

# Cannabis Evidence Series

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An Evidence Synthesis

The Health Technology Assessment Unit, University of Calgary

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**Acknowledgements**

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## Issue

Cannabis is the most widely used illicit drug in Canada; however, it is illegal to possess, produce or sell it <sup>1</sup>. In 2015, the Liberal government of Canada formed a majority government and announced their plan to legalize cannabis. In June of 2016, a nine-member federal task force on cannabis was announced. The task force, chaired by Anne McLellan, includes representation from Quebec, British Columbia, Newfoundland and Labrador, Ontario, and Saskatchewan <sup>2</sup>. Guided by this task force, cannabis legislation is expected to be introduced in 2017.

## Objective

To inform Alberta's response to the federal decision to legalize cannabis, the University of Calgary Health Technology Assessment (HTA) Unit is developing a series of evidence syntheses to support policy development by the Government of Alberta. This evidence series consists of five reports that address:

- Canadian Context
- Health effects and harms
- Medical cannabis
- Advertisement and communication regulations
- Experience with legalization among jurisdictions who have legalized including economic, sales and use regulations

## Executive Summary and Policy Messages

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## Background

Cannabis is the most widely used illicit drug in Canada; however, it is illegal to possess, produce, or sell cannabis <sup>1</sup>. In 2015, the Government of Canada announced plans to legalize cannabis for non-medical use. In June of 2016, a nine-member federal task force on cannabis was established. The task force, chaired by Hon. Anne McLellan, includes representation from Quebec, British Columbia, Newfoundland and Labrador, Ontario, and Saskatchewan <sup>2</sup>. The Task Force released its Framework for the Legalization & Regulation of Cannabis in Canada on November 30, 2016. Guided by input from this Task Force, cannabis legislation is expected to be introduced in 2017.

To inform Alberta's preparation for the federal decision to legalize cannabis, the University of Calgary Health Technology Assessment (HTA) Unit has completed a series of evidence syntheses to support policy development by the Government of Alberta. The five evidence syntheses focus on the following topics:

1. Current Canadian context
2. Health harms and effects
3. Medical cannabis
4. Advertising and communication
5. Experience with legalization

The purpose of this current report is to highlight the key findings and gaps from these evidence syntheses emerging policy options.

### Summary of Topic 1: Current Context

*Cannabis sativa*, also known as cannabis, cannabidiol, weed, pot, or bud, is a multi-use crop that has been cultivated by humans for thousands of years. Today, there are three varieties of cannabis, *C. sativa*, *C. indica*, and 'hybrid strains', each of which induce different psychological and physiological effects depending on which cannabinoids they contain <sup>3</sup>. The two most notable cannabinoids commonly investigated for medicinal use are tetrahydrocannabinol (THC) and cannabidiol (CBD).

There are three broad categories of regulation for the non-medical use of cannabis: criminalization, decriminalization and legalization. When cannabis is criminalized, it is regulated as an illegal substance; the purchasing, selling and use of cannabis is prohibited and enforced <sup>4</sup>.

Levers for enforcement may include fines, incarceration, and/or mandatory treatment <sup>4</sup>. Individuals found possessing, using or selling cannabis will have a criminal record <sup>4</sup>. In places where cannabis is decriminalized, it is still considered an illegal substance; however, penalties are non-criminal in nature for some or all offenses <sup>4,5</sup>. Some countries that have decriminalized use have regulations on ages of use, what products may be used, how much cannabis may be possessed, and potency <sup>4</sup>. Fines may be used as an enforcement lever, but are not related to a criminal record <sup>4</sup>.

Legalization refers to a regulatory approach where cannabis is identified as a legal substance for non-medical use under the law <sup>4</sup>, and all legal prohibitions against it have been removed <sup>5</sup>. Where cannabis is legal, it may be regulated by regional jurisdiction, the country, or it may be unregulated (free-market) <sup>4</sup>. When regulated by regional jurisdiction or country, elements that may be regulated include: production, distribution, minimal age to purchase, possession limits, cultivation for personal use, and driving while under the influence. <sup>4</sup>.

### *International Context*

Internationally, there is a continuum of cannabis regulatory approaches from criminalization to decriminalization and legalization. The possession of non-medical cannabis is legal in Uruguay, eight American states and one American jurisdiction, including Washington State, Colorado, Oregon, Alaska, Washington D.C., California, Maine, Massachusetts, and Nevada, and has been decriminalized in 31 countries and 18 states.

Cannabis continues to be included within the United Nations (UN) drug control regime. When any UN nation chooses to legalize cannabis, it violates international law. Accordingly, that country is required to formally withdraw from these treaties <sup>6</sup>.

### *Canadian Context*

Within Canada, medical use of cannabis became legal with the passing of the Marijuana Medical Access Regulation in 2001. However, non-medical use has remained illegal since it was added to the Opium and Narcotics Drug Act in 1923. The debate on legalizing, decriminalizing or maintaining the status quo of non-medical cannabis largely began in the 1960s. However, no significant steps were taken towards legalizing, until the current Liberal Party of Canada formed a majority Federal Government in 2015 and announced their plan to legalize cannabis. On June

20<sup>th</sup>, 2016 a Federal Task Force on Cannabis chaired by Hon. Anne McLellan was struck with the purpose of collecting input on how to legalize non-medical cannabis. If the federal government decides to legalize cannabis, Canada would be the second country in the world to consider it a legal substance (Uruguay being the first).

Although it is illegal, cannabis is a widely used substance in Canada. Nationally, 10.5% of Canadians self-report using cannabis within the last 12 months and 33.7% report lifetime use. In Alberta, 8.9% used cannabis within the last 12 months. Sixty-five percent of Canadians support legalization of cannabis; support is highest in British Columbia and lowest in Quebec. Individuals are more likely to support legalization if they have used cannabis in the past 12 months, are under 35 years old, are male, have an annual income over \$80,000, and have a university degree. Most Canadians who support legalization for non-medical use say they do so because they do not believe alcohol, tobacco and cannabis are different, and because they do not think cannabis possession should be penalized with a criminal record. Those who do not support legalization feel primarily that we need to protect children and youth, are particularly concerned about driving while under the influence, and do not believe the Federal Government should be involved in decisions such as these.

## **Summary of Topic 2: Health Effects and Harms**

There is a considerable amount of research on physical and mental health harms related to non-medical cannabis use; a review of the literature found 64 systematic reviews on health effects and harms related to cannabis. The evidence suggests that cannabis may be associated with harm to physical and mental health. Specifically, there is an association with an increased risk of: testicular cancer; increased risk of mental health problems (including psychosis, mania, relapse of psychosis or schizophrenia); and, poor outcomes during pregnancy, such as low birth-weight babies, birth complications, pulmonary dysfunction, neurocognitive brain changes and functional brain changes. There is inconclusive evidence on many harms such as brain changes, bladder, prostate, penile, cervical and childhood cancers, bone loss, atrial fibrillation, suicide, depression, anxiety, and all-cause mortality. There is evidence that cannabis does not increase the risk of arteritis, lung, and head and neck cancers.

A systematic review on the effects of second-hand cannabis smoke found that inhalation of second-hand smoke can result in detectable cannabinoids and metabolites in blood and urine.

Non-smokers may experience psychoactive effects when exposed to a high volume of second-hand smoke in enclosed spaces. In extreme smoking conditions, individuals may experience psychoactive effects. There is evidence of a dose-response relationship between THC content and cannabinoid metabolite concentrations in the urine; this is mediated by a number of factors, including ventilation, air volume, and number of cigarettes lit at one time. No studies on health outcomes of individuals exposed to second or third-hand cannabis smoke were found. However, three studies investigated the toxicity and chemical composition of passive cannabis smoke compared to tobacco smoke<sup>7-9</sup>. Evidence from these comparative studies concluded that cannabis smoke produces more changes to genetic material (mutagenic) and is more toxic to living cells (cytotoxic) than tobacco smoke<sup>7-9</sup>.

#### *Pathways of Substance Use*

There are multiple pathways of drug use. Most commonly, cannabis use directly precedes other illicit drug use and is closely associated with the use of alcohol. Forty-three articles reported on the position of cannabis in the pathway of substance use, from initiation to experimentation and regular use. Among the many mediating factors, including social and genetic factors, early age of use is a consistently reported factor associated with higher likelihood to progress to other types of illicit drug use. Daily or near-daily cannabis use in other cohorts has been shown to be a risk factor for using other illicit drugs.

#### *Public perception of harm*

Within Canada, the majority of residents perceive non-medical cannabis consumption to be as harmful to physical and mental health as cigarettes and alcohol, but not as harmful as prescription drug abuse or use of other illicit drugs. Moreover, the Canadian public perceives cannabis to be addictive, but no more addictive than cigarettes or alcohol.



### **Summary of Topic 3: Medical Cannabis**

#### *Therapeutic Effect*

A systematic review of the effectiveness of cannabis for treating clinical conditions found 79 randomized controlled trials. The 79 included studies from the Whiting systematic review contained 104 separate trials. Of these trials, 43 used synthetic cannabis forms and 61 trials used natural forms of medical cannabis. Despite a vast literature, there is only low to moderate quality evidence to suggest that cannabis is an effective treatment for most medical conditions. Medical cannabis has been found effective by some studies for symptom control, such as treating nausea and vomiting due to chemotherapy, chronic pain, spasticity due to multiple sclerosis or paraplegia, sleep disorders and Tourette syndrome. There is inconclusive evidence on appetite stimulation for HIV/AIDS, anxiety disorders and glaucoma, and there is evidence of harm from depression (when using high doses of THC). The majority of the included studies were evaluated as being at high risk of bias; therefore, we conclude that there is moderate- to very low-quality evidence to suggest that cannabinoids are effective treatment options for these medical conditions.

#### *Canadian Context*

Canada was the first country to legalize medical cannabis use in 2001. Although Canada has a fifteen-year history of legalized use of medical cannabis, there have been frequent and significant legislative changes during this time. Since its use was first sanctioned, these legislative changes have impacted accessibility, production and use.

The 2001 Medical Marihuana Access Regulations were replaced by the Medical Purposes Regulations in 2014 and again in August 2016, with the Access to Cannabis for Medical Purposes Regulations. The key change between the two regulations is that individuals may now produce their own cannabis or designate another individual to produce it for them. There is one producer in Alberta, and 35 licensed nationally. Cannabis for medical purposes can only be accessed if prescribed by a physician; there are 5,950 patients registered to use medical cannabis in Alberta and 56% of these prescriptions come from one authorized physician. Patients may possess up to thirty times the daily authorized quantity of cannabis at one time, up to a maximum of 150 grams. The prescribing guidelines and regulations for physicians vary by Province. It is unclear what would happen to the current system in place for medical cannabis if

non-medical cannabis were legalized. As has been the case in other places that have legalized cannabis, medical users may be permitted special privileges including where it may be used, possession amounts, and whether patients can grow it for their own purposes.

Approximately 3% of Canadians, and Albertans are using medical cannabis to treat a clinical condition. Fifty-four percent of those using it for medical purposes use it at least once per day. Most individuals use it for symptom management, including nausea and vomiting due to chemotherapy, appetite stimulation in wasting caused by AIDS, chronic pain, and sleep disorders. It is least commonly used for neurological conditions, such as spasticity due to multiple sclerosis, epilepsy, and movement disorders due to Tourette syndrome. Fifty-three percent of Canadians think that if cannabis were legalized, the cost of purchasing medical cannabis should be reimbursed under health plans. Support for reimbursement was highest in Alberta (65%).

#### **Summary of Topic 4: Advertising**

Advertising regulations vary among the regions that have legalized cannabis, and are enforced by various regulatory bodies within each state and country (). Broadly, outdoor advertising and promotional items are prohibited. Restrictions are placed on media advertising, sponsorship of events, and advertising targeted at minors. Specific rules around signage displayed at dispensaries are also heavily emphasized. Of all regions that have legalized cannabis, Washington State has the most restrictive regulations, including the requirement of health-warning labels on packages. The United States has two federal acts that place limitations on the advertising of tobacco within the country, as well as federal laws that primarily prohibit certain statements on products. If cannabis is legalized in Canada, advertising regulations would be necessary in a variety of areas. Considerations may include, populations most impacted by advertising, who advertising can target, who it is prohibited from targeting, alignment of advertising to other regulations such as age restrictions for use, and where cannabis can be used.

A systematic review was conducted regarding the effects of corporate advertising, public health campaigns and public services announcements in mass media on the use of alcohol, tobacco, cannabis, prescription drugs and illicit substances. This review found considerable evidence on the effects of media and advertising on substance use, however found minimal evidence regarding the effects of advertising bans. Such results demonstrate that most campaigns

influence intention to quit and have a modest effect on actual behavioral outcomes. Of all studies assessing mass media campaigns, all but one reported positive outcomes and none reported negative outcomes. The one study considering advertisement for cannabis found that those people who were exposed to a community-level health promotion campaign both in school and through posters, banners, and pamphlets were less likely to use cannabis.<sup>10</sup> Most of the included research came from experience with alcohol and tobacco. The outcomes of this research may be used in a variety of ways. Since the evidence shows that mass media campaigns can be an effective way of delivering a public health message, public service announcements may be useful tools for providing Canadians with information about risks and harms associated with use. However, advertising may also be used promotionally by companies selling cannabis products. Thus following from existing tobacco legislation it will be necessary to tightly regulate promotional advertising.

Among Canadians who support advertising, most prefer print or social media. Overall, 70% of Canadians think that if cannabis was legalized, it should not be advertised in any public media.

### **Summary of Topic 5: Experience with Legalization**

In July 2013, Uruguay became the first country in the world to legalize cannabis for non-medical use. Cannabis has now been legalized in six jurisdictions: Uruguay, Alaska, Colorado, Oregon, Washington and Washington D.C. On November 8, 2016, five US States voted on the proposal to legalize non-medical cannabis; the proposal was passed by Nevada, California, Maine and Massachusetts and failed in Arizona. Similar to alcohol, legal age of cannabis consumption is 21 years in all jurisdictions with the exception of Uruguay, where the legal age is 18 years. Regulations surrounding use, production, and sales differ across all places that have legalized (Table 20). For instance, the amount of cannabis an individual may possess at any given time ranges from one ounce (Alaska) to 8 ounces (Oregon). However, public consumption, as well as driving under the influence of cannabis, is prohibited in all jurisdictions.

For non-medical cannabis, there is no taxation in Uruguay, there is also no tax in Washington D.C. since sale of non-medical cannabis is prohibited. In Washington State the tax rate is 37% at the point of sale in Oregon there is a 17% excise tax with an additional local tax up to 3%, and in Colorado there is a 15% excise tax from producers and a 10% tax on retail. For

medical cannabis, there was no information on tax rate for Washington D.C., Alaska or Uruguay, tax rate is 6.5% in Washington State, 2.9% in Colorado, and it is not taxed in Oregon. With the exception of the District of Columbia, all regions have created a regulatory board or council for controlling the sale of cannabis, the majority of which are fused with or modelled after the regulatory board responsible for controlling the sale of alcohol in that region.

Once cannabis is legalized in Canada, regulations will be required on where it can be used, how it can be used, and how it can be bought and sold. It is not yet clear whether these regulations would be set federally or provincially. If it is the later, every effort should be made to harmonize the regulatory regime.

A systematic review was conducted on the impact of cannabis legalization. Broadly, legalization of cannabis results in more burn cases reported to the local burn center, more calls to pediatric poison control centers, and more cannabis-related emergency department visits.

Studies involving law enforcement and impaired driving found increases in impaired driving cases, with confirmed THC and carboxy-THC. In studies that examined the association between self-reported risk-factors and substance use, cannabis use remained stable while use of alcohol and cigarettes decreased. These studies also reported lower perceived harm and increased approval of cannabis use - outcomes that were concerning to treatment providers.

Overall, there is some evidence that experience with cannabis legalization may have negative repercussions with respect to: resource utilization; law enforcement and impaired driving cases; self-reported cannabis-specific risk-factors; and, other substance use including, but not limited to, cannabis. Unpublished studies/data found that after legalization, states reported: a stable level of self-reported cannabis use, a decrease in alcohol and cigarette use, an increase in cannabis use disorders, an increase in the number of arrests for cannabis-related crimes, increase in the number of drivers testing positive for THC, and an increase in health care resource utilization associated with cannabis use.

The impact of legalization in other places provides insight into the impact it may have within Canada. Poison control centers, burn centers and emergency departments may experience an increase in demand. Increased law enforcement may also be required to enforce safe driving, use or sales regulations. However, less law enforcement will be required for possession.

Survey results showed that the majority of Canadians believe cannabis to be equivalent to alcohol and cigarettes in terms of use, sales and economic regulations. Of note, over 70% of

respondents believed that driving under the influence of cannabis is equally as harmful as driving under the influence of alcohol. Public service advisories may be one mechanism for educating the public on the hazards of using cannabis and driving.

## Emerging Policy Messages

**Health Effects:** Use of cannabis in Canada is high by international comparisons. Based on experiences elsewhere, rates of use are likely to remain stable, or moderately increase after legalization. To the extent that cannabis use increases due to legalization, the healthcare system can expect an increase in patients presenting with: testicular cancer; mental health problems (including psychosis, mania, relapse of psychosis or schizophrenia); poor outcomes during pregnancy, such as low birthweight babies and birth complications, pulmonary dysfunction, neurocognitive brain changes, and functional brain changes. Jurisdictions that legalize cannabis will have to consider the potentially significant societal and economic impact of this burden, including its corresponding effects on financial and human resources. The Federal Task Force has recommended evidence-informed public education campaigns, in hopes of mitigating some of the potential harms related to cannabis use, and to inform the public about the risks associated with using cannabis.

**Minimum Legal Age:** The Federal Task Force has recommended that the minimum age for cannabis consumption in Canada should be 18, or align with the age of legal alcohol consumption in the province. This aligns with the practices in all jurisdictions that have legalized non-medical cannabis, although notably in many of the jurisdictions the minimum age for alcohol purchasing and consumption is 21 years. The Task Force further recommends discouraging use in those 15 to 25 years old, due to the risks associated with early use. Within Alberta, youth and young adults (those aged 15-24) are the most likely to have used cannabis in the past twelve months. Research suggests that earlier age of first use is associated with higher risk of dependency, higher risk of health harms, and a higher likelihood of using other illicit drugs. Given the high use and high risk of harms in those between 15-24 years old, targeted public health messages using best-evidence on how to reach youths should be developed.

**Passive exposure:** Passive exposure to cannabis smoke leads to cannabinoid metabolites in bodily fluids, sufficient for those passively exposed to test positive. Moreover, some exposed individuals experience intoxication. There is evidence of a dose-response relationship between THC content and cannabinoid metabolite concentrations in the urine. A higher THC content results in higher metabolite concentrations. It should be stressed that urinary testing is qualitative and confirms presence or absence, but is not quantitative. For second hand smokers, who may test positive, increased ventilation, larger air volume, and fewer cannabis cigarettes lit at one time all decrease metabolite concentrations in urine. When considering when and where cannabis can be consumed, these environmental factors should be considered as they may impact the health of cannabis smokers and non-smokers.

Second-hand cannabis smoke is more mutagenic and cytotoxic than tobacco smoke, and therefore second-hand inhalation should be considered a health risk. This knowledge is particularly important for children and individuals who are unable to control their exposure to others' smoke. The long-term effects of passive inhalation are unknown; with unknown long-term health effects, caution with policy making should be taken until further studies can be conducted. Alignment of smoking bylaws, with a combined policy approach to exposures to smoke of any kind – especially tobacco and cannabis are often co-used - may result in the most effective public policies. The Federal Task Force has recommended that current restrictions on tobacco smoking be applied to cannabis use, and that dedicated places to smoke cannabis should be permitted.

There is no established threshold that law enforcement could use to reliably differentiate between those who have actively smoked cannabis, and those who have been passively exposed. This raises important questions regarding whether there should be tolerance for individuals who produce positive urine tests. Further studies with realistic smoking conditions are required to provide data that may inform appropriate urine testing cutoff levels.

**Substance use:** There are multiple pathways of drug use. Most commonly, cannabis use directly precedes other illicit drug use. In addition, daily or near-daily cannabis use and early onset of use that have been shown to be strong predictors of using other illicit drugs. This suggests that it is not simply cannabis use that affects likelihood of using other illicit drugs, rather, it is frequency of use and multiple other factors that may cause some users to show a progressive

pattern in their use, while others do not. Where and when to intervene to reduce the potential harms associated with substance use is multi-factorial; the individual, their social context, genetic factors and environmental interplay. In the case of a substance like cannabis where prevalence is widespread, prioritizing prevention to pre-adolescent populations (before use is initiated) and developing harm minimization interventions that target reductions in the frequency of use, may be effective for reducing future illicit substance use and dependency.

**Dependency and Addiction:** Debates over the degree of cannabis addictiveness have been ongoing, partially due to difficulties in producing quantitative evidence. A systematic review of epidemiologic evidence reports that the global burden of cannabis dependence was 13.1 million people in 2010, which equates to 0.20% of the population <sup>11</sup>. Dependence is higher amongst males than females <sup>11</sup> and is more prevalent in high-income areas, compared to low-income areas <sup>11</sup>. There is evidence that a number of factors contribute to the development of cannabis dependence, including psychosocial, geographic, biologic, and socioeconomic variables <sup>11-15</sup>. Notably, our survey findings indicate that the Canadian public perceives cannabis to be addictive, but no more addictive than cigarettes or alcohol. Recognition amongst the public that cannabis is possibly addictive is an important step towards reducing harms.

**Medical Cannabis:** Due to the lengthy process required to become authorized to use medical cannabis, there may be an increase in people using non-medical cannabis to treat a clinical condition if it were legalized and easily accessible to non-medical users. However, it may become difficult to ensure patients are using it safely, with appropriate dosages, and for appropriate conditions. Consideration must be given to the fact that patients may begin using cannabis to treat a clinical condition, without the supervision of a physician or health care practitioner. The Federal Task Force has recommended maintaining two separate systems: one for medical access and one for non-medical access, and to monitor patient's ability to easily access cannabis for medical purposes.

**Conclusions:** Based on the limited experience in other jurisdictions, Canada can expect: negligible or modest increases in cannabis use; increased demand on health care resources, specifically burn centers, poison control centers, and emergency departments; increase in the

number of drivers under the influence; need for more law enforcement to enforce safe driving, and use or sales regulations; and, higher demand for addiction services. Before legalizing cannabis, it may be valuable to proactively increase the ability of these services to handle higher than average demand and be clear on the process of establishing impairment under the influence of cannabis. Public education campaigns may also help reduce how much of an impact cannabis legalization has on demand for these services.



## Topic 1: Current Canadian Context

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## Key Messages

- In Canada, cannabis is an illegal substance, classified as a schedule II drug under the Controlled Drugs and Substances Act
- There are a variety of lay terms and methods of use for cannabis; of those who have used cannabis in the past 12 months, the most frequent method of consumption was smoking, edibles and using a vaporizer
- Internationally, the possession of non-medical cannabis is legal in one country and five American states, including Washington D.C., and has been decriminalized in 31 countries and 18 states
- Key stakeholder groups include the Center for Addictions and Mental Health, the Canadian Center on Substance Abuse, Norml Canada, Cannabis in Canada/Cannabis Life Network, Alberta 420, Sensible BC.
- Nationally, 10.5% of Canadians report using cannabis within the past 12 months and the prevalence has decreased slightly since 2008. Canada's past-12-month-use is double the global prevalence.
- In Alberta, the prevalence of cannabis use in the past 12 months based on survey data is 20.1%
- In Alberta, groups that have a higher prevalence of cannabis use when compared to the national average, include 15 to 24 years, aboriginal people, individuals who work part-time or are unemployed, and individuals who have a household income between \$30,000 and \$49,000 per year
- Nation-wide, 65.1% of individuals support legalization. Legalization support varies by province: 63.8% in Alberta, 71.5% in British Columbia, 64.4% in Ontario and 58.8% in Quebec
- Support for legalization does not vary statistically by any demographic characteristic; only by use within the past 12 months

## Cannabis: An Introduction

*Cannabis sativa*, also known as cannabis, cannabis, weed, pot, or bud, is a multi-use crop that has been cultivated by humans for thousands of years. “Cannabis” is used to refer to the plant as a whole, while “marijuana” refers to the dried leaves of the cannabis plant <sup>16</sup>. Today, there are three varieties of cannabis, *C. sativa*, *C. indica*, and ‘hybrid strains’, each of which induce different psychological and physiological effects depending on which cannabinoids they contain <sup>3</sup>. The two most notable cannabinoids commonly investigated for medicinal use are tetrahydrocannabinol (THC) and cannabidiol (CBD). The psychoactive properties of THC are well known while the effects of CBD are still being investigated.

Hemp plants, which contain very small amounts of psychoactive cannabinoids, are commonly used to create fiber for use in cloth making, and hemp seeds are ingested by both humans and animals as a source of protein. For this reason, industrial hemp has been regulated and cultivated legally in Canada since 1998 <sup>17</sup>.

However, cannabis remains the most frequently trafficked, cultivated, and used illicit drug in the world<sup>18</sup> due to higher concentrations of the psychoactive cannabinoid (THC) in the dried flowers of female cannabis sativa and indica plants. There is a variety of lay terms for cannabis and various methods of use (Table 1). A survey of the public conducted by the University of Calgary in July of 2016 found that of those who have used cannabis in the past 12 months (19.7% of Canadians, 20.1% of Albertans), the most frequent methods of consumption were smoking (78.8%), edibles (31.0%) and using a vaporizer (25.1%).

In recent years, there has been increasing evidence published on the safety and medicinal use of cannabis products and derivatives <sup>19</sup>. As a result, there have been calls to reconsider the legal status of cannabis use at regional, national, and international levels.

Table 1: Delivery Modes and Devices by Cannabis Product

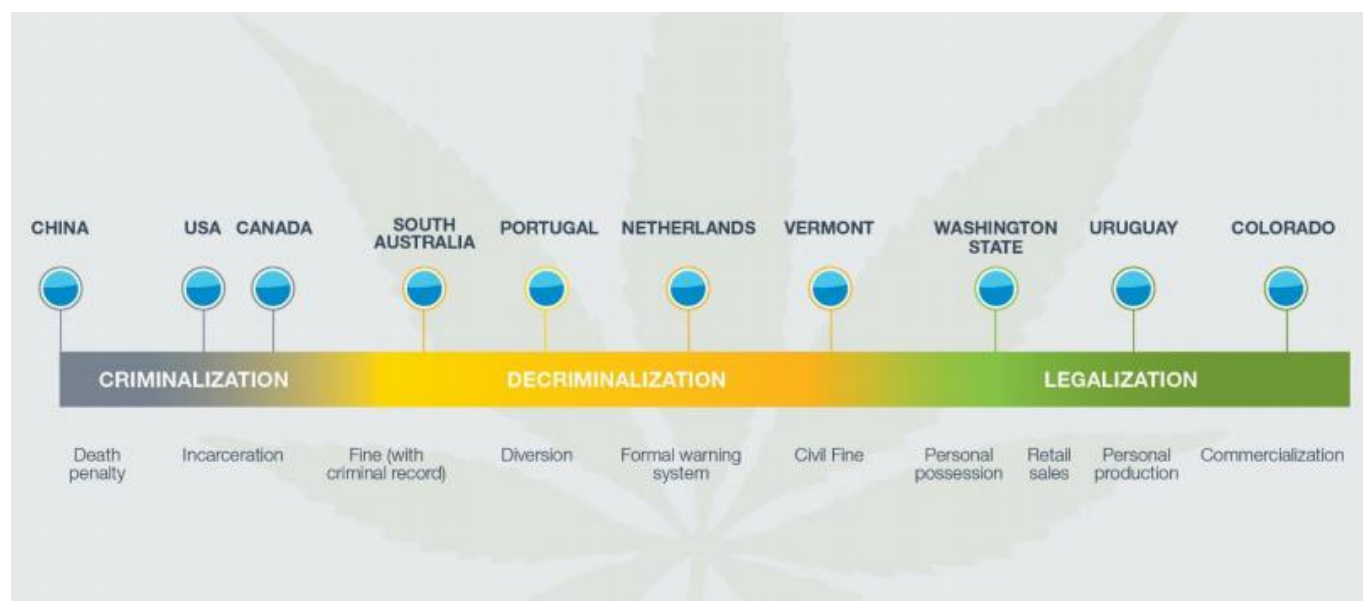
Cannabis Product	Description of Cannabis Product	Production	THC concentration	Other names used to describe product	Mode of consumption	Devices
<b>Dried cannabis</b>	Cured cannabis flower (the “bud” of the plant)	At harvest time, cannabis plants are cut and cured (hung to dry) <sup>20</sup>	<1% - ~30%	Pot, weed, grass, ganga, dope, herb, reefer, Mary Jane, chronic <sup>21</sup>	-Smoking -Vaporizing (“vaping”)	-Pipe -Water pipe (bong) -Rolling paper (joint) -Vaporizer
<b>Cannabis concentrate</b>	Made from the oils produced by trichome on the cannabis flowers	There are a number of methods for extracting cannabis concentrates, and the product depends on the method chosen <sup>22-25</sup>	20%-80%, depending on the process <sup>22,26</sup>	Hash oil, Butane hash oil, live resin, rosin, CO2 oil, kief, water hash <sup>22</sup>	-Smoking -Vaporizing -Dabbing <sup>27</sup>	-Butane torch device -“Dabbing rig” -Vaporizer -Hash pipe -Joint (with dried cannabis) <sup>28</sup>
<b>Hashish</b>	Made from cannabis resin or the cannabinoid-producing trichomes on the cannabis flowers. It is a fine powder that covers the surface of the flowers <sup>27</sup>	Made by compressing resin/kief. Ethanol or other solvents might be used as a method to strip the plant of kief more effectively <sup>26</sup>	20%-60% <sup>22</sup>	Hasheesh, hashisha, hash, rosin hash	-Smoking -Vaporizing	-Pipe -Water pipe (“bong”) -Rolling paper -Vaporizer
<b>Hash oil</b>	Made from dried cannabis material (usually not the seeds or stalks, but they may be included) <sup>29</sup>	Plant material is mechanically broken up, then heated to decarboxylate the cannabinoids. A solvent is then used to extract the cannabinoids from the plant material <sup>29</sup>	10%~50% <sup>30</sup>	N/A	-Smoking -Vaporizing -Dabbing -Ingestion -Topical	-Butane torch device -“Dabbing rig” -Vaporizer -Hash pipe -Joint (with dried cannabis) -Mixed with food preparation products <sup>28</sup>
<b>Butane Hash Oil (BHO)</b>	Oils and cannabinoids from trichomes on dried cannabis plants, may contain traces of solvent <sup>23</sup>	The cannabis plant is washed in pressurized butane to dissolve the oils, then heated to get rid of the excess solvent <sup>23</sup>	60%-90% <sup>23</sup>	Shatter, wax, crumble, budder, oil, errl, honeycomb, moon rock, nectar <sup>22</sup>	-Smoking -Vaporizing -Dabbing <sup>28</sup>	-Butane torch device -“Dabbing rig” -Vaporizer -Hash pipe -Joint (with dried cannabis) <sup>28</sup>
<b>Live resin</b>	Made from fresh-frozen plants	Same extraction process as BHOs, but using fresh-frozen plants. The fresh-frozen plants have different terpene content than dried cannabis plants, creating a different flavor and texture <sup>24,25</sup>	60%-90% <sup>25</sup>	N/A	-Smoking -Vaporizing -Dabbing <sup>28</sup>	-Butane torch device -“Dabbing rig” -Vaporizer -Hash pipe -Joint (with dried cannabis) <sup>28</sup>
<b>Rosin</b>	May be extracted from dried flowers, trim, water has, or kief <sup>23</sup>	Cannabis product is placed between two sheets of parchment paper, heated (may be done with a straightening iron), then applied pressure to. This kind of concentrate is often made at home <sup>23</sup>	50%-70% <sup>23</sup>	N/A	-Smoking -Vaporizing -Dabbing <sup>28</sup>	-Butane torch device -“Dabbing rig” -Vaporizer -Hash pipe -Joint (with dried cannabis) <sup>28</sup>
<b>CO2 Oil</b>	Made of cannabis oils produced by trichomes	THC-containing oils are dissolved through a process called supercritical fluid extraction, where the cannabis plant is washed in supercritical CO2	50%-95% <sup>23</sup>	N/A	-Smoking -Vaporizing -Dabbing <sup>28</sup>	-Butane torch device -“Dabbing rig” -Vaporizer -Hash pipe

		(scCO2) and the cannabinoids and terpenes are dissolved within it <sup>23</sup>				-Joint (with dried cannabis) <sup>28</sup>
<b>Kief</b>	Made of dried trichomes <sup>22</sup>	Processors break the trichomes away from the plant using a sifting screen <sup>22</sup>	20%-60% <sup>22</sup>	Dry sieve/dry sift hash <sup>22</sup>	-Smoking -Vaporizing -Dabbing <sup>28</sup>	-Butane torch device -“Dabbing rig” -Vaporizer -Hash pipe -Joint (with dried cannabis) <sup>28</sup>
<b>Water Hash</b>	Made of trichomes from dry or fresh-frozen cannabis plant <sup>22</sup>	Processors use a machine or manually break trichomes off, which are then sifted to remove excess plant material using “microscreen” fabric bags <sup>22</sup>	50%-80% <sup>22</sup>	Bubble hash, solventless wax, ice wax <sup>22</sup>	-Smoking -Vaporizing -Dabbing <sup>28</sup>	-Butane torch device -“Dabbing rig” -Vaporizer -Hash pipe -Joint (with dried cannabis) <sup>28</sup>
<b>Cannabis Butter/Oil</b>	A cannabis and butter product that is usually made by mixing butter with dried buds from the cannabis plant <sup>31</sup>	Processing involves baking the cannabis buds and then mixing them in a boiling mixture of water and butter to decarboxylate the psychoactive ingredients in cannabis. The butter product may then be used as an ingredient in edible cannabis products <sup>31</sup>	Depends on the strain of cannabis used (>1% to ~30%)	Cannabutter <sup>31</sup>	For use in preparation of edible cannabis products <sup>31</sup>	-Additional cooking/food preparation ingredients
<b>Fresh cannabis (all parts of the plant)</b>	All parts of a fresh cannabis plant (not dried or frozen) <sup>24</sup>	Contain THCA and CBDA, which have less psychoactive properties than THC and CBD. THCA and CBDA must be decarboxylated to release the psychoactive ingredients for oral ingestion <sup>24</sup>	Much lower than when cured, with higher % of the carboxylated form <sup>32</sup>	(see alternative names for dried cannabis)	Juicing	-Blender -Juicer
<b>Tincture</b>	Decarboxylated cannabis, mixed with a solvent (usually alcohol) for administration <sup>24,33</sup>	Cannabis extracts are mixed with either alcohol or glycerin <sup>24</sup>	Depends on the strain of cannabis used, and the method used to make the tincture <sup>33</sup>	N/A	-Topical, often under the tongue <sup>24</sup>	-Dropper
<b>Spray</b>	Made with decarboxylated cannabis plant	See instructions for tinctures	Example: one 10mL spray vial holds 10 doses of 25 mgs of THC <sup>34</sup>	Sativex (a well-known drug brand) <sup>35</sup>	-Topical, usually administered orally (under the tongue) <sup>34</sup>	-Spray bottle -Applicator
<b>Salves/ Ointment/ Balm</b>	May be made from all parts of the cannabis plant, depending on the desired potency <sup>36</sup>	Often used by medical cannabis users, it is made of cannabis oil (e.g. cannabis mixed with coconut oil), beeswax, and Vitamin E oil <sup>36</sup>	Depends on the strain of cannabis used, and the method used to make the salve <sup>36</sup>	N/A	-Topical, often directly onto trouble area <sup>36</sup>	-Applicator (e.g. pen)
<b>Cannabis patches</b>	Contain cannabis concentrates (e.g. terpenes, cannabinoids) <sup>32</sup>	Manufacturers produce cannabis concentrate-infused adhesive patches <sup>32</sup>	Mary’s Medicinals Half-and-Half patches deliver 5mg THC and 5mg CBD; dosages change depending on the patch <sup>32</sup>	Transdermal patch <sup>32</sup>	Transdermal	-Patch (resembles nicotine patch) <sup>37</sup>

## Cannabis: Criminalization, Decriminalization and Legalization

There are three broad categories of regulation for cannabis: criminalization, decriminalization and legalization. Internationally, countries have adopted frameworks across the entire spectrum of these regulatory approaches (Figure 1) When cannabis is criminalized, it is regulated as an illegal substance; the purchasing, selling and use of cannabis is prohibited and enforced <sup>4</sup>. Levers for enforcement may include fines, incarceration, and/or mandatory treatment <sup>4</sup>. Individuals found possessing, using or selling cannabis will have a criminal record <sup>4</sup>. Currently, countries such as China, the USA and Canada are regulating cannabis within a criminal regulatory approach.

Figure 1: Global Continuum of Regulatory Approaches (from the Canadian Center on Substance Abuse) <sup>4</sup>



In places where cannabis is decriminalized, it is still considered an illegal substance; however, penalties are non-criminal in nature for some or all offenses <sup>4,5</sup>. There is a broad array of approaches to decriminalization ranging from lenient to strict regulation (Table 2). Some decriminalized countries have regulations on ages of use, what products may be used, how much cannabis may be possessed, and potency <sup>4</sup>. Fines may be used as an enforcement lever, but are not related to a criminal record <sup>4</sup>. In some countries that have decriminalized cannabis, as in the

Netherlands, there are regulated sites, where cannabis can be used <sup>4</sup>. Other decriminalized states, such as Vermont, have adopted strict regulation such that civil fines are issued for any personal possession <sup>4</sup>. In the most lenient states, such as the United Kingdom, individuals are given warnings increasing in severity and the first several police encounters are not usually associated with fines <sup>4</sup>.

Table 2: Summary of Decriminalization Approaches <sup>38-40</sup>

	Belgium	Netherlands	Portugal	Spain	Vermont	United Kingdom
Year of Decriminalization	2003	2012	2001	1992	2013	
Decriminalization (General)		✓	✓	✓	✓	✓
Regulated sites (i.e., cafes)		✓				
Collectives or private members' clubs	✓			✓		
Notes	Less than 3g is a fine of 75-125 euros <sup>40</sup>	Less than 5g is confiscated with a police dismissal <sup>39,40</sup>	Quantity associated with up to 10 days of personal use allowed <sup>39</sup>	Public use and possession is a fine between EUR 601 and 30,000 <sup>39</sup>	Civil fines, but no criminal charges	Warning usually issued for possession less than 1 ounce

Legalization refers to a regulatory approach where cannabis is identified as a legal substance under the law <sup>4</sup>, and all legal prohibitions against it have been removed <sup>5</sup>. Where cannabis is legal, it may be regulated by regional jurisdiction, the country, or it may be unregulated (free-market) <sup>4</sup>. When regulated by regional jurisdiction or country, elements that may be regulated include: production, age of purchase, amount of cannabis that can be possessed, and growing for personal use <sup>4</sup>. This is the least adopted regulatory framework with only eight US states (Washington State, Colorado, Oregon, Alaska, California, Maine, Massachusetts, and Nevada), one US jurisdiction (Washington DC) and one country (Uruguay) adopting this approach <sup>4</sup>.

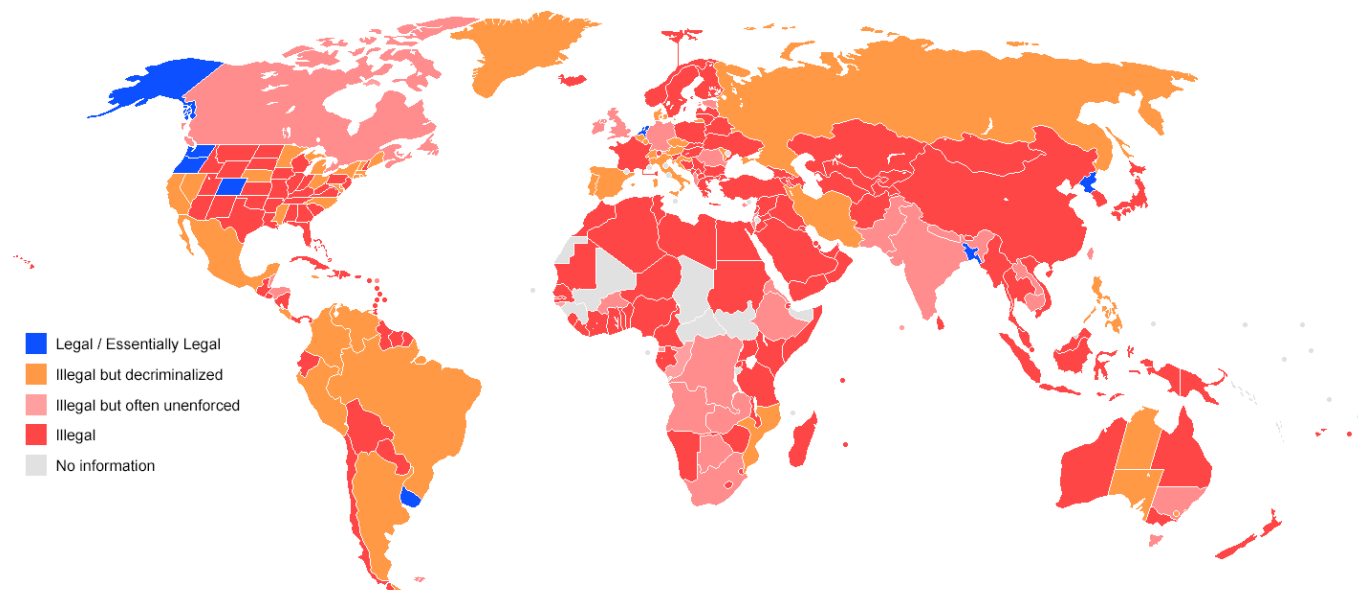
## Cannabis: Current Context

### International

#### *International Legalization and Decriminalization of non-Medical Cannabis*

Internationally, the possession of non-medical cannabis is legal in one country (Uruguay), eight American States (Washington State, Colorado, Oregon, Alaska, California, Maine, Massachusetts, and Nevada) and one American jurisdiction (Washington DC), and has been decriminalized in 31 countries and 18 states. Cannabis is decriminalized and essentially legal in Bangladesh, North Korea, and the Netherlands; however, it has not yet been legalized. Medical cannabis is legal or tolerated in 12 countries <sup>41</sup> (Figure 2).

Figure 2: Summary of Global non-Medical Cannabis Legislation<sup>42</sup>



### *International Law*

Cannabis is included within the United Nations (UN) drug control regime, which is made up of three treaties: the 1961 Single Convention on Narcotic Drugs, the 1971 Convention on Psychotropic Substances, and the 1988 Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances <sup>43</sup>. If Canada legalizes cannabis, it would violate international law and would be required to formally withdraw from these treaties <sup>6</sup>. Each of these treaties allows some deviation if it is required by a country's constitution; however, there is nothing in Canada's



constitution allowing the possession of cannabis for personal use <sup>6</sup>. Therefore, the constitution would need to be amended if cannabis is legalized to avoid opposing the UN conventions <sup>6</sup>.

