several inflammatory cytokines in healthy individuals (8-1a)

There is limited evidence of *no* statistical association between cannabis use and:

• The progression of liver fibrosis or hepatic disease in individuals with viral Hepatitis C (HCV) (daily cannabis use) (8-3)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- Other adverse immune cell responses in healthy individuals (cannabis smoking) (8-1b)
- Adverse effects on immune status in individuals with HIV (cannabis or dronabinol use) (8-2)
- Increased incidence of oral human papilloma virus (HPV) (regular cannabis use) (8-4)



SUMMARY

There is substantial evidence of a statistical association between cannabis use and:

• Increased risk of motor vehicle crashes (9-3)

There is moderate evidence of a statistical association between cannabis use and:

• Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal (9-4b)

There is no or insufficient evidence to support or refute a statistical association between cannabis use and:

- All-cause mortality (self-reported cannabis use) (9-1)
- Occupational accidents or injuries (general, non-medical cannabis use) (9-2)
- Death due to cannabis overdose (9-4a)

Chapter 10 Conclusions—Prenatal, Perinatal, and Neonatal Exposure

There is substantial evidence of a statistical association between maternal cannabis smoking and:

• Lower birth weight of the offspring (10-2)

There is limited evidence of a statistical association between maternal cannabis smoking and:

- Pregnancy complications for the mother (10-1)
- Admission of the infant to the neonatal intensive care unit (NICU) (10-3)

There is insufficient evidence to support or refute a statistical association between maternal cannabis smoking and:

• Later outcomes in the offspring (e.g., sudden infant death syndrome, cognition/academic achievement, and later substance use) (10-4)

Chapter 11 Conclusions—Psychosocial

There is moderate evidence of a statistical association between cannabis use and:

• The impairment in the cognitive domains of learning, memory, and attention (acute cannabis use) (11-1a)

There is limited evidence of a statistical association between cannabis use and:

- Impaired academic achievement and education outcomes (11-2)
- Increased rates of unemployment and/or low income (11-3)
- Impaired social functioning or engagement in developmentally appropriate social roles (11-4)

There is limited evidence of a statistical association between *sustained abstinence from* cannabis use and:

• Impairments in the cognitive domains of learning, memory, and attention (11-1b)



S-14

THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS

Chapter 12 Conclusions—Mental Health

There is substantial evidence of a statistical association between cannabis use and:

• The development of schizophrenia or other psychoses, with the highest risk among the most frequent users (12-1)

There is moderate evidence of a statistical association between cannabis use and:

- Better cognitive performance among individuals with psychotic disorders and a history of cannabis use (12-2a)
- Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use) (12-4)
- A small increased risk for the development of depressive disorders (12-5)
- Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users (12-7a)
- Increased incidence of suicide completion (12-7b)
- Increased incidence of social anxiety disorder (regular cannabis use) (12-8b)

There is moderate evidence of *no* statistical association between cannabis use and:

• Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders (12-2c)

There is limited evidence of a statistical association between cannabis use and:

- An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders (12-2b)
- The likelihood of developing bipolar disorder, particularly among regular or daily users (12-3)
- The development of any type of anxiety disorder, except social anxiety disorder (12-8a)
- Increased symptoms of anxiety (near daily cannabis use) (12-9)
- Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (12-11)

There is no evidence to support or refute a statistical association between cannabis use and:

- Changes in the course or symptoms of depressive disorders (12-6)
- The development of posttraumatic stress disorder (12-10)

SUMMARY

Chapter 13 Conclusions—Problem Cannabis Use

There is substantial evidence that:

- Stimulant treatment of attention deficit hyperactivity disorder (ADHD) during adolescence is *not* a risk factor for the development of problem cannabis use (13-2e)
- Being male and smoking cigarettes are risk factors for the progression of cannabis use to problem cannabis use (13-2i)
- Initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use (13-2j)

There is substantial evidence of a statistical association between:

- Increases in cannabis use frequency and the progression to developing problem cannabis use (13-1)
- Being male and the severity of problem cannabis use, but the recurrence of problem cannabis use does not differ between males and females (13-3b)

There is moderate evidence that:

- Anxiety, personality disorders, and bipolar disorders are *not* risk factors for the development of problem cannabis use (13-2b)
- Major depressive disorder is a risk factor for the development of problem cannabis use (13-2c)
- Adolescent ADHD is *not* a risk factor for the development of problem cannabis use (13-2d)
- Being male is a risk factor for the development of problem cannabis use (13-2f)
- Exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use (13-2g)
- Neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use (13-2h)
- During adolescence the frequency of cannabis use, oppositional behaviors, a younger age of first alcohol use, nicotine use, parental substance use, poor school performance, antisocial behaviors, and childhood sexual abuse are risk factors for the development of problem cannabis use (13-2k)

There is moderate evidence of a statistical association between:

- A persistence of problem cannabis use and a history of psychiatric treatment (13-3a)
- Problem cannabis use and increased severity of posttraumatic stress disorder symptoms (13-3c)

There is limited evidence that:

• Childhood anxiety and childhood depression are risk factors for the development of problem cannabis use (13-2a)



S-16

THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS

Chapter 14 Conclusions—Abuse of Other Substances

There is moderate evidence of a statistical association between cannabis use and:

• The development of substance dependence and/or a substance abuse disorder for substances including, alcohol, tobacco, and other illicit drugs (14-3)

There is limited evidence of a statistical association between cannabis use and:

- The initiation of tobacco use (14-1)
- Changes in the rates and use patterns of other licit and illicit substances (14-2)

Chapter 15 Conclusions—Challenges and Barriers in Conducting Cannabis and Cannabinoid Research

There are several challenges and barriers in conducting cannabis and cannabinoid research, including:

- There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research (15-1)
- It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use (15-2)
- A diverse network of funders is needed to support cannabis and cannabinoid research that explores the beneficial and harmful health effects of cannabis use (15-3)
- To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observational studies) are needed (15-4)



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