The 1961 Single Convention on Narcotic Drugs states that the “production, manufacture, export, import, distribution of, trade in, use, and possession” of cannabis should be limited to scientific and medical uses only <sup>41</sup>. This treaty recognizes that narcotic drugs may be required for medical purposes, allowing countries to legalize medical cannabis. Countries must provide an estimate in the amount of cannabis they will require in a year and may not import more than that quantity. There is also a limit to the growth and production of cannabis plants in order to protect public health and welfare and to control the production of cannabis if it is allowed. The manufacturing and distribution of cannabis must be done by licensed groups only, and importing and exporting require authorization. Each country must enforce state punishment for the possession, production, sale, and delivery of illicit substances <sup>41</sup>. Legalizing cannabis contradicts this article <sup>6</sup>.

The 1971 Convention on Psychotropic Substances also recognizes that psychotropic substances may be needed for medical and scientific purposes and access should not be completely restricted <sup>44</sup>. Under this treaty, the use of all schedule I drugs, including cannabis, should be prohibited except for scientific or medical use. Individuals cannot be given more than required for medical use and medical or scientific use must be recorded. Production, distribution, and trade requires licensing <sup>44</sup>. Cautions and warnings about use must be provided on packaging, and the advertisement of all psychotropic substances to the public is banned <sup>44</sup>.

The most recent treaty addressing cannabis is the 1988 Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances <sup>45</sup>. This convention provides measures addressing illicit drug trafficking and combating organized crime. All drugs involved in illicit trafficking must be confiscated. All international trade of illicit substances must be controlled and permitted only in the countries involved. Countries should limit the use of mail delivery for illicit drug trafficking. Production, possession, or purchasing of illicit substances for personal use is prohibited, but this article is often questioned <sup>45</sup>.

## **Canada**

### *Policies, Regulations and Legislation on Cannabis Use, Sale, and Purchase*

Within Canada, cannabis is classified as a schedule II drug under the Controlled Drugs and Substances Act (CDSA) <sup>46</sup>. This act governs the penalties for the possession, production, and trafficking of cannabis. The maximum penalties are six months for possession of less than 30 grams, five years for possession of more than 30 grams, 14 years for production, and a life sentence for trafficking more than 3 kilograms <sup>46</sup>. The harshness of the penalty depends on the amount possessed, produced, or trafficked, the criminal history of the person, and the circumstances surrounding the crime. Only two groups of people can legally possess cannabis other than cannabis: a licensed producer or an individual who requires cannabis in connection with their employment for testing producers <sup>47</sup>.

### *Medical Cannabis*

Medical cannabis is legal in Canada. Medical cannabis is exempt from the above regulations under the Access to Cannabis for Medical Purposes Regulations (ACMPR) <sup>48</sup>. The ACMPR provides regulations for everything relating to medical cannabis including sales, production, possession, product labelling, and client and license registration. Medical cannabis will be further discussed in Cannabis Evidence Series Topic 3.

### *Accessibility of non-Medical Cannabis*

There are several “compassion clubs” and dispensaries that produce and sell cannabis illegally <sup>49</sup>. Some of these would include grow operations, which are generally run out of houses or residential buildings <sup>50</sup>. Between 2007 and 2011, there was an estimated 793 illegal grow-ops throughout Alberta, 662 of which were in Calgary and Edmonton <sup>50</sup>.

Compassion clubs operate in different ways. For example, Natural Health Services in Calgary and Edmonton functions similarly to a primary care network; however, the physicians only prescribe medical cannabis to clients. This is not illegal, but the physicians often prescribe cannabis after a very short consultation <sup>51</sup>. Other compassion clubs operate under the guise of wellness centres that offer acupuncture and yoga, and also allow users to purchase cannabis <sup>52</sup>. Though these clubs are not legal, many are ignored by law enforcement if they are not part of

organized crime and there are no complaints from the public <sup>52</sup>. There are about 50 compassion clubs across Canada <sup>52</sup>.

Mail-order cannabis is also a growing issue <sup>53</sup>. There are several websites where cannabis can be ordered online and shipped to the address provided. Examples would include Mary Jane Mail, Best BC Bud, Herbal Dispatch, and Weedism. Canada Post publicly provides regulations for shipping medical cannabis, which allow these websites to ship cannabis discreetly <sup>54</sup>.

## History of Cannabis Control in Canada

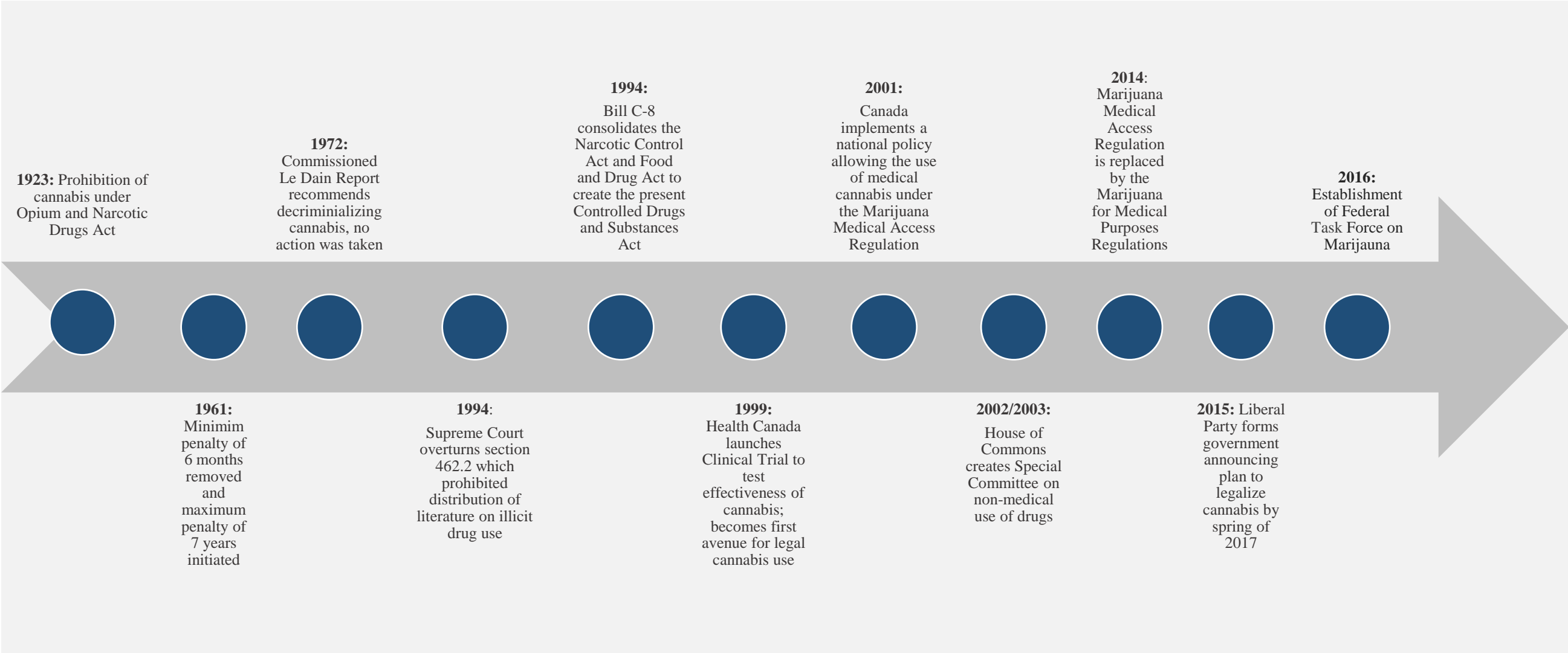
A visual depiction of key events in the development of cannabis control in Canada is shown in Figure 3. The first account of drug control in Canada occurred in 1908, when the manufacture and sale of smoking opium became prohibited following the anti-Asiatic riots in Vancouver. The Minister of Labour introduced Bill 205 as the *Opium and Drug Act* <sup>55</sup>. In 1923, cannabis was added, and the act was renamed the *Opium and Narcotic Drugs Act* <sup>55</sup>, wherein the maximum penalty for the possession of cannabis was two years, with a minimum penalty of six months imprisonment <sup>55</sup>. In 1961, the *Narcotic Control Act* replaced the *Opium and Narcotic Drugs Act* <sup>55</sup>. The six-month minimum penalty for cannabis possession was removed and the maximum penalty increased to seven years. Consequences doubled for repeat offences <sup>55</sup>. In 1974, the Senate proposed Bill S-19, intending to amend the *Narcotic Control Act*. The bill intended to remove cannabis from the act and include it in the *Food and Drugs Act* instead, which would make possession of cannabis a summary conviction, reducing the maximum penalty <sup>55</sup>. Trafficking, possession with intent to traffic, cultivation, and importing or exporting without a proper license would still remain illegal. The maximum penalty for indictment was to be more severe, increasing to thirteen years for importing and exporting and from seven to ten years for other infractions; however, the bill was defeated by the House of Commons in 1975 and did not take effect <sup>55</sup>.

The Commission of Inquiry into the Non-Medical Use of Drugs, also referred to as the Le Dain Commission, began in 1969 <sup>55</sup>. This review examined the effects of cannabis and other drugs, including health effects, sensory, cognitive and intellectual effects, and effects on aggression and crime. The interim report proposed the decriminalization of all drugs, suggesting an alternate

fine for possession <sup>55</sup>. The final report recommended removing criminal penalties for the possession of cannabis. This recommendation was largely ignored and no changes were made <sup>55</sup>.

In 1994, the Supreme Court overturned Section 462.2 of the criminal code which prohibited the distribution of literature on illicit drug use, saying it unjustly infringed upon the guarantee of freedom of expression provided by the *Canadian Charter of Rights and Freedoms* <sup>55</sup>. This ruling aided several activist groups by allowing the promotion of cannabis <sup>55</sup>.

Figure 3: Timeline of Key Cannabis Events in Canada



At the same time, Bill C-7 was introduced by the Liberal government <sup>55</sup>. This bill consolidated the *Narcotic Control Act* and much of the *Food and Drugs Act* to create the *Controlled Drugs and Substance Act* (CDSA), which is the current act in place. Cannabis remained illegal and was considered a schedule II drug. The sentence for possession remained the same and the maximum penalty for trafficking and possession with intent to traffic was reduced from life imprisonment to five years minus one day <sup>55</sup>.

Following the introduction of the act, several court cases challenged the CDSA. The three most prominent cases were heard in the provincial courts of Ontario, British Columbia and Alberta with the judge ruling in each case that prohibiting the cultivation of cannabis is unconstitutional <sup>55</sup>.

In June 1999, Canada's Minister of Health announced a clinical trial to test cannabis as a medicinal treatment and a potential avenue for those who require medical cannabis to be exempt from the law <sup>55</sup>. In July of 2001, Canada implemented a national policy allowing the use and paid supply of medical cannabis, becoming the first country to do so <sup>55</sup>. The *Marijuana Medical Access Regulation* (MMAR) is annexed to the CDSA. Cannabis can be accessed for medical use in the treatment of severe nausea, cachexia, anorexia, or weight loss associated with cancer or HIV/AIDS; persistent muscle spasms from multiple sclerosis, or a spinal cord injury or disease; seizures associated with epilepsy; and severe pain associated with cancer, HIV/AIDS, multiple sclerosis, spinal cord injury or infection, or severe arthritis <sup>56</sup>. It can also be accessed for compassionate end-of-life care or to treat a debilitating symptom associated with a medical condition not previously mentioned. All patients accessing medical cannabis must be ordinary residents of Canada <sup>56</sup> and there are regulations for producers and suppliers <sup>55,56</sup>.

In 2002, the House of Commons created a Special Committee on the Non-Medical Use of Drugs, which recommends the eventual decriminalization of possession and cultivation of less than thirty grams for personal use <sup>55</sup>. In 2003, the Liberal government proposed Bill C-38, which aimed at amending the CDSA and decriminalizing the possession of up to fifteen grams of cannabis. The bill was terminated when elections were called in June of 2004, primarily because

the United States' Drug Enforcement Administration threatened to increase the frequency of searches at Canada-United States borders <sup>55</sup>.

In 2015, the Liberal government of Canada formed a majority government and announced their plan to legalize cannabis. On June 20<sup>th</sup>, 2016 a Federal Task Force on Marijuana chaired by former deputy prime minister Anne McLellan was announced <sup>2</sup>. This nine-member board consists of representation from Quebec, British Columbia, Newfoundland and Labrador, Ontario, and Saskatchewan. The objective of the task force is to collect input on how to legalize cannabis and produce recommendations. Their findings will be considered by the federal government. Cannabis is expected to be legalized by the spring of 2017.

## **Stakeholders**

### **Government of Alberta Initiatives**

Few initiatives were identified regarding cannabis use in Alberta. One initiative, called Grow-op Free Alberta, was launched in May of 2014 with the objective of shutting down illegal grow-ops <sup>50</sup>. Grow-op Free Alberta put forth thirty-seven recommendations; the overall goal being a reduction in the number of illegal cannabis grow operations (MGOs), or grow-ops, in Alberta <sup>50</sup>. Recommendations came from discussions with stakeholders in a broad variety of organizations including police agencies, fire officials, public health safety code officers, home inspectors, mortgage lenders and real estate companies, and utility companies and associations <sup>50</sup>. An online survey was utilized to gain public opinion and input. All recommendations fall under eight broad categories: detection, notification, and disclosure; community and environmental impact, inspection and remediation; child protection; safety and health hazards; utility usage and theft; licensed grow-ops and medical cannabis access program; and implementation the recommendations <sup>50</sup>. Specific recommendations include creating public awareness campaigns to increase knowledge about the health risks associated with MGOs, requiring real estate agents to disclose when a property was previously used as an MGO, and improving upon the Drug Endangered Child Act <sup>50</sup>. Though the final recommendation was to develop progress reports every six months to ensure the recommendations are being implemented, no such report could be found and no information was found on whether this initiative has reduced grow-ops in Alberta <sup>50</sup>.

### Government of Canada Initiatives

The exclusion of cannabis from the Food and Drug Act is one example of a federal initiative <sup>57</sup>. Under the Marijuana Exemption (FDA) Regulations (2013), cannabis has been exempt from food and drug regulations if it is produced, imported, or exported by a licensed producer <sup>57</sup>. Because of this, the rules of production, storage, packaging, labelling, and shipping under the Food and Drug Regulations (FDR) do not apply to cannabis; however, these regulations are covered under the Marijuana for Medical Purposes Regulations (MMPR) <sup>47</sup>.

Perhaps the largest federal initiative regarding cannabis in Canada is the promise of the Liberal government to “legalize, regulate, and restrict access to” cannabis <sup>58</sup>. Cannabis is expected to be legalized by Spring 2017 <sup>59</sup>. The Liberal Party Platform states that the consumption and incidental possession of cannabis is to be removed from the criminal code in conjunction with the enactment of more severe laws to punish those who provide to minors, drive while impaired, and sell outside the regulatory framework <sup>58</sup>. A task force was initiated in June 2016 to inform the federal decision on cannabis legalization <sup>2</sup>.

### Canadian Organizations with Cannabis-related Mandates

There are a number of Canadian organizations that have mandates related to cannabis and its use (Table 3). Many of these organizations have ongoing research related to cannabis legalization and use within Canada. Broadly, these groups focus on influencing the policy development for cannabis within Canada.

Table 3: Examples of Canadian Organizations with Cannabis-related Mandates

Agency	Focus	Cannabis-related Work
Canadian Center on Substance Abuse (CCSA) (Health Canada funded)	Focus on issues related to substance use and abuse that affect the health and safety of Canadians, including alcohol, cannabis, and prescription drugs	<ul style="list-style-type: none"><li>• Maternal cannabis use</li><li>• Cannabis and driving</li><li>• Impact on mental health and cognitive functioning</li><li>• Impact on respiratory functioning</li><li>• Cannabis and youth</li><li>• Regulatory approaches (summary of global regulatory models)</li></ul>
Center for Addiction and Mental Health (CAMH)	Public teaching hospital in Toronto, and leading research center	<ul style="list-style-type: none"><li>• Policy framework which examines evidence on cannabis, legalization etc.</li></ul>



Canadian Drug Policy Coalition	“Support the development of a drug policy for Canada that is based in science, guided by public health principles, is respectful of the human rights of all...”	<ul style="list-style-type: none"> <li>• Regulatory approaches</li> <li>• Drug policy</li> </ul>
Mental Health Commission of Canada (MHCC)	Funded by Health Canada, with 10-year mandate to improve mental health in Canada	<ul style="list-style-type: none"> <li>• Research on cannabis and psychosis</li> </ul>
Healthy Canadians	Government of Canada initiative	<ul style="list-style-type: none"> <li>• Prevalence/incidence data and surveys</li> </ul>
The Canadian Consortium for the Investigation of Cannabinoids	Federally registered Canadian not-for-profit. “...basic and clinical researchers and health care professionals established to promote evidence-based research and education concerning the endocannabinoid system and therapeutic application”	<ul style="list-style-type: none"> <li>• Not available</li> </ul>
Canadian Medical Cannabis Council	Committed to providing safe, quality, access, and security to those who need medical cannabis	<ul style="list-style-type: none"> <li>• Created a code of ethics promoting safety, integrity, easier access, security, and research</li> </ul>

### **Pro-Legalization Groups in Alberta**

A number of groups that support cannabis decriminalization and legalization exist in Alberta and Canada. Some, such as Norml Canada, Cannabis in Canada/Cannabis Life Network, Canadian Students for Sensible Drug Policy, Marc and Jodie Emery of Cannabis Culture magazine and Pot TV, Alberta 420, and Sensible BC advocate specifically for the legalization of non-medical cannabis. These advocacy groups are not-for-profit member operated and member funded groups. Others, such as the Canadian National Medical Marijuana Association advocate for the use and users of medical cannabis.

### **General Public**

The general public, both cannabis users and non-users, may be impacted by a decision to legalize or not legalize cannabis and are therefore important stakeholders. Within the general public there are a variety of opinions on use, and legalization (see page 40).

## **Utilization of Cannabis across Canada**

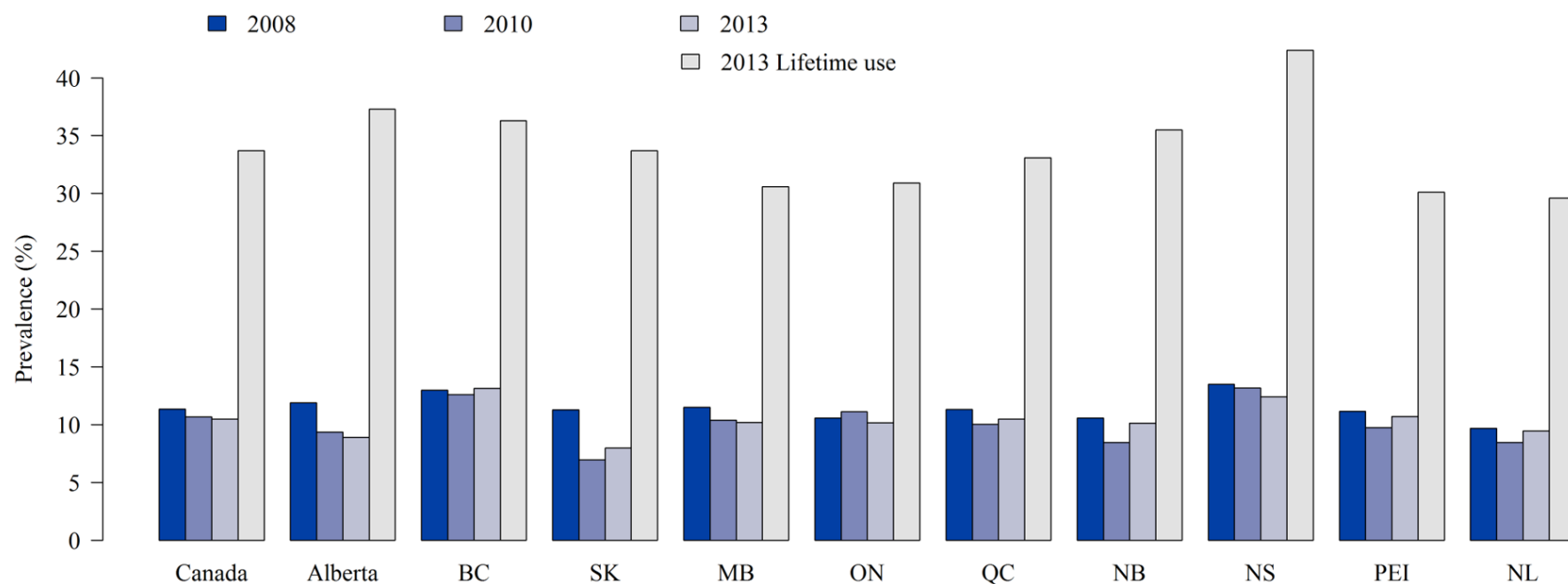
An analysis of cannabis use, in comparison to other substances, was completed using data from two national surveys conducted by Statistics Canada (the Canadian Alcohol and Drug Use Monitoring Survey (CADUMS) and the Canadian Tobacco, Alcohol and Drugs Survey (CTADS)). CADUMS is a national survey conducted annually from 2008 to 2012. It provides an estimate of current drug use trends across Canada and by province over time. The total sample size is 11,090 individuals, and includes individuals 15 years of age and older. CTADS is a national survey conducted in 2013 (replacing CADUMS) and provides the most recent estimates of use. While both these surveys provide the best estimates available of use in Canada, it is likely that these data under-report frequency of use as the data are self-reported and people are likely to under-report their use of illicit substances <sup>60,61</sup>.

### **Cannabis use across Canada**

Nationally, 10.5% of Canadians report using cannabis within the last 12 months and 33.7% report lifetime use (Figure 4). The prevalence of use within the last 12 months has decreased slightly since 2008 (11.7% in 2008 vs. 10.5% in 2013). Iceland has the highest past-12 months-use prevalence at 18.3%, followed by the United States at 15.4%, then Italy and New Zealand at 14.6% <sup>62</sup>. Spain and Australia each report past-12 months-use prevalence at 10.6%, and 10.16%, respectively <sup>62</sup>.

In Alberta, the use is lower than the national average, and the second lowest provincial use rate, with 8.9% reporting use within the last 12 months. However, Alberta has amongst the highest lifetime use (37.3%), second only to Nova Scotia (42.4%). Use has declined across all provinces from 2008 to 2013, with the exception of BC (Figure 4).

Figure 4: National and Provincial Prevalence of Cannabis Use in the Past 12 Months

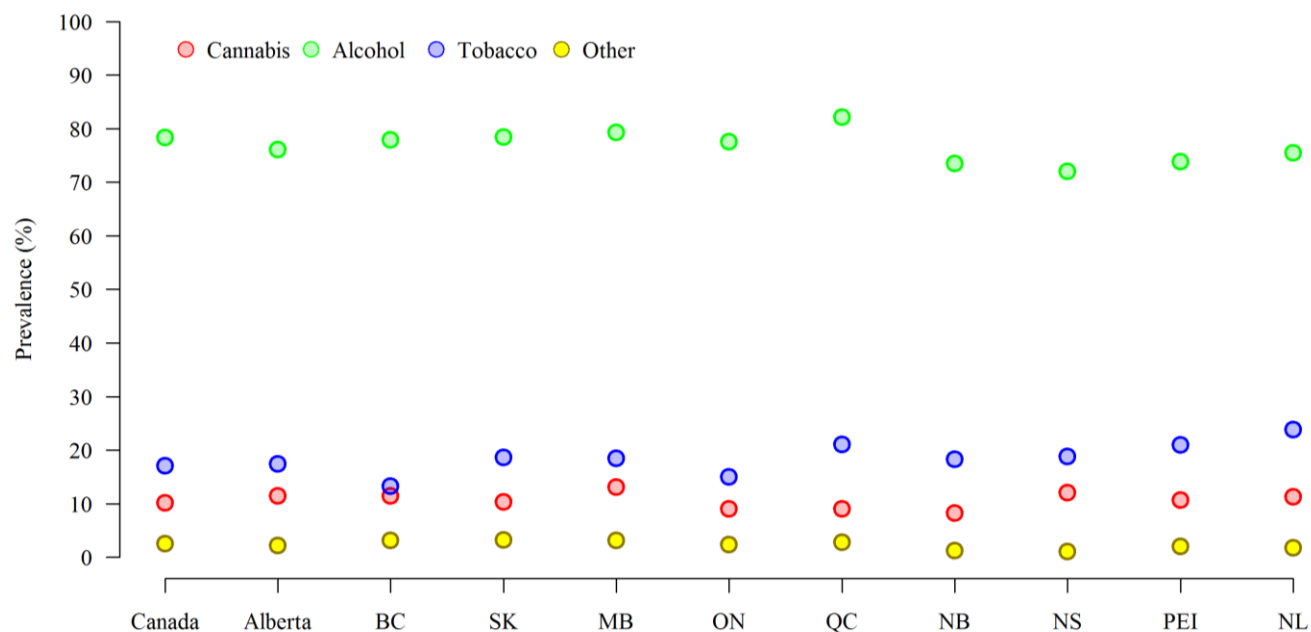


		Canada	Alberta	BC	SK	MB	ON	QC	NB	NS	PEI	NL
Lifetime use	2013	33.7%	37.3%	36.3%	33.7%	30.6%	30.9%	33.1%	35.5%	42.4%	30.1%	29.6%
	2008	11.4%	11.9%	13.0%	11.3%	11.5%	10.6%	11.3%	10.6%	13.5%	11.2%	9.7%
	2010	10.7%	9.4%	12.6%	7.0%	10.4%	11.1%	10.1%	8.5%	13.2%	9.8%	8.5%
	2013	10.5%	8.9%	13.2%	8.0%	10.2%	10.2%	10.5%	10.1%	12.4%	10.7%	9.5%
Change in past 12 months use 2008 to 2013		-0.9%	-3.0%	0.2%	-3.3%	-1.3%	-0.4%	-0.8%	-0.4%	-1.1%	-0.5%	-0.2%

### Cannabis use compared to other substances

In 2012, substance use in Alberta is not significantly different from Canadian national averages or from other provinces. Nationally, 78% report using alcohol, 17% report using tobacco, 10% report using cannabis, and 3% report using other substances (Figure 5). The use of cannabis is slightly lower than that of tobacco. Alberta has similar rates of substance use (alcohol 76%, tobacco 17%, cannabis 11%, and other 2%) compared to the national average.

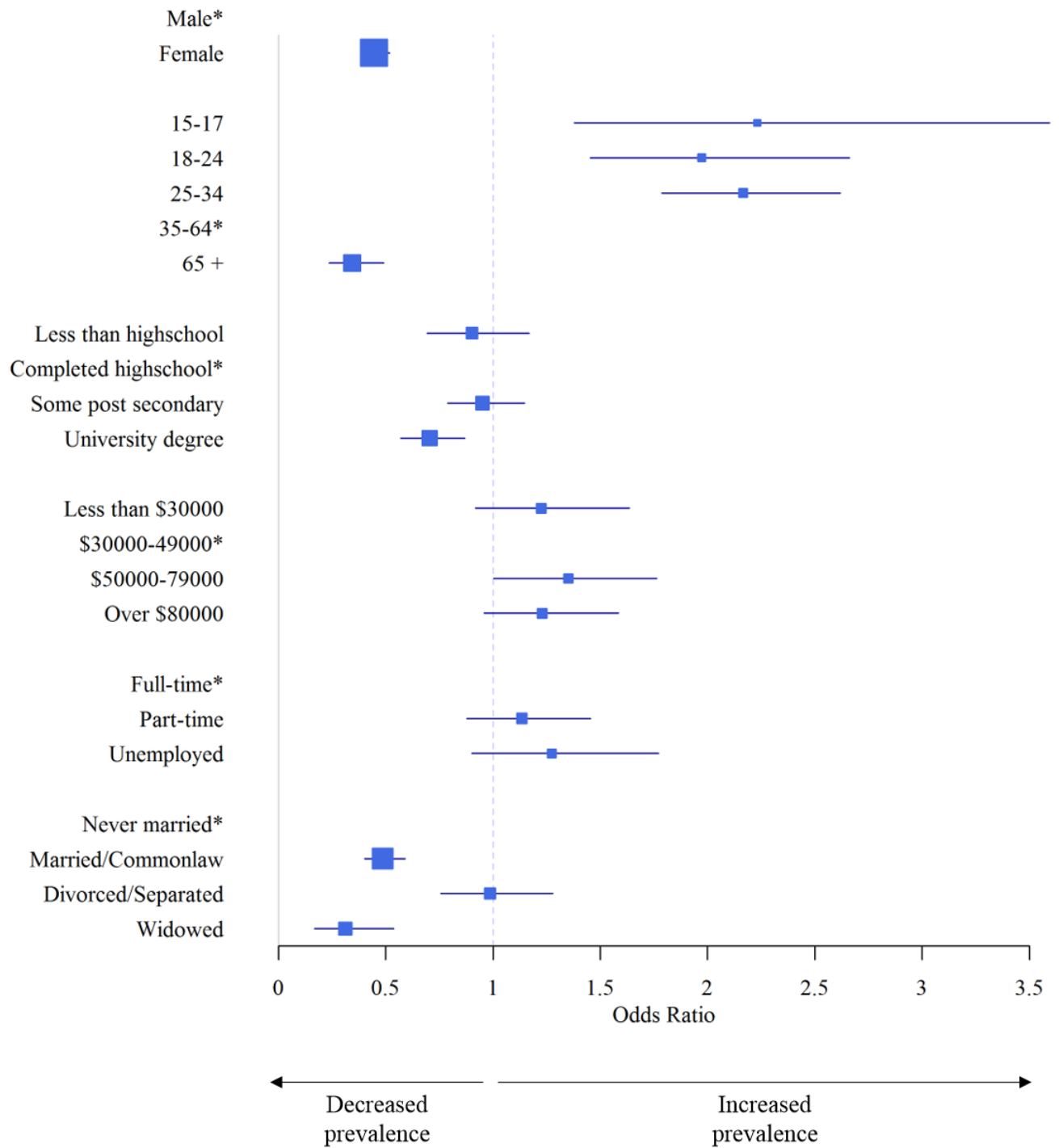
Figure 5: Cannabis Use Compared to Other Substances within the Past 12 Months (2012; most recent data available)



### Factors associated with use across Canada

Factors, including sex, age, level of education, income, employment status, and marital status may affect the likelihood of cannabis use. Nationally, females, individuals aged 35 to 64, and those who are married are less likely to use cannabis (Figure 6). There is no statistically significant association between use and educational attainment, income or level of employment.

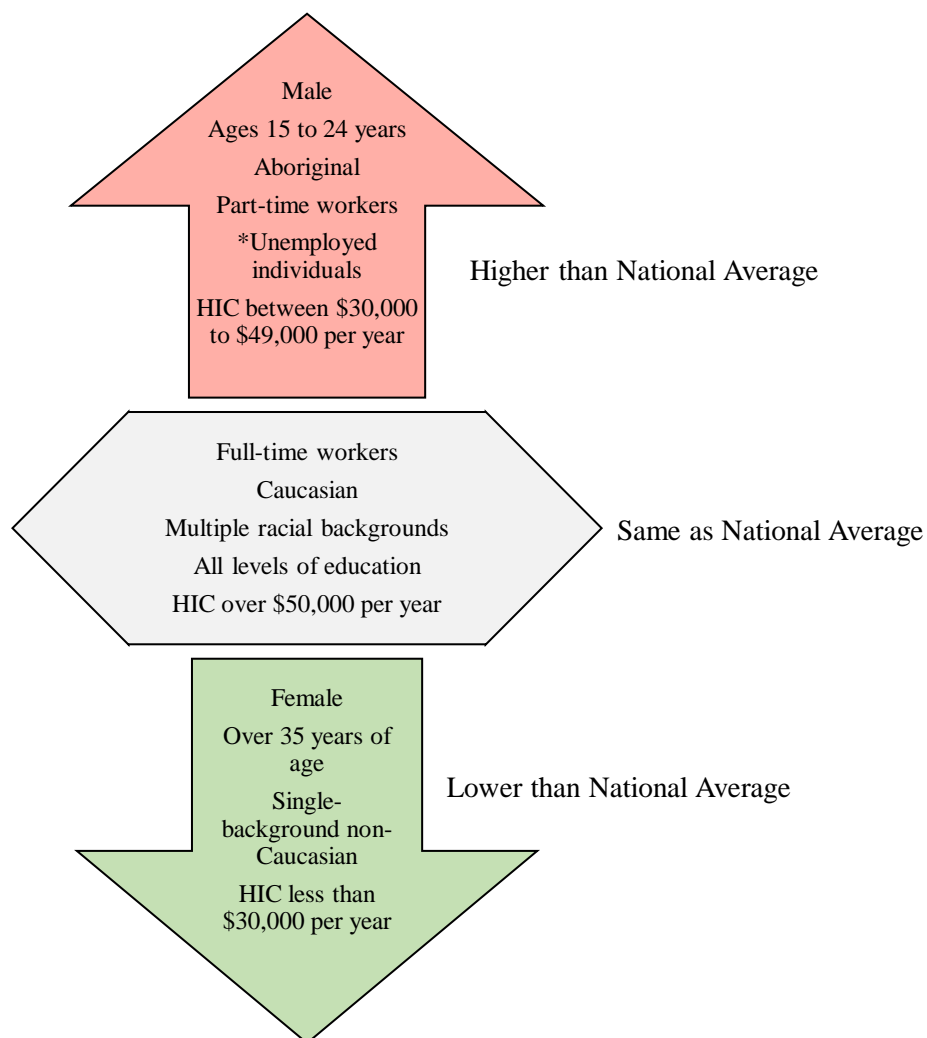
Figure 6: Odds Ratios of Cannabis Use in the Last 12 Months by Demographic Characteristics



### High cannabis use groups in Alberta

In Alberta, males, individuals aged 15 to 24 years, aboriginal people, individuals who work part-time or are unemployed, and individuals who have a household income between \$30,000 and \$49,000 per year report higher rates of use of cannabis within the last 12 months when compared to the national average (Figure 7; detailed information in Appendix 1 Table 1. These groups may represent particularly vulnerable groups with an existing pattern of higher than average use.

Figure 7: Likelihood of Cannabis Use in the Past 12 Months Amongst Albertans by Demographic Characteristics Compared to Canadian Average

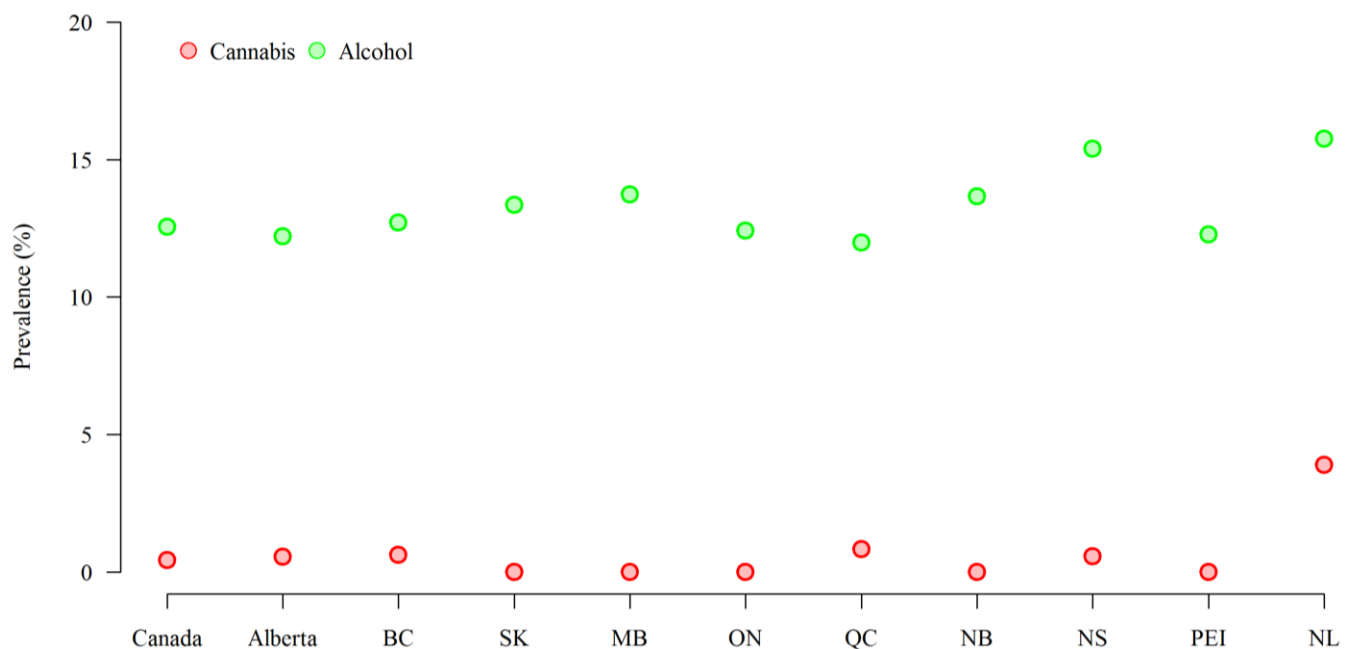


## Risk of Dependence

Cannabis dependence was compared to alcohol dependency across provinces. The ASSIST score, used to measure cannabis dependency, uses three dependence risk groups: low (0-3), moderate (4-26) and high (27+). This score was developed by the World Health Organization to assist substance users to assess their risk of social, financial, legal, or relationship problems based on patterns of use. The AUDIT score, used to measure alcohol dependency, uses two dependence risk groups: low (<8), and hazardous (>8). This score was also developed by the World Health Organization and was developed to assess harmful or hazardous patterns of alcohol use on physical and mental health.

Of those who have used cannabis in the past 12 months in Alberta, 1% have a “high” score for dependency (Figure 8), and 53% have a “moderate” or “high” score. Of those who have used alcohol in the past 12 months, 12% have a “hazardous” score. The distribution of “high” and “moderate” scores for cannabis dependency is similar between Alberta and the rest of the provinces.

Figure 8: Risk of Cannabis or Alcohol Dependence Amongst Those Who have Used in the past 12 Months



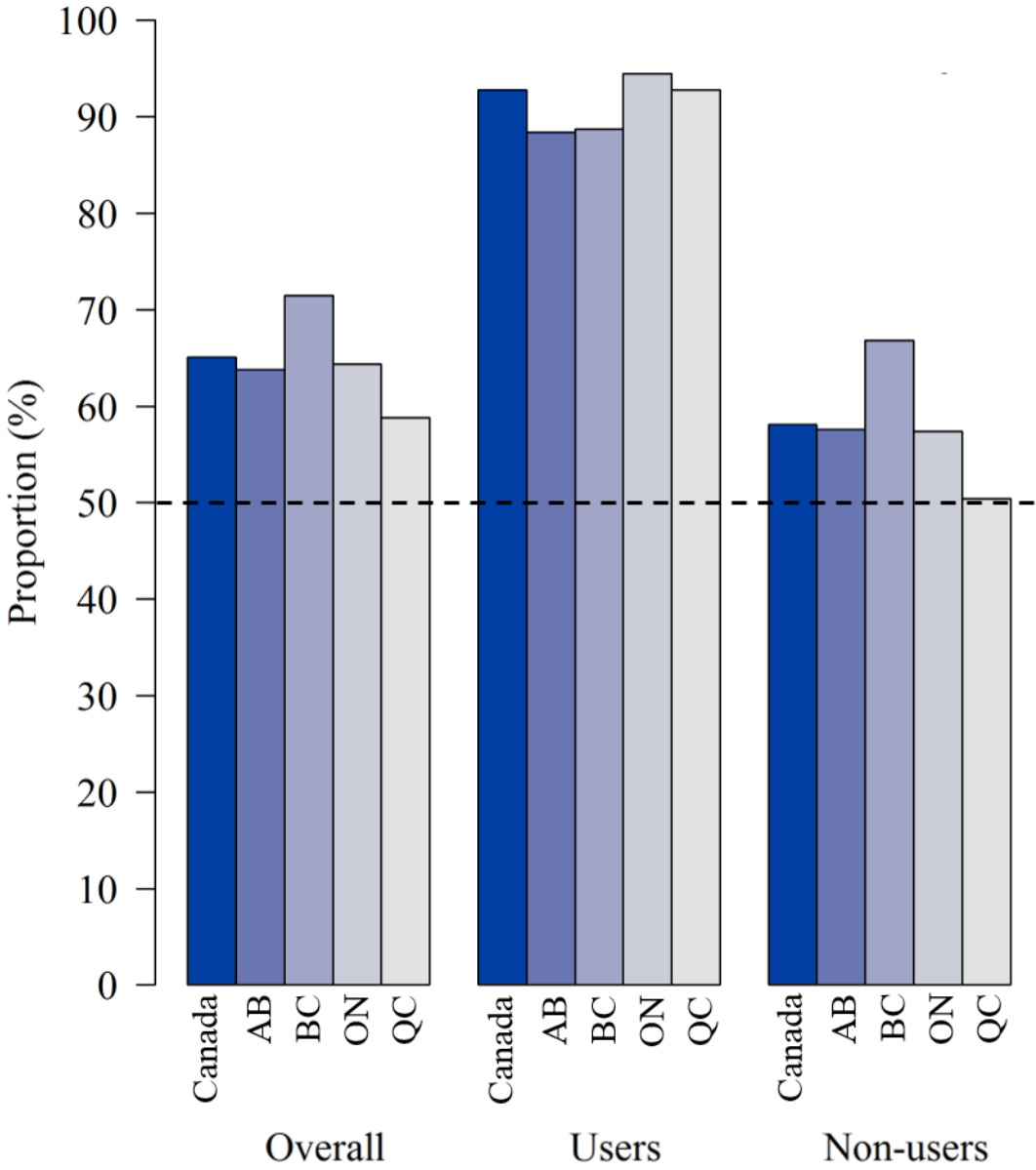
## **Public Perspective on the Legalization of Cannabis**

A survey was commissioned by the University of Calgary HTA Unit in July 2016 to understand current public perceptions of cannabis and cannabis legalization. This survey of 2,008 people, is weighted to be a representative sample nationally and for the populations of British Columbia, Alberta, Ontario, and Quebec.

Nation-wide, 65.1% of individuals support legalization of cannabis. Legalization support varied across the provinces: 63.8% in Alberta, 71.5% in British Columbia, 64.4% in Ontario and 58.8% in Quebec (Figure 9). Support for legalization varied with reported cannabis use in the past 12 month; 92.5% of those who have used cannabis in the past 12 months supported legalization compared to 58.1% among non-users. Generally, those who are under 35 years old, male, have an annual income over \$80,000 per year, and have a university degree are most supportive of cannabis legalization although the changes in levels of support are not statistically different by demographic characteristic (Figure 10). These trends are generally consistent across all four provinces examined (Alberta, British Columbia, Ontario, and Quebec).

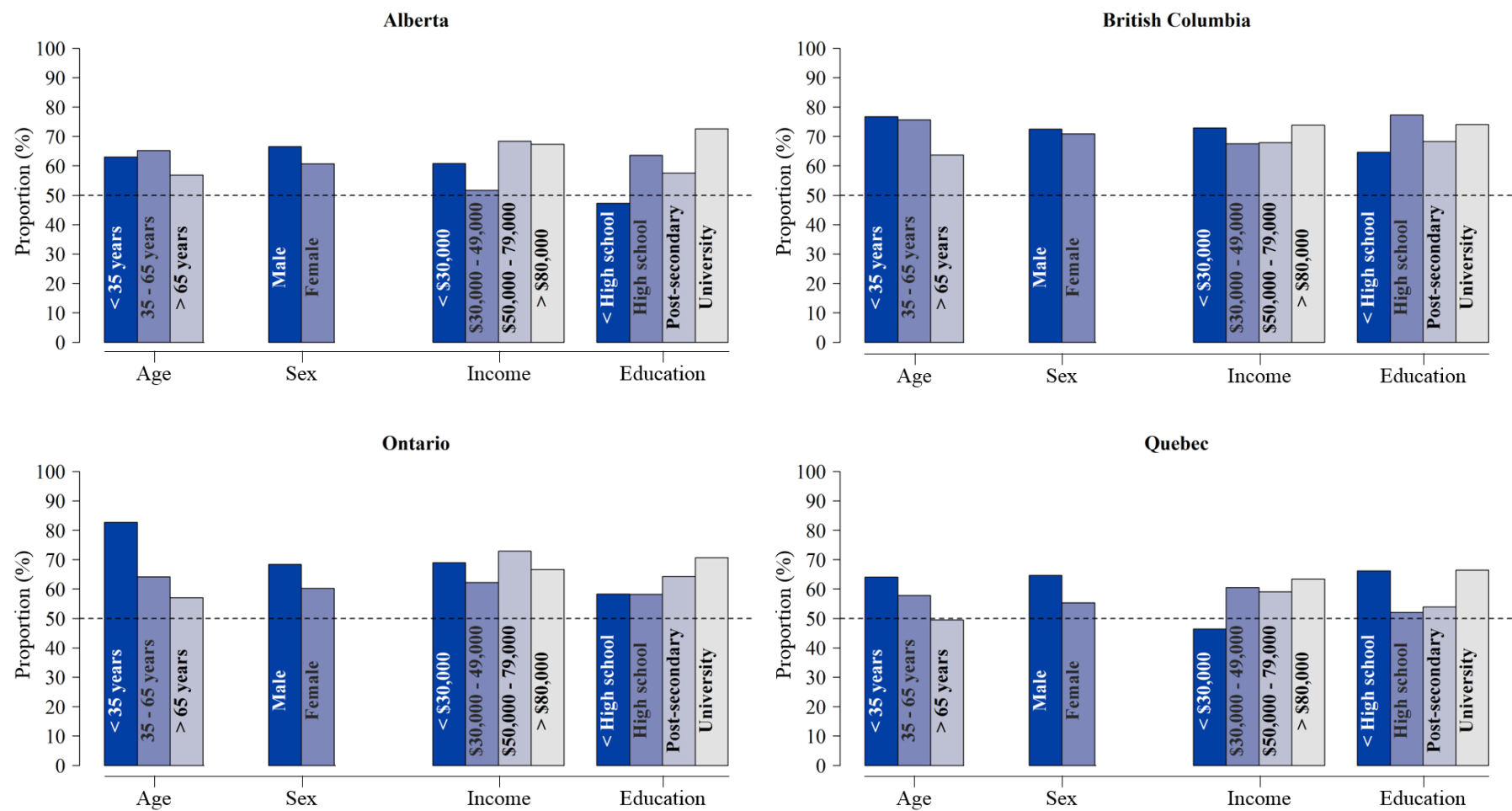


Figure 9: Proportion of Canadians who Support Cannabis Legalization Overall and by Cannabis Use in the Past 12 Months



	Canada	AB	BC	ON	QC
<b>Overall</b>	65.1%	63.8%	71.5%	64.4%	58.8%
<b>Users</b>	92.8%	88.4%	88.7%	94.5%	92.8%
<b>Non-users</b>	58.1%	57.6%	66.8%	57.4%	50.4%

Figure 10: Proportion in Each Province who Support Cannabis Legalization, by demographic



	<35	35 - 65	65+	Male	Female	< \$30,000	\$30,000-49,000	\$50,000-79,000	> \$80,000	< High school	High school	Post-secondary	University
AB	63.0%	65.2%	56.9%	66.6%	60.7%	60.8%	51.7%	68.4%	67.3%	47.3%	63.6%	57.5%	72.6%
BC	76.7%	75.7%	63.7%	72.5%	70.9%	72.9%	67.5%	67.9%	73.9%	64.6%	77.3%	68.3%	74.1%
ON	82.7%	64.2%	57.1%	68.4%	60.2%	69.0%	62.2%	72.9%	66.7%	58.3%	58.2%	64.3%	70.7%
QC	64.1%	57.8%	49.5%	64.6%	55.3%	46.4%	60.5%	59.1%	63.4%	66.2%	52.1%	53.9%	66.5%

## **Rationale for Support of Legalization**

We also assessed the reasons why respondents support or do not support legalization. Among those who support legalization, the most common three reasons were: 1) cannabis is no different than alcohol or tobacco (70.0%), 2) people should not have criminal records for cannabis use or possession (69.9%), and 3) it will ensure a safer product (61.7%). The most common reasons for not supporting legalization were: 1) the need to protect children and youth (53.9%), 2) government should not be involved in these kinds of decision (50.5%), and 3) concern about public safety (46.1%).

## **Conclusion**

Non-medical cannabis use in Canada has a lengthy history dating back to the early 1900s. Largely beginning on the 1960's, the debate on legalizing, decriminalizing or maintaining the status quo (illegal) of non-medical cannabis has been ongoing. When the Liberal government of Canada formed a majority government and announced their plan to legalize cannabis, this debate came to the forefront. If the liberal government were to decide to legalize cannabis, Canada would be amongst the first in the world to consider it a legal substance. Internationally, possession of non-medical cannabis is legal in only Uruguay, eight American states, and one American jurisdiction.

Within Canada, the majority of residents support legalization. They believe that the substance is no different than alcohol or tobacco, and that possession should not be penalized with a criminal record. On the other hand, those who do not support legalization feel that we need to protect children and youth and think that the government should not be involved in decisions such as these. With high frequency of use amongst Canadians, and many stakeholder and advocacy groups, the current Canadian context is complex, multi-faceted and dynamic.

## Topic 2: Health Effect and Harms of Cannabis Use

**Key Messages**

- There is evidence that cannabis is associated with increases in the risk of testicular cancer, mental health problems, poor outcomes of pregnancy, and functional changes such as memory loss and anhedonia.
- Evidence suggests that cannabis consumption is not associated with lung, head or neck cancer, or arteritis.
- Cannabinoids and metabolites can be found in the urine and blood of individuals who are exposed to second-hand smoke in extreme conditions. There is evidence of a dose-response relationship between the THC content of the smoked cannabis and cannabinoid metabolite concentrations in the urine of those passively exposed; this relationship is mediated by whether the environment is ventilated or not, and the volume of air in the room.
- Broadly, Canadians perceive cannabis to be comparable to cigarettes and alcohol in terms of negative physical and mental health effects. Cannabis is perceived to be less harmful than prescription drug abuse or other illicit drugs such as ecstasy and cocaine.
- There are multiple pathways from substance use initiation to other illicit drug use (such as cocaine, heroin and ecstasy) although the most commonly reported pathway was cannabis use immediately preceding other illicit drug use. This pathway is mediated by multiple social and genetic factors.
- The majority of Canadians believe that cannabis is an addictive substance; however, most believe that consumption of cannabis does not necessarily lead to use of other illicit drugs

## **Addictiveness and Dependency on Cannabis**

Debates over the degree of cannabis addictiveness have been ongoing, partially due to difficulties in producing quantitative evidence. An epidemiological systematic review reports that the global burden of cannabis dependence was 13.1 million people in 2010, which equates to 0.20% of the entire population <sup>11</sup>. Dependence is higher amongst males than females <sup>11</sup> and is more prevalent in high-income areas, compared to low-income areas <sup>11</sup>. Australasia and North America have a significantly higher cannabis dependence prevalence than other regions, nearly eight times higher than the region with the lowest prevalence, Sub-Saharan Africa <sup>11</sup>.

A number of cannabis scales, drug scales, structured interviews, and tools for quantifying cannabis use can be used for diagnosing cannabis dependence <sup>12</sup>, including: the Cannabis Use Disorder Identification Test, Cannabis Problems Questionnaire, Drug Use Disorder Identification Test, and the Psychiatric Research Interview for Substance and Mental Disorders <sup>12</sup>. Many of these instruments face criticism, as they fail to measure data on frequency and amount of use <sup>12</sup>. Further development of these instruments to increase reliability and validity is required <sup>12</sup> and epidemiologic estimates that solely rely on tools should be interpreted with caution.

Another potential indicator of the addictiveness of cannabis is the prevalence of risk factors for abuse. Individual risk factors for dependence include stress, age of onset of cannabis use, comorbid mental disorders, and alcohol or tobacco use and dependence <sup>13</sup>. Social risk factors for dependence include experiencing a negative life event (e.g. divorce of parents, death of a family member), mental and social conflicts, and peer use patterns <sup>13,15</sup>. Genetic predispositions to substance dependence have been proposed in the literature <sup>14</sup>, but there is limited evidence to support the role of genetic factors in cannabis dependence <sup>63,64</sup>.

There is evidence that a number of factors contribute to the development of cannabis dependence, including psychosocial, geographic, biological, and socioeconomic variables <sup>11-15</sup>. Many of the currently available diagnostic tools face criticism, and current quantitative literature on the burden of cannabis dependence and the degree of addictiveness of cannabis is lacking. Further evidence is required to determine the addictiveness of cannabis.

## Harms and Health Effects of Cannabis

A systematic review regarding cannabis harms, health effects and adverse health effects was conducted. A systematic review comprehensively searches the available literature to identify all relevant knowledge. The identified knowledge is then synthesized into key messages. Following best practices for systematic reviews <sup>65</sup>, all abstracts and full-texts were reviewed by two reviewers to determine eligibility and all papers deemed eligible were included (see Figure 11). As many systematic reviews of specific harms and adverse events have been completed, only other systematic reviews were included. Data on author, country and year of publication, objective, search strategy and results, and main outcomes were extracted by one reviewer and verified by another.

Figure 11: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"><li>• Systematic review design</li><li>• Assesses at least one of the following:<ul style="list-style-type: none"><li>○ Acute and chronic health effects related to cannabis use</li><li>○ Addictiveness of cannabis</li><li>○ Cannabis dependence compared to other drugs</li><li>○ Safety of cannabis use for the general population and for special populations (e.g. pregnant women, youth)</li><li>○ Health effects, harms and safety of drug delivery modes</li><li>○ Cross-interactions with other substances</li></ul></li><li>• Adults, children or animal models</li></ul>	<ul style="list-style-type: none"><li>• Any study design other than a systematic review</li><li>• Does not examine impact on humans or animals</li><li>• Not written in English or French</li></ul>

## Findings

The systematic review yielded 552 abstracts. Of those, 64 systematic reviews were included in the final data analysis (Appendix 2 Figure 1). Detailed information on all 64 included systematic reviews can be found in Appendix 2 Table 1.

The evidence was grouped into seven categories of health effects:

- overall health effects which included outcomes such as overall mortality, overall health, and cardiovascular health
- mental illness including psychosis, schizophrenia, anxiety, and suicide
- cancer of all types
- social effects which included motor vehicle accidents and social problems
- brain changes including physical, functional, and chemical changes within the brain
- neurocognitive changes such as learning, memory, and psychomotor functioning
- prenatal exposure including birthweight and birth complications

Figure 12 summarizes the health effect within each category. Evidence of harm was reported for testicular cancer, several mental health outcomes, pregnancy outcomes, brain changes, and neurocognitive outcomes. No evidence of harm was reported for lung, head and neck cancers, or arteritis. Inconclusive evidence was found for other types of cancers, all-cause mortality, and some mental health outcomes (psychosis in high risk individuals and worsening psychotic symptoms). There was no evidence found on the safety of various delivery modes, nor on the safety of use among children.



Figure 12: Overview of health effects associated with cannabis consumption.

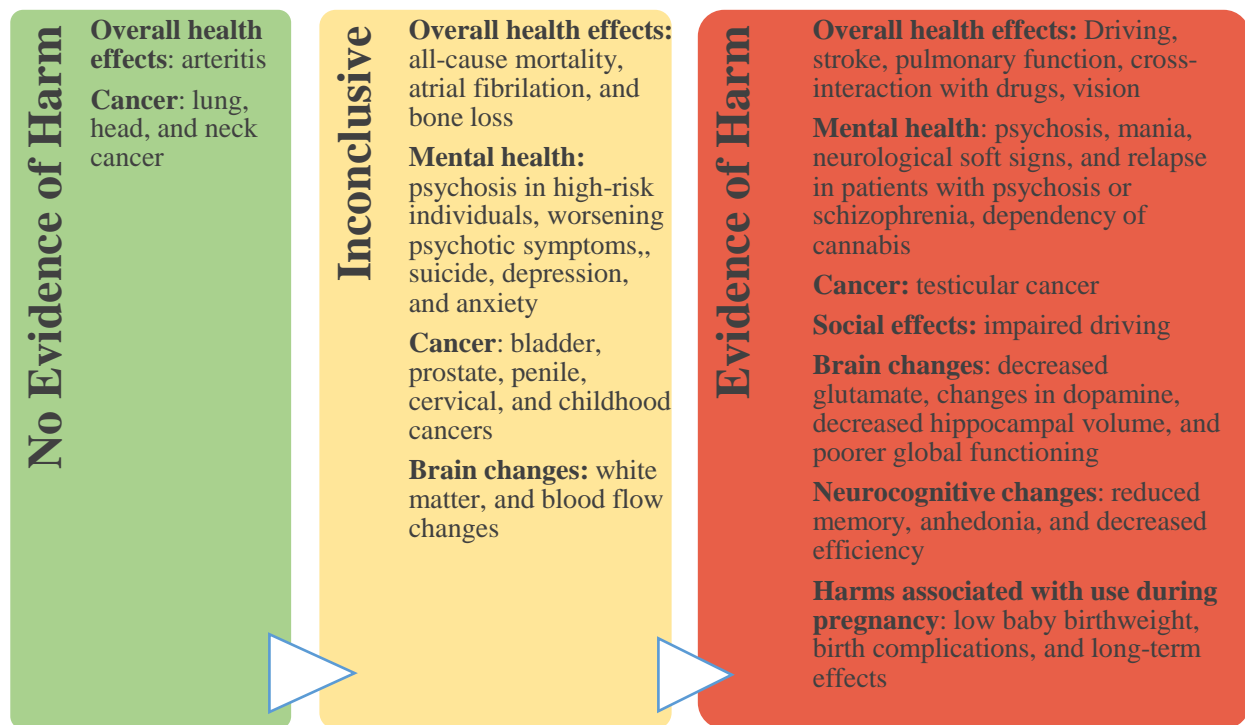
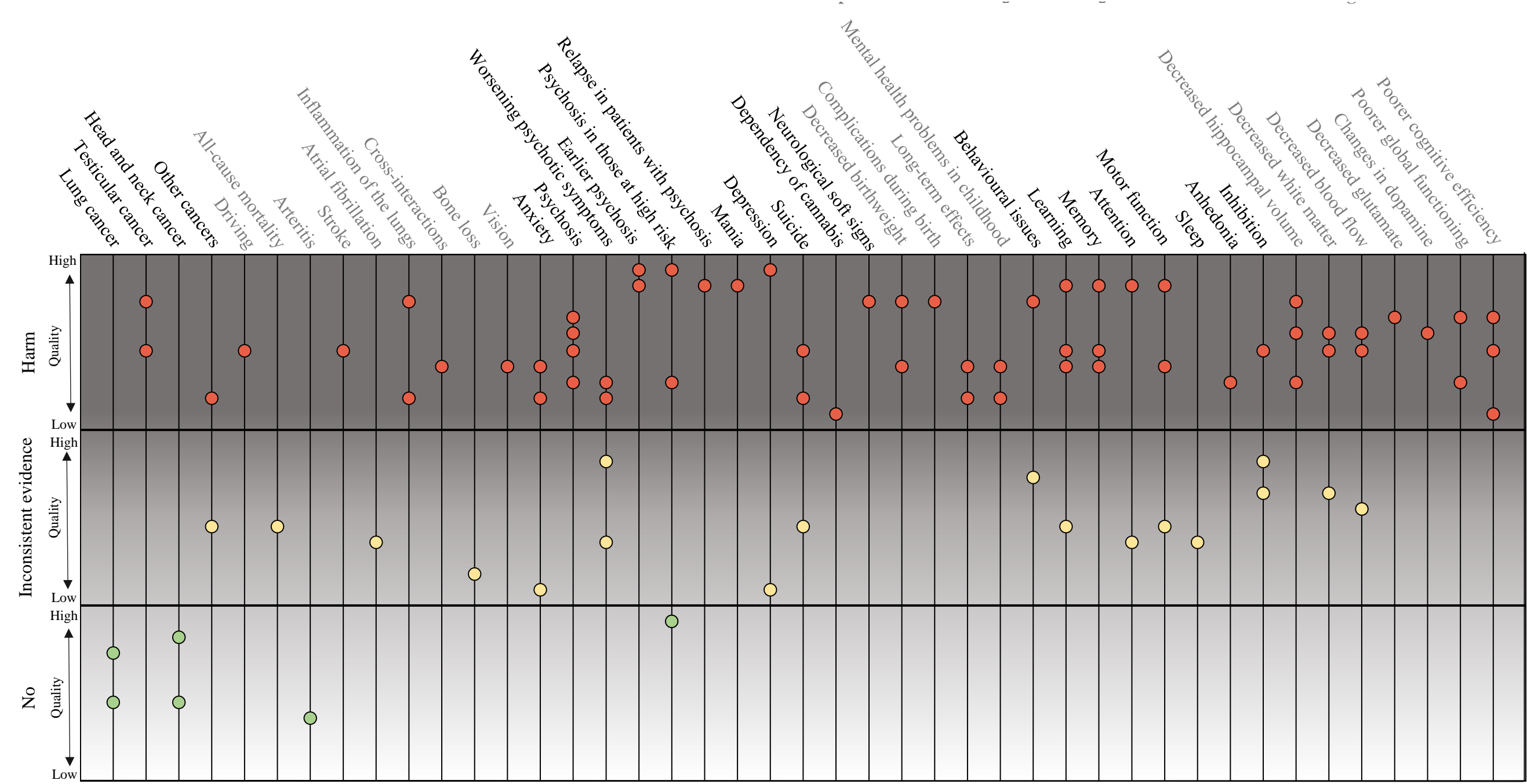


Figure 13 presents the outcome assessed in each identified systematic review, grouped by conclusion (no evidence of harm, inconsistent evidence, harmful) and quality. Quality was assessed using the AMSTAR quality checklist. Systematic reviews with scores of 0-4 were considered poor quality, 5-8 were moderate quality, and 9-11 were considered high quality (total maximum score 11). Among the 64 included systematic review, 26 were of low quality, 28 were of moderate quality, and 10 were of high quality. Sixty-one concluded harm, 18 concluded there was inconsistent evidence, and 6 concluded no evidence of harm. Some reported more than one outcome and are represented once for each outcome in the figure. The majority of the evidence is from epidemiological studies (not randomized control trials) limiting the evidence to assessment of associations not causation. Each of the health categories are summarized below.

Figure 13: Synthesis of Findings



### **Overall health effects**

Eight systematic reviews examined overall health effects. Harm was reported in six systematic reviews: one examining each outcome of driving <sup>66</sup>, stroke <sup>67</sup>, pulmonary function<sup>68</sup>, cross-interactions with drugs <sup>69</sup>, and vision <sup>70</sup>; and two reported on the inflammation of the lungs <sup>67,71</sup>. Inconsistent findings were reported for all-cause mortality <sup>66</sup>, atrial fibrillation <sup>72</sup>, and bone loss <sup>67</sup>. No harm was found for arteritis <sup>73</sup>.

### **Mental illness**

There were 21 systematic reviews examining cannabis and mental illness. The systematic reviews examined psychosis or schizophrenia (n=14), anxiety (n=2), suicide or depression (n=2), mania (n=1), neurological soft signs (n=1), and cannabis dependence (n=1). In total, eleven outcomes were assessed.

Thirteen systematic reviews reported harm associated with psychosis in general <sup>74-82</sup>, early-onset psychosis, relapse of psychosis in patients with schizophrenia <sup>83,84</sup>, mania <sup>85</sup>, and neurological soft signs <sup>86</sup>, which are markers of schizophrenia. Additionally, one study found evidence to suggest that between 9-10% of those exposed to cannabis become dependent <sup>87</sup>.

For five outcomes, the evidence was inconsistent. For anxiety, one low-quality systematic review reported there was inconsistent evidence while two medium-quality systematic reviews studies reported harm for anxiety <sup>87-89</sup>. Two low- to medium-quality systematic reviews reported evidence of worsening psychotic symptoms in those with schizophrenia, whereas one medium and one high quality systematic review reported inconsistent evidence <sup>84,90-92</sup>. One high-quality systematic review reported no risk for psychosis in those at high risk and two high-quality systematic reviews reported harm <sup>84,92</sup>. For depression, one low-quality systematic review reported inconsistent evidence and one high-quality systematic review reported an increased association <sup>87,93</sup>. Two low- to medium-quality systematic reviews reported a risk of suicide and one medium quality systematic review reported inconsistent evidence <sup>67,93,94</sup>. Importantly, none of the identified systematic reviews reported a positive effect of cannabis on the measured mental health outcomes.

## **Cancer**

Four systematic reviews examined cannabis use and cancer. The cancers examined included head and neck cancer, testicular cancer, overall cancers, and lung cancer. Current, weekly, and chronic cannabis use was associated with nearly double the odds of testicular cancer<sup>95,96</sup>. There was insufficient evidence to suggest a significant association between cannabis use and bladder, prostate, penile, cervical, and childhood cancers<sup>96</sup>. There was no association between cannabis use and the risk of head and neck or lung cancers<sup>96-98</sup>.

## **Social effects**

Two systematic reviews examined social effects of cannabis exposure: one examined motor vehicle collisions<sup>99</sup> and one examined social problems<sup>100</sup>. Cannabis use was associated with increased motor vehicle collision<sup>100</sup>, reduced educational attainment<sup>100</sup>, and increased use of other drugs<sup>100</sup>. There were inconsistent associations for overall psychological problems, antisocial behaviour, and other problematic behaviour<sup>100</sup>.

## **Brain changes**

15 systematic reviews examined changes to the brain: three reviewed chemical changes, five reviewed structural changes, three examined functional changes, and four reviewed both structural and functional changes.

Cannabis use was associated with decreased glutamate<sup>101</sup>, dopamine<sup>102</sup>, N-acetylaspartate<sup>103</sup>, myo-inositol<sup>103</sup>, and choline<sup>103</sup> levels. These are associated with poorer cognitive functioning<sup>101,103</sup> and drug addictions<sup>102</sup>. Decreased blood flow was reported by three medium quality systematic reviews, two of which reported an association and one which reported inconsistent evidence<sup>104-106</sup>. This could affect attention, decision making, psychomotor speed, and cognitive efficiency<sup>104,105</sup>. Three medium- to high-quality systematic reviews reported decreased hippocampal volume, which can have effects on memory<sup>104,107,108</sup>. Two medium-quality systematic reviews reported decreased white matter and one medium- to high-quality systematic review reported inconsistent evidence regarding white matter changes, which is related to overall efficiency<sup>105,109-111</sup>.

### **Neurocognitive changes**

Ten systematic reviews examined the neurocognitive changes associated with cannabis use. Five examined learning and memory, three examined motor functioning, three examined inhibition, two examined attention, one examined anhedonia, and one examined sleep.

Two medium and one high-quality systematic reviews reported impairments in memory associated with cannabis use <sup>112-114</sup>. One low- to medium-quality systematic review reported anhedonia was higher in cannabis users compared to non-users, and decreased with abstinence <sup>115</sup>. There was inconsistent evidence regarding behavioural issues, learning <sup>116,117</sup>, attention <sup>116,117</sup>, motor function <sup>116-118</sup>, sleep <sup>119</sup>, and inhibition <sup>117,120</sup>.

### **Prenatal exposure**

There were four systematic reviews examining prenatal cannabis exposure. Two examined effects on children in childhood, one examined birth weight, and one examined birth complications. Cannabis use was associated with low birthweight among frequent users and high birthweight among those using cannabis once or less than once per week <sup>121,122</sup>, complications during birth <sup>121</sup>, physical anomalies, gastroschisis, and ventricular septal defect <sup>123</sup>, and mental health problems such as inattention and impulsivity during childhood <sup>123,124</sup>.

### **Summary**

There is substantial evidence of harm associated with cannabis. Overall, cannabis was seen to be associated with testicular cancer, impaired driving, low birthweight, complications during birth, and a variety of mental health effects such as increased psychosis, relapse of psychosis, and mania. There was inconclusive evidence regarding all-cause mortality, other cancers, and anxiety. Cannabis was not associated with head and neck or lung cancers or arteritis.

### **Second- and Third-Hand Smoke**

Second-hand smoke exposure is exposure to smoke inhaled by those immediately in the area. Third-hand smoke exposure is exposure to smoke that has been deposited on fabrics such as carpet or clothes <sup>125</sup>. To determine the effects of exposure to second- and third-hand cannabis smoke, a systematic review of the published literature was completed. Six electronic databases were searched. Studies were included if they reported human or animal models with more than

one case, original data on the effects of second- or third-hand cannabis smoke exposure, and any outcome (e.g. blood or urine analysis, tetrahydrocannabinol (THC) levels in the air). The quality of the included studies was assessed using the Downs and Black Checklist <sup>126</sup>. Eighteen studies were included (Appendix 2 Figure 2). For full details on included studies, see Table 2 in Appendix 2.

### **Immediate outcomes from passive exposure**

#### *Cannabinoids and cannabinoid metabolites in bodily fluids*

Thirteen studies were identified that assessed the dose-response relationship between the amount of THC in the cannabis and the amount of cannabinoid metabolites in urine samples from passively exposed individuals (Figure 14) <sup>125,127-137</sup>. The majority of studies used an immunoassay test with 20ng/mL threshold to determine how much THC was passively absorbed, which is less than the US Federal Workplace Cutoff value of 50 ng/mL (based on the Drug-Free Workplace Act 1988, a person with more than 50ng.mL of THC in their urine sample will fail the drug test) <sup>138</sup>. Four hours after exposure to cannabis with 1.5% THC, only one of five of the individuals passively exposed to cannabis smoke tested over the 20 ng/mL threshold, while four hours after exposure to cannabis with 11.3% THC resulted in a maximum test value of 28.3 ng/mL. In studies that compared urine samples of those exposed to passive smoke and active smokers, those passively exposed to cannabis smoke had a smaller cannabinoid metabolite concentration in their urine <sup>128,139</sup>. Blood concentrations of THC were measured in six studies but these results were reported too inconsistently to be able to synthesize <sup>7,129</sup>.

#### *Effect of ventilation on atmospheric cannabinoid uptake*

The amount of THC and metabolites found in bodily fluids of individuals passively exposed to cannabis smoke is also determined by the environment. Factors such as ventilation and the size of the room may influence the degree of exposure of passive inhalers to smoke <sup>128,139</sup>. In studies that included multiple trials in both ventilated and unventilated environments, the results showed that urine cannabinoid metabolite concentrations and blood THC levels were higher in individuals that were passively exposed to cannabis smoke in an unventilated environment compared to a ventilated environment <sup>127-130</sup>.

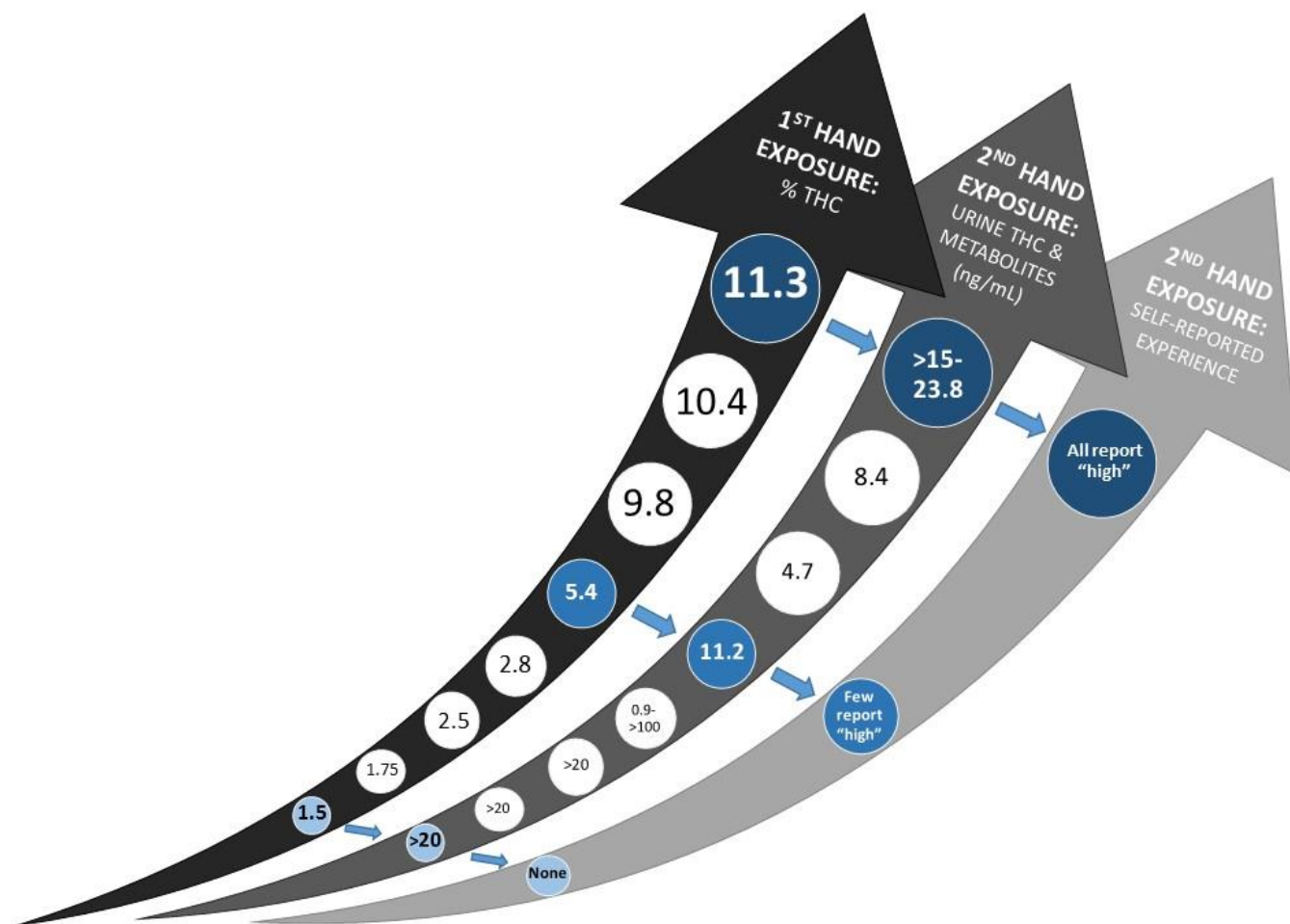
### *Subjective (self-reported) effects*

Individuals who were exposed to smoke from cannabis with higher THC content reported feeling more drug effects than those exposed to smoke with lower THC content <sup>127,132</sup>. Furthermore, in one exposure session in an unventilated environment, individuals expressed discomfort and eye irritation as a result of the amount of smoke in the room <sup>128</sup>.

### **Health outcomes of passively-exposed individuals**

No studies on health outcomes of individuals exposed to second or third-hand cannabis smoke were found. However, three studies investigated the toxicity and chemical composition of passive cannabis smoke compared to tobacco smoke <sup>7-9</sup>. Evidence from the comparative studies concluded that cannabis smoke produces more changes to genetic material (mutagenic) and is more toxic to living cells (cytotoxic) than tobacco smoke <sup>7-9</sup>.

Figure 14: Impact of percent THC in smoked cannabis on THC metabolites and subjective effects in individuals passively exposed. Note the US Federal Workplace Cutoff value is 50 ng/mL in urinalysis.





## **Summary**

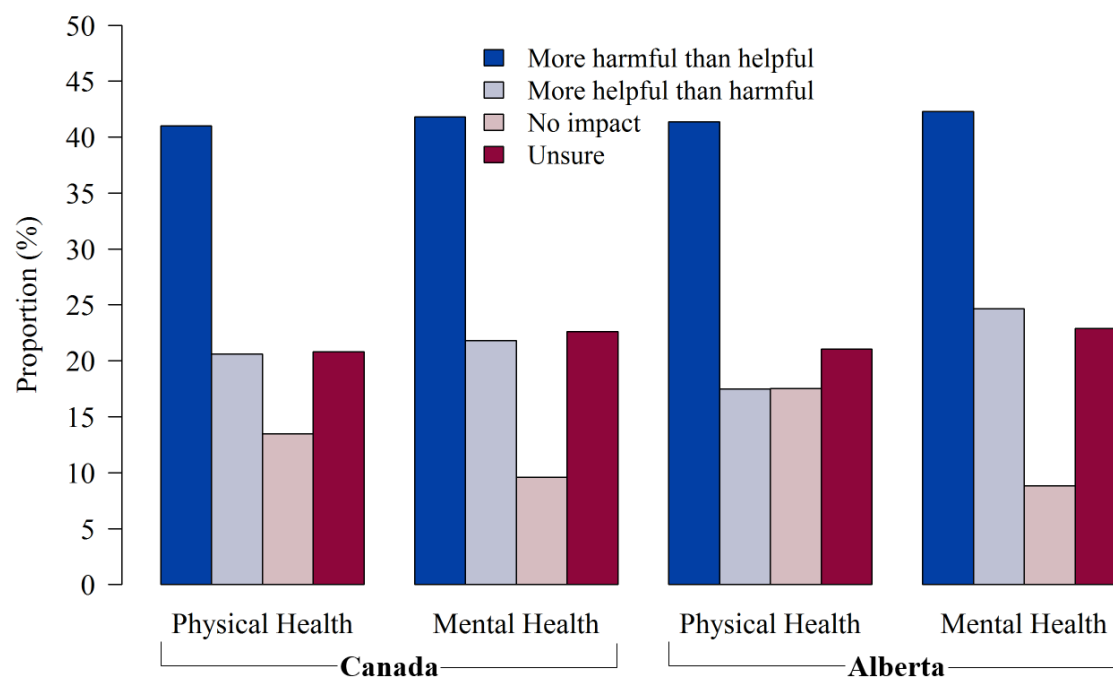
Although there is evidence of a dose-response relationship between the percent THC content of smoked cannabis and resulting concentrations of cannabinoid metabolites in the urine of those passively exposed, this relationship is mediated by whether the environment is ventilated or not and the volume of air in the room. It is possible for cannabinoids and metabolites to be found in the urine and blood of individuals who were passively exposed to cannabis smoke. In extreme smoking conditions, it is possible that individuals experience psychoactive effects of cannabis as well. These effects are also typically less dramatic compared to those experienced by active smokers. It appears that passive exposure to cannabis smoke could be chemically similar to tobacco smoke, and therefore may carry similar health concerns.

## **Public Perceptions on Health and Harms of Cannabis**

A survey was commissioned by the University of Calgary HTA Unit in July 2016 to understand current public perceptions of cannabis and cannabis legalization. This survey of 2,008 people was weighted to be a representative sample nationally and for the populations of British Columbia, Alberta, Ontario, and Quebec.

Canada-wide, 41% perceive non-medical cannabis as being more harmful to physical health than it is helpful, 21 % think it is more helpful than harmful, 13% think there is no impact on physical health, and 21% are unsure (Figure 15). The perception of the impact of non-medical cannabis on mental health was similar to physical health (Figure 15). Similar proportions are observed in Alberta (Figure 15). Data for other provinces are available in Appendix 2.

Figure 15. Canadians' perception of harms and health effects of non-medical cannabis use.



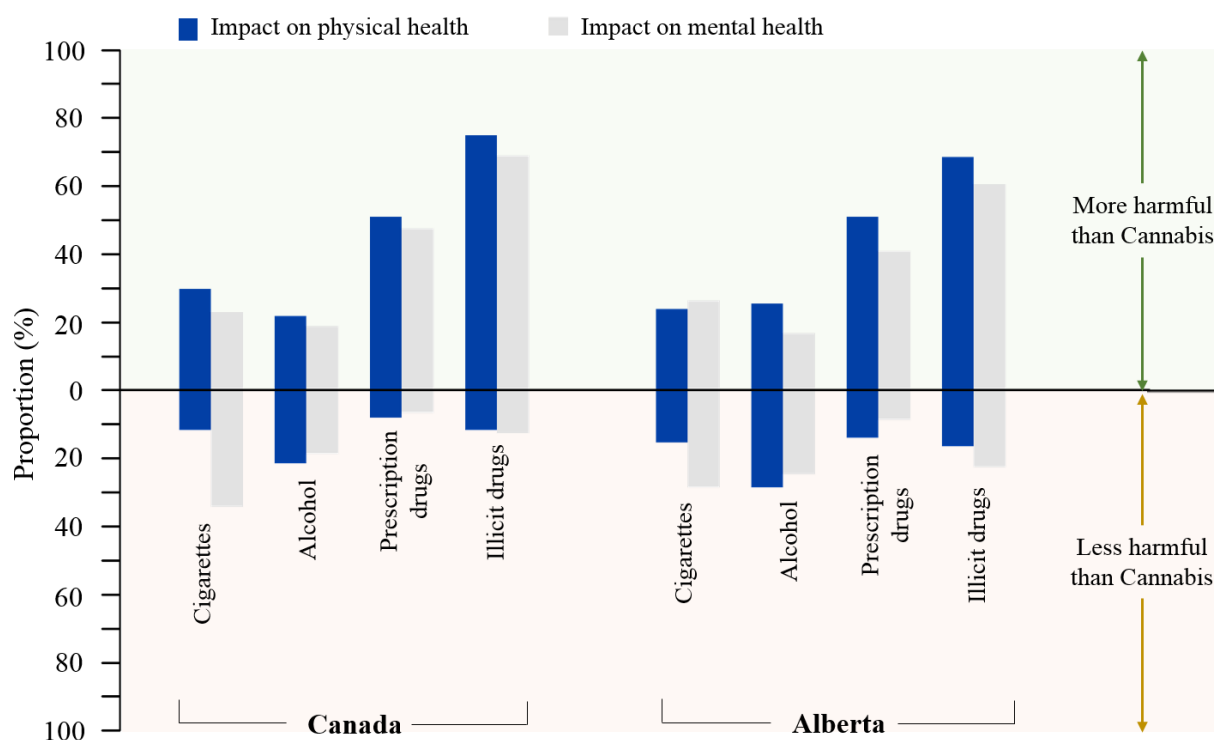
\*No response rate: 4%

The survey asked respondents the perceived impact of cannabis compared to other substances on physical and mental health. Three categorical responses were available; “more harmful”, “similarly harmful”, and “less harmful.” Figure 16 shows the proportion that responded “more harmful” or “less harmful” (complete table of responses available in Appendix 2).

When considering physical health, 30% of Canadians think that cigarettes are more harmful than cannabis, 22% think alcohol is more harmful than cannabis, 51% think prescription drugs are more harmful than cannabis and 75% think illicit drugs (such as methamphetamine, ecstasy and heroin) are more harmful than cannabis (Figure 16). Notably, 12% of Canadians think that the cigarettes are less harmful to physical health than cannabis, 22% think alcohol is less harmful to physical health than cannabis, 8% think prescription drugs are less harmful to physical health than cannabis, and 12% think illicit drugs are less harmful to physical health than cannabis. The

findings are similar for mental health (Figure 16). The trends were similar when analyzed by province (Appendix 2)

Figure 16. Perceived impact of cannabis on physical and mental health compared to other substances.



\*See Appendix 2 for more detailed information

\*No response rate: cigarettes physical health (1%), mental health (2%), alcohol physical and mental health (1%), Prescription drugs physical and mental health (2%), Illicit drug use physical and mental health (0.5%)

## Cannabis as a “Gateway Drug”

Generally, two dominant theories have emerged mapping the sequence of substance use: the Gateway Model (GM) and the Correlated Liabilities Model (CLM). The GM proposes that drug use follows a specific pattern, beginning with licit substances, then cannabis (classified as a “soft drug”), followed by experimentation and use of other “harder” illicit substances such as cocaine or methamphetamine<sup>140</sup>. Conversely, the CLM suggests that there are biological and environmental factors that influence substance use by affecting an individuals’ ‘normality’ and propensity to alternative use patterns, and therefore the progression of drug use may not be

universal<sup>141-143</sup>. We sought to assess the evidence supporting each theory and document the substance use pathways reported in the literature.

A systematic review of the literature was completed using six electronic databases. Abstract and full-text review were both completed in duplicate. Studies were included if they reported original data in either humans or animals, reported data on the sequence of substance use, or reported data on the factors that affected sequence of substance use.

## **Findings**

Five types of articles were identified: studies assessing the substance pathways, studies assessing the social factors that influence use, studies assessing the impact of frequency of use and age of initiation of use, studies assessing genetic factors, and animal studies to assess biological plausibility. Some articles fit into more than one category, and therefore may have been included in the summary of findings more than once.

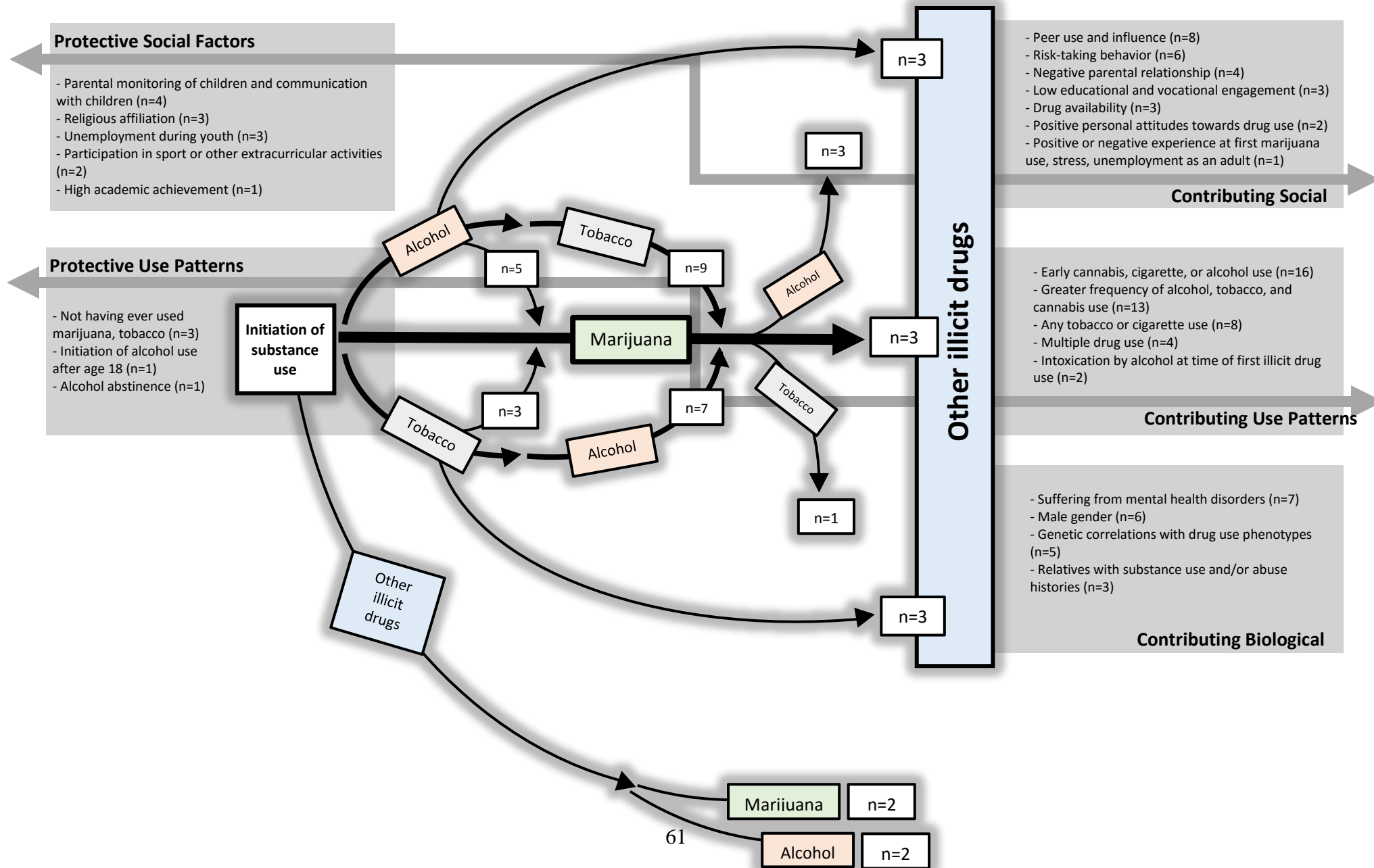
### *Pathways of substance use*

Forty-three articles reported on the position of cannabis in the pathway of substance use, from initiation to experimentation and regular use. The pathways reported are presented in Figure 17. The number of articles confirming the pathway is presented in the box associated with each pathway. Articles reporting more than 1 pathway were counted in each pathway reported.

The most reported pathway was the movement from cannabis use to other illicit drugs, regardless of prior reported licit substance use (n=30). The pathway beginning with alcohol, followed by tobacco and cannabis respectively was reported in nine studies and tobacco to alcohol to cannabis by seven studies (Figure 17).

Other less common pathways include: initiating other illicit drug use immediately following alcohol use (n=3), other illicit drug use immediately following tobacco initiation (n=3), initiating use of other illicit drugs before cannabis (n=2), and initiating use of other illicit drugs before alcohol (n=2). These findings support that there are multiple pathways to illicit substance use.

Figure 17. Substance initiation and use pathways reported (n=number of articles that provide evidence for each pathway).



### *Social factors*

The majority of the included studies (n=44) identified factors that mediated substance use progression (see Figure 17 for details). These factors include:

- peer group use
- delinquent attitudes
- living in a single parent household
- parental disapproval of peers
- lack of communication with a parent/parents
- low socioeconomic status
- sensation-seeking behaviour
- high stress
- low education level
- unemployment
- early onset mental disorders
- rebelliousness
- early age of cannabis, alcohol or tobacco use
- male sex

### *Frequency of drug use and age of initiation*

Twenty-six of the studies reported the effects of age of substance initiation as well as the effect of frequency of use. Most studies found that earlier initiation of substance use predisposed individuals to substance use progression and experimentation later on <sup>140-158</sup>. Additionally, earlier initiation was associated with atypical substance sequencing <sup>159</sup>. It was also found that frequency of use of a specific substance could influence the further initiation and use of other substances <sup>143,146,160-163</sup>.

### *Genetic factors*

Seven of the included studies observed twins to investigate the role of genetics in substance use and dependence. These studies showed that common genetic, shared, and unique environmental factors are responsible for the association between cannabis experimentation, early use, repeated use, and experimentation with other illicit drugs <sup>147,149,157,158</sup>.

### *Biological Plausibility from Animal Models*

Only one study examined an animal model to assess the biological plausibility for cannabis as the “gateway” drug. Techniques of molecular biology were applied to reveal the action of nicotine compared to cannabis in the brain of mice <sup>143</sup>. Locomotor sensitization showed that priming mice with nicotine enhances the effect of cocaine <sup>143</sup>. The conclusion of this study states that the priming effect that nicotine exerts on cocaine establishes nicotine as a more likely gateway drug <sup>143</sup>.

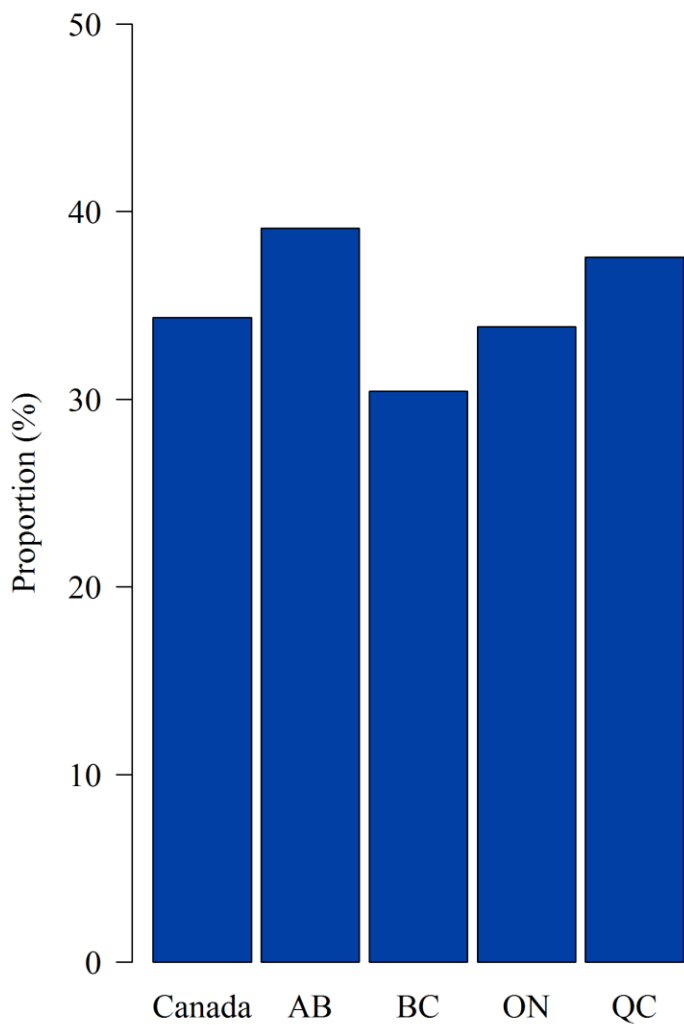
### **Summary**

The most commonly reported pathway identifies cannabis as the immediate precursor to other illicit drug use. However, there are multiple pathways of substance use reported. Therefore, decision makers should consider alternate routes when crafting public health initiatives and policies regarding substance use. Among the many mediating factors, including social and genetic factors, early age of use is a consistently reported factor associated with higher likelihood to progress to illicit drug use. Thus, efforts to prevent substance use progression should be directed at youth and school-age individuals.

### **Public Perceptions on Addictiveness and Dependency**

Figure 18 and Figure 19 present the perceptions of Canadians regarding the gateway effect and cannabis dependency. Fifty-eight percent of Canadians perceive cannabis to be an addictive substance. However, 55% of Canadians believe that consumption of cannabis does not lead to the use of other illicit drugs (58% of those in British Columbia, 55% in Alberta, 54% in Ontario and 54% in Quebec) (Figure 18). Broadly, 37% of Canadians think that cannabis is less addictive than cigarettes. 23% of Canadians think alcohol is more addictive than and 15% think alcohol is less addictive than cannabis. Cannabis is considered less addictive than prescription drug abuse (44%) and other illicit drugs (65%) (Figure 19).

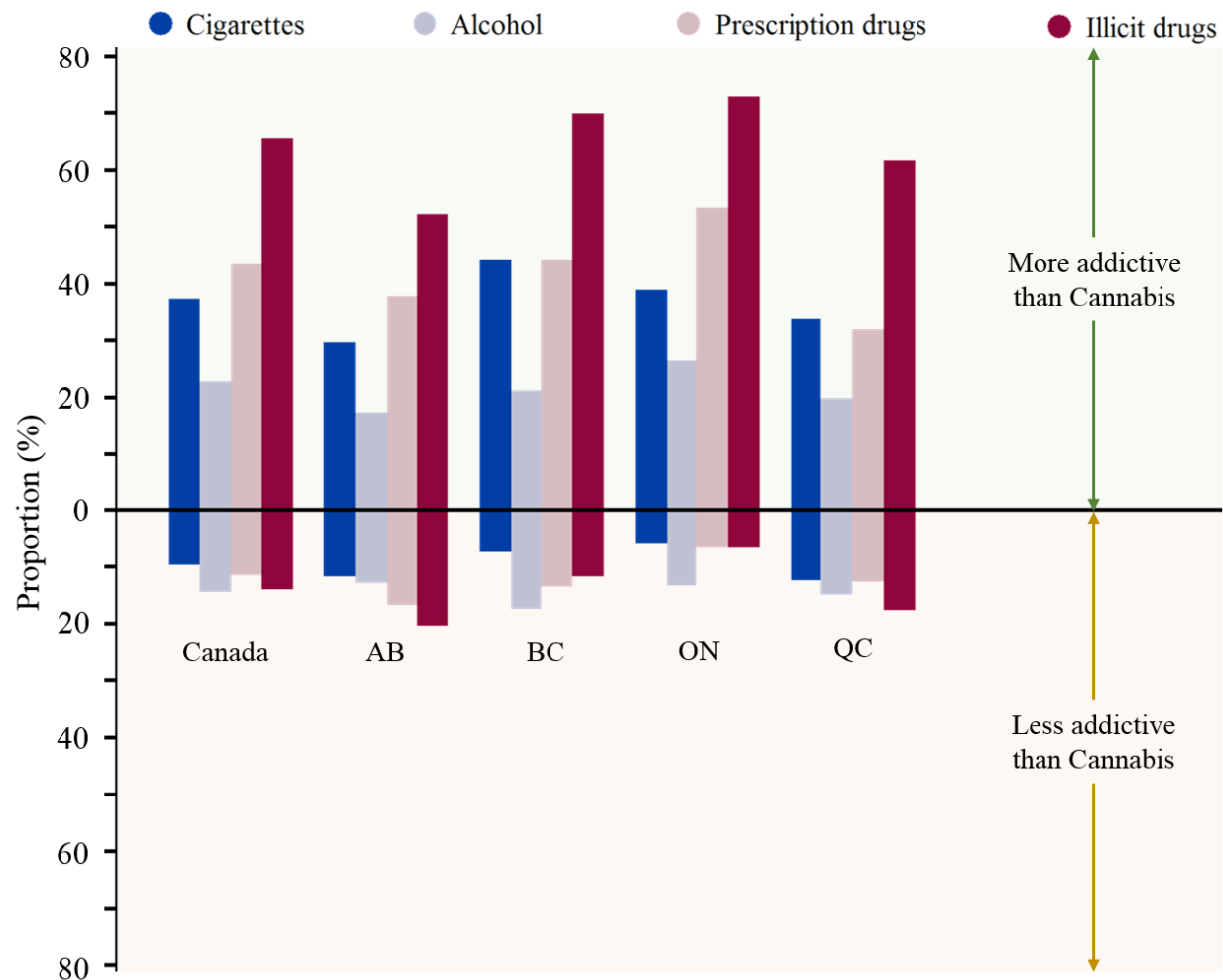
Figure 18. Proportion of Canadians who think that using cannabis leads to using other illicit substances.



**\*No response rate: 10%**



Figure 19. Perceived addictiveness of cannabis compared to other substances.



\*See Appendix 2 for more detailed information

\*No response rate: cigarettes (2%), alcohol (2%), prescription drugs (3%), illicit drugs (1%)

## Conclusions

There is a considerable amount of research on physical and mental health harms related to non-medical cannabis use. The evidence suggests that cannabis is associated with harm to physical and mental health. Specifically, there is an association with an increased risk of testicular cancer, increased risk of mental health problems, poor outcomes during pregnancy, and functional brain changes. There is inconclusive evidence on many harms such as brain changes, bone loss, and all-cause mortality.

Second-hand smoke can result in detectable cannabinoids and metabolites in blood and urine. Environmental factors, such as ventilation and THC concentration, directly impact the effects of second-hand smoke on non-smokers. Under extreme conditions, it is possible for individuals exposed to second-hand smoke to experience psychoactive effects of cannabis. Second-hand cannabis smoke is more mutagenic and cytotoxic than tobacco smoke, and therefore passive inhalation should be considered a health risk.

There are multiple pathways of drug use, although the most common is cannabis use immediately before other illicit drugs. This pathway is mediated by many social and genetic factors. A very commonly reported finding is that early age of initiation of any substance is associated with a higher likelihood of illicit drug initiation. This finding supports a need to focus on youth drug use prevention.

Within Canada, the majority of residents perceived non-medical cannabis consumption to be as harmful to physical and mental health as cigarettes and alcohol, and less harmful than prescription drug abuse or use of other illicit drugs. Cannabis is perceived to be addictive, but no more addictive than cigarettes or alcohol. The addictiveness of cannabis has not been quantified in the literature, but epidemiologic studies suggest that cannabis is an addictive substance.

## Topic 3: Medical Cannabis

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**Key Messages**

- In 2001, Canada was the first country to legalize medical cannabis use with access through the Medical Marihuana Access Regulations
- The Medical Marihuana Access Regulations were replaced by the Medical Purposes Regulations in 2014, and again in August of 2016 with the Access to Cannabis for Medical Purposes Regulations.
- Thirty-five licensed producers are legally allowed to produce and sell cannabis for medical purposes in Canada; one producer is in Alberta.
- There is moderate to very low-quality evidence to suggest that cannabinoids are effective treatment options for nausea and vomiting due to chemotherapy, chronic pain, spasticity due to multiple sclerosis, sleep disorder and Tourette syndrome.
- The evidence suggests that cannabis is harmful in the treatment of depression and that it causes a higher incidence of adverse events in treatment as compared to control groups.
- Guidelines for medical cannabis use across Canadian Provinces vary widely in physician and patient requirements.
- Nation-wide, 3% of Canadians report use of cannabis prescribed by a doctor, with most using it once daily.
- Medical cannabis is most often used for symptom management.
- 53% of Canadians think that if cannabis were legalized, the cost of purchasing medical cannabis should be reimbursed under health plans; support for reimbursement was highest in Alberta.

## Medical Cannabis: Overview

In 2000, an Ontario court ruled Canadians have a constitutional right to use cannabis for medical reasons. Subsequently, in 2001, legal access to cannabis was granted through the Medical Marihuana Access Regulations (MMAR)<sup>164</sup>. Medical cannabis was predominantly accessed by those with HIV/AIDS, cancer, multiple sclerosis, spinal cord injuries or diseases, epilepsy, and severe arthritis<sup>164,165</sup>. It was most commonly prescribed for symptom control, such as severe nausea and pain, anorexia, weight loss, cachexia, persistent muscles spasms, and seizures associated with these illnesses<sup>165</sup>. Only dried cannabis or cannabis seeds were accessible and cannabis could be produced or grown at home<sup>165</sup>. THC, a chemical in cannabis, is approved by the FDA for use to increase appetite and reduce nausea<sup>166</sup>.

In 2014, the Marihuana for Medical Purposes Regulations (MMPR) replaced the MMAR<sup>167</sup>. As a result, clients could no longer grow cannabis at home<sup>167</sup> and cannabis could only be accessed by licensed commercial growers<sup>167,168</sup>. The number and variety of products available increased to include: dried cannabis, cannabis oil, and edibles<sup>168</sup>. The MMPR was challenged in 2016 by the *Allard v. Canada* case, which stated that those who use it often for medical purposes should be allowed to grow and produce their own cannabis<sup>169</sup>. This case resulted in the development of the Access to Cannabis for Medical Purposes Regulations (ACMPR), which is the current legislation governing the access to medical cannabis<sup>170</sup>.

## Accessibility of Medical Cannabis

In Canada, cannabis is legally accessible only if prescribed by a physician<sup>171</sup>. In Alberta, there are multiple health clinics facilitating access medical cannabis (Table 4). These clinics offer assistance in accessing cannabis for medical purposes; they have physicians that prescribe cannabis. In addition, medical cannabis may also be accessed in some hospitals<sup>171</sup>. In Alberta, there are 295 physicians authorized to prescribe medical cannabis [personal communication, College of Surgeons and Physicians of Alberta, September 15, 2016]. Fifty-six percent of the total number of prescriptions have been authorized by the same physician. There are 5950 patients registered in Alberta

Table 4: Clinics offering assistance in accessing cannabis for medical purposes within Alberta  
172-175

Calgary	Edmonton	Other
<ul style="list-style-type: none"> <li>• Natural Health Services</li> <li>• Calgary Medicinal Cannabis Center</li> <li>• 420 Clinic</li> <li>• CannApply Medical Service</li> <li>• Lift Resource Centre</li> <li>• Cannabis Health Institute</li> <li>• DKF Med Care</li> </ul>	<ul style="list-style-type: none"> <li>• Natural Health Services</li> </ul>	<ul style="list-style-type: none"> <li>• Natural Health Services – Medicine Hat</li> </ul>

## Legislation of Medical Cannabis Use, Production and Sales

As of August 24, 2016, the ACMPR regulates the possession, production, and sale of medical cannabis. The major change resulting from the ACMPR, compared to the previous legislation, is that individuals who have been prescribed cannabis for medical reasons may now produce their own cannabis or designate another person to produce it for them <sup>176</sup>.

### Obtaining Cannabis

Individuals wishing to access cannabis for medical reasons must have a prescription from a physician or authorized nurse practitioner (nurse practitioners require special authorization to prescribe medical cannabis). The health care professional will complete a document outlining the dosage, length of time for which cannabis is needed, and contact information for the health care professional and patient <sup>48</sup>. Upon successful submission, a certificate will be provided to the patient, who can then submit this to a licensed producer to obtain cannabis plants or seeds <sup>48</sup>. The patient must register as a client of a licensed producer and supply medical documentation to that producer <sup>48</sup>. Only Canadian residents can apply to a licensed producer <sup>48</sup>. The patient can also register with Health Canada to grow their own cannabis or designate another person to do so for them <sup>48</sup>. The registration expires when the medical document or registration certificate expires <sup>48</sup>.

### Possession

Fresh or dried cannabis or cannabis oil can be possessed by a person who obtained the substance for medical reasons, a person who requires the substance for their profession as a health care practitioner, or a hospital employee who possesses for the purposes of and in connection with

their employment <sup>48</sup>. Cannabis plants or seeds may be provided to a person who has been authorized to produce cannabis for their own medical purposes or those of a person for whom they are responsible <sup>48</sup>. Individuals may designate someone else to produce their cannabis for them, but this person must be a resident of Canada and must register as the producer <sup>48</sup>.

Thirty times the daily quantity of dried cannabis needed, or a maximum of 150g, can be possessed at one time <sup>48</sup>. Each licensed producer must determine how much cannabis oil is equivalent to one gram of dried cannabis <sup>48</sup>. All persons possessing cannabis, cannabis oil, or cannabis plants or seeds must be able to show proof of authorization when asked by a police officer <sup>48</sup>. Fresh or dried cannabis, cannabis oil, or cannabis plants or seeds may only be obtained from one source at a time <sup>48</sup>.

### **Altering Cannabis**

A person that possesses and produces cannabis for either their own medical purposes or the medical purposes for another person may alter the chemical and physical properties (e.g. turn dried or fresh cannabis into oil or another product), complying with the regulations set in the ACMPR <sup>48</sup>.

### **Production and Sale**

Cannabis can be produced by licensed producers or persons who have been authorized to produce cannabis for medical reasons <sup>48</sup>. Only licensed producers and sellers may legally sell cannabis, albeit not all producers are allowed to sell directly to patients <sup>48</sup>. There are currently 35 licensed producers and sellers across Canada (Figure 20) <sup>177</sup>. There is one producer in Alberta, Aurora Cannabis Enterprises Inc.

Figure 20: Licensed Medical Cannabis Producers in Canada <sup>177</sup>



Adults living in Canada, or a corporation that has head offices, or operates a branch office, in Canada are eligible to apply for a license <sup>48</sup>. All licenses expire a maximum of three years after the effective date <sup>48</sup>. The site of all licensed producers comply with the security measures set out by the ACMPR to ensure that no unauthorized persons can access it <sup>48</sup>.

Cannabis and cannabis oil may not be sold with any additives <sup>48</sup>. A licensed producer can sell cannabis to another licensed producer, a licensed dealer, or an appointed government representative. Fresh or dried cannabis or cannabis oil can be sold to a client or a person responsible for a client, or a hospital employee for the purposes of their employment. Cannabis plants or seeds can be sold to a client who has been authorized to produce cannabis for medical purposes <sup>48</sup>. Cannabis may not be produced or sold from a place of dwelling <sup>48</sup>.



Labelling of products is regulated by the ACMPR and must be followed by licensed producers. Two labels are required for all products: the product label and the client label <sup>48</sup>. The product label must include: the name and contact information of the producer; information about the cannabis; notice of the narcotic nature of the contents; warnings to keep away from children; and directions to read the Health Canada document on medical cannabis. All information must be provided in both French and English. Client labels must include client information, shipping and expiry date, information on dosage, and contact information for their healthcare practitioner <sup>48</sup>.

Licensed producers may apply for a import and export permit within Canada, separately from their production license <sup>48</sup>. Information about the producer, the substance to be imported or exported, the port of entry or exit, the address of where it is being shipped, and the mode of transportation used must be provided <sup>48</sup>. A permit is valid until its expiry date, the expiry date of the producer's license, or the expiry date of the import or export permit of the person the substance is being shipped to or from, whichever comes first <sup>48</sup>.

## **Systematic Review on the Effectiveness of Medical Cannabis for Treating Clinical Conditions**

### **Methods**

This review built on a high-quality systematic review and meta-analysis conducted in 2015 by Whiting et al. on the effectiveness of cannabis for treating clinical conditions <sup>178</sup>. Whiting's search included literature from database inception until April 2015 <sup>178</sup>. To update this systematic review, we conducted an updated search, which captured literature from April 2015 until July 5, 2016, using the search strategy developed by Whiting et al. <sup>178</sup>.

Twenty-eight databases were searched for randomized controlled trials (RCTs) investigating the use of cannabinoids on ten pre-specified conditions compared to standard of care or placebo: nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis (MS) or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, intraocular pressure in glaucoma, or Tourette syndrome <sup>178</sup>. In cases where no published RCTs were found on a clinical condition, non-randomized trials with over 25

participants were included (depression, anxiety disorder, sleep disorder, psychosis, intraocular pressure in glaucoma, and Tourette syndrome).

## **Results**

A total of 79 randomized controlled trials were included in the 2015 systematic review (see Appendix 3 Figure 1) <sup>178</sup>. The de novo search identified five additional RCTs published after April 2015 that were not included in the 2015 systematic review (Appendix 3 Table 1). Multiple cannabinoids were evaluated within the identified literature. Table 5 summarizes the evidence identified for each cannabinoid. The outcome measures reported in the newly identified studies were not the same as the outcomes reported in the 2015 systematic review, so it was not possible to add any of the newly identified studies to the original pooled analysis.

The 79 included studies contained 104 separate trials. Of these trials, 43 used synthetic cannabis forms, 38 of which were administered orally in capsules and 5 of which were administered intramuscularly. Sixty-one trials used natural forms of medical cannabis, with 30 trials administering the cannabis through oromucosal spray, 15 trials through oral capsules, 9 through smoking, 2 through vaporizing, and one through oral tablets. The number of trials that used synthetic and not synthetic cannabis by intervention and method of administration for each type of trial are reported in Figure 2, in the Appendix.

Table 5 Included Studies by cannabinoid (modified from Whiting et al., with authors permission) <sup>178</sup>

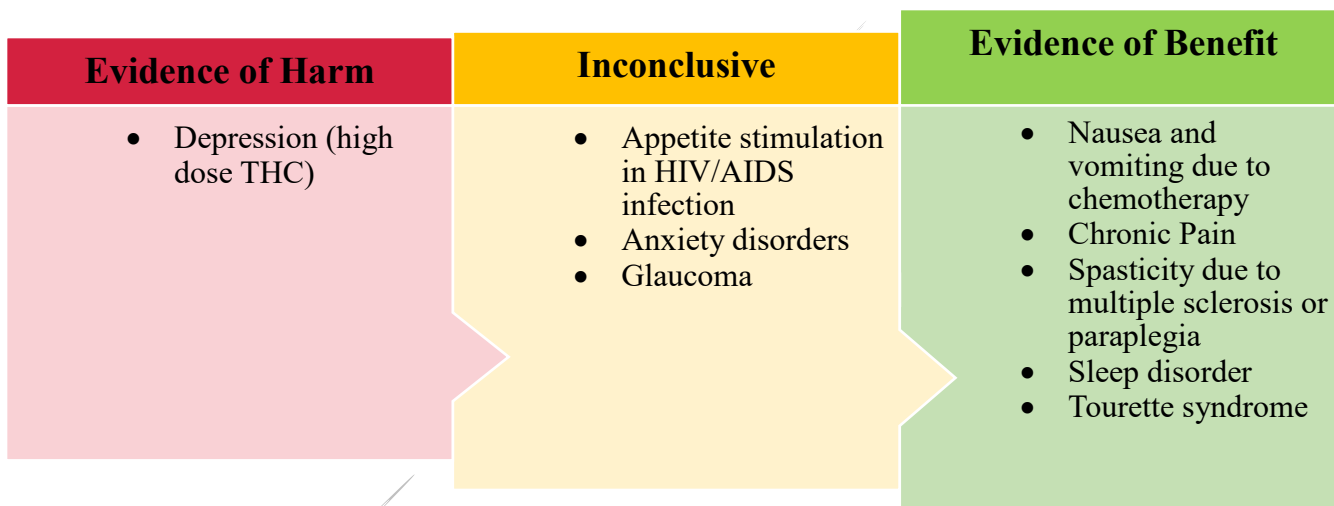
Cannabis Product	Cannabis related properties	Administration Method	Dose Evaluated	Comparator	N	Indications
Ajulemic acid (JBT-101, CT3)	Synthetic non-psychoactive cannabinoid derivate of the THC metabolite 11-nor-9-carboxy-THC	Capsules (oral)	Max 40 mg 2x/day	Placebo	1	Pain
CBD	Active cannabinoid, part of cannabis	Capsules (oral)	200-800mg/day	Placebo	2	Psychosis, anxiety
				Amisulpride	1	Pyschosis
		Oromucosal spray	20 or 40 mg 1x/day (2 doses evaluated)	Placebo	1	Glaucoma
Cannabis (Marijuana)	Numerous active cannabinoids which will vaporise at different temperatures	Vaporised	$\Delta^9$ - THC concentration between 1% and 7%	Placebo	2	Pain
		Smoked	Max 3 cigarettes/day	Placebo	1	HIV
Dronabinol (Marinol® (Unimed Pharmaceuticals))	Synthetic THC	Capsules (oral)	Max 5-30mg/day given as 1-4 doses/day, most common 2 doses	Placebo	11	N&V, pain, spasticity, HIV, sleep
				Dronabinol + prochlorperazine or prochlorperazine	1	N&V
				Megestrol acetate	1	HIV
				Dronabinol + ondansetron or ondansetron, or placebo	1	N&V
Levonantradol (Pfizer)	Synthetic analogue of dronabinol	Capsules (oral)	Max 5mg: 1 mg 2 hours before chemotherapy then every 4 hours.	Prochlorperazine	1	N&V
		IM	Max 1.5-4mg: 0.5-1mg 1-2 hours before chemotherapy then every 4 hours	Prochlorperazine	1	N&V
				Chlorpromazine	1	N&V
				Metoclopramide	1	N&V
Nabilone (Cesamet®, Valeant Pharmaceuticals International)	Synthetic cannabinoid derivate mimicking THC	Capsules (oral)	Max 0.5-8mg. Most common dose 2mg 2x daily	Placebo	8*	Spasticity, pain, sleep, N&V
				Alizapride	1	N&V
				Amitriptyline	1	Pain, sleep

Cannabis Product	Cannabis related properties	Administration Method	Dose Evaluated	Comparator	N	Indications
				Chlorpromazine	1	N&V
				Dihydrocodeine	1	Pain
				Domperidone	2	N&V
				Prochlorperazine	7	N&V
Nabiximols (Sativex®, GW Pharmaceuticals)	Each mL contains 27 mg THC and 25 mg CBD	Oromucosal spray	Titrated to max 4-48 sprays/24h. Most common maximum was 8 sprays/3 hours or 48 sprays/24h.	Placebo	20	Spasticity, pain, N&V
ECP002A (Namisol, Echo Pharmaceuticals)	Pure (≥98%), natural Δ9-THC	Oral tablet	Individualised, titrated, dose	Placebo	1	Spasticity
					1	Pain
THC	Active cannabinoid, part of cannabis	Capsules (oral)	Max 5-60mg/ day. Given 1x daily or every 4-6h in chemotherapy patients	Placebo	3	Pain, Tourette's
				Placebo and codeine	1	Pain
				Placebo and prochlorperazine	2	N&V
				Prochlorperazine	3	N&V
				Hydroxyzine	1	N&V
		Smoked	1-5 cigarettes/ day. Potency, where reported, ranged from 2.5%-9.4%	Placebo	5	Spasticity, pain
		Oromucosal spray	Single daily dose – max 8 actuations/24 h. Concentration ranged from 1-7%	Placebo	4	Pain, glaucoma
THC/CBD	Combination of CBD and THC	Capsules (oral)	Max 10-60mg/day given as 2 doses	Placebo	4	Spasticity

### *Clinical Conditions*

Most of the included RCTs evaluated the use of cannabinoids as treatment for symptoms, such as chronic pain (28 studies, 63 reports), followed by nausea and vomiting due to chemotherapy (28 studies, 37 reports), and spasticity due to MS (14 studies, 33 reports) <sup>178</sup>. Broad findings by clinical category are presented in Figure 21. The studies found in the updated review included: two RCTs which investigated the effect of cannabinoids on MS (one on spasticity and one on disease progression) <sup>179,180</sup>, two which investigated effects on chronic pain <sup>181,182</sup>, and one which investigated the effects on nausea due to chemotherapy <sup>183</sup>. A synthesis by clinical indication is presented narratively and in Figure 21.

Figure 21: Summary of Findings



### **Nausea and Vomiting**

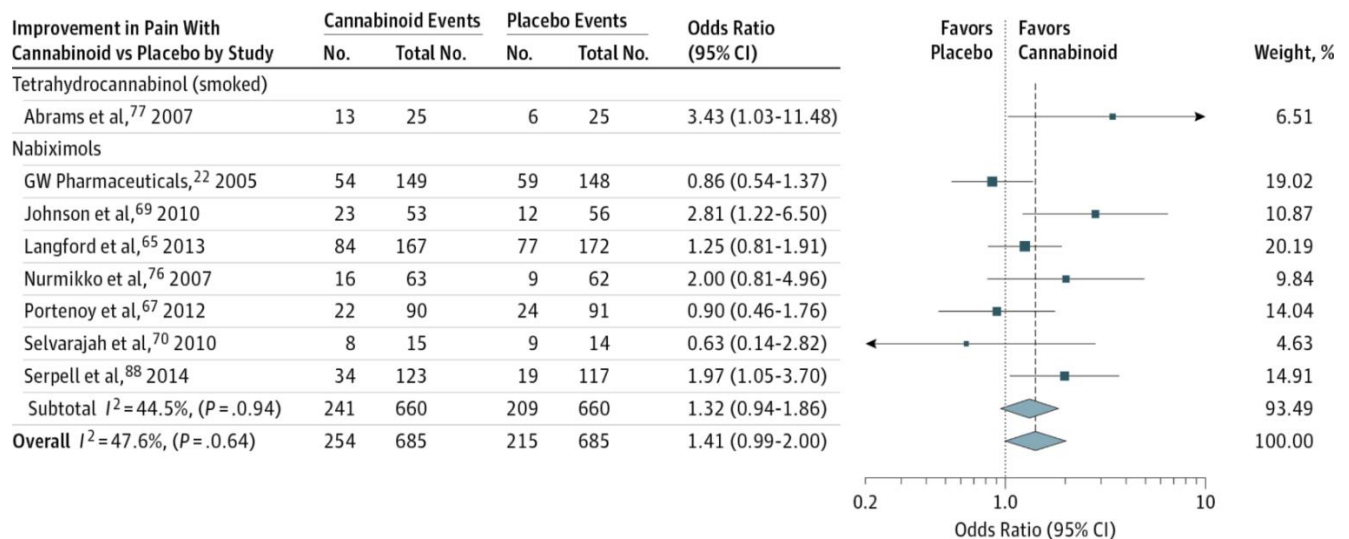
29 randomized controlled trials investigated the effectiveness of cannabinoids on alleviating nausea and vomiting in patients receiving chemotherapy. All studies report beneficial effects of cannabinoids when compared to placebo or active comparators such as prochlorperazine, chlorpromazine and domperidone. Patients taking cannabinoids were 3.82 times more likely than patients taking only placebo to have complete relief from nausea (95% CI: 1.55 to 9.42) <sup>178</sup>. The de novo search yielded one additional article that investigated the effectiveness of nabilone (Cesamet®) for nausea and vomiting on patients with oral squamous cell carcinoma receiving radiotherapy or radiochemotherapy <sup>183</sup>. This study reported no significant differences between

treatment and placebo groups for any of the outcome measures including quality of life, pain, appetite and body weight, nausea, sleep, mood, and adverse effects <sup>183</sup>.

### **Chronic Pain**

In the 30 randomized controlled trials that evaluated chronic pain, patients taking cannabinoids were 1.41 times more likely (Figure 22) than patients taking a placebo to experience >30% reduction in pain (95% CI: 0.99 to 2.00); however, this result was not statistically significant <sup>178</sup>. There was a difference in the reported effectiveness depending on the method of use. One trial that evaluated the effectiveness of vaporized dried cannabis compared to placebo on pain relief reported the highest effect (OR: 3.43, 95% CI: 0.99-2.00). Nabiximols (Sativex®) and other cannabinoids reported a lower effect on pain relief compared to placebo (OR: 1.32, 95% CI: 0.94-1.86) <sup>178</sup>. The updated search yielded two additional articles. One study investigated the effectiveness of ECP002A (Namisol®) on patients with chronic pancreatitis <sup>181</sup>. In this cross-over study, patients in the treatment group were given both the treatment and the active placebo, diazepam over two days <sup>181</sup>. The authors found no significant difference between treatment and placebo groups with the frequency of adverse events and improvement of condition as measured by the VAS pain score <sup>181</sup>. The second study was also a cross-over design, with three eight-hour exposure periods to vaporized dried cannabis, separated by at least 3 days <sup>182</sup>. This study was conducted in patients with chronic pain due to spinal cord injury or disease <sup>182</sup>. This study reported that patients who received either the higher or lower dose of vaporized cannabis had higher rates >30% pain reduction when compared to the placebo group <sup>182</sup>. There was a significant dose-response relationship between the dose received and pain relief including the placebo ( $p < 0.05$ ), but the difference of effect between the higher and lower dosage was not statistically significant ( $p > 0.11$ ) <sup>182</sup>.

Figure 22: Chronic pain forest plot comparing cannabinoids versus placebo (Whiting et al.)<sup>178</sup>

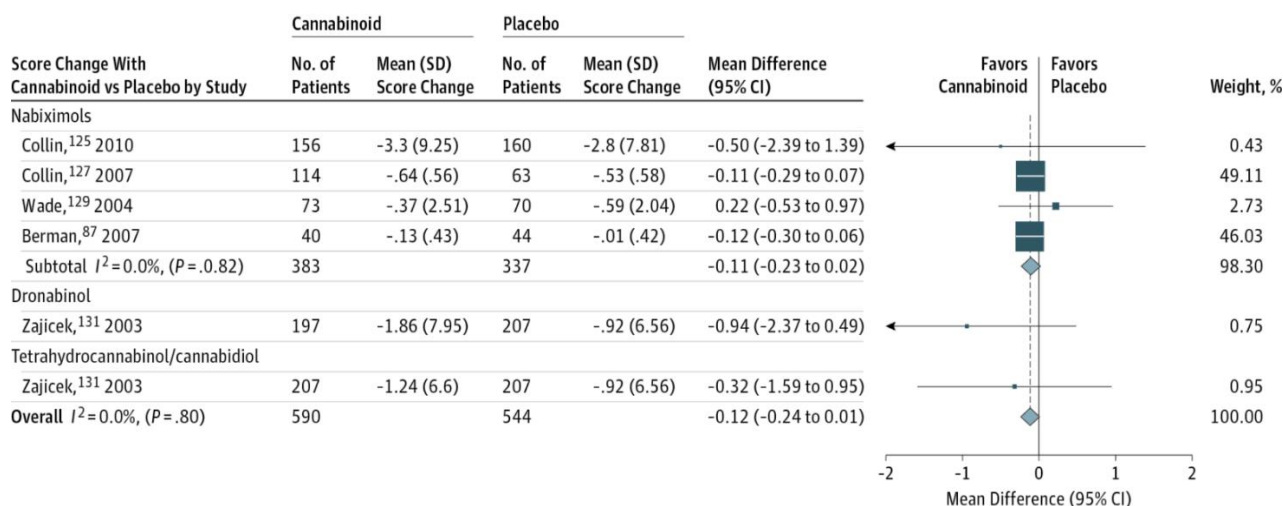


## Spasticity

In the sixteen studies evaluating the effects of cannabinoid treatment on muscle spasticity, RCTs generally reported that cannabinoids were associated with an improvement in muscle spasticity, but the differences were not statistically significant (Figure 23)<sup>178</sup>. Overall, treatment with nabiximol appeared to improve muscle spasticity on a Patient Global Impression of Change scale (patient reported outcome) compared to placebo (OR: 1.44, 95% CI: 1.07-1.94). This finding is supported in other studies using dronabinol (Marinol®) and other cannabinoids as treatment<sup>178</sup>. There were no significant differences in effectiveness between cannabinoids<sup>178</sup>. The updated search yielded two additional articles. One investigated dronabinol as an agent to slow the progression of MS<sup>179</sup>. This study lasted three years and no statistically significant differences in disease progression between patients taking dronabinol compared to placebo were reported for any outcome measures<sup>179</sup>. The second study used a cross-over design to investigate the effectiveness of nabiximol for treating muscle spasticity resulting from progressive MS<sup>180</sup>. This study lasted 10 weeks and found that patients who received nabiximol had significant improvement in the lower limb modified ashworth scale (LL-MAS) score from baseline, when compared to the placebo group ( $-21.73\% \pm 29.45$  in treatment compared to  $-5.99\% \pm 24.75$  in placebo)<sup>180</sup>. However, this was the only test out of sixteen that evaluated neurophysiological response, treatment response, and overall muscular function that showed the treatment group had significantly different results from baseline<sup>180</sup>. Both studies reported that adverse events were

more frequent in the treatment group when compared to the placebo group, but the differences were not statistically significant<sup>180</sup>.

Figure 23: Spasticity forest plot comparing cannabinoids versus placebo (Whiting et al.)<sup>178</sup>



## Anxiety and Depression

No RCTs assessing the use of cannabis to treat anxiety or depression were found. Five non-randomized studies that looked at cannabis use for chronic pain, and one that looked at cannabis use for spasticity evaluated depression as a secondary outcome<sup>178</sup>. These studies found that there was no difference between cannabinoids and placebo in depression outcomes. One study found that higher doses of cannabinoids were associated with a more negative depression outcome.

One non-RCT was found on treatment of anxiety disorder with cannabidiol<sup>178</sup>. This study found that cannabidiol resulted in lower anxiety compared to placebo during a public speaking test.

## Adverse Events

Sixty-two of the studies included in the systematic review report adverse events. A meta-regression and stratified analysis was conducted. Patients receiving cannabinoids were 3.03 times as likely to experience an adverse event compared to patients receiving placebo (95% CI: 2.42-3.80)<sup>178</sup>. Only two studies reported a higher rate of adverse events in placebo groups compared to cannabinoids, both of which evaluated dronabinol as treatment for wasting due to HIV<sup>184</sup> and for nausea and vomiting<sup>185</sup>. The most frequent adverse events were: dizziness, dry mouth, nausea, fatigue, drowsiness and euphoria<sup>178</sup>.

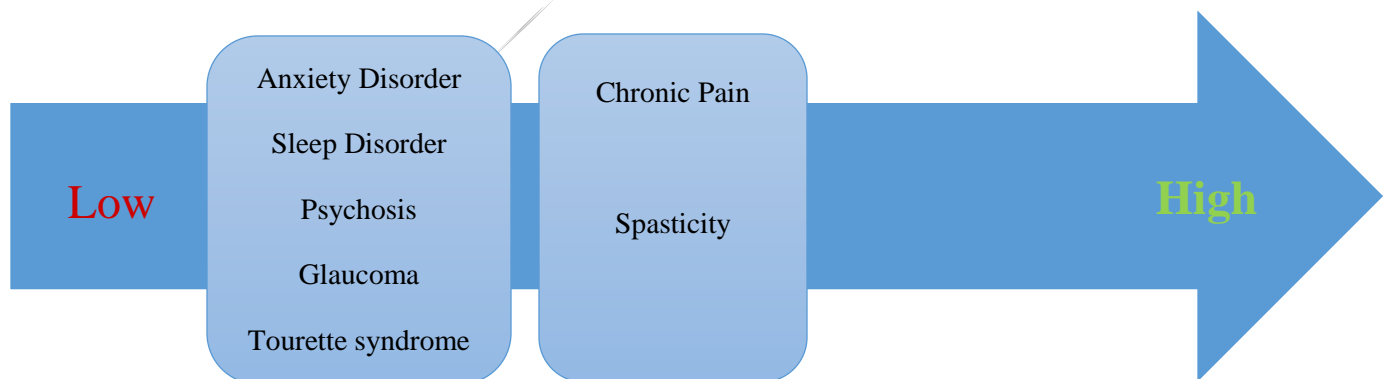


## Quality of Evidence

Quality assessment was conducted using the Cochrane Risk of Bias Tool <sup>176</sup>. The majority of trials included in the systematic review were judged at a high risk of bias (70%) with only 5% of trials judged at low risk of bias; 25% of studies were judged at unclear risk of bias <sup>178</sup>.

Incomplete outcome data was the main source of risk of bias, as 50% of trials reported withdrawals that were not accounted for in analysis <sup>178</sup>. There was moderate-quality evidence that cannabinoids can alleviate chronic pain and spasticity resulting from MS and that cannabinoids were more effective at alleviating chronic pain than placebo <sup>178</sup> (Figure 24). For the remainder of the health conditions, there was low-quality evidence for the effectiveness of cannabinoids as treatment for the health conditions <sup>178</sup>. No RCTs investigating depression, anxiety disorder, sleep disorder, psychosis, intraocular pressure in glaucoma, and Tourette syndrome met inclusion criteria for in this systematic review. As a result, there was low- and very low-quality evidence to support the use of cannabinoids as treatment for these health conditions <sup>178</sup>.

Figure 24: Quality of Included Studies



## Limitations

There was high heterogeneity between studies in terms of with the types of cannabinoids used as treatment and the measures used to determine treatment effectiveness <sup>178</sup>. Furthermore, inconsistencies with reporting made quantitative data synthesis difficult for most conditions. For example, some studies that produced continuous data reported differences in measures from

baseline, while others report differences between treatment and placebo groups, and others only reported p-values for any kind of measure. Studies that produced categorical outcomes also had factors that complicated data synthesis, such as reporting heterogeneous measures and using varying comparison groups.

One concern with study designs that compare cannabinoids to placebo is that there are marked and well-documented psychoactive properties of tetrahydrocannabinol, which may have caused unblinding. As none of the included RCTs used an active placebo, it is possible that patients and health care professionals could identify when they were given or gave out cannabinoids versus placebo due to these effects. While studies did not report on this directly, Whiting and colleagues mention this potential limitation to the study design<sup>178</sup>. Accordingly, to the extent there is a potential for unblinding of participants and health care professionals, quality assessment should be interpreted with caution.

## **Conclusions**

Despite there being a large number of published studies on the effectiveness of medical cannabis, there is only moderate to limited evidence for the effectiveness of cannabinoids for each of the medical conditions of interest. The RCTs identified in the updated search did not provide robust enough evidence to change the conclusions reached in the previous systematic review. There are a number of limitations to the evidence for the effectiveness of cannabinoids on the ten medical conditions of interest in the literature. Therefore, we conclude that there is moderate- to very low-quality evidence to suggest that cannabinoids are effective treatment options for these medical conditions, and that further high-quality studies are required to establish effectiveness of cannabinoids as medical treatment for the specified conditions. This is because of differences for a number of factors including differing measures and reporting strategies, differences in inclusion and exclusion criteria, and varying patient characteristics. In addition to inconclusive evidence on the effect of cannabinoids on medical conditions and symptoms, there is also lack of evidence on the effects and adverse events as a result of the use of cannabis on healthy individuals, especially for short-term adverse events. There are limited studies on smoking cannabis or using cannabis oil for treating clinical conditions; most studies assess synthetic cannabinoids.

## Provincial Insurance Reimbursement

### Methods

A review was conducted of current pharmaceutical benefits and coverage of cannabis products in each Canadian Province. The Canadian Agency for Drugs and Technologies in Health (CADTH) Common Drug Review (CDR) was searched for reports on cannabis and drug products containing cannabinoids. Websites for provincial drug plans were searched to determine the status of cannabis drug coverage in each Province. Drug plans for Canadian Territories were not searched. Product monographs were used to verify findings from each of the provincial websites, and to fill gaps in drug coverage information.

### Results

The Common Drug Review has only completed an assessment of one pharmaceutical cannabis product, Sativex®, which is an oral-mucosal spray containing two kinds of cannabinoids, tetrahydrocannabinol and cannabidiol (Table 6). Although no drug review has been conducted on the pill-form Cesamet® (nabilone), it is publically funded in nine Provinces across Canada with application approval. Veterans Affairs Canada health plan is the only publically funded health insurance plan that will cover expenses for dried cannabis in Canada.

Table 6: Drug Coverage by Cannabis Product

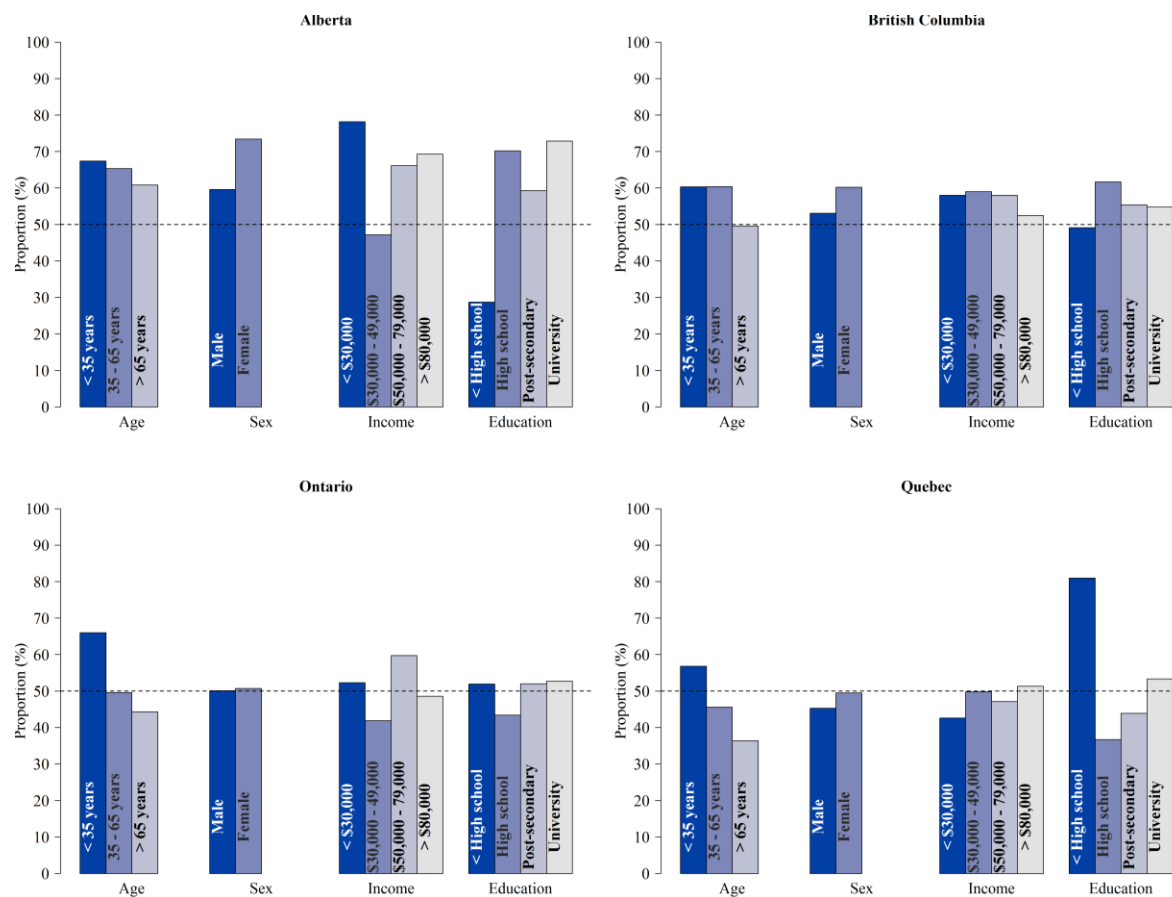
	CDR decision	Publicly funded drug plans that reimburse	Notes
<b>Dried Cannabis</b>	No review conducted	Veterans Affairs Canada health plans	May be claimed as a health expense on federal tax return <sup>187</sup>
<b>Sativex®</b>	Do not list <sup>188,189</sup>	Ontario <sup>190,191</sup>	
<b>Cesamet® (nabilone)</b>	No review conducted	Alberta, British Columbia, Saskatchewan, Manitoba, Ontario, Quebec, Nova Scotia, PEI, Newfoundland, Canadian Forces Health Services, Veterans Affairs Canada <sup>192</sup>	Non-Insured Health Benefits (Federal coverage for First Nations and recognized Inuit) may cover this drug

### **Public Perception of Reimbursement Coverage**

Based on a survey commissioned by the University of Calgary HTA Unit in July 2016, 53% of Canadians think that if cannabis was legalized, the cost of purchasing medical cannabis should be reimbursed under health plans. The support for reimbursement was highest in Alberta (65%), followed by British Columbia (57%), Ontario (50%) and Quebec (48%). Those who are under 35 years old, and female tend to be more supportive of medical cannabis reimbursement (Figure 25).



Figure 25: Proportion of individuals who think that the cost of medical cannabis should be reimbursed under health plan



	<35	35 - 65	65+	Male	Female	< \$30,000	\$30,000- 49,000	\$50,000- 79,000	> \$80,000	< High school	High school	Post- secondary	University
<b>AB</b>	67%	65%	61%	60%	73%	78%	47%	66%	69%	29%	70%	59%	73%
<b>BC</b>	60%	60%	50%	53%	60%	58%	59%	58%	52%	49%	62%	55%	55%
<b>ON</b>	66%	50%	44%	50%	51%	52%	42%	60%	49%	52%	43%	52%	53%
<b>QC</b>	57%	46%	36%	45%	50%	43%	50%	47%	51%	81%	37%	44%	53%

## Provincial Medical Cannabis Prescribing Guidelines

Guidelines for prescribing cannabis for medical use, from the College of Physicians and Surgeons from each Canadian province were reviewed. This information was retrieved from each website from July 13-28, 2016. Data were extracted from each document, and the content was compiled into a table for descriptive and comparative analysis.

All provincial medical licensure bodies have guidelines, follow a similar format, and had similar requirements for prescribing cannabis for medical purposes as the documents circulated by the Canadian College of Family Physicians of Canada (Table 7). Beyond these similarities, there was wide variability in physician and patient dimensions.

Within Alberta, a physician who chooses to treat a patient using cannabis must:

- Register with the College as a prescriber of medical cannabis
- Treat the patient using conventional therapies and find them ineffective
- Assess the risk of addiction
- Receive informed consent
- Obtain a patient medication profile
- Comply with provincial and federal regulations
- Evaluate each patient on a regular basis to assess the benefits and risks of using cannabis as a treatment
- See the patient once every three months at minimum
- Provide ongoing care for the clinical condition being treated and assess misuse or abuse of cannabis

Guidelines for all provinces, except Alberta, require physicians to have established a continuing professional relationship with the patient, prior to prescribing cannabis<sup>193-201</sup>. However, only the Alberta guidelines require physicians to register as cannabis prescribers<sup>202</sup>. The remainder of the requirements vary between Provinces. For example, all provincial guidelines, except for Manitoba and New Brunswick, state that physicians should check in with patients to monitor use and potential dependence; however, only Alberta and British Columbia guidelines have explicit timelines for follow-up<sup>193,202</sup>. Alberta physicians are advised to check in with patients every three months after their dose is stabilized, and British Columbia physicians are advised to check

in with patients every three to six months<sup>193,202</sup>. While physicians in most Provinces are required to use a dependency risk assessment tool prior to prescribing cannabis, Manitoba and New Brunswick have no such provisions<sup>193-197,199,201,202</sup>.

The College of Physicians and Surgeons of Alberta provide information and support on when medical cannabis may be beneficial to a patient and when it may not be. Risks outlined include precipitation of psychotic symptoms, impaired pulmonary function, impaired cognition, dependence, infertility, neurodevelopmental disorders due to in utero exposure, impaired driving, and impact on insurance and benefit coverage<sup>203</sup>. The College recommends that Health Canada guidelines are followed, and cannabis is not prescribed to patients: under the age of 18; with severe cardiopulmonary disease or respiratory insufficiency; have a history of psychiatric disorder, history of substance abuse, or family history of schizophrenia; are pregnant or breast feeding; or with renal or liver disease<sup>203</sup>. They suggest potential benefits for appetite stimulation for HIV/AIDS, pain and spasticity related to multiple sclerosis, chronic pain and neuropathic pain<sup>203</sup>.

Table 7: College of Physicians and Surgeons guidelines for prescribing dried cannabis for each province

	Physician must register as a prescriber?	Physician must have a continuing relationship with patient?	Physician must submit to an audit process?	Patient treatment agreement required?	Patient medical document (PMD) requirements:			
					Periodic follow-up required?	Risk assessment for dependency required?	Disclosure of dose per day required?*	Disclosure of medical condition for which cannabis was prescribed required?
Alberta <sup>202</sup>	✓	Not explicit	✓	-	✓	✓	✓	✓
British Columbia <sup>193</sup>	-	✓	✓	-	✓	✓	-	-
Saskatchewan <sup>195</sup>	-	✓	✓	✓	✓	✓	✓	✓
Manitoba <sup>200</sup>	-	✓	✓	-	-	-	✓	✓
Ontario <sup>197</sup>	-	✓	✓	✓	✓	✓	✓	-
New Brunswick <sup>198</sup>	-	✓ <sup>1</sup>	Not explicit	- (recommended)	-	Not explicit	✓	Not explicit
Newfoundland <sup>201</sup>	-	✓	Not explicit	✓	✓	✓	-	✓
Nova Scotia <sup>194</sup>	-	✓	-	-	✓	✓	✓	-
Prince Edward Island <sup>196</sup>	-	✓	✓	✓	✓	✓	✓	✓
Quebec <sup>199</sup>	Physicians may only prescribe cannabis to patients who are participating or agree to participate in research on cannabis for medical use.							

<sup>1</sup> Or by recommendation from one physician practicing in NB to another, where there has been direct communication between the physicians and the prescribing physician has conducted their own patient assessment.

\* Period of use, as specified in the medical document, is limited to one year according to federal law (Marihuana for Medical Purposes Regulations).



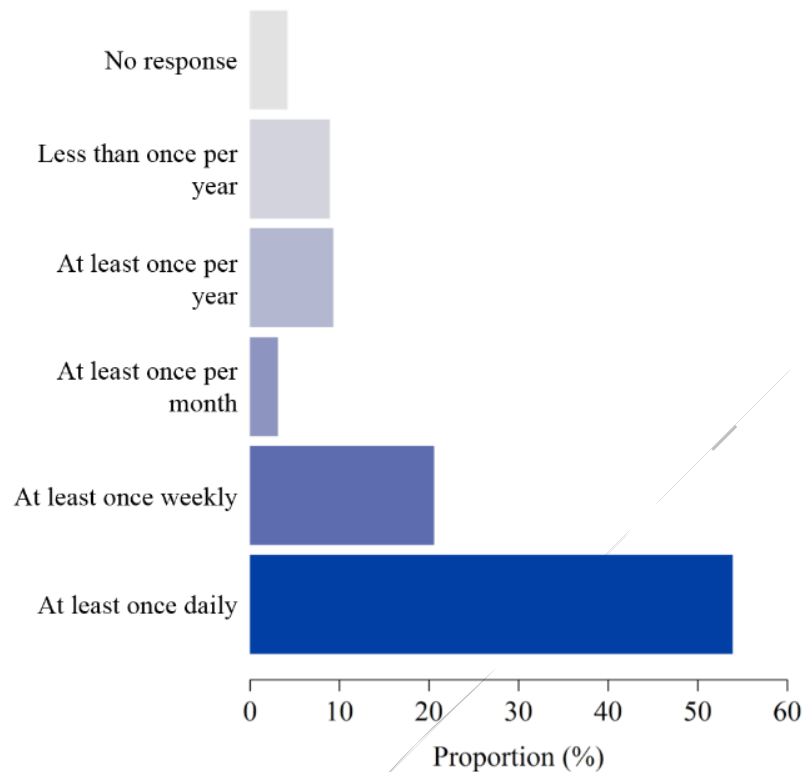
There were also some outlying cases. For example, the Collège des médecines du Québec guidelines are unlike all other Provinces in that patients seeking medical cannabis are required to participate in research in order to obtain a prescription <sup>199</sup>. Furthermore, some guidelines were more detailed than others. Nova Scotia's professional standards were four sentences long, while Alberta, British Columbia, PEI, Ontario, Quebec, and Manitoba's guidelines were more comprehensive and provided explicit guidelines for conduct <sup>193,196,197,199,200,202</sup>.

## **Public Perspective on the Use of Medical Cannabis**

A survey was commissioned by the University of Calgary HTA Unit in July 2016 to understand current public perceptions of cannabis and cannabis legalization. This survey of 2,088 people, is weighted to be a representative sample nationally and for the populations of British Columbia, Alberta, Ontario, and Quebec.

Nation-wide, 3% of Canadians report using cannabis prescribed by a doctor. The prevalence of medical cannabis use differed across Provinces: 3% in Alberta, 5% in British Columbia, 3% in Ontario, and 2% in Quebec. The majority of people who reported using cannabis prescribed by a doctor used it at least once daily (54%) (Figure 26). Twenty-one percent reported using it once per week while 9% used it at least once per year, 9% less than once per year, and 3% at least once per month.

Figure 26: Frequency of use among individuals who report using cannabis prescribed by a physician



Medical cannabis is most commonly used for symptom management (Figure 27), including nausea and vomiting due to chemotherapy, appetite stimulation in wasting caused by AIDS, chronic pain, and sleep disorders. It was least commonly used for neurological conditions such as spasticity due to multiple sclerosis, epilepsy, and movement disorders due to Tourette syndrome. The majority of patients use medical cannabis to manage one condition (Figure 28). However, 16.7% report using medical cannabis to manage three conditions and 1.9% report managing four types of conditions.

Figure 27: Use of medical cannabis by medical condition

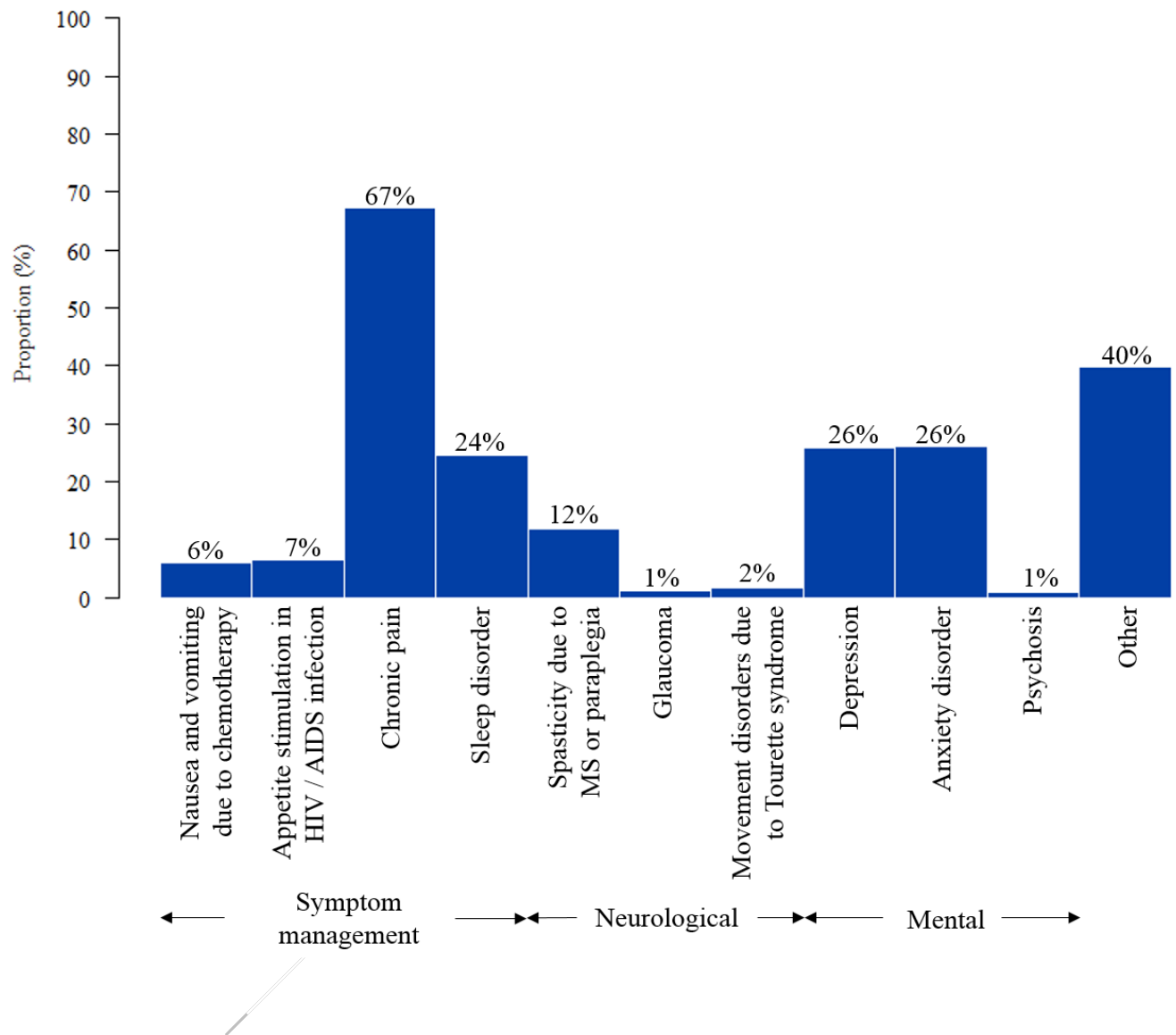
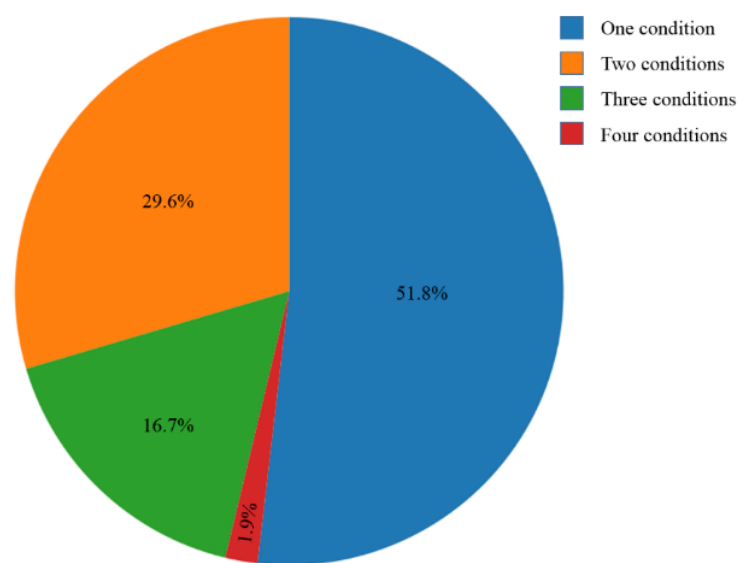


Figure 28: Proportion of individuals using cannabis for different numbers of conditions



## Conclusions

Although Canada has a fifteen-year history of legalized use of medical cannabis, there have been frequent and significant legislative changes during this time. Since its use was first sanctioned in 2001, these legislative changes have impacted accessibility, production and use. Approximately 3% of Canadians are using medical cannabis to treat a clinical condition, most of whom are using it for symptom management. Despite a large amount of literature, there is only moderate to limited evidence to suggest that cannabis is an effective treatment for some medical conditions. The guidelines and regulations for physicians vary by province.

## Topic 4: Advertising and Communication

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


































### **Key Messages**

- Advertising regulations in regions that have legalized marijuana are varied, with Washington State having the most restrictive regulations.
- Broadly, most advertising regulations are targeted towards preventing misleading claims and youth viewership.
- Evidence regarding the effects of advertising on substance use, including tobacco and alcohol, demonstrates that most campaigns can influence thoughts about quitting but have a modest effect on actual behavioural outcomes. Packaging, and bans consistently result in decreased use and fewer calls to quit lines.
- Evidence examining effects of anti-marijuana advertising is very limited

## Background

Regulations on tobacco and alcohol advertising vary significantly among countries and states. Among the 6 jurisdictions that have legalized cannabis (Uruguay, Alaska, Colorado, Oregon, Washington State, and Washington DC), the regulations for cannabis also vary (Table 8).

**Table 8: Overview of Allowances in Cannabis Advertising**

	Uruguay	Alaska	Colorado	Oregon	Washington State	Washington DC	US Federal Law
Restrictions around Media Advertising (TV, Radio, print media)?	Yes		Yes*				** 
Regulate Against Deceptive, False and/or Misleading Claims?			Yes		Yes		
Outdoor Advertising Generally Permitted?	No		No		No		
Point of Sale Advertising Permitted?	No						
Sponsorship of Charitable, Sports or Other Events Permitted?	No		Yes*				
Regulation Against Content Targeting Minors?			Yes		Yes		
Sign Restrictions for Dispensaries?			Yes	Yes	Yes	Yes	
Restrictions around Schools, Playgrounds?					Yes		
Restrictions around Public Transit/ Public Parks/Recreation Centers?					Yes		
Promotional Items Permitted?	No				No		
Mandatory Health Warnings on Packages?					Yes		
Mandatory Health Warnings at Point of Sale?				Yes			

\* Colorado state law allows media advertising and sponsorship of charitable, sports or similar events only under the condition that the Retail Marijuana Establishment has reliable evidence that more than 70% of the audience is over the age of 21.

\*\* US Federal Law prohibits all cannabis ads from being sent through the postal service.



--: No regulations found

Broadly, advertising of cannabis, tobacco and alcohol is prohibited outdoors, and is allowed on licensed premises, subject to conditions such as no targeting towards minors, and specific rules around the language and graphics used on advertising products. Provided their execution and intent are lawful, the primary forms of permitted advertising include: signage and interior displays on retail licensed premises, coupons and other promotional items from suppliers, and advertising at sponsored, retailer, and certain public events. The advertising of tobacco, alcohol and cannabis is typically regulated by either a state's Liquor Control Commission, Control Board or Enforcement Division, the Ministry or Department of Public Health, or by the State Department of Revenue. While each state's advertising laws vary in the degree of regulation and the specificities expressed within these regulations, all substances and all states are subject to the same federal laws on advertising.

The following section outlines how cannabis, tobacco and alcohol advertising is in each of the six places that have legalized recreational cannabis use: Uruguay, Alaska, Colorado, Oregon, Washington State, and Washington DC.

### **Uruguay**

Uruguay has no legally binding regulations on alcohol advertising<sup>204</sup>. However, between 2004 and 2010, the Uruguay government passed anti-tobacco legislation: smoking in public places was banned, risk warnings had to cover 80% of cigarette packs, and all tobacco advertising and sponsorships were banned<sup>205</sup>.

In 2013, Uruguay became the world's first country to legalize and regulate the cannabis market. The legal cannabis market in Uruguay is entirely government controlled. Federal law forbids all advertising of cannabis as well as contests, tournaments or public events that promote cannabis consumption<sup>206</sup>.

## **US Federal Laws on Alcohol Advertising**

The primary federal laws on alcohol advertising in the United States (US) prohibit certain statements on products. These include statements that are false or untrue, statements that are inconsistent with approved product labels, false or misleading statements that are disparaging or a competitor's product, health-related statements that are false or misleading, as well as any misleading guarantees (although money back guarantees are not prohibited) <sup>207</sup>.

## **US Federal Acts Regulating Tobacco Advertising**

Two key US federal acts place limitations on the advertising of tobacco within the country: the 2009 Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) and The Tobacco/Smokeless Tobacco Master Settlement Agreements (MSA and STMSA) of 1998 <sup>208,209</sup>.

The Tobacco Control Act, signed in 2009, gave the Food and Drug Administration (FDA) the power to regulate the tobacco industry. FDA regulations are designed to restrict advertising and promotions that are likely to be heard or seen primarily by youth. The main laws within the Act that focus on advertising are stated as follows:

- only black text on a white background may be used in print and video advertising and labelling of cigarettes and smokeless tobacco
- audio advertising is limited to words only
- no gifts or other items may be provided in exchange for purchasing cigarettes or a smokeless tobacco product; non-tobacco items may not bear the brand name, logo, symbol, motto, or recognizable color or pattern of colors identifiable with any cigarette or smokeless tobacco brand
- no free samples of tobacco products may be distributed, except smokeless tobacco in a "qualified adult-only facility"
- sampling is prohibited to any sports team or entertainment group, or at any sporting or entertainment event
- a tobacco product is considered "misbranded" if it's labelling is false or misleading in any way <sup>210</sup>

The 1998 Tobacco/Smokeless Master Settlement Agreements (MSA and STMSA) regulating tobacco advertising center around prohibiting manufacturers from targeting youth with the advertisement, promotion, or marketing of tobacco. Specific rules include prohibiting the use of cartoon characters in advertisement, promotion, packaging, or labeling of tobacco products, and prohibiting the promotion of tobacco products in movies, TV shows, theater or live performances, and videos or video games. Transit advertising and most outdoor forms of advertising are also prohibited, including tobacco brand names for stadiums and arenas, and sponsorship of any events with a significant youth audience or team sports. Tobacco companies may not authorize third parties to use or advertise tobacco brand names. No gifts or other items may be offered to youth in exchange for purchasing a tobacco product, and gifts may not be distributed through the mail without proof of age. Cigarettes and tobacco products may not be marketed in combination with any other product regulated by the FDA. No distribution or sale of non-tobacco merchandise with tobacco brand-name logos except at the site of permitted brand-name sponsorships, and no free samples of tobacco products may be distributed except in "adult-only" facilities <sup>209</sup>.

### **US Federal Laws on Cannabis Advertising**

The primary federal law on cannabis advertising in the US prohibits distribution of cannabis ads through postal service. Ads promoting the sale of cannabis are considered illegal by the postal services; this applies to all ads and all states, even those that have legalized the drug <sup>211</sup>.

### **Alaska**

In regards to alcohol, Alaska strictly limits outdoor advertising without reference to ad content <sup>212</sup>. Section 15 Pricing and Marketing of Alcoholic Beverages, of the Alaska Statutes, prohibits a licensed premise from offering or delivering free alcoholic beverages to a patron, as a marketing tool to the public. However, other than these two rules Alaska has no state laws in other areas of alcohol advertising <sup>213</sup>. Alaska also has no state laws or regulations around advertising and promotion of tobacco <sup>214</sup>. Nor, as of 2016, are there are laws set around advertising and promotion of cannabis <sup>215</sup>.

## Colorado

The state of Colorado has extensive and comprehensive laws regarding alcohol advertising <sup>216</sup>. Below are stated the primary regulations within each of advertising's three main sections.

### 1) Advertising Practice:

- Suppliers are allowed to provide consumer advertising specialties, contest information, supplier rebates and coupons without cost to a licensed retailer, though subject to certain conditions such as reaching the customer only through allowed advertising practices.
- Suppliers are prohibited from directly or indirectly paying for advertising for any retail licensee, except as provided for on-site sales promotions and sponsored events

### 2) Signs and Interior Displays

- Advertising statements on signs and interior displays shall primarily consist of a supplier's name, brand or trade name or trademark, and permitted language

### 3) Unfair Trade Practices and Competition

- Conditions around the allowance of on-site sales promotions and sponsored consumer sampling of beverages, and lawful advertising at sponsored events and retailer events <sup>216</sup>

Colorado has no state laws regarding the advertising/promotion of tobacco products <sup>217</sup>.

In Colorado, state laws regarding advertising of retail cannabis state that a Retail Marijuana Establishment (RME) shall not engage in advertising that is deceptive, false or misleading. An RME shall not make any deceptive, false or misleading assertions or statements on any product, any sign, or any document provided to a customer. An RME shall not utilize television, radio or print media or internet advertising unless the RME has reliable evidence that more than 70% of the audience is expected to be over the age of 21. An RME shall not engage in advertising that specifically targets persons located outside the state of Colorado. No RME shall engage in advertising or utilize signage that asserts its products are safe because they are regulated by the State Licensing Authority or because they are tested by a retail cannabis testing facility. Outdoor advertising is generally prohibited; however, the prohibitions do not apply to any fixed sign that is located on the same zone lot as an RME and that exists solely for the purpose of identifying the location of the RME. An RME cannot utilize unsolicited pop-up advertising on the internet. An RME may sponsor a charitable, sports, or similar event, as long as the RME has reliable

evidence that more than 70% of the audience at the event and/or viewing advertising in connection with the event is over the age of 21. Any content that targets minors is prohibited. Finally, no advertising is allowed via marketing directed towards location-based devices unless on an application installed by the owner of the device who is 21 year of age or older <sup>218</sup>.

## Oregon

The Oregon Liquor Control Commission regulates alcohol advertising through the “Advertising Media, Coupons” state law. The key regulations within this law are stated as follows:

- Advertising is prohibited through flyers that are posted/passed out in public areas, and point of sale items (such as displays and signs), on premises where the advertised product is not sold, and in some additional media
- Suppliers are allowed to provide customers with coupons but under certain criteria.
- Advertising the regular price of an alcoholic beverage outside the licensed premises, such as on a menu in the window or on a website, is allowed as long as there is no mention of a specified limited time period for those prices and no mention of an alcoholic beverage’s price or discount <sup>219</sup>

Oregon’s only State Law on tobacco advertising regards “sampling” and states the following: free tobacco products may not be distributed to people under 18 as part of a marketing strategy. Additionally, free samples of smokeless tobacco may not be given to anyone under the age of 21 or distributed in any area in which people under the age of 21 are allowed <sup>220</sup>.

The Oregon Liquor Control Commission’s function includes regulating and prohibiting and advertising by manufacturers, processors, wholesalers, or retailers of cannabis items <sup>221</sup>. Oregon has one set of primary laws on the advertising of medical and non-medical cannabis that relate to signage. Cannabis signage rules include the following general principle: the registered dispensary must post the applicable entry sign on the exterior of the dispensary in a conspicuous location that can be easily seen by the public from outside the dispensary at any point of public entry, in bold, 80 point Times New Roman font. Point of Sale signage must also include 1) a pregnancy warning poster, 2) a poisoning prevention poster and 3) a colour copy of the “Educate Before You Recreate”

poster. If a dispensary has properly notified the authority that it intends to sell limited cannabis retail products, the dispensary must post signs that read: “Medical Marijuana Patients and Persons 21 and Older Permitted” and “no person under 21 permitted on the premises without an OMMP card”<sup>222</sup> [the Oregon Medical Marijuana Program or OMMP, oversees the medical cannabis cardholder registry for patients and regulates medical cannabis dispensaries, processors and grow sites]<sup>223</sup>.

## **Washington State**

Washington State’s alcoholic beverage advertising laws are as follows:

- All liquor advertising is prohibited from promoting over consumption, or referring to Washington state liquor control board, except where required by law
- Also prohibited is advertising that depicts liquor as having curative or therapeutic effects; is targeted principally to minors, or uses subliminal or similar techniques
- Subject to specific limitations, Washington State allows liquor advertising that offers consumers premium or prizes, advertising in public and civic events, displays on retail licensed premises, by retail licensees, and at sports entertainment facilities<sup>224</sup>
- On March 3 2010 Washington’s Liquor Control Board (WSLCB) adopted revised alcohol advertising rules that restricted outdoor advertising at licensed locations<sup>225</sup>

Washington State previously had restrictions tobacco advertising in publicly visible locations; however these have been suspended and are pending further review by the King County Board of Health<sup>226</sup>.

Laws on the advertising of cannabis in Washington State are divided between two main categories: advertising by retail licensees, and general rules. The WSLCB limits each retail licensed premises to a maximum of two signs identifying the retail outlet by the licensee's business name or trade name. Both signs must be affixed to the building or permanent structure and each sign is limited to sixteen hundred square inches. General rules on cannabis advertising include the following: all cannabis advertising and labels of usable cannabis, cannabis concentrates, and cannabis-infused products sold in the state of Washington must not contain any statement, or illustration that: is false or misleading, promotes over consumption represents the

use of cannabis having curative or therapeutic effects; depicting a child or other person under legal age consuming cannabis, or includes objects suggesting the presence of a person under legal age to consume cannabis, or is designed in any manner that would be especially appealing to children or other persons under twenty-one years of age. Cannabis advertising is also prohibited in all forms within certain distances of schools, playgrounds, recreation centers, public parks, on or in public transit vehicles and public transit shelters, on or in a publicly owned or operated property. All promotional items are also banned, and all advertising must contain specific warnings regarding the product's intoxicating and habit-forming effects, regarding the impairment of concentration, coordination and judgement and warning against operating a vehicle under the influence, general health risks, and a statement regarding use only for persons age 21 years of older <sup>227</sup>.

### **Washington, DC**

The Washington Metropolitan Area Transit Authority, which runs the District of Columbia's subway and bus system, has prohibited alcohol advertising on all system rail cars and buses <sup>228</sup>.

DC's other laws on the advertising of alcoholic beverages fall under the District of Columbia Municipal Regulations; the primary of which are as follows:

- Prohibited statements are those depicting or designed to be appealing to a child or immature person, referring to any religious symbol, or intending to mislead the public into believing that the advertiser is authorized to sell alcoholic beverages as a wholesaler
- Restrictions on signage in terms of distance from licensed premise and time illuminated
- Prohibited advertisements are those being displayed on the exterior of any window or interior of any door of the licensed premise, and those with statements that are false or misleading with respect to any material fact <sup>229</sup>

DC has one main law on the advertising and promotion of tobacco, also set by the Washington Metropolitan Area Transit Authority; all tobacco advertising on all system rail cars and buses is prohibited <sup>228</sup>.

DC has one set of primary laws on the advertising of medical cannabis that relate to signage. These laws are as follows: advertisements relating to the prices of medical cannabis shall not be displayed in the window of a registered establishment, advertisements relating to medical cannabis shall not be displayed on the exterior of any window or on the exterior or interior of any door, and no sign advertising medical cannabis on the exterior or visible from the exterior of any registered establishment or elsewhere in the District shall be illuminated at any time <sup>230</sup>.

### **Enforcement of Advertising Laws**

The laws on the advertising of tobacco, alcohol and cannabis are enforced by various regulatory bodies within each state and each country. In Uruguay, the federal government has total control over all advertising of tobacco, alcohol and cannabis <sup>205,206</sup>. Within the five states described above that have legalized cannabis, exist different regulatory bodies that have control over the advertising of the three substances. These bodies include the Alaska Legislature, the Oregon Liquor Control Commission, the Colorado Department of Revenue and Enforcement Division, the Washington State Liquor Control Board, and the Washington (DC) Metropolitan Area Transit Authority.

### **Alcohol Advertising Regulations in Canada and Alberta**

#### *Canada*

Table 9 provides a summary of the Canadian and Alberta allowances for alcohol and tobacco advertising. Alcohol advertising is regulated by the Federal government through the Canadian Radio-Television and Telecommunications Commission (CRTC) and the Canadian Food Inspection Agency (CFIA). The CRTC regulates alcoholic beverage advertisement under the Radio Regulations and Television Broadcasting Regulations <sup>231</sup>. All broadcasters must maintain a CRTC license in order to advertise alcohol. The regulation is broad in design and includes directions which clearly outline that broadcast advertising cannot be appealing to those under the legal drinking age, attempt to influence people, show individuals consuming the product or demonstrates the product in a beneficial manner. The CFIA is responsible for the labelling of alcoholic products and requires that all alcoholic beverages containing 1.1% or more alcohol by volume to declare the percentage by volume of alcohol on the label <sup>232</sup>.



### *Alberta*

Alcohol advertising is regulated by the Alberta Gaming and Liquor Commission (AGLC) <sup>233</sup>. There are several different licenses you can obtain in Alberta which outline guidelines for the use and advertisement of alcohol. Special event licensing can also be obtained on a temporary basis. Price and brand promotions may occur and specific guidelines are outlined according to the different licenses in effect. All advertising, at minimum, must meet the guidelines outlined by the CRTC.

## **Tobacco Advertising Regulations in Canada and Alberta**

### *Canada*

Canada passed the *Tobacco Act* in 1997 which regulates the sale, labelling and promotion of tobacco products <sup>234</sup>. The purpose of this Act is to protect the health of Canadians and protect young persons by restricting access and use. The Act outlines the manufacturing, access, labelling and promotion of all tobacco products in Canada stipulating that no advertising shall depict a tobacco product (except by direct mail to an adult who is identified by name) or in signs where young persons are present and no event or facility sponsorship is allowed. In 2011, the *Tobacco Products and Labelling Regulations* came into effect requiring graphic health warnings that cover 75% of the front of back of packages, easy to understand health information and toxic emission statements <sup>235</sup>.

### *Alberta*

Alberta amended the *Smoke-free Places Act* in 2002 and adopted the *Tobacco Reduction Act* in 2008 <sup>236</sup>. The Act limits where tobacco is sold, does not allow for advertising or association of tobacco and does not allow for the promotion of tobacco (Table 2). In places where tobacco products are sold, a sign may indicate tobacco products are available for sale as long as the sign complies with the regulations. Tobacco is prohibited for sale in health facilities, post-secondary institutions, pharmacies and retail stores where a pharmacy is in operation.

**Table 9: Overview of Allowance in Tobacco and Alcohol Advertising.**

	Alcohol		Tobacco	
	Canada*	Alberta	Canada	Alberta
Restrictions around Media Advertising (TV, Radio, print media)?	✓	✓	✓	✓
Regulate Against Deceptive, False and/or Misleading	✓	✓	✓	✓
Outdoor Advertising Generally Permitted?	—	✓	X	X
Point of Sale Advertising Permitted?	—	—	X	X
Sponsorship of Charitable, Sports or Other Events	—	—	X	X
Content Targeting Minors Permitted?	X	X	X	X
Sign Restrictions for Dispensaries?	—	—	—	✓
Restrictions around Schools, Playgrounds?	—	—	—	✓
Restrictions around Public Transit/ Public Parks/Recreation	—	—	—	✓
Promotional Items Permitted?	—	✓	—	—
Mandatory Health Warnings on Packages?	—	—	✓	—
Mandatory Health Warnings at Point of Sale?	—	—	—	—

## Effects of Advertising on Use

### Methods

A systematic review was conducted regarding the effect of advertisements on use alcohol, tobacco, cannabis, prescription drugs, and illicit substances was conducted. Published peer-reviewed literature was reviewed by searching 6 databases. Studies that examined real world

data, had a control group that was not exposed to the advertising, and reported on either intention to quit or use were included.

Abstracts were screened independently by one reviewer. The review team (7 independent reviewers) calibrated to an initial set of 200 abstracts; the team was considered calibrated when there were no disagreements in any of the inclusion/exclusion decisions. All abstracts identified as “include” or “potentially include” were subsequently reviewed in duplicate by two independent reviewers. All abstracts included by either reviewer were included for full text review. All full texts were reviewed in duplicate. Full texts included by both reviewers were included in the final data analysis and any differences were resolved via discussion. Data extraction was conducted by a single reviewer and then independently verified. Quality assessment was not completed due to the diversity of study designs which are unable to be assessed using the same quality assessment instrument.

## **Results**

The initial search identified 28,799 potentially relevant articles (Appendix 4, Figure 1). Seventy-eight full texts were included in the final dataset. Overall, 12 studies examined alcohol, 62 studies examined tobacco, one study examined cannabis, three studies examined prescription drugs, and one study examined unspecified “legal and illegal” drugs (Table 10). Fifty-one examined effects on the general population, 17 targeted youth, and the rest targeted specific populations including pregnant women and ethnic minorities. Types of advertising were divided into bans (n=9), mass media (n=47), packaging (n=18), or other (n=4).

Mass media articles included advertisements on TV, radio, websites, public billboards, buses, or newspapers and point-of-sale warnings. Social media was included in the search; only one study utilized Facebook and YouTube<sup>237</sup>. Both pro-substance and anti-substance advertisements were searched for, but only anti-substance interventions were reported in the literature.

Bans included banning of pro-substance advertisements in public places or on mass media platforms. There was one study<sup>238</sup> that examined banning anti-substance messages. Another

study <sup>239</sup> examined the effect of banning price advertising. One <sup>240</sup> examined lifting an advertising ban.

Packaging included the implementation of graphic health warning labels that warned about the risk of use and increasing the size of labels.

**Table 10. Summary of Included Studies**

Type of media	Substance	Outcome	Country
<b>Ban (n=9)</b>	Alcohol	Use (n=3)	<ul style="list-style-type: none"> <li>• Canada (n=1) <sup>240</sup></li> <li>• US (n=2) <sup>239,241</sup></li> </ul>
	Tobacco	Intent to quit (n=1)	<ul style="list-style-type: none"> <li>• UK (n=1) <sup>238</sup></li> </ul>
		Use (n=5)	<ul style="list-style-type: none"> <li>• Australia (n=1) <sup>242</sup></li> <li>• Brazil (n=1) <sup>243</sup></li> <li>• Ireland (n=1) <sup>244</sup></li> <li>• NZ (n=1) <sup>245</sup></li> <li>• Taiwan (n=1) <sup>246</sup></li> </ul>
<b>Mass Media (n=47)</b>	Alcohol	Intent to quit (n=1)	<ul style="list-style-type: none"> <li>• Australia (n=1) <sup>247</sup></li> </ul>
		Use (n=3)	<ul style="list-style-type: none"> <li>• Australia (n=1) <sup>248</sup></li> <li>• NZ (n=1) <sup>249</sup></li> <li>• US (n=1) <sup>250</sup></li> </ul>
	Tobacco	Intent to quit (n=15)	<ul style="list-style-type: none"> <li>• Australia (n=1) <sup>251</sup></li> <li>• China (n=1) <sup>252</sup></li> <li>• Scotland (n=1) <sup>253</sup></li> <li>• UK (n=2) <sup>254,255</sup></li> <li>• US (n=10) <sup>256-265</sup></li> </ul>
		Use (n=28)	<ul style="list-style-type: none"> <li>• Australia (n=3) <sup>251,266,267</sup></li> <li>• Canada (n=2) <sup>268,269</sup></li> <li>• Switzerland (n=1) <sup>270</sup></li> <li>• Norway (n=2) <sup>237,271</sup></li> <li>• UK (n=1) <sup>272</sup></li> <li>• US (n=2) <sup>273-289</sup></li> </ul>
	Other	Use (n=3)	<ul style="list-style-type: none"> <li>• Australia (n=1) <sup>290</sup></li> <li>• US (n=2) <sup>291,292</sup></li> </ul>
<b>Packaging (n=18)</b>	Alcohol	Use (n=2)	<ul style="list-style-type: none"> <li>• US (n=2) <sup>293,294</sup></li> </ul>
	Tobacco	Intent to quit (n=10)	<ul style="list-style-type: none"> <li>• Australia (n=3) <sup>295-297</sup></li> <li>• Canada (n=4) <sup>298-301</sup></li> <li>• Iran (n=1) <sup>302</sup></li> </ul>

<b>Other*(n=4)</b>			<ul style="list-style-type: none"> <li>• Taiwan (n=2) <sup>303,304</sup></li> </ul>
		Use (n=9)	<ul style="list-style-type: none"> <li>• Australia (n=3) <sup>305-307</sup></li> <li>• Canada (n=3) <sup>300,308,309</sup></li> <li>• HK (n=1) <sup>310</sup></li> <li>• Taiwan (n=1) <sup>304</sup></li> </ul>
	Alcohol	Use (n=2)	<ul style="list-style-type: none"> <li>• Sweden (n=1) <sup>311</sup></li> <li>• US (n=1) <sup>312</sup></li> </ul>
	Other	Use (n=2)	<ul style="list-style-type: none"> <li>• Canada (n=1) <sup>313</sup></li> <li>• Netherlands (n=1) <sup>314</sup></li> </ul>

\*"Other" substances include studies on alcohol and antidepressants

† Use was measured using outcomes such as smoking prevalence, number of average cigarettes smoked, and cigarette sales.

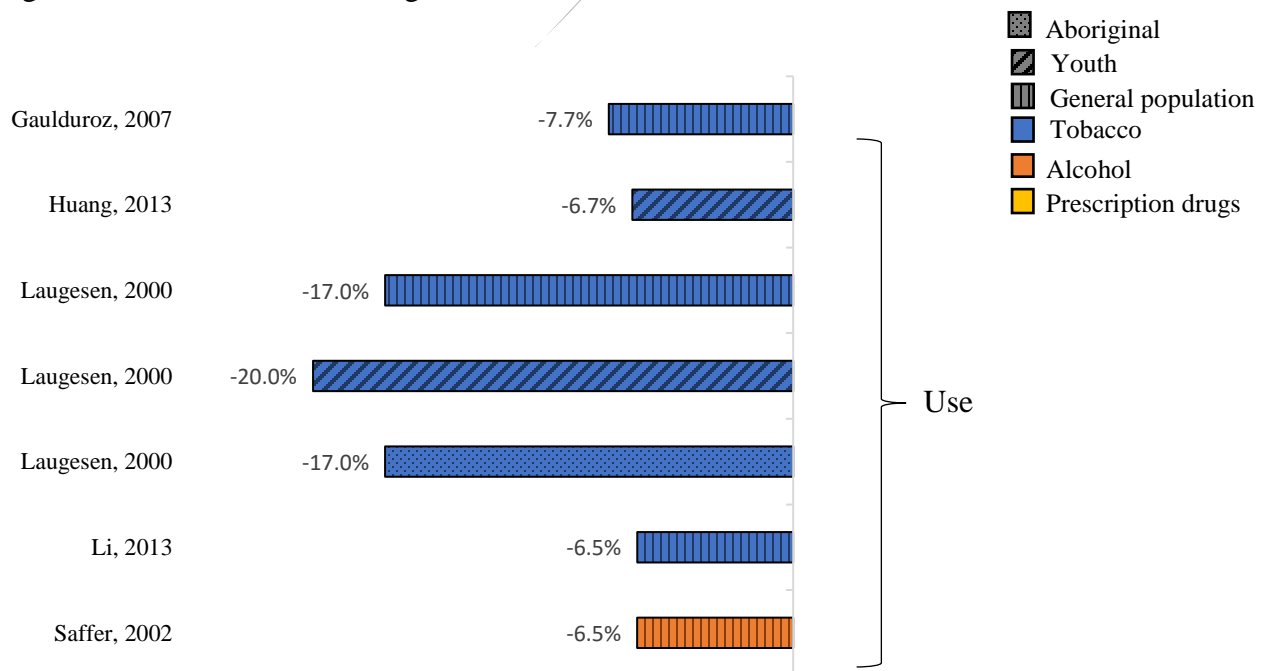
Intent to quit was measured using outcomes such as self-reported quit attempts, and calls to quit lines.

## Bans

Of the nine included studies examining advertising bans, five reported decreased use, four reported no change in use or consumption, and one reported decreased calls to a quitline.

One study <sup>240</sup> examined lifting an advertising ban on alcohol and determined there were no changes in sales. Another examined a suspension in anti-tobacco advertising and determined that those seeking help to quit decreased <sup>238</sup>. All studies reported a decrease in use across all population and substances studied (Figure 29).

Figure 29: Effects of Advertising Bans



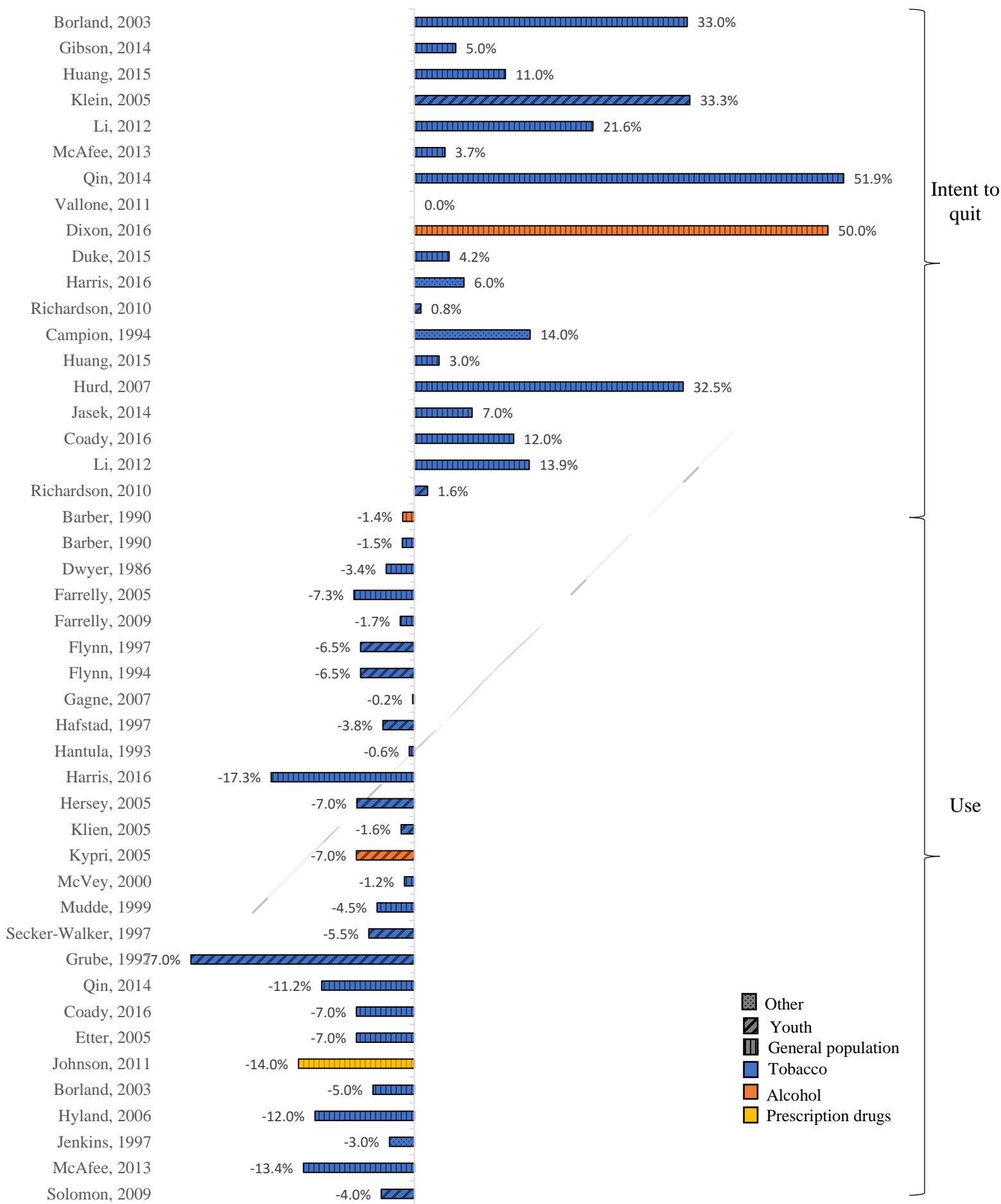
## Mass Media Campaigns

Fifty-four outcomes were reported within the 47 identified studies; 46 were positive outcomes and 8 reported no change. None reported negative outcomes. Most mass media interventions used TV and radio advertisements.

One study examined cannabis <sup>292</sup>. Those who were exposed to a community-level health promotion campaign both in school and through posters, banners, and pamphlets were less likely to use cannabis <sup>292</sup>.

One study conducted in Canada <sup>269</sup> examined a health promotion campaign aimed at reducing children's exposure to tobacco in the home through print adverts, television, etc. This study reported no difference post-campaign and suggested that public health campaigns should aim at changing behaviours and not just attitudes and knowledge <sup>269</sup>. Similarly, all studies reported either an increase in intention to quit or a decrease in use across all populations and substances studied (Figure 30).

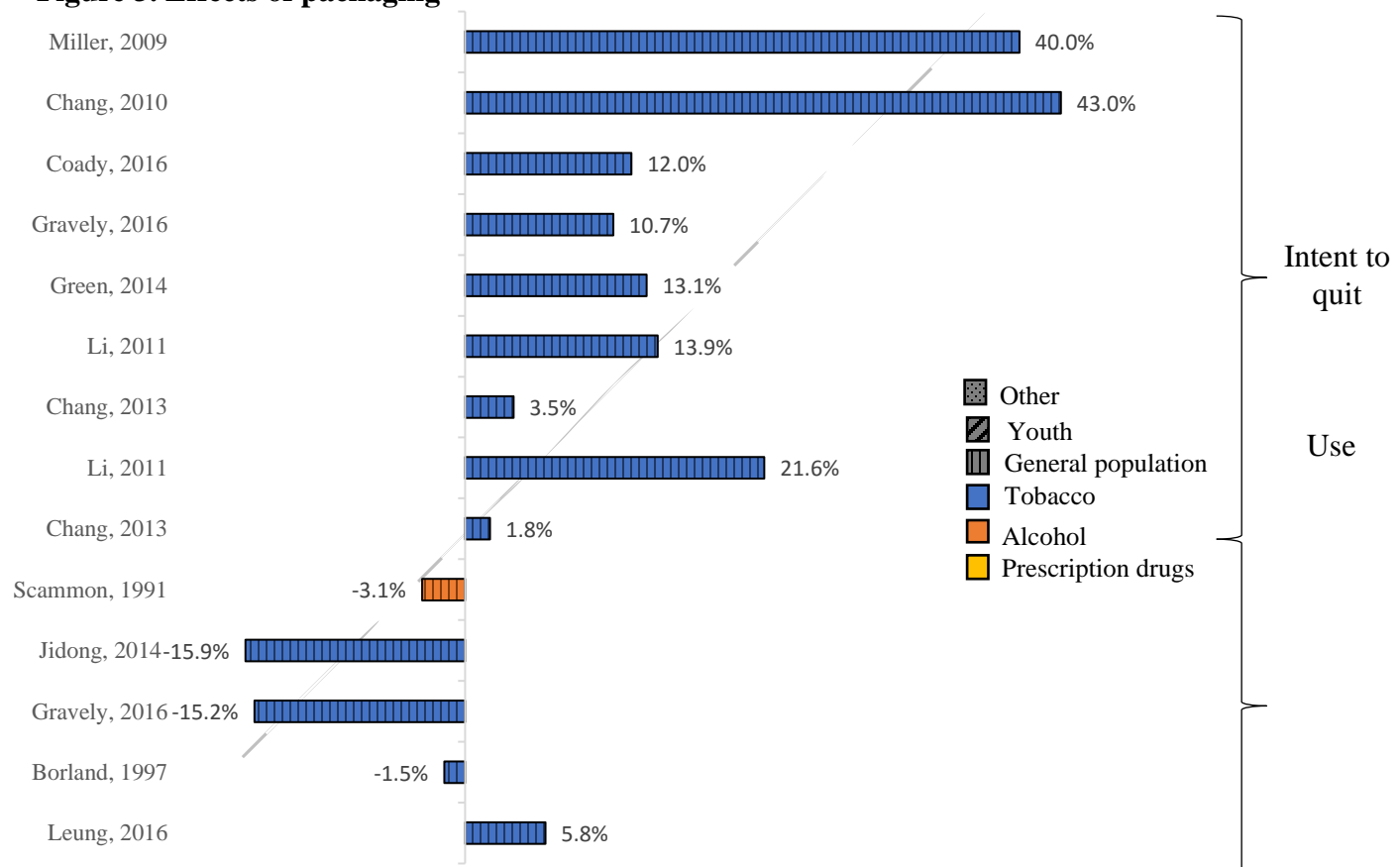
Figure 30: Effects of Mass Media



## Packaging

Of the 18 identified studies, all studies reported positive outcomes. One study reported no change in a subgroup of the total population; this study<sup>310</sup> found there was no change in “hardcore” smokers (daily smokers who smoke an average of 11 cigarettes per day, with a history of greater than six years with no intent to quit or quit attempts), but found positive outcomes in the general population.

**Figure 3. Effects of packaging**



## Other

Of the four studies classified as “other,” two examined alcohol and two examined antidepressants.



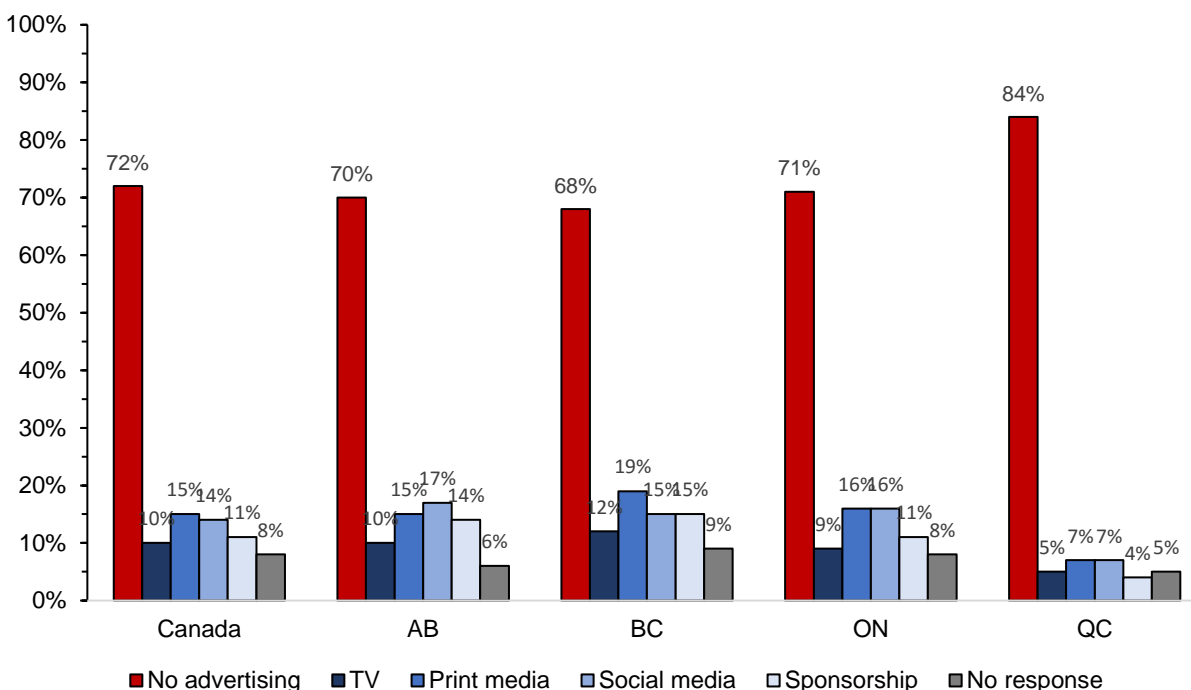
One study examining alcohol <sup>312</sup> educated two residence halls in a university on alcohol-related laws and the risks of alcohol. One group (the intervention group) got several related media (bookmarks, stickers, posters). Alcohol intake increased in both halls and there was no significant change <sup>312</sup>. The other study examining alcohol utilized media advocacy, social and emotional training, media and police reports, and motivational interviewing to decrease alcohol intake in youth <sup>311</sup>. There was no significant decrease in alcohol intake over time or between the two groups <sup>311</sup>.

Both of the studies on antidepressants examined the effects of media and attention to a warning against using antidepressants in pediatrics and young adults <sup>313,314</sup>. In one, the rate of overall prescriptions decreased after the warning, but the rate of completed suicides increased <sup>314</sup>. In the other study, the rate of prescriptions decreased slightly but increased to the original level, indicating no longitudinal change <sup>313</sup>.

## **Perspectives on Advertising Across Canada**

A survey was commissioned by the University of Calgary HTA Unit in July 2016 to understand current public perceptions of cannabis advertising. Overall, 70% of Canadians think that if cannabis was legalized, it should not be advertised in any public media and this proportion was much higher in Quebec (84%) compared to other provinces. Among those who supported cannabis advertising, majority preferred it to be advertised on print media (15% nationally) and in social media (14% nationally), and only 10% of respondents think it is suitable to advertise in television. The provincial response pattern is not significantly different from the national level results.

Figure 31. Opinion on advertising across Canada



## Conclusions

Places that have legalized cannabis have different regulations on advertising. In general, outdoor advertising and promotional items are not allowed. There are restrictions on media advertising, sponsorships of events, and advertising targeted to minors. Signs for dispensaries are regulated. Only Washington State requires health warning labels on packages.

There is considerable evidence regarding the effects of media and advertising on substance use, but there is minimal evidence regarding the effects of advertising bans. In general, advertising seems to have effects on intention to quit; however, there is modest effects on actual behavioural outcomes.

In Canada, most people do not support advertising for cannabis. Of those who do support advertising, most support advertising in print or social media.

## Topics 5: Experience with Legalization Economic, Sales and Use Regulation

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## **Key Messages**

### *Experience with Legalization and Regulation*

- Cannabis has been legalized in six jurisdictions: Uruguay, Alaska, Colorado, Oregon, Washington and Washington D.C.
- Legal age of consumption is 21 years in all jurisdictions except in Uruguay, where the age limit is 18 years.
- Public consumption is prohibited in all jurisdictions and the amount of cannabis an individual may possess at any given time varies from 1 ounce (Alaska) to 8 ounces (Oregon).
- All jurisdictions that have legalized non-medical marijuana use, first legalized medical marijuana use.
- In jurisdictions where home cultivation is permitted, users are usually restricted to 4-6 plants.
- All jurisdictions that have legalized marijuana prohibit public consumption
- After legalization, States with data available reported:
  - self-reported cannabis use remained stable
  - alcohol and cigarette use decreased
  - cannabis use disorders increased
  - number of arrests for cannabis-related crimes decreased
  - number of drivers testing positive for THC increased
  - health care resource utilization associated with cannabis use increased

### *Perceptions of Regulations*

- Approximately 50% of Canadians prefer cannabis to be taxed similarly to alcohol and cigarettes

## **Legal Cannabis: Current Jurisdictions**

Since 2012, one country (Uruguay) and four US States (Washington State, Colorado, Alaska, and Oregon) and on US jurisdiction (Washington DC) have legalized cannabis for non-medical use. On November 8, 2016, five States voted on the proposal to legalize non-medical cannabis; four States passed the proposal (Figure 32). Generally, regions that have legalized cannabis follow a similar legislative progression and have developed similar regulations (Table 11). Public cannabis consumption is illegal in all jurisdictions, and age restrictions for purchasing cannabis are the same as those set for alcohol. Oregon, Colorado, Alaska and Washington State decriminalized possession and legalized the medical use of cannabis prior to legalizing the use of cannabis for non-medical use, while Uruguay legalized cannabis for both medical and non-medical use at the same time. Only Uruguay has chosen not to tax the retail sale of non-medical cannabis, while other regions have imposed various tax rates on retail sales and/or wholesales. With the exception of the District of Columbia, all regions have created a regulatory board or council for controlling the sale of cannabis, the majority of which are fused with or modelled after the regulatory board responsible for controlling the sale of alcohol in that region. A brief overview of the trajectory to legalization in each jurisdiction is described below.

Figure 32: Overview of timeline for legalization of cannabis

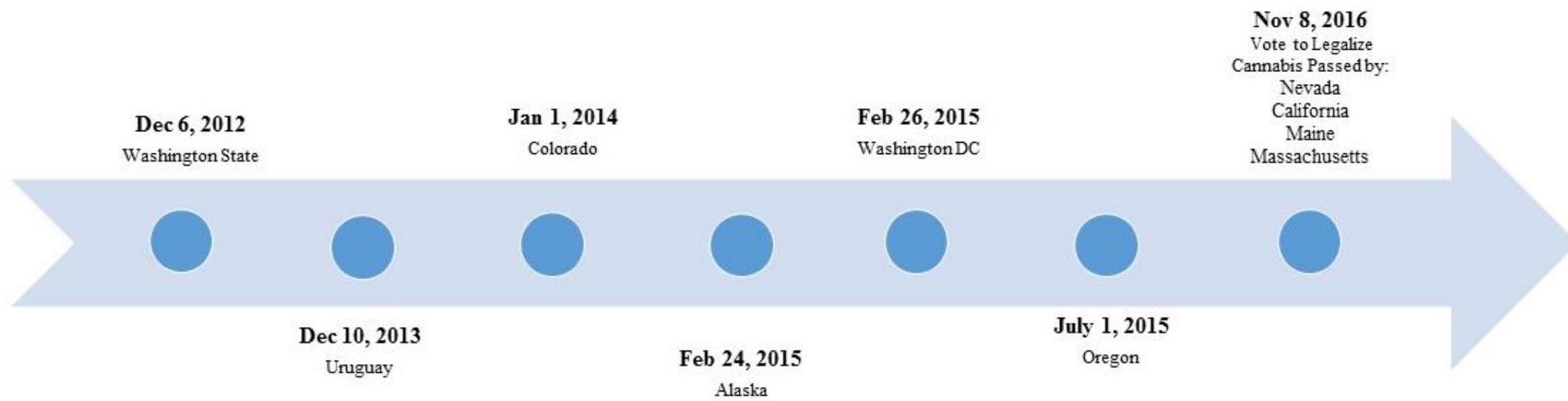


Table 11: Alcohol and Tobacco Regulations Compared to Cannabis Regulations by Jurisdiction

Country Regulation	Washington State	Colorado	Uruguay	Alaska	Washington DC	Oregon
What is the legal age minimum for recreation cannabis?	21	21	18	21	21	21
What is the legal age minimum for medical cannabis?	18*	18*	18	18*	18*	18*
What is the legal age minimum for alcohol?	21	21	18	21	21	21
What is the legal age minimum for tobacco?	18	18	18	19	18	18
Is the legal age minimum the same for cannabis and tobacco?	X	X	✓	X	X	X
Is cannabis governed by the same body as alcohol?	✓	✓	NR	X	X	✓
Is cannabis governed by the same body as tobacco?	✓	✓	X	X	X	X
Are there separate regulatory systems for the medical and recreation use of cannabis?	X	X	NR	NR	X	X
Tax rate for cannabis	37% at the point of sale	15% excise tax from cultivator; 10% excise tax on retail	0%	US\$50 per ounce on parts transferred to product manufacturing	NA	17% excise tax; additional 3% potential to local governments
What is considered driving under the influence?	5ng THC/mL blood	5ng THC/mL blood	Detectable THC in body	Relies on field sobriety tests	Impairment in the slightest degree	Relies on field sobriety tests

\*Individuals under the age of 18 require additional steps in order to be granted access

NR: Not reported, THC: Tetrahydrocannabinol, NA: Not Applicable

Uruguay: Overview of regulations

Figure 33: Timeline of Cannabis Legalization in Uruguay

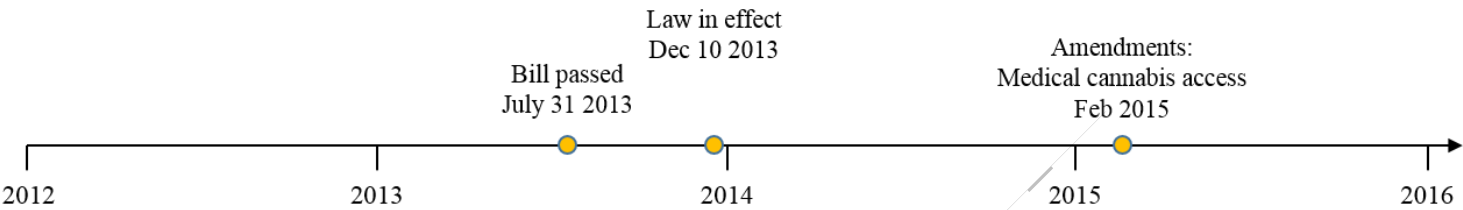


Table 12: Cannabis, Alcohol and Tobacco Regulations in Uruguay <sup>315-327</sup>

	Non-medical Cannabis Regulation	Medical Cannabis Regulation	Alcohol Regulation	Tobacco Regulation
<b>Regulation of Sales</b>	<i>Control over sale:</i> Only sold at licensed pharmacies to registered individuals; adults permitted up to 10g per week from pharmacy; overseen by the Institute for Regulation and Control of Cannabis <i>Control over growing:</i> Six licensed commercial growers allowed, allowed 6 plant maximum in personal grow-op <i>Retail licensing:</i> Limited to pharmacies only <i>Number of licensed retailers:</i> Approximately 40 pharmacies have registered as cannabis distributors <i>Number of licensed cultivators:</i> 2 <i>Production estimates:</i> 2 tons per year from each licensed cultivator <i>Sales over time:</i> N/A	<i>Control over sale:</i> Dried cannabis may be sold from pharmacies (cannabis oil must be requested by form, and imported from the United States) <i>Control over growing:</i> State-controlled, limited commercial production licenses permitted, medical and non-medical cannabis to be grown separately and have separate licensing programs <i>Patient requirements:</i> Prescription from licensed physician <i>Physician restrictions:</i> N/A	<i>Control over sale:</i> NR <i>Control over production:</i> A production license is required. Government produces Scotch, rum, vodka, cognac <i>Retail licensing:</i> A sale license is required	<i>Control over sale:</i> Ministry of Public Health <i>Control over production:</i> <i>Retail licensing:</i> NR
<b>Regulation of Use</b>	<i>Age for legal consumption:</i> 18+ <i>Amount allowed:</i> Six plants/household, adults permitted 40g/month (10g/week), annual cap 480g/member of a cannabis club <i>Consumption:</i> Follows tobacco regulation. Use at work or during the work day is prohibited <i>DUI definition:</i> Detectable THC in the body	<i>Patient age:</i> 18+ <i>Amount allowed:</i> Not specified <i>Consumption:</i> Same as non-medical cannabis	<i>Age for legal consumption:</i> 18+ <i>Where can you consume:</i> Restrictions on consumption are voluntary in health care establishments, educational building, public transport, workplaces and government offices. Not allowed in parks, streets, sporting events and leisure events <i>When can you consume:</i> Off-premise sales have hourly restrictions and are banned from midnight to 6am <i>DUI definition:</i> 0.03% for amateur drivers (since March 2009); 0.0% BAC law in effect Jan 2016	<i>Age for legal consumption:</i> Prohibits sale of tobacco products to persons under 18 <i>Where can you consume:</i> Designated Smoking Areas that exclude all enclosed public places and workplaces, public transportation, & the outdoor premises of health & educational institutions
<b>Economic Regulation</b>	<i>Taxation rate:</i> 0% - categorized as an agricultural product; no luxury item tax (like there is with cigarettes and alcohol)	<i>Taxation:</i> Unclear	<i>Taxation:</i> Excise taxes as a % of retail price: Beer 27%, Wine (no tax), Spirits 18%	<i>Taxation:</i> Excise tax on cigarettes: 49% of retail price

DUI: Driving under the influence; NR: Not reported; N/A: Not applicable; THC: tetrahydrocannabinol



The Executive branch of Uruguay's Government passed Law 19.172 on July 31, 2013, making Uruguay the first country in the world to legalize cannabis for non-medical use. Medical cannabis provisions were included in Law 19.172 as well, allowing individuals with a prescription to access cannabis for medical use <sup>328</sup>. Further plans for the structure of medical cannabis access were released in February 2015 <sup>329</sup>. Legislation was initially proposed as a solution to illegal drug trafficking throughout the country. Unlike Canada, nearly two-thirds of the population of Uruguay opposes legalization. There were no referendums held to determine whether the legalization process should begin, if at all. Once the bill was drafted by the executive branch, public hearings were conducted, the outcomes of which were incorporated into the bill by the Lower House <sup>323</sup>.

There was no previous body to oversee liquor or gaming control in Uruguay. Accordingly, the Government created the Institute for Regulation and Control of Cannabis (IRCC) in 2013 to oversee the production, distribution and sale of cannabis <sup>323</sup>. The IRCC has a high degree of control over the industry, as well as freedom to regulate as they deem necessary <sup>323</sup>. Uruguay set up four methods of supply: through medical prescription, registration with the IRCC as a non-medical user and then obtaining cannabis from a pharmacy, at-home growing for personal use, and by joining a "Cannabis Club" <sup>323</sup>. This results in three points of supply for non-medical users in Uruguay: at-home cultivation, cultivation in a Cannabis Club, or by licensed, commercial growers <sup>324</sup>. Uruguay has capped the number of licensed producers to six, and have auctioned off commercial growing licenses with strict regulations, such as the growers being responsible for paying to have mandatory military security watch over the crops <sup>323,325</sup>. So far, the government in Uruguay has licensed two commercial growers, SIMbiosys and International Cannabis Corp, to grow non-medical cannabis for distribution through pharmacies <sup>326</sup>.

Uruguay's leaders have stated that they will not tax cannabis, unlike alcohol and cigarettes, which are subject to a non-essential goods tax in Uruguay. Cannabis will remain untaxed to keep consumer prices competitive with the illegal market. This is because the primary goal of legalization is to divert capital from mafias who are illegally trafficking throughout Uruguay. The price of cannabis is affected by revenue raised from licensing fees, income tax, and security fees from the commercial growing companies <sup>325</sup>.

Adults (aged over 18) who register with the IRCC will be permitted to access non-medical cannabis through the pharmacy distribution system <sup>323</sup>. There are strict limits on the amount of cannabis that individuals are permitted to buy or take home from both Cannabis Clubs and state-controlled pharmacies. Pharmacies are allowed to sell 10g of cannabis per week to an individual who has registered with the IRCC, and the amount that an individual purchases is recorded in the registry set up by the IRCC <sup>324</sup>. Cannabis Clubs are required to have between 5 and 45 members, may only possess 99 plants at a time, and limit each member to 480g of cannabis per year <sup>323</sup>.

Restrictions on cannabis consumption in public places follow the laws around tobacco, which prohibits use in the workplace during work hours, on public transportation, in educational centers, health centers, sports centers, and in closed public spaces <sup>323</sup>. Penalties for use in these areas are the same for both cannabis and tobacco <sup>323</sup>. Driving under the influence of cannabis is strictly prohibited and there is a zero-tolerance policy for motorists found with any amount of THC in their system <sup>323</sup>.

Alaska: Overview of Regulation

Figure 34: Timeline of Cannabis Legalization in Alaska

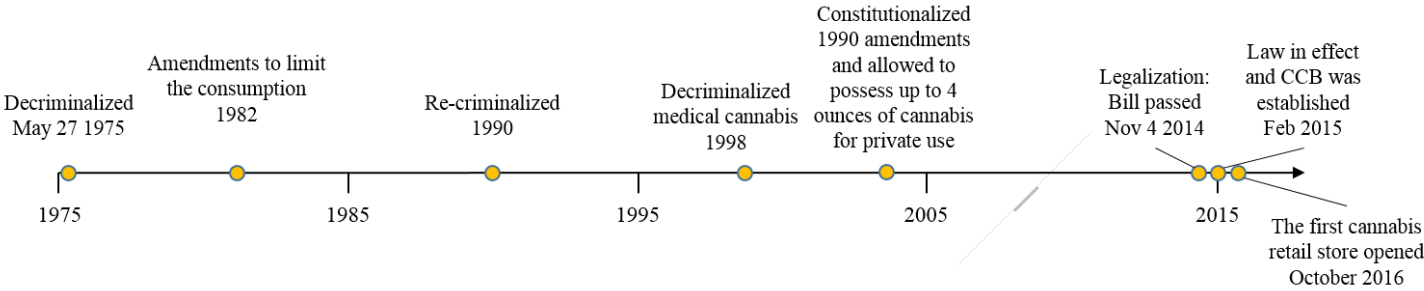


Table 13: Cannabis, Alcohol and Tobacco Regulations in Alaska <sup>330-340</sup>

	Cannabis Regulation	Medical Cannabis Regulation	Alcohol Regulation	Tobacco Regulation
Regulation of Sales	<i>Control over sale:</i> First retail licenses issued in Fall 2016, cannabis clubs in operation currently, ‘Cannabis Cafes’ are permitted under law but yet to open; activity overseen by the Cannabis Control Board <i>Control over growing:</i> 6 plants/household for personal use; businesses may apply for cultivation licenses <i>Retail licensing:</i> Candidates must meet zoning requirements, pay fees, and pass inspections before being awarded a license <i>Number of licensed retailers:</i> 4 licensed <i>Number of licensed cultivators:</i> 18 licensed <i>Production estimates:</i> It is estimated that for the first year, 4 tons of cannabis will be supplied by the retail market, with this figure increasing to 13 tons by 2020 <i>Sales over time:</i> N/A	<i>Control over sale:</i> Dispensaries that solely provide medical cannabis are not permitted, applications to use medical cannabis are through the Alaskan Division of Public Health <i>Control over growing:</i> Up to six plants for at-home cultivation, no more than three mature at one time <i>Patient requirements:</i> Diagnosed with cachexia, cancer, chronic pain, glaucoma, HIV/AIDS, multiple sclerosis, nausea, or a condition where one experiences seizures <i>Physician restrictions:</i> N/A	<i>Control over sale:</i> Alcoholic Beverage Control board oversees manufacture, possession, & sale. <i>Control over production:</i> Alcoholic Beverage Control board. <i>Retail licensing:</i> Issuance of licenses by the ABCB to private business. License must be operated at least 30, 8hr days, each year.	<i>Control over sale:</i> Department of Commerce, Community and Economic Development <i>Control over production:</i> Department of Commerce, Community and Economic Development <i>Retail licensing:</i> Department of Revenue provides 6 types of cigarette licenses (buyer-\$25/year, direct-buying retailer, cigarette distributor, manufacturer, vending machine operator, wholesale-distributor, and tobacco products only distributor- all \$50/year.)
Regulation of Use	<i>Age for legal consumption:</i> 21+ <i>Amount allowed:</i> One ounce at any time <i>Consumption:</i> Public consumption prohibited <i>DUI definition:</i> Relies on field sobriety tests; may be ticketed for operating a vehicle with a motor, or any aircraft or watercraft with or without a motor	<i>Patient age:</i> Any age, patients under 18 must have a parent or legal guardian to consent to the use of cannabis as treatment for the minor, and serve as the primary caregiver for the minor <i>Amount allowed:</i> No more than one ounce of usable cannabis <i>Consumption:</i> Public consumption prohibited, use on federal land prosecuted under federal law	<i>Age for legal consumption:</i> 21+ <i>Where can you consume:</i> Illegal in public places other than licensed premises <i>When can you consume:</i> Licensed businesses open 8am-5pm every day of the year except election days. Local governing bodies can limit hours of operation by ordinance <i>DUI definition:</i> driving while under the influence of alcohol or other chemical substances, or driving with a blood or breath alcohol level of .08 or >	<i>Age for legal consumption:</i> 19+ <i>Where can you consume:</i> Designated Smoking Areas that exclude in all portions elementary and secondary schools & children’s day care facilities, state & local government public meeting & assembly rooms, private & public washrooms, health care offices, institutions & hospitals, and elevators. Smoking is also not allowed in food service establishments having a seating capacity of at least 50 person or grocery stores.
Economic Regulation	<i>Taxation rate:</i> US\$50 per ounce on parts of the cannabis plant transferred from the cultivation facility to either a product manufacturing facility or a retail store. A rate lower than \$50 may be established for certain parts of the plant	<i>Taxation:</i> No information available	<i>Taxation:</i> Excise Tax Rates by Gallon: Liquor (>21% Alcohol): \$12.80 Wine (<21% Alcohol): \$2.50 Beer, Malt Beverages, Hard cider: \$1.07 Approved Reduced Rate Brewery: \$.35	<i>Taxation:</i> Excise tax on manufacture, importation, acquisition, distribution and/or sale of cigarettes is \$.10 per cigarette or \$2.00 per pack of 20. Excise tax on tobacco products other than cigarettes is 75% of the product’s wholesale price.

AIDS: Acquired immune deficiency syndrome; DUI: Driving under the influence; N/A: Not applicable; NR: Not reported; THC: tetrahydrocannabinol

An Alaskan Supreme Court decision on May 27, 1975 (*Ravin v. State*) interpreted the Alaska State Constitution right to privacy as upholding an adult's right to have a small amount of cannabis in their homes<sup>336</sup>. Following this decision, the Alaska Supreme Court decriminalized cannabis<sup>336</sup>. In 1982, legislation passed that revised the criminal code to limit the amount of cannabis that an adult could possess in private to four ounces. However, a 1990 referendum that was supported by the federal government passed, which allowed amendments to re-criminalize cannabis possession in the state<sup>336</sup>. Under this provision, possession of any amount of cannabis was classified as a Class B misdemeanor, even in the private home<sup>336</sup>. However, it was unclear whether the amended statute would override *Ravin*, and this problem remained for the next decade<sup>336</sup>.

In 1998 Measure 8, a referendum that allowed the Alaskan Government to move forward with an initiative to decriminalize cannabis for medicinal use was passed with 58.67% support from those who voted (Alaska Statute 17.37)<sup>341,342</sup>. This allowed registered patients to possess up to one ounce of cannabis and six plants, three of which could be flowering. Medical cannabis users are also permitted special privileges regarding possession of cannabis in public, where it is permitted but must be in a sealed container, concealed, and the individual must be in transit to an area where they are allowed to use it. The law did not allow medical cannabis users to buy or sell cannabis, only grow it for their own purposes<sup>336</sup>. In 2003, two cases (*Noy v. State*, and *Crocker v. State*) highlighted the unconstitutionality of the 1990 amendments in accordance with *Ravin*. The court ruled that the statute amendments in 1990 were unconstitutional, and reinstated the *Ravin* ruling, whereby possession of up to four ounces for personal use is permitted under the constitution. This established that neither legislation or public referendum could overturn the constitutional right to privacy that protects personal cannabis possession<sup>336</sup>.

Alaska is the first state with Republican leadership to legalize cannabis, which was done in 2014 with the passing of Measure 2: "An Act to regulate the production, sale, and use of cannabis" (Alaska Statute 17.38). The ballot measure passed with 53.23% of voters in support and 46.77% against on November 4, 2014 and was enacted on February 24, 2015<sup>343</sup>. It is speculated that this

is because of the popular belief in the importance of the role of the Alaskan Constitution to protect individuals' privacy <sup>336</sup>.

After the referendum and legalization in 2014, Alaskan law now limits possession of cannabis more for non-medical use than under the precedent set by *Ravin* <sup>336</sup>. Adults are allowed to possess one ounce of cannabis in their homes, as well as up to six cannabis plants, which are the same guidelines in the 1998 law that decriminalized medical use of cannabis <sup>336</sup>.

The enforcement of new cannabis laws is overseen by the Cannabis Control Board MCB, which was established on February 23, 2015 <sup>335</sup>. The current Chair of the Alcoholic Beverage Control Board sits as one of the five members of the MCB, but the two are not formally fused. One of the MCB's duties is to oversee the allocation of business licenses. The approval process for business licenses began on May 24, 2016, with priority placed on applications for cultivation and testing licenses. The first cannabis retail store in Alaska opened on October 29, 2016 after being licensed in early September. Cannabis will be taxed under Alaska Statute 43.61.010 at \$50 USD per ounce <sup>338</sup>.

The legal age for possession, use and purchase of cannabis for non-medical use in Alaska is 21 years. Individuals are prohibited from consuming in public, as well as in national parks, as these locations are subject to federal law <sup>344</sup>. The Cannabis Control Board is still working on rules around onsite consumption of cannabis, which would allow cannabis cafes to operate in Alaska <sup>168,345</sup>. Determining if an individual operating a vehicle is under the influence of cannabis relies on field sobriety tests, and applies to the operation of any vehicle with a motor, or any aircraft or watercraft, with or without a motor <sup>344</sup>.

Colorado: Overview of Regulation

Figure 35: Timeline of Cannabis Legalization in Colorado

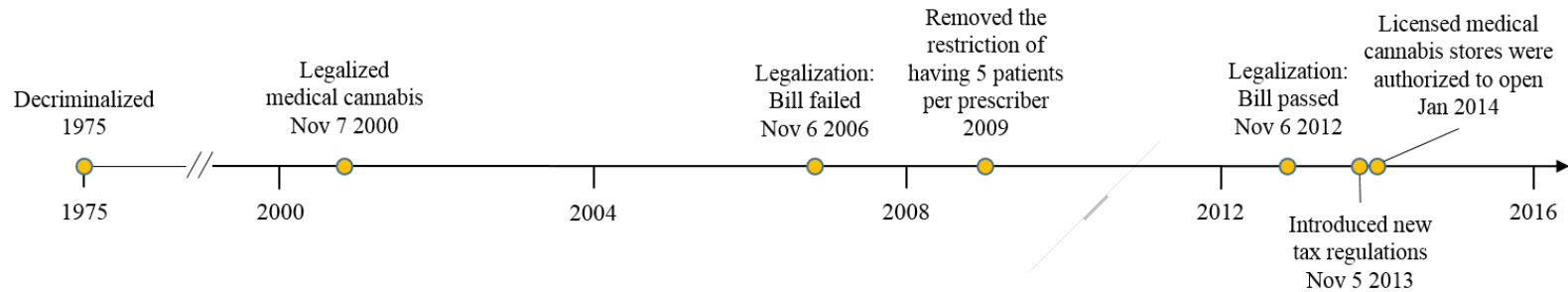


Table 14: Cannabis, Alcohol and Tobacco Regulations in Colorado 323,346-352

	Cannabis Regulation	Medical Cannabis Regulation	Alcohol Regulation	Tobacco Regulation
Regulation of Sales323,346-352	<p><i>Control over sale:</i> Department of Revenue oversees sale of cannabis similarly to alcohol. Only one ounce is allowed to be purchased at one time by Colorado residents</p> <p><i>Control over growing:</i> Department of Revenue oversees manufacturers, cultivators, and labs. Residents over 21 are allowed to grow up to 6 plants</p> <p><i>Retail licensing:</i> City and county governments can deny licensure requests by individuals within their jurisdiction. Licensing fees are several hundred dollars.</p> <p><i>Number of licensed retailers:</i> 454</p> <p><i>Number of licensed cultivators:</i> 613</p> <p><i>Production estimates:</i> An average of 597,415 plants were cultivated each month in 2015 (medical and non-medical)</p> <p><i>Sales over time:</i> An average of 8,911 pounds of bud/flower for non-medical purposes were sold each month in 2015</p>	<p><i>Control over sale:</i> Patients are required to obtain cannabis from dispensaries (not permitted to fill prescriptions for a Schedule I substance at a pharmacy). Department of Revenue oversees sale of cannabis.</p> <p><i>Control over growing:</i> Patients permitted to grow up to six cannabis plants, three or fewer mature at one time</p> <p><i>Patient requirements:</i> Possession of a state-issued Medical Cannabis Registry Identification Card, recommended by a physician</p> <p><i>Physician restrictions:</i> Until 2009, physicians were only permitted to prescribe cannabis to five patients at a time, a restriction that has since been removed</p>	<p><i>Control over production:</i> Liquor Enforcement Division, Department of Revenue</p> <p><i>Retail licensing:</i> Retailers excluding chain stores or multiple liquor licenses must first obtain license approval at local government level with an initial background investigation.</p>	<p><i>Control over sale:</i> Tobacco Enforcement Unit, Department of Revenue</p> <p><i>Control over production:</i> Tobacco Enforcement Unit, Department of Revenue</p> <p><i>Retail licensing:</i> A Colorado retailer does not need a Colorado cigarette tax license if the retailer only purchases cigarettes with the stamps already affixed for sales to consumers.</p>
Regulation of Use	<p><i>Age for legal consumption:</i> 21+</p> <p><i>Amount allowed:</i> Purchase and possess up to one ounce</p> <p><i>Consumption:</i> Public consumption prohibited</p> <p><i>DUI definition:</i> 5ng THC/mL blood</p>	<p><i>Patient Age:</i> Any age, patients under 18 must be diagnosed by two separate doctors with a debilitating medical condition and have a parent primary caregiver to administer the medication</p> <p><i>Amount Allowed:</i> Possess up to two ounces</p> <p><i>Consumption:</i> Public consumption prohibited</p>	<p><i>Age for legal consumption:</i> 21</p> <p><i>Where can you consume:</i> All alcohol except 3.2% beer is illegal to consume in public other than a place which is licensed for that purpose.</p> <p><i>When can you consume:</i></p> <p>Off-Premises Licenses: 8am-midnight all days</p> <p>On-Premises Licenses: 7am-2am all days</p> <p><i>DUI definition:</i> Maximum BAC level 0.08%.</p> <p><i>Control over sale:</i> Liquor Enforcement Division, Department of Revenue</p>	<p><i>Age for legal consumption:</i> 18</p> <p><i>Where can you consume:</i> Private homes residences and automobiles, certain hotel rooms, any retail tobacco business, a cigar-tobacco bar, an airport smoking concession, outdoor area of any business, a non-public place of employment with three or fewer employers, private non-residential buildings on a farm/ranch, floor plan of a licensed casino.</p>
Economic Regulation	<p><i>Taxation rate:</i> 15% excise tax from cultivator to processors or retailers; 10% excise tax on retail (plus existing local or state sales tax). Local governments may impose additional retail taxes on cannabis.</p>	<p><i>Taxation:</i> 2.9% state sales tax (on all goods), and any local sales tax</p>	<p><i>Taxation:</i> Excise Tax Rates:</p> <p>Beer and Hard Cider: 8 cents/gallon</p> <p>Wine: 7.33 cents/liter</p> <p>Spirituuous Liquors: 60.26 cents/liter</p> <p>Winery Grape/Produce Tax: 10 cents/ton</p>	<p><i>Taxation:</i> Wholesalers are required to collect and remit to the Colorado Department of Revenue 4.2 cents on each cigarette sold, evidenced by affixing of stamps to cigarette packs. Retailers charge state sales tax on all retail sales of cigarettes.</p>

BAC: Blood Alcohol Content; DUI: Driving under the influence; THC: tetrahydrocannabinol

Cannabis was decriminalized in Colorado in 1975, after the National Commission on Cannabis and Drug Abuse recommended Congress reduce penalties against cannabis use<sup>353,354</sup>. After decriminalization, possession of less than an ounce of cannabis was considered a petty offence and carried a \$100 fine. Colorado legalized medical cannabis on November 7, 2000 when the proposal, Amendment 20 (Medical Use of Cannabis Act), was passed (53.5% vs 46.5%)<sup>355</sup>. After this proposal was passed, patients and caregivers were allowed to possess up to two ounces of cannabis or up to six cannabis plants. In order to be authorized, patients required a state-issued Medical Cannabis Registry Identification Card, which could only be obtained with a doctor's recommendation. After an increase in prescriptions, Colorado sought to limit consumption in the early 2000s, limiting prescribers to having no more than five patients each<sup>356</sup>. In 2009, Colorado's Board of Health removed the restriction of having five patients per prescriber. Because of this, the number of licensed users grew by nearly ten times, between 2008 and 2009<sup>353</sup>.

A proposal to legalize non-medical cannabis (Amendment 44: Cannabis Possession) originally failed on November 6, 2006 by a state-wide ballot (60% against)<sup>353,357</sup>. This proposal would have legalized the possession of up to one ounce of cannabis by individuals aged 21 and over. Another proposal (Amendment 64 (Use and Regulation of Cannabis)) was passed by ballot initiative on November 6, 2012 (55% in favor)<sup>353</sup>. This legalized the purchase, possession and use of up to one ounce of cannabis and the growth of up to six cannabis plants for individuals aged 21 years and over, with valid government identification. Out-of-state residents were restricted to purchasing 0.25 ounces of cannabis. However, after June 2016, the limit placed on non-residents was removed, allowing for anyone over 21 in Colorado to purchase one ounce of cannabis<sup>358</sup>. On November 5, 2013, a ballot referendum introduced new regulations and taxes. Specifically, Proposition AA (Taxes on the Sale of Cannabis) imposed sales taxes on producers and retailers, while also allowing local governments to introduce additional taxes (65% in support)<sup>353,359</sup>.

The Colorado Department of Revenue controls the regulation of cannabis sales<sup>360</sup>. Specifically, the Cannabis Enforcement Division of the Colorado Department of Revenue administers and



enforces medical and retail cannabis laws and regulations. There are four types of Retail Cannabis Business Licenses for which an individual can apply, including: Retail Cannabis Store, Retail Cannabis Product Manufacturing, Retail Cannabis Cultivation, and Retail Cannabis Testing Facility. Licensing fees are generally several hundred dollars, and city and county governments can deny licensure requests made by individuals within their jurisdiction. New Permanent Rules have been adopted regarding cannabis regulations, and will become effective on January 1, 2017. Stores are restricted to the sale of “retail cannabis”, which has been sourced from a licensed Retail Cannabis Cultivation Facility or a Retail Cannabis Products Manufacturing Facility. Licensed stores are not allowed to sell any other consumable product (including alcohol and tobacco). Licensed medical cannabis stores were authorized to start non-medical sales in January 2014, and prior to January 2016, only existing medical cannabis centers, manufacturers and cultivators were eligible to apply for a retail license. City and county- specific regulatory boards oversee the sales of cannabis-infused food products. There are currently 613 licensed cultivators and 454 licensed retailers <sup>352</sup>. An average of 597,415 plants were cultivated and 8,911 pounds of buds/flowers were sold for non-medical purposes each month in 2015 <sup>352</sup>. Cultivators, producers and retailers currently have a 15% excise tax on cannabis <sup>353</sup>. There is also a minimum 10% sales tax on cannabis, which may be increased by local governments <sup>353</sup>. Adults can grow up to 6 cannabis plants per person in their own home, as long as no more than 3 are in the mature/flowering stage at one time<sup>360</sup>. A maximum of 12 plants are allowed per residence, regardless of the number of adults living in the household. All plants must also be stored in an enclosed and locked area <sup>360</sup>.

Only individuals over the age of 21 are authorized to purchase, possess and use cannabis. Residents of Colorado are permitted to purchase up to one ounce of retail cannabis at a time <sup>324</sup>. All public consumption of cannabis is illegal in Colorado. This includes ski slopes, national parks, national forests and national monuments. Driving under the influence of cannabis is illegal, and is defined as 5ng THC/mL blood.



Oregon: Overview of Regulation

Figure 36: Timeline of Cannabis Legalization in Oregon

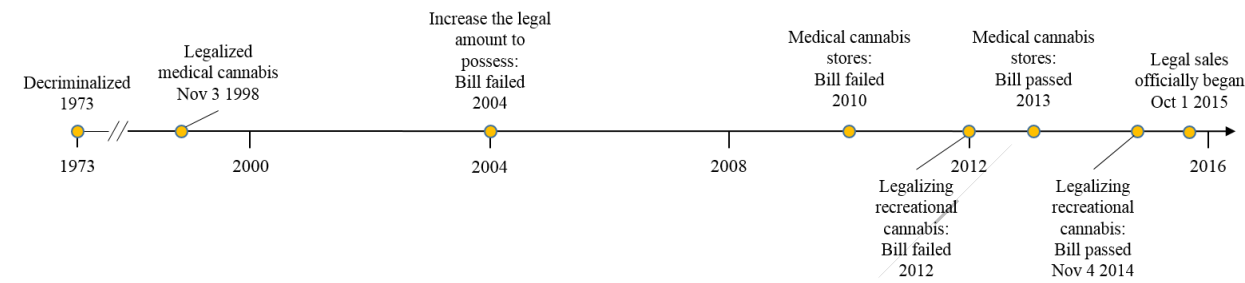


Table 15: Cannabis, Alcohol and Tobacco Regulations in Oregon 361-367

	Cannabis Regulation	Medical Cannabis Regulation	Alcohol Regulation	Tobacco Regulation
Regulation of Sales	<i>Control over sale:</i> Oregon Liquor Control Commission oversees all businesses that ‘serve adults’ <i>Control over growing:</i> Oregon Liquor Control Commission oversees cultivators; up to 4 plants for personal use <i>Retail licensing:</i> Oregon Liquor Control Commission is taking applications as of January 2016 <i>Number of licensed retailers:</i> 48 <i>Number of licensed cultivators:</i> 306 <i>Production estimates:</i> Not found <i>Sales over time:</i> \$22,970,868 October 2015 sales (112% increase from medical sales only)	<i>Control over sale:</i> Oregon Health Authority provides licenses to dispensaries allowing them to control sale <i>Control over growing:</i> Up to six mature cannabis plants for home cultivation <i>Patient requirements:</i> Diagnosis with a debilitating medical condition <i>Physician restrictions:</i> N/A	<i>Control over sale:</i> Oregon Liquor Control Commission <i>Control over production:</i> Oregon Liquor Control Commission <i>Retail licensing:</i> License Services within the Oregon Liquor Control Commission is responsible for issuing and renewing licenses to Oregon businesses involved in the manufacture, distribution, and retail sale of alcoholic beverages.	<i>Control over sale:</i> Department of Revenue <i>Control over production:</i> Department of Revenue <i>Retail licensing:</i> All business, except for sole proprietorships, are required to have a federal tax identification number. There is no fee to be licensed.
Regulation of Use	<i>Age for legal consumption:</i> 21+ <i>Amount allowed:</i> 8 ounces at home; 1 ounce on person form purchased at a retail store <i>Consumption:</i> Public consumption prohibited <i>DUI definition:</i> No limit on level of THC. Relies on field sobriety tests and police officer observations	<i>Patient age:</i> Any age, patients under 18 must have a parent or guardian who consents to the use of medical cannabis as treatment for the minor, and serve as the primary caregiver for the minor <i>Amount allowed:</i> Not more than 24 ounces of usable cannabis <i>Consumption:</i> N/R	<i>Age for legal consumption:</i> 21 <i>Where can you consume:</i> No law against public intoxication. <i>When can you consume:</i> 7 a.m. to 2:30 a.m. every day on licensed premises. <i>DUI definition:</i> Motorists will fail a DUI field test if their blood alcohol reading is 0.08% or higher. For drivers under 21 years old, any amount of alcohol in the bloodstream. For new drivers the legal limit is a BAC of 0.04%.	<i>Age for legal consumption:</i> 18 <i>Where can you consume:</i> Certified smoke shops and cigar bars, and up to 24% of motel/hotel rooms, and smoking of non-commercial tobacco for American Indian ceremonial purposes.
Economic Regulation	<i>Taxation rate:</i> 17% excise tax; local governments may tax up to an additional 3%	<i>Taxation:</i> Not taxed	<i>Taxation:</i> Excise Tax Rates: Beer: 8 cents/gallon Wine (<14%): 67 cents/gallon Spirits: \$22.73 per gallon	<i>Taxation:</i> \$1.31 per pack of 20 cigarettes

DUI: Driving under the influence; N/A: Not applicable; NR: Not reported; THC: tetrahydrocannabinol

In 1973, Oregon became the first state to decriminalize cannabis <sup>353</sup>. Once the Oregon Decriminalization Bill was passed, the possession of cannabis was considered a violation and not a crime. Possessing cannabis was a \$500 to \$1000 fine. State law makers tried to recriminalize cannabis in 1997; however, this bill did not pass. On November 3, 1998, medical cannabis was legalized when the Oregon Medical Cannabis Act (Measure 67) was passed in a ballot initiative (54.6% in favor) <sup>368</sup>. This act allowed for the growth, possession and use of cannabis for patients with specific medical conditions. Voters turned down a bill to increase the legal amount a patient could possess to 6 pounds in 2004. In 2010, voters also turned down a bill to permit medical cannabis dispensaries; however, these were legalized in 2013 <sup>353</sup>.

Oregon initially tried to legalize non-medical cannabis on November 4, 1986 (Oregon Cannabis Legalization for Personal Use, Measure 5) and again in 2012 (Oregon Cannabis Tax Act Initiative, Measure 80); however, both of these initiatives failed with 74% and 53% of voters being against legalization, respectively <sup>353,369,370</sup>. The 2012 initiative would have allowed cannabis cultivation and use without a license. There would also have been unlimited possession for adults over the age of 21. The use of cannabis for non-medical purposes eventually passed in 2014 with the approval of Measure 91 (Oregon Legalized Cannabis Initiative – 56% in favor) <sup>371</sup>. Following the passing of Measure 91, Oregon's legislature introduced several laws to regulate the industry. Individual counties were also given the authority to ban cannabis sales if more than 55% of voters in that county opposed Measure 91. Legal sales officially began on October 1, 2015 <sup>353</sup>.

The Oregon Liquor Control Commission oversees the cultivation and selling of non-medical cannabis <sup>372</sup>. The Oregon Liquor Control Commission started accepting applications for licenses in January 2014; however, currently only medical cannabis dispensaries are participating in non-medical cannabis sales. There are five types of licenses available: Producer, Processor, Wholesaler, Retail, Laboratory and Certificate for Research. There is a non-refundable application fee of \$250 for all license types, with additional licensing fees ranging from \$1000-\$5750. Each type of license is subject to its own set of rules and regulations as specified by the Oregon Liquor Control Commission. There are currently 48 licensed retailers and 206 licensed

cultivators <sup>367</sup>. After moving from medical to non-medical cannabis, Oregon experienced a 112% increase in sales <sup>366</sup>. Non-medical cannabis currently being sold at medical dispensaries is subject to a 25% sales tax. Once licensed retailers open, sales from retailers will be subject to a 17% sales tax at the state level and up to an additional 3% at the local level <sup>372</sup>.

Current regulations specify that Oregon residents aged 21 and over are allowed up to four plants per residence, can possess up to 8 ounces of usable cannabis (dried flowers or leaves) in their homes, and can possess up to one ounce on their person <sup>372</sup>. As of June 2016, edible cannabis products containing up to 15 mg of THC have been available for sale at registered medical cannabis dispensaries. All public consumption of cannabis remains illegal <sup>372</sup>. Driving Under the Influence laws have not changed, which includes the impairment from the use of cannabis <sup>373</sup>. There is no limit on the level of THC in the bloodstream. Instead driving under the influence is based on field sobriety tests and police officer observations <sup>373</sup>.

Washington State: Overview of Regulation

Figure 37: Timeline of Cannabis Legalization in Washington State



Table 16: Cannabis, Alcohol and Tobacco Regulations in Washington State <sup>323,324,374-387</sup>

	Cannabis Regulation	Medical Cannabis Regulation	Alcohol Regulation	Tobacco Regulation
Regulation of Sales	<i>Control over sale:</i> Sale of cannabis is overseen by the Washington Liquor and Cannabis Control Board <i>Control over growing:</i> At-home cultivation prohibited; businesses may apply for a cultivation license <i>Retail licensing:</i> Number of businesses determined by population density; limits on number of licenses one individual holds at one time <i>Number of licensed retailers:</i> 453 <i>Number of licensed cultivators:</i> 908 <i>Production estimates:</i> 59,394 pounds of cannabis harvested from producers (Jul 2014 – Jun 2015) <i>Sales over time:</i> 22,654 pounds of useable cannabis sold (Jul 2014 – Jun 2015)	<i>Control over sale:</i> State-licensed dispensaries no longer permitted, medical patients may access cannabis from licensed retail stores <i>Control over growing:</i> Up to 6 plants permitted for at-home cultivation and 8 ounces of prepared cannabis from those plants <i>Patient requirements:</i> Recommendation from a physician for use of cannabis as treatment for any debilitating condition, registering as a medical patient is voluntary <i>Physician restrictions:</i> Must write recommendation on tamper-resistant paper	<i>Control over sale:</i> Washington State Liquor and Cannabis Board <i>Control over production:</i> Washington State Liquor and Cannabis Board <i>Retail licensing:</i> An endorsement on a Business License, issued by the Washington State Department of Revenue Business Licensing Service.	<i>Control over sale:</i> Washington State Liquor and Cannabis Board <i>Control over production:</i> Washington Office of the Attorney General <i>Retail licensing:</i> Issued through the Department of Revenue’s Business Licensing Services, then the Liquor & Cannabis Board’s Enforcement Division
Regulation of Use	<i>Age for legal consumption:</i> 21+ <i>Amount allowed:</i> Adults can possess 1 ounce of cannabis, 7 grams of cannabis concentrate/extract for inhalation, 16 ounces of cannabis infused product in solid form, 72 ounces of cannabis infused product in liquid form <i>Consumption:</i> Public consumption prohibited <i>DUI definition:</i> 5ng THC/mL blood	<i>Patient age:</i> 18+; if under 18, the patient may appoint a designated provider over the age of 21 who must purchase and administer the cannabis, who is authorized by the health care provider <i>Amount allowed:</i> 48 ounces of cannabis-infused product, 3 ounces of dried cannabis, 216 ounces of cannabis-infused liquids, or 21 grams of cannabis concentrate <i>Consumption:</i> Public consumption prohibited	<i>Age for legal consumption:</i> 21 <i>Where can you consume:</i> Illegal in public places other than licensed premises. <i>When can you consume:</i> Licensed premises between 6am-2am all days. <i>DUI definition:</i> Maximum blood alcohol level 0.08%; 0.04% for commercial vehicle drives; and, 0.02% for minors (under 21).	<i>Age for legal consumption:</i> 18 <i>Where can you consume:</i> Designated areas excluding all bars, restaurants, non-tribal casinos, private residences used to provide childcare, foster care, adult care, or similar social services, and at least 75% of sleeping quarters within a hotel. Also excludes within 25 feet of enclosed prohibited areas.
Economic Regulation	<i>Taxation rate:</i> 37% tax at the point of sale	<i>Taxation:</i> Subject to retail sales tax, which is 6.5%	<i>Taxation:</i> Beer tax high rate (producers): \$8.08/barrel; low tax rate \$4.782 per barrel. Beer and Wine Tax (consumers): 9.5% state and local sales tax. Table wine 22.67 cents per liter Spirits (for consumers): 20.5% Spirits (for retailers): 13.7%	<i>Taxation:</i> Cigarette tax rate of \$30.25 for a carton of cigarettes. In addition to cigarette tax, cigarettes are also subjective to sales or use tax.

DUI: Driving under the influence; N/A: Not applicable; NR: Not reported; THC: tetrahydrocannabinol

Washington commenced decriminalization of cannabis in 1971, by softening its cannabis laws such that the possession of less than 40 grams would be considered a misdemeanor<sup>353</sup>. Medical cannabis was legalized on November 3, 1998, following the passing of Ballot Initiative 692 (Washington Medical Cannabis Initiative – 59% in favor)<sup>388</sup>. The passing of Initiative 692 meant that the use, possession, distribution and growth of cannabis was legal for patients with specific medical conditions who had been approved by a licensed clinician. Dosage limits were placed on patients using medical cannabis<sup>353</sup>.

Similarly, to Colorado, Washington legalized non-medical cannabis in 2012 when the Ballot Initiative 502 (Washington Cannabis Legalization and Regulation Initiative) was passed (56% in favor)<sup>353,389</sup>. While legalized possession began in late 2012, the first retail stores did not open until July 8, 2014. There are currently several hundred non-medical cannabis shops across the state<sup>353</sup>.

The Washington State Liquor and Cannabis Board regulates the cultivation and distribution of medical and non-medical cannabis in Washington<sup>390</sup>. The regulatory and licensing framework used in this state is similar to the control of alcohol. There are three types of licenses that can be applied for through the Liquor and Cannabis Board, including: Producer, Processor and Retailer. There is a mandatory \$266 application fee and a \$1062 annual license renewal fee for all three types of licenses. The total amount of production is also regulated to stay on par with in-state demand. 908 licensed cultivators harvested approximately 59,394 pounds of cannabis between July 2014 and June 2015<sup>384</sup>. Similarly, 453 licensed retailers sold approximately 22,654 pounds of useable cannabis during the same time period<sup>384</sup>. As of July 2015, there is an excise tax of 37% on all taxable sales of cannabis, cannabis concentrates, useable cannabis and cannabis-infused products<sup>390</sup>. This tax is the responsibility of the consumer and not the retailer. This is different from the original taxation plan proposed with Initiative 502. The original taxation plan was a 25% excise tax at each 'stage' of sale (including: production, processing and retail); however, this plan was deemed to be particularly tough on retailers, who paid federal income tax on the cannabis tax they paid to the state<sup>391</sup>.

Current non-medical cannabis laws allow individuals over the age of 21 to possess 1 ounce of usable cannabis, 7 grams of cannabis concentrate/extract for inhalation, 16 ounces of cannabis infused product in solid form, 72 ounces of cannabis infused product in the liquid form, and cannabis-related drug paraphernalia <sup>390</sup>. At-home cultivation is currently prohibited; however, House Bill 2629, which concerns the possession and transfer of cannabis plants, is still being considered <sup>392</sup>. Public consumption of cannabis is illegal, as is driving under the influence, which is defined as THC levels of 5 ng/mL of blood <sup>390</sup>.

Washington D.C.: Overview of Regulation

Figure 38: Timeline of Cannabis Legalization in Washington, D.C.

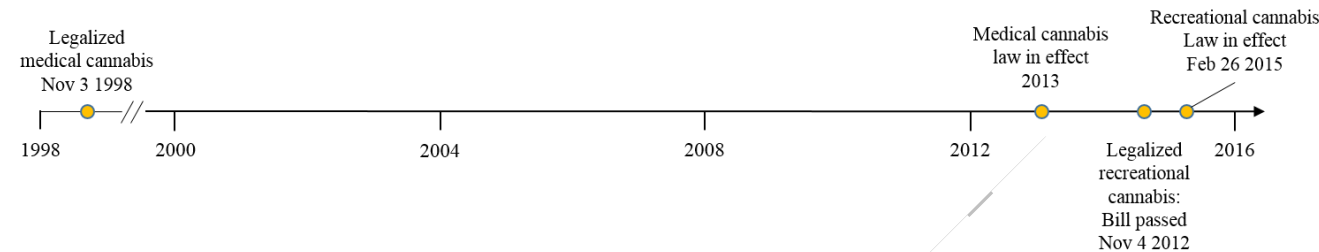


Table 17: District of Columbia (Washington D.C.) 393-400

	Cannabis Regulation	Medical Cannabis Regulation	Alcohol Regulation	Tobacco Regulation
Regulation of Sales	<i>Control over sale:</i> Sale of cannabis is prohibited at this time <i>Control over growing:</i> 6 plants/household for personal use (Note: residents growing in federal housing projects may be subject to prosecution under federal law) <i>Retail licensing:</i> N/A <i>Number of licensed retailers:</i> N/A <i>Number of licensed cultivators:</i> N/A <i>Production estimates:</i> N/A <i>Sales over time:</i> N/A	<i>Control over sale:</i> Must be from non-governmental, not-for-profit corporations <i>Control over growing:</i> Home cultivation not permitted <i>Patient requirements:</i> Diagnosis with a debilitating condition, as recommended by a licensed physician practicing in D.C. <i>Physician restrictions:</i> N/A	<i>Control over production:</i> Alcoholic Beverage Regulation Administration <i>Retail licensing:</i> Issued by the Alcoholic Beverage Regulation Administration	<i>Control over sale:</i> Department of Health <i>Control over production:</i> Department of Health <i>Retail licensing:</i> Administered by the Department of Consumer and Regulatory Affairs, for the sale of cigarettes to consumers in original packages from a place of business.
Regulation of Use	<i>Age for legal consumption:</i> 21+ <i>Amount allowed:</i> No more than two ounces at one time <i>Consumption:</i> Public consumption prohibited; but consumption in private events and clubs would be permitted <i>DUI definition:</i> Impairment of the slightest degree will qualify an individual as being impaired under the law, determined using field sobriety tests	<i>Patient age:</i> Any age, patients under 18 must have written consent from a parent or guardian that they understand the medical conditions, risk for use, and consent to the use of cannabis as treatment for the medical condition <i>Amount allowed:</i> No more than two ounces at one time <i>Consumption:</i> Public consumption prohibited, consumption on federal land prohibited under federal law	<i>Age for legal consumption:</i> 21 <i>Where can you consume:</i> Illegal in public places other than licensed premises. <i>When can you consume:</i> Liquor can be served by a licensed business from 8am-2am on Monday - Thursday, from 8am to 3am on Friday and Saturday and 10am-2am on Sundays. The day before a federal holiday, alcohol may be served from 8am-4am. Off-premises retailers, such as grocery and other stores, may sell liquor from 9am-10pm daily. <i>DUI definition:</i> BAC 0.07% or lower. <i>Control over sale:</i> Alcoholic Beverage Regulation Administration	<i>Age for legal consumption:</i> 18 <i>Where can you consume:</i> Retail tobacco stores, tobacco bars, outdoor area of a restaurant, club, brew pub, most hotel rooms, theatrical productions, establishments granted an “economic hardship waiver” by the mayor.
Economic Regulation	<i>Taxation rate:</i> There is currently no tax rate as the retail sale of cannabis is prohibited in D.C. at this time	<i>Taxation:</i> No information available	<i>Taxation:</i> Beer: \$2.79/barrel Distilled Spirits: \$1.50/gallon Light Wine (14% or less): \$0.30/gallon	<i>Taxation:</i> \$2.50 per pack of 20 cigarettes

DUI: Driving under the influence; N/A: Not applicable; THC: tetrahydrocannabinol



Residents of the District of Columbia (D.C.) voted to pass an initiative to legalize the medical use of cannabis on November 3, 1998 <sup>401</sup>. The law was implemented in 2013, after United States Congress passed the Barr Amendment, which blocked funding to the program until it was overturned in 2009 <sup>402</sup>. The “Legalization of Cannabis for Medical Treatment Initiative of 1998” prevented patients, their caregivers, and employees of businesses that operate in the medical cannabis supply market from being detained for possessing cannabis <sup>402</sup>. This act also set out the requirements around which doctors could prescribe cannabis to patients: if they have a “bona-fide physician-patient relationship”, the physician should not have an office at a dispensary or receive any compensation from a dispensary, and the patient should have HIV/AIDS, cancer, glaucoma, multiple sclerosis, seizure disorders, or any condition diagnosed as “debilitating” by a physician <sup>402</sup>. Medical cannabis patients are limited to possess up to 2 ounces of dried cannabis at one time <sup>402</sup>.

On November 4, 2014, residents of D.C. voted and passed legislation to legalize personal possession and cultivation of small amounts of cannabis, with plans for the regulation of cultivation, processing, and retail sales of cannabis as well. The “Legalization of Possession of Minimal Amounts of Cannabis for Personal Use Initiative” <sup>400</sup>, passed with 64.87% voting for and 27.72% voting against <sup>403</sup>. However, legalization in D.C. has looked more like decriminalization, where possession, cultivation, and ‘gifting’ of cannabis are permitted but there has yet to be any movement towards regulating commercial cultivation and sales by the municipal government <sup>400</sup>.

Unlike the other U.S. regions that have legalized cannabis, Initiative 71 did not include any provisions to allow the regulation of commercial production and retail sale of cannabis, and further legislation to control this appears unlikely <sup>400</sup>. This is because D.C.’s City Council is under pressure from Congress to repeal the law, and they are threatening to pursue legal action against D.C. City Council members who supported the law <sup>404</sup>. This is on the grounds that the United States Congress has “plenary powers” over D.C. <sup>404,405</sup>, where Congress must approve of all legislation proposed by City Council. Further, Section 809 (b) of the “Consolidated and Further Continuing Appropriations Act, 2015” states that no funds implicated in the Act can “be used to enact or carry out any law, rule, or regulation to legalize or otherwise reduce penalties



associated with the possession, use, or distribution of any schedule I substance under the Controlled Substances Act or any tetrahydrocannabinols derivative for non-medical purposes”<sup>399</sup>. This clause restricts City council from using funds to enact regulatory laws or taxation laws, to hold formal City Council hearings, and reduce penalties associated with cannabis<sup>406</sup>.

There is also disagreement between D.C. City Council and United States Congress as to whether the Appropriations Act has any power over Initiative 71 due to the timing of the legislation. City Council claims that though Initiative 71 came into force after the Appropriations Act, it was legislated prior to the Act’s legislation, and therefore is not subject to Congress’s budget restrictions. However, some in Congress argue that although the provision in the Appropriations Act is not retroactive, it will apply to the provision of the laws as they will be enacted, which would be proactive. Legal action is still a possibility in this conflict, especially as four members of Council have sponsored the “Cannabis Legalization and Regulation Act of 2015” which provides a framework for how the cannabis industry would operate in D.C.<sup>407</sup>, while Congress is looking to include stricter provisions against further action on cannabis legalization in the 2017 Appropriations Act<sup>408</sup>.

### **Emerging jurisdictions**

On November 8, 2016, nine states voted on the legalization of cannabis. Of those nine, five voted on the non-medical use of cannabis and four voted on the use of medical cannabis. All four of the states voting on medical cannabis (Montana, North Dakota, Arkansas, and Florida) passed their respective measures. Of the states voting on non-medical cannabis, only Arizona did not pass, with 52% of voters voting against legalization. The history and legalization details for the other four states (California, Maine, Massachusetts, and Nevada) are described below.

#### *California*

California first legalized medical cannabis by passing Proposition 215 (The Compassionate Use Act) by popular vote in 1996<sup>409</sup>. This Act became part of the Health and Safety Code Section 11362.5<sup>410</sup>. In 2003, Senate Bill 420 was passed, which legislated an ID card system to help patients avoid harassment from law enforcement officers<sup>411</sup>. Senate Bill 420 also strengthened the protections for cannabis cultivators to align more with the intent of the original law<sup>411</sup>.

Patients who are under the age of 18 must have a guardian's permission to access medical cannabis, but are permitted to access it through their guardian and caregiver <sup>411</sup>. Patients can possess eight ounces of dried cannabis and either eight mature plants or twelve immature plants <sup>412</sup>. Smoking cannabis in public is not illegal; however, patients must comply with smoking regulations, not operate motor vehicles and be over 1000 feet from a school <sup>413</sup>. Currently, medical cannabis sales are not-for-profit <sup>414</sup>, and medical cannabis is not taxed beyond the regular sales tax, which is 7.5-10% depending on the municipality <sup>415</sup>. Dispensaries may not be within 600 feet of a school <sup>416</sup>. People growing private supplies would be exempt from this stipulation <sup>417</sup>.

Cannabis possession was decriminalized in 1975 under Senate Bill 95, also known as the Moscone Act, in which possession of one ounce of cannabis became an infraction instead of a felony <sup>418</sup>. Today, possession of less than one ounce of cannabis is punishable by no more than a \$100 dollar fine, under section 11357b of the California Health and Safety Code <sup>419</sup>. This is in part due to the signing of Senate Bill 1449, which downgraded possession of up to an ounce of cannabis to an infraction, punishable by a fine no more than \$100 USD <sup>420</sup>.

California first tried to legalize non-medical cannabis in 2010, with Proposition 19 (Regulate, Control and Tax Cannabis Act of 2010); however, this initiative failed with 53.5% of voters being opposed <sup>421-423</sup>. On November 8, 2016 California voted on Proposition 64 (the California Cannabis Legalization Initiative) <sup>422,424</sup>. In contrast to the 2010 initiative, this proposition clearly laid out taxation plans and did not occur during a mid-election year, which generally has lower voter turnout <sup>423</sup>. Proposition 64 passed with 56.1% of voters being in favor <sup>425</sup>. California's proposed non-medical cannabis law is expected to come into effect January 1, 2018 <sup>424</sup>. Under the proposed legislation, non-medical cannabis would be available to all persons over 21 years of age and possession of cannabis for personal, non-medical use would be limited to one ounce and 6 plants <sup>426</sup>. Smoking would be permitted in areas that currently allow smoking with the exception of any area within 1000 feet of a school zone <sup>426</sup>. California has proposed a 15% excise tax on non-medical cannabis as well as a cultivation tax of \$9.25/ounce on flowers and \$2.75/ounce on leafs <sup>426</sup>. Individual counties may also tax the cultivation of cannabis as they wish. California also restricts the sale of non-medical cannabis to retailers that do not sell

tobacco or alcohol <sup>426</sup>. California law relies on officer judgement to determine impairment of individuals who are operating motor vehicles and does not use biological tests for cannabinoids.

### *Maine*

Medicinal cannabis was legalized in Maine on November 1, 1999 under Chapter 558-C: Maine Medical use of Marijuana Act <sup>427</sup>. Medicinal cannabis use is limited to individuals over 18 years of age who have a valid prescription from a doctor <sup>427</sup>. If the patient is under 18, a parent or guardian must consent to the minor's use of cannabis, confirm that they are the patient's caregiver, and administer cannabis to the minor <sup>427</sup>. The only places permitted to sell cannabis are licensed non-profit dispensaries <sup>427</sup>. Patients are permitted to purchase up to two and a half ounces of dried cannabis at one time and grow up to six plants, as long as they are stored in a locked, secure area <sup>427</sup>. Medical cannabis is not taxed at a rate above any taxes incidental to other medications, as it is not legal to tax prescription drugs under Maine law <sup>428</sup>.

Legal non-medical cannabis would be made available in Maine by the "Marijuana Legalization Act", which was proposed as Question 1 on Maine's November 8, 2016 state ballot <sup>429</sup>. The initiative passed with 50.2% voter support <sup>429</sup>. In Maine, if the ballot passes by a margin of less than 1.5%, it qualifies for a state-funded re-count <sup>429</sup>. Groups, such as the State Attorney General Janet Mills and the Maine Cannabis Patients and Caregivers Defeating MPP organization, that previously declared opposition to the bill have petitioned for an official recount for this ballot initiative <sup>430</sup>. The recount is expected to be completed in mid-December 2016 <sup>430</sup>.

The legal age to purchase and/or possess cannabis for non-medical use is 21 years, and like medical users, individuals are permitted to have six plants for personal production and can carry as much as two and a half ounces at one time <sup>431</sup>. A tax at the point of sale of 10% would be enacted as well. No other taxes are to be imposed on the consumer; however, producers and retailers are required to pay application, licensing, and license renewal fees ranging from \$250 to \$2,500 <sup>431</sup>. Maine would also allow for the operation of "social clubs" which would allow consumers to purchase and smoke cannabis on the business premises in a common area <sup>431</sup>. Under the proposed Act, operating a motor vehicle with any detectable amount of cannabinoids

in one's system is illegal and may be charged with an "Operating Under the Influence" offense<sup>431,432</sup>.

### *Massachusetts*

Massachusetts legalized cannabis for medical use on January 1, 2013 under the Act for Humanitarian Medical Use of Marijuana<sup>433</sup>. Medical cannabis use is limited to persons over the age of 21; however, if a parent or guardian over 21 years of age agrees to act as the patient's caregiver, then minors may be permitted access<sup>433</sup>. The amount one patient is permitted at any one time is defined as "the amount necessary for a sixty-day supply" for the patient's treatment<sup>433</sup>. The Act states that consumption of medical cannabis may be prohibited in areas of employment, around schools, at youth centers, in correctional facilities, and in any public space<sup>433</sup>.

The ballot initiative Question 4 passed with 53.57% support from voters on November 8, 2016<sup>434</sup>. Legislation to legalize the use of cannabis for non-medical use (The Regulation and Taxation of Marijuana Act) is expected to be implemented on December 15, 2016<sup>435</sup>. Legal non-medical cannabis possession and use is restricted to individuals over 21 years of age<sup>435</sup>. Consumers may possess up to one ounce of dried cannabis or up to five grams of concentrated cannabis product at one time, and may cultivate up to six plants for cannabis for personal use<sup>435</sup>. Having any detectable amount of cannabinoid in the body is considered a DUI and is punishable by fine and imprisonment<sup>436</sup>.

Cannabis licenses for commercial operations will be granted to firms with existing experience in the medical cannabis industry<sup>435</sup>. After January 1, 2018, licenses will be granted by lottery system<sup>435</sup>. Cannabis establishments would not be allowed within 500 feet of any school that provides kindergarten or grades 1 to 12 education, and may not be operated by any individual who has previously been convicted of a felony offense other than a cannabis personal possession charge<sup>435</sup>. The proposed legislation sets a 3.75% sales tax on top of the existing tax on the 6.25% tax rate on the "sale of property or services" in Massachusetts<sup>70,435</sup>, and the possible addition of 2% added at the county level. There are also additional charges, some yearly, on cannabis establishments. Firms applying for a license for a cannabis establishment of any kind

must pay a fee of \$3,000 <sup>435</sup>. After this is approved, there is a \$15,000 fee for retail, processor, and cultivator licenses and a \$10,000 fee for a testing facilities <sup>435</sup>.

### *Nevada*

On November 7, 2000 Nevada passed the Medical use of Cannabis Act, which legalized the use of cannabis prescribed by a physician <sup>437</sup>. Under this Act, patients could only legally access cannabis for personal medical use by growing their own <sup>437</sup>. The act was revised on June 12, 2013 by the passage of Senate Bill 374, which allows for the commercial sale of medical cannabis <sup>438</sup>. Furthermore, the bill permits patients qualifying for medical cannabis to cultivate up to twelve mature plants if they are over 25 miles from a dispensary or are otherwise unable to reach one <sup>438</sup>. Nevada is unlike other states who have legalized medical cannabis in that Nevada imposes a 2% tax on medical cannabis, while other states usually do not tax medical cannabis. Nevada also levies a \$25 application fee and a \$75 renewal fee on medical cannabis card holders <sup>437</sup>. Nevada only allows the sale of medical cannabis to persons over 21 years old, and anyone requiring a prescription for medical cannabis who is under 21 must rely on a care giver to purchase and transport their prescription <sup>437,438</sup>.

Medical cannabis must be grown in a secure environment and comply with regulations governing sale to minors and employing felons <sup>437,438</sup>. Retailers must be at least 1000 feet from schools and 300 feet away from community centers <sup>438</sup>. Felons are not legally allowed to be owners, officers, or board members of a medical cannabis establishment; however, some exceptions are made for employees with felony records on a case-by-case basis <sup>437</sup>.

In 2006, Nevada voters defeated Question 7, which would have legalized the possession, sale, and use of less than one ounce of cannabis for individuals over 21 years old <sup>439</sup>. One decade later on November 8, 2016 Nevada voters approved (55% in favor) the Nevada Cannabis Legalization Initiative (Question 2) <sup>440</sup>, which legalized non-medical consumption of cannabis. The project date for the implementation of the law is January 1, 2017. The proposed model for non-medical sale is similar to the model currently in place for medical use and sales.

Non-medical cannabis retailers must also locate their stores in accordance with the regulations set out in SB 374 <sup>438,440</sup>. Additionally, there are regulations on the number of dispensaries allowed in a municipality based on its population. For example, up to 80 retail licenses are permitted in a county with over 700,000 residents, while in a county of less than 55,000 residents, up to 2 retail cannabis licenses will be issued, unless the county requests additional licenses <sup>440</sup>. There is a proposed US\$5000 initial licensing fee, and a US\$3000-30,000 fee for renewing a commercial license, depending on the type of license <sup>440</sup>. Nevada also proposed that municipalities have the ability to restrict cannabis sales in their jurisdictions and ban the sale of cannabis in residential areas. Nevada has proposed a 15% tax on the sale of non-medical cannabis <sup>440</sup>, which does not impact the current 2% tax on cannabis sold from medical dispensaries.

Individuals are permitted to possess one ounce of cannabis or one-eighth of an ounce of concentrated cannabis <sup>440</sup>. Personal cultivation for non-medical use is limited to six plants <sup>440</sup>. Public consumption will be illegal under the proposed legislation, and cannabis sale is limited to individuals over 21 years of age <sup>440</sup>. The definition of intoxicated driving will not be changed by the proposed legislation. Nevada sets the legal bar for intoxication at .08% blood alcohol. For cannabis the limit is set a 10 nanograms/milliliter of urine or 2 nanograms/milliliter for blood <sup>441</sup>. There is also specialized drug recognition evaluation training available for some police officers that has already been implemented <sup>442</sup>.

### **Alcohol Regulations in Canada and Alberta**

Canada and Alberta's laws regarding tobacco and alcohol are similar to those in place in the US in terms of where the substances can be consumed (prohibited to consume either in unlicensed public places), and when alcohol can be sold and consumed (before 3:00am on licensed premises). Laws around the advertising of tobacco and alcohol are also similar in Canada and the US, primarily regarding health warnings on packaging and the prohibition of certain statements. However, laws in Canada, Alberta and the US vary in terms of the age of legal consumption, the rate of tax on the two substances, and also vary in terms of the different regulatory bodies that govern each industry. Table 18 provides a summary of alcohol and tobacco regulations in Canada and Alberta.

### *Canada*

Regulations for alcohol in Canada vary; each province and territory defines their own laws for purchasing, possessing, consuming and supplying alcohol, as well as issues such as driving under the influence of alcohol. The legal drinking age for alcohol in Alberta, Manitoba and Quebec is 18 years of age, and is 19 years in all other provinces and the three territories <sup>443</sup>. The set of general laws regarding alcohol in Canada are as follows. It is illegal to <sup>444</sup>:

- Drive while under the influence of alcohol
- Drink or possess alcohol if you are below the legal drinking age
- Use a fake ID to buy alcohol or get into a bar
- Buy alcohol for, or serve alcohol to someone who is under the legal drinking age

The Canadian federal government also imposes an excise tax on wine, beer and spirits <sup>445</sup>.

### *Alberta*

Alberta's liquor industry is regulated by the Alberta Gaming & Liquor Commission (AGLC). The industry was privatized in 1993 permitting the private sector to retail, warehouse and distribute liquor within the province. The AGLC has control over regulations such as the issuing of liquor licenses, registration of liquor suppliers, inspecting liquor operation, as well as setting and collecting the provincial markup from sales (Table 8) <sup>446</sup>. The legal age for possessing and consuming alcohol in Alberta is 18. Liquor may be sold, provided and served on licensed premises before 2:00am, and all liquor must be consumed before 3:00am. Consumption of alcohol in non-licensed public places is prohibited. A comprehensive set of regulations around the sale of liquor on licensed premises has been implemented by the AGLC; namely the Gaming and Liquor Act, the Gaming and Liquor Regulation, and various other Alberta Gaming and Liquor Commission policies <sup>447</sup>. Lastly, Alberta laws prohibit new drivers from having any alcohol in their system, and impose various charges for drivers with a BAC between 0.05% - 0.08% and a BAC over 0.08% <sup>448</sup>.

## **Tobacco Regulations in Canada and Alberta**



### *Canada*

Under the 1997 Tobacco Act and the additions that followed, the following key federal regulations were implemented regarding the manufacture, sale, promotion and labeling of tobacco products (Table 18). The Tobacco Products Labelling Regulations (Cigarettes and Little Cigars) (TPLR-CLC) specify requirements for health-related labels on packages and prohibit certain terms such as “light” and “mild” on packaging and in advertising. In 2000, the Tobacco Act instated the Tobacco Products Information Regulations (TPIR), which were the first regulations to require graphic health warnings to be displayed. The TPIR also expanded the requirements for presenting toxic emission/constituent levels. The Tobacco Act furthermore contains a regulation that requires all cigarettes manufactured to have a reduced likelihood of igniting a fire. In regards to legal age, the Act states that the legal age for purchasing tobacco in Canada is 18 years, and requires tobacco product retailers to post signs that inform the public of this law. Under the Tobacco Reporting Regulations, tobacco manufacturers and importers must provide Health Canada with comprehensive annual reports<sup>449</sup>. The Act also bans advertising on TV and radio, and in print media. The federal excise tax per 200 cigarettes in Canada is \$21.03. Under sub-national legislation, smoking in Canada is banned in indoor public spaces and workplaces with a few limited exceptions. Otherwise, smoking restrictions in workplaces and public places are in general the responsibility of provincial and territorial as well as municipal governments<sup>450</sup>.

### *Alberta*

Alberta amended the *Smoke-free Places Act* in 2002 and adopted the *Tobacco Reduction Act* in 2008. Smoking is prohibited in all public places and workplaces including outdoor patios (Table 18). Minors caught carrying or consuming tobacco products may be fined up to \$100<sup>451</sup>. As of Sept 30 2015, the sale of menthol flavoured tobacco has also been prohibited<sup>452</sup>. In 2015, Alberta’s excise tax per 200 cigarettes was increased to \$45.00.



Table 18: Summary Alcohol and Tobacco Regulations in Canada and Alberta

Regulation	Alcohol		Tobacco	
	Canada	Alberta	Canada	Alberta
<b>What is the legal age minimum?</b>	Varies by province (18 in Alberta, Manitoba and Quebec, 19 in all other provinces and territories)	18 years	18 years	18 years
<b>What is the governing body?</b>	Varies by province /territory	Alberta Gaming & Liquor Commission (AGLC)	Federal Government	Provincial Government
<b>Where you can consume</b>	Varies by province /territory	Public consumption in non-licensed premises prohibited	Banned in indoor public spaces and workplaces with a few limited exceptions	Prohibited in all public places and workplaces including outdoor patios
<b>When you can consume</b>	Varies by province/territory	All liquor must be sold on licensed premises by 2:00 am, and consumed by 3:00 am.	N/A	N/A
<b>Retail Licensing</b>	Varies by province/territory	The AGLC issues five class of licenses and a special event license, for sale and manufacture.	Varies by province/territory	Licenses administered by the Alberta Treasury Board and Finance, Tax and Revenue Administration
<b>Tax Rate</b>	Liquor excise tax rate: Spirits: \$11.066 per liter of absolute ethyl alcohol Wine: (>7%): \$0.5122/ liter Beer: (<2.5%):\$27.985/ hectoliter	Liquor Markups: Spirits- \$10.35-\$18.33 depending on % alcohol Wine (<=16%): \$3.91 Beer (<= 9%): \$1.25	\$21.03 per 200 cigarettes	\$45.00 per 200 cigarettes
<b>Regulations Regarding Driving Under the Influence</b>	Varies by province/territory. In general, it is illegal to drive with a BAC >0.08%	License suspension and vehicle impoundment for BAC over 0.08%, 3 day license suspension and vehicle impoundment for drivers with a BAC between 0.05%-0.08%	N/A	N/A

AGLC: Alberta Gaming and Liquor Commission, N/A: Not applicable

## **Experiences with Economic Regulation of Cannabis**

A systematic review on experiences with economic regulation of cannabis was conducted to understand the impact of cannabis legalization. Medline, Embase, Psychinfo, NHSeed, and Econlit were searched from inception until October 24, 2016. Studies were included if they looked at experiences with economic regulation of cannabis, presented experiences from a country, state or jurisdiction that has legalized non-medical cannabis (Washington State, Colorado, Alaska, Oregon, Washington DC, Uruguay), reported original data pre-legalization and post-legalization, were qualitative or quantitative in study design, and reported any outcome. Following best practices for systematic reviews, two reviewers independently determined eligibility. The full-search strategy is available in the Appendix. Of the 88 citations retrieved, ten were duplicates, so 78 were reviewed in duplicate (see Appendix 5, Figure 1). No studies were included after abstract review. There are no known studies examining the experiences with economic regulation of cannabis.

## **Experience with Cannabis Legalization**

To determine the experience with and impact of cannabis legalization, a systematic review of the published literature was completed. Eight electronic databases were searched. Studies were included if they assessed the impact of legalizing non-medical cannabis, based on a country, state or jurisdiction that has legalized non-medical cannabis (Washington State, Colorado, Alaska, Oregon, Washington DC, Uruguay), original data reporting pre-legalization and post-legalization results, qualitative or quantitative in study design, and any outcome (e.g., economic impact, cannabis usage, social impact, safety or health effects). Following best practice for systematic reviews, all abstracts and full-texts were reviewed in duplicate to determine eligibility, and all papers deemed eligible were included. Data on author, year of publication, objective, location, study design, participant selection/data collection, outcomes assessed, participant characteristics, key findings and conclusions were extracted by one reviewer and verified by another.

The quality of the included studies was assessed using the Downs and Black Checklist for non-randomized controlled trials<sup>126</sup>. Using the Downs and Blacks checklist, each study was assessed based on 27 criteria, widely covering areas reporting quality, external and internal validity, and

power. Studies are assigned a value of “1” if they meet the question criteria, “0” if they do not or if it is not possible to determine whether they meet the criteria, with one exception where one question may be given “2” points.

## Results

The search yielded 668 abstracts of which 69 were read in full-text. Nine studies were included in the final data analysis (see appendix 5, Figure 2).

The evidence was grouped into three categories of impact:

- Resource utilization
- Law enforcement
- Risk-factors and substance use

Figure 39 broadly summarizes the findings. The nine studies included in the review report outcomes from Colorado (n=5) and Washington State (n=4)<sup>453-461</sup>. Three studies examined resource utilization (emergency department (ED) visits and poison control cases), two articles evaluated law enforcement and impaired driving, and four articles studied the impact of legalization on cannabis-related risk-factors and substance use (cannabis, alcohol, cigarette smoking, and/or other drugs). Five were cohort studies<sup>453-455,457,461</sup>, three were cross-sectional studies<sup>456,458,460</sup>, and one was a qualitative interview study<sup>459</sup>. Using the Downs and Black Checklist<sup>126</sup>, the nine studies had a median total score of 18 which represents moderate quality (range of 6 to 21). All nine studies were clear in their objectives and main outcomes to be measured. None of the included studies reported reasons for participant lost to follow-up or randomized participants. The percent changes pre- and post- legalization for each specific outcome are illustrated in Figure 40. Detailed information on all nine articles can be found in Appendix 5, Table 1.

Figure 39: Overview of impact associated with cannabis legalization

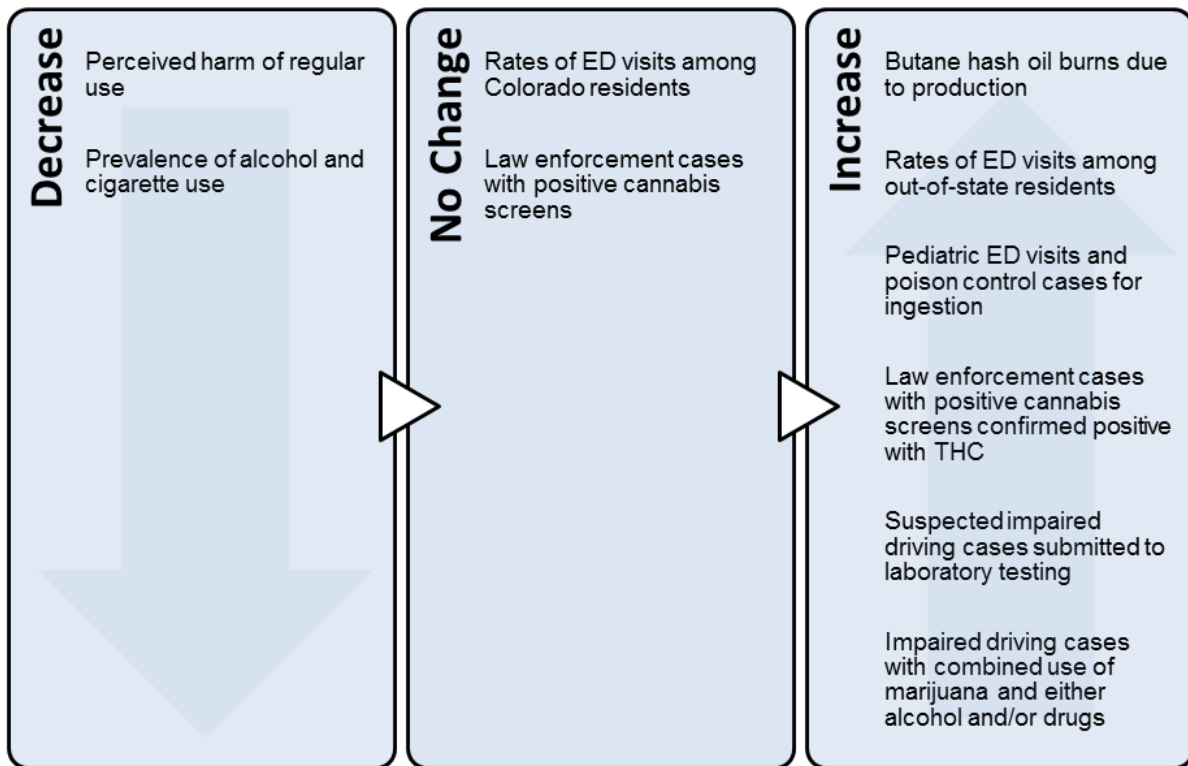
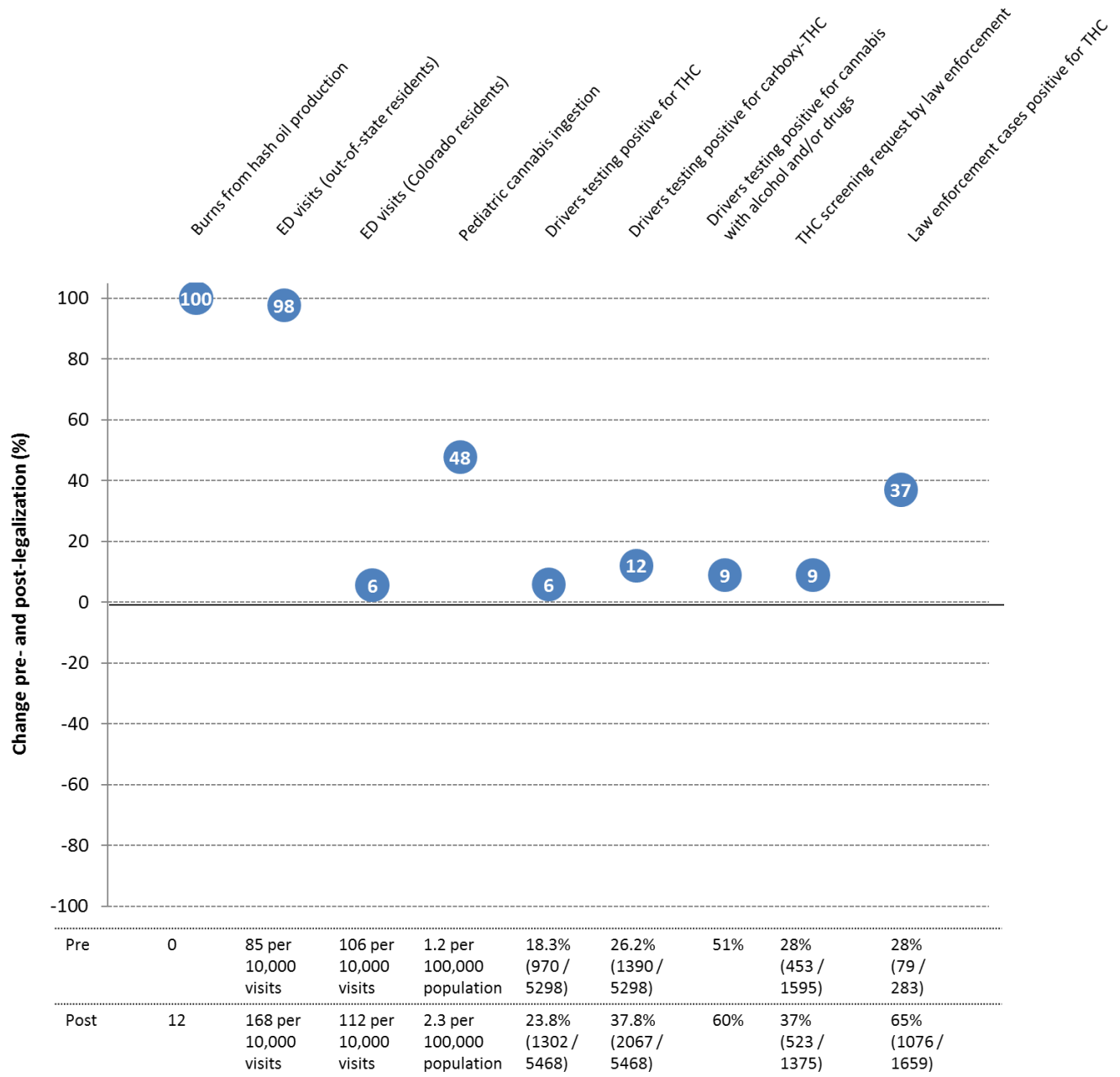


Figure 40: Percent change of impact associated with cannabis legalization



### Healthcare Resource Utilization

Two cross-sectional<sup>456,460</sup> and one retrospective cohort study<sup>453</sup> examined healthcare resource utilization in Colorado before and after legalization. Broadly, legalization resulted in increases in healthcare resource utilization of burn cases reported to the local burn center, ED visits related to cannabis use, and pediatric exposure visits to the hospital as well as the regional poison center.

A cross-sectional study of hydrocarbon burns captured in the National Burn Repository from January 1, 2008 through August 31, 2014 was conducted. Twenty-nine cases of butane hash oil burns were admitted to the local burn center during this time period; zero cases prior to legalization, 19 (61.3%) during legalization, and 12 (38.7%) in 2014 since legalization. The median total-body-surface-area burn size was 10% and the median length of hospital admission was 10 days.

A cross-sectional study of Emergency Department (ED) visits (state-wide and academic hospital-specific) among Colorado and out-of-state residents was conducted from 2011 through 2014. State-wide data were based on inputs from more than 100 hospitals to the Colorado Hospital Association from 2011 through 2014. Academic hospital-specific data were based on an urban academic hospital in Aurora, Colorado from 2012 to 2014. There was a significant increase in state-wide ED visits, related to cannabis use for Colorado, with 61 to 70 to 86 to 101 per 10,000 visits in 2011 through 2014, respectively ( $p < 0.001$  for all comparisons). Similar results were seen for out-of-state residents with 78 to 112 to 163 per 10,000 visits in 2012 through 2014, respectively ( $p < 0.001$  for all comparisons). Academic hospital-specific ED visits related to cannabis use also significantly increased for out-of-state residents (85 to 168 per 10,000 visits in 2013 and 2014, respectively; rate ratio=1.98,  $p=0.001$ ). There was no significant increase among Colorado residents.

A retrospective cohort study of hospital admissions and regional poison center (RPC) cases was conducted at Children's Hospital Colorado, Aurora, between January 1, 2009 and December 31, 2015. Participants were patients aged 0 to 9 years and had been evaluated at the hospital's emergency department, urgent care centers, or inpatient unit and RPC cases for single-substance cannabis exposures. There was an increase in pediatric cannabis-related ED visits to hospital with a mean rate of 1.2 per 100,000 population two years prior to legalization to 2.3 per 100,000 population two years after legalization ( $p=0.02$ ). There was a five-fold increase in annual RPC pediatric cannabis cases (9 in 2009 to 47 in 2015). Compared to the rest of the United States, Colorado had a greater increase in RPC per year, 34% for Colorado versus 19% for the remainder of the United States <sup>453</sup>.

## **Law Enforcement**

Two studies, one in Washington State <sup>454</sup> and one in Colorado <sup>461</sup>, examined contents of blood samples submitted to toxicology laboratories for testing of impaired driving law enforcement cases before and after cannabis legalization.

In Washington State, blood samples from all suspected impaired driving cases submitted by law enforcement officers over a five-year period (2009-2013) were examined <sup>454</sup>. The average yearly rate of cases positive for THC and for carboxy-THC significantly increased before and after legalization (19% to 25% and 28% to 40%, respectively) <sup>454</sup>. Over the five-year period, the prevalence of alcohol and the majority of other drugs in suspected impaired drivers in Washington State did not change, with the exception of an increase in frequency of cannabis.

In Colorado, driving under the influence (DUI) and DUI drugs (DUID) law enforcement cases were submitted to a laboratory in Boulder, Colorado from January 2011 to February 2014. The laboratory is responsible for more than 160 law enforcement agencies in Colorado <sup>461</sup>. There were increases in the percentage of cases with requests for cannabis screening <sup>461</sup>. The rate of cannabis screens, with THC confirmed, significantly increased by 37% (from 28%) between 2011 and 2013.

## **Risk-factors and Substance Use**

Four studies evaluated risk-factors and substance use prior to and after legalization of cannabis in Washington State and Colorado <sup>455,457-459</sup>. Three studies based in Washington State were self-reported surveys of adolescents and one study based in Colorado qualitatively explored the substance misuse treatment provider experience. After legalization, these studies reported lower perceived harm and increased approval with cannabis use. Self-reported cannabis use remained stable while there was a decrease in alcohol and cigarette use; however, among past-year users, the rate of cannabis use per month and prevalence of cannabis use disorder or dependence disorder increased.

The Longitudinal Seattle Social Development Project in Washington State interviewed adolescents at age 10, into adulthood, and up to age 39 to evaluate the change in attitudes/behaviors after retail outlets for nonmedical cannabis were opened <sup>457</sup>. There was a

significant increase in the approval of adult cannabis use and decrease in perceived harm of regular use. However, there was wide opposition against teen use and use around children. Among past-users, participants over time reported an increase in frequency of use and cannabis use disorder as adults <sup>457</sup>. The rate of cannabis use through adolescence was “up to six times” per month at age 21. Six years later, coinciding with retail cannabis availability, monthly use among current past-year users almost doubled to “over 10 times” per month.

Similarly, the 2000-2014 yearly results of the Washington State Healthy Youth Survey for tenth graders were examined with respect to cannabis-specific questions. Over the time period, there was an increase in cannabis-specific risk factors: low perceived harm with cannabis use, youth favorable attitudes about use, and perceived community favorable attitudes about use <sup>458</sup>. Results also illustrated stable cannabis use prevalence and a decrease in the prevalence of alcohol and cigarette use <sup>458</sup>. Authors reported the decrease in alcohol and cigarette use largely accounted for the stability in cannabis use during a period where risk factors for cannabis use increased.

A longitudinal study with two successive cohorts of eighth grade students was conducted in Tacoma, Washington. During the time frame of the study, the first grade eight cohort did not experience any cannabis law changes, while the second cohort experienced the Washington State non-medical cannabis law change. At follow-up, compared with students who did not experience the law change, students who did reported a higher rate of cannabis use (6.8% versus 11.8%, respectively), this was not statistically significant <sup>455</sup>. There was also a lower rate of alcohol use and cigarette smoking in this cohort which authors suggest may be a substitution effect.

The results of these three survey studies in Washington State align with the concerns voiced by Colorado-based adolescent substance misuse treatment providers <sup>459</sup>. In Colorado, a qualitative study interviewed 11 adolescent substance misuse treatment providers, including psychologists, social workers, and counsellors <sup>459</sup>. These treatment providers had at least two years of clinical practice in Colorado before non-medical cannabis was available. Seven core concepts related to cannabis use emerged from this study: normalizing, increasing access, rising addiction potential, linking laws to opioids and other drugs, diversity issues, complicating adolescent substance treatment, and responding to laws in treatment.



## **Experience with Legalization: Current state analysis**

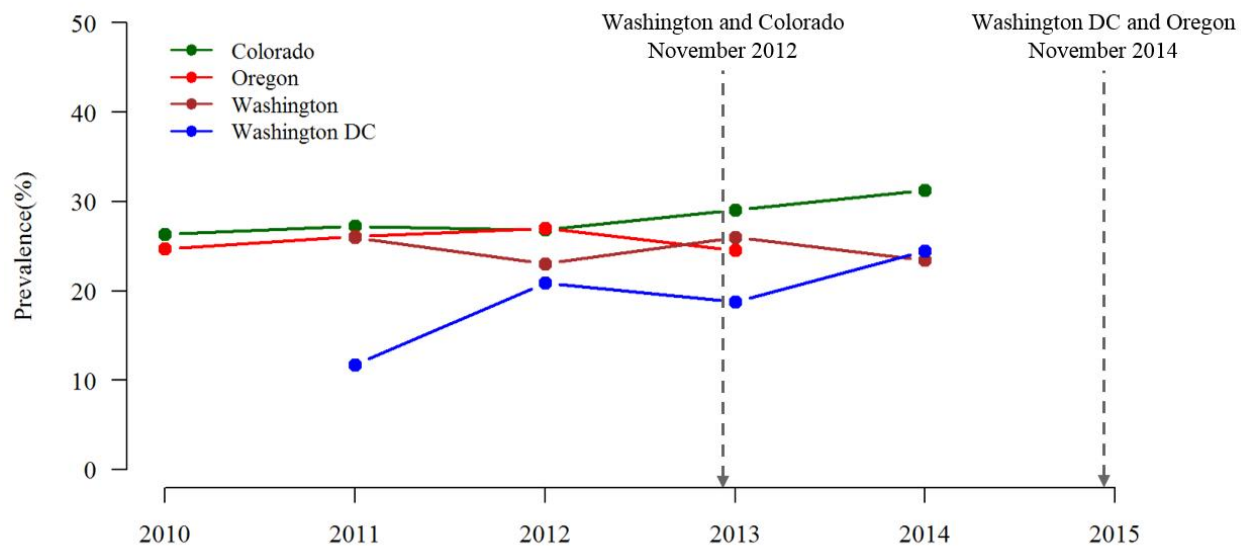
A grey literature review was completed to capture government reports, non-published papers and other literature to understand the impact of legalizing cannabis, using the experiences of places that have already undertaken legalization.

Government websites were searched for all six places that have legalized cannabis (Washington State, Colorado, Alaska, Oregon, Washington DC, Uruguay). Additionally, targeted Google searches were conducted using terms such as “marijuana”, “impact”, and “legalization” to identify additional grey literature not available on government websites. To be included, reports had to include original data, and they had to report at least one data point pre-legalization and one post-legalization. Any outcome was included (e.g., economic impact, cannabis usage, social impact, safety or health effects). Data on state and outcome were extracted, and synthesized.

### **Prevalence of Use**

Four documents reported the prevalence of past month cannabis use in adults 18 and older before and after legalization <sup>462-465</sup>. From 2010 to 2014, prevalence of use increased in both Colorado (26.4% to 31.2%) and Washington D.C. (11.7% to 24.49%), while prevalence decreased or remained level in Washington State (26% to 23.44%) and Oregon (24.7% to 24.5%) (Figure 41).

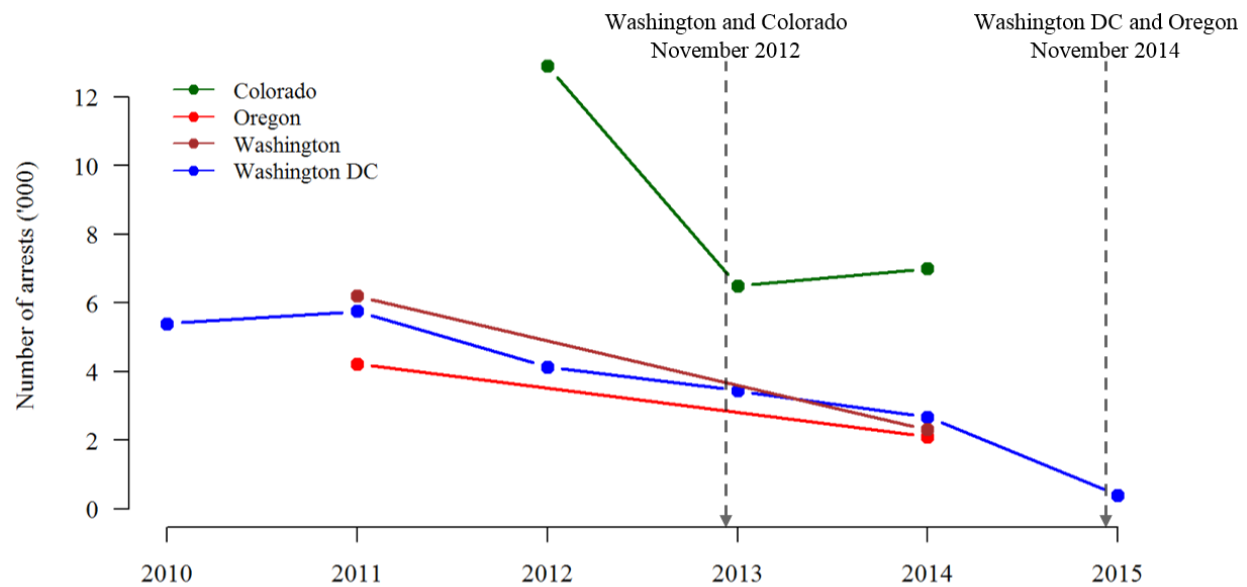
Figure 41: Prevalence of cannabis use over time, past month (ages 18+)



## Arrests

Four reports presented data on arrests for cannabis-related crimes pre- and post- legalization. Washington D.C.<sup>384</sup>, Oregon<sup>465</sup>, and Washington State<sup>466</sup> all showed trends towards decreased arrests leading up to and following legalization (Figure 42). Arrests in Washington State decreased from 6196 to 2316, arrests in Oregon decreased from 4223 to 2109, and Washington D.C. decreased from 5376 to 408. Colorado<sup>467</sup> experienced a decrease immediately following legalization from 12,894 to 6502, but an increase the year after legalization.

Figure 42: Number of arrests for cannabis-related crimes



### Impact on Driving Safety

Two driving related outcomes were measured by the reports identified: number of drivers who test THC positive at a level higher than 2ng/mL<sup>387,462</sup>, and number of fatalities with drivers testing positive for THC<sup>462</sup>. The number of drivers testing positive for THC levels over 2ng/mL increased after legalization in both Colorado and Washington (Figure 43). Similar trends were shown for the number of fatal accidents with drivers testing positive for THC (Figure 43).

Fatalities substantially increased after legalization in Colorado and Washington, from 49 to 94 in Colorado, and from 40 to 85 in Washington. These outcomes suggest that after legalization, more people are driving while impaired by cannabis.

Figure 43: Number of drivers who test positive for THC levels greater than 2ng/mL

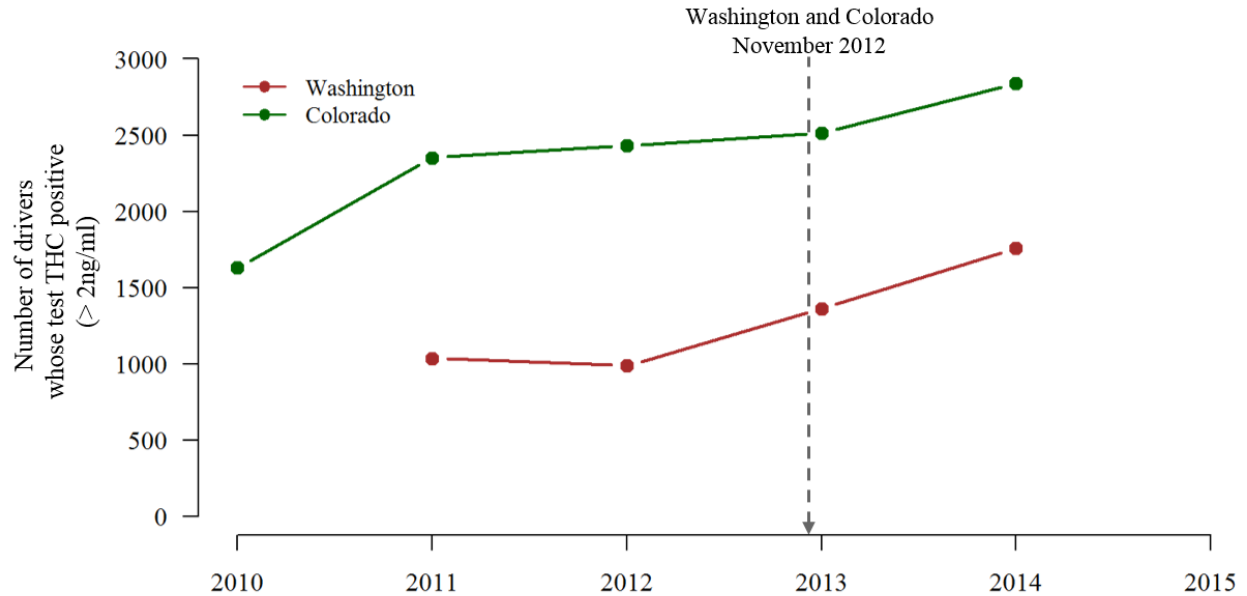
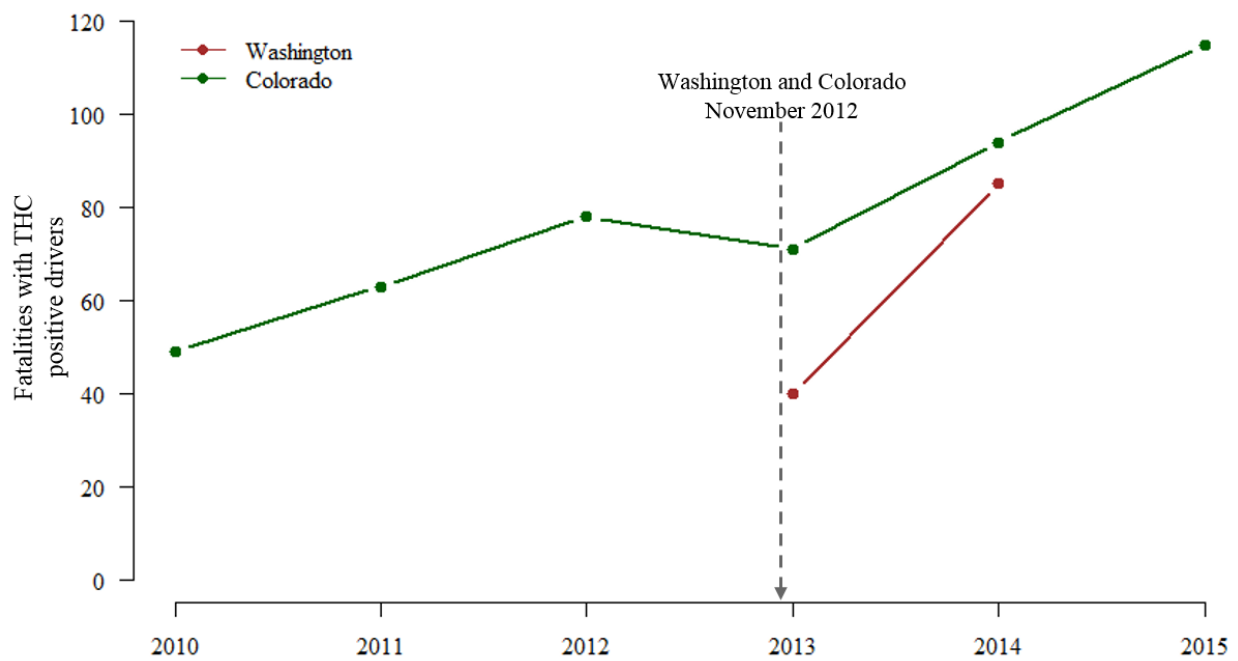


Figure 44: Fatalities with drivers who test positive for THC



### **Health Care Resource Utilization**

Data on health resource utilization prior to and after legalization were extracted from the grey literature search. Consistent trends were found after legalization of cannabis (Table 19).

Washington State, Oregon and Colorado all experienced an increase in cannabis-related poison control calls after legalization. Admissions for cannabis decreased amongst both adult and youth populations in Colorado and Washington State. However, there was an increase in cannabis-related emergency department and hospital visits after legalization, and an increase in hash oil explosion-related injuries, caused by the production of home-made hash oil. Across all age groups and all states, there was a substantial increase in accidental cannabis ingestion.

Table 19: Health Care Resource Utilization Pre- and Post- Legalization

Category	Location	Year										Trend
		2006	2007	2008	2009	2010	2011	2012  Washington Legalizes	2013	2014  Colorado Legalizes	2015  Washington DC and Oregon Legalize	
								●		●	●	
Cannabis-related poison control calls (N)	<b>Colorado</b> <sup>176</sup>	44	68	58	43	94	86	109	123	221	227	▲
	<b>Washington State</b> <sup>168,468,469</sup>					150	146	162	158	246	272	
	<b>Oregon</b> <sup>470</sup>								112	105	158	
Treatment admissions for cannabis (All ages and adults) (N)	<b>Colorado</b> <sup>471</sup> (all ages)	5,708	6,144	6,900	7,074	6,903	6,687	7,056	6,877	6,907	6,267	▼
	<b>Washington State</b> <sup>472</sup>					5,730	5,354	4,621	4,154	3,996		
Treatment admissions for cannabis (Youth) (N)	<b>Washington State</b> <sup>472</sup>					5,047	5,448	5,214	4,984	4,469		▼
	<b>Colorado</b> <sup>471</sup> , % (ages 12-17)	31.2	28.2	28.3	28.7	29	27.7	24.1	22.4	19.8	18.8	
Cannabis-related emergency room/ hospital visits (N)	<b>Colorado</b> <sup>471</sup>	3,876	3,895	4,438	4,694	6,019	6,305	6,715	8,272	11,429		▲
	<b>Oregon</b> <sup>473</sup> , yearly average patients per month							21	32	121	196	
Cannabis ingestion among children and teens (N)	<b>Colorado</b> <sup>468</sup> (Poison control calls ages 0-8)	4	4	4	7	12	19	16	26	44	49	▲
	<b>Colorado</b> <sup>471</sup> (ages 0-8)				1	3	10	9	7	16	16	
	<b>Washington State</b> <sup>474</sup> - King County* (ages 0-5)							3	10	11	6	
	<b>Washington State</b> <sup>474</sup> - King County* (ages 6-17)								2	9	8	
	<b>Oregon</b> <sup>214</sup> (ages ≤5)									13	25	
	<b>Oregon</b> <sup>214</sup> (ages 6-19)									33	46	
Hash oil explosions (N)	<b>Colorado</b> <sup>475</sup> , explosions [injuries]								12 [18]	32 [30]		▲
	<b>Washington State</b> <sup>472</sup>									17		
	<b>Oregon</b> <sup>476</sup>						2	2	4	1		

\*Edible cannabis intoxication reports with 2015 data through May

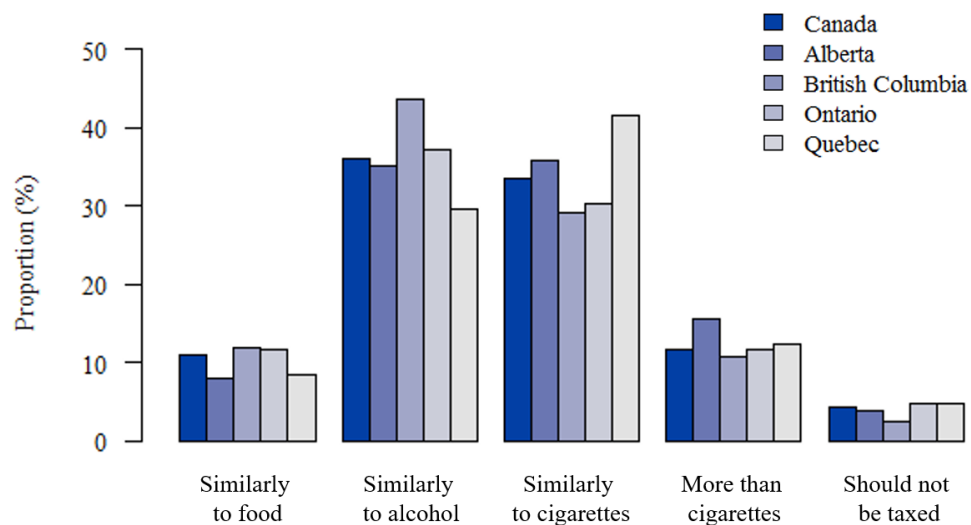
## Public perspective on Economic, Use and Sales Regulations

A survey was commissioned by the University of Calgary HTA Unit in July 2016 to understand current public perceptions of cannabis use and sales. This survey of 2088 people was weighted to be a representative sample nationally and for the populations of British Columbia, Alberta, Ontario, and Quebec. The survey included demographic questions as used on the Canadian Census (age group, sex, province of residence, income category and educational attainment). Further questions were developed to understand respondents' perspectives on economic regulation of legalized cannabis and cannabis use and sales.

### Economic Regulation

Nation-wide, 68% of Canadians think that if cannabis were legalized, it should be taxed similarly to alcohol (35%) or cigarettes (33%). Twelve-percent of Canadians think that it should be taxed more than cigarettes (Figure 45). Preferences for taxation varied by province. In British Columbia, most (44%) respondents indicated cannabis should be taxed similarly to alcohol, and only 29% indicated that it should be taxed similarly to cigarettes. Respondents from Quebec show an opposite opinion; 29% think it should be taxed similarly to alcohol and 42% think it should be taxed similarly to cigarettes. Respondents' opinion about economic regulations on legalized cannabis was not significantly different across age groups, sex, and different income and education categories.

Figure 45: If cannabis was legalized, how should it be taxed?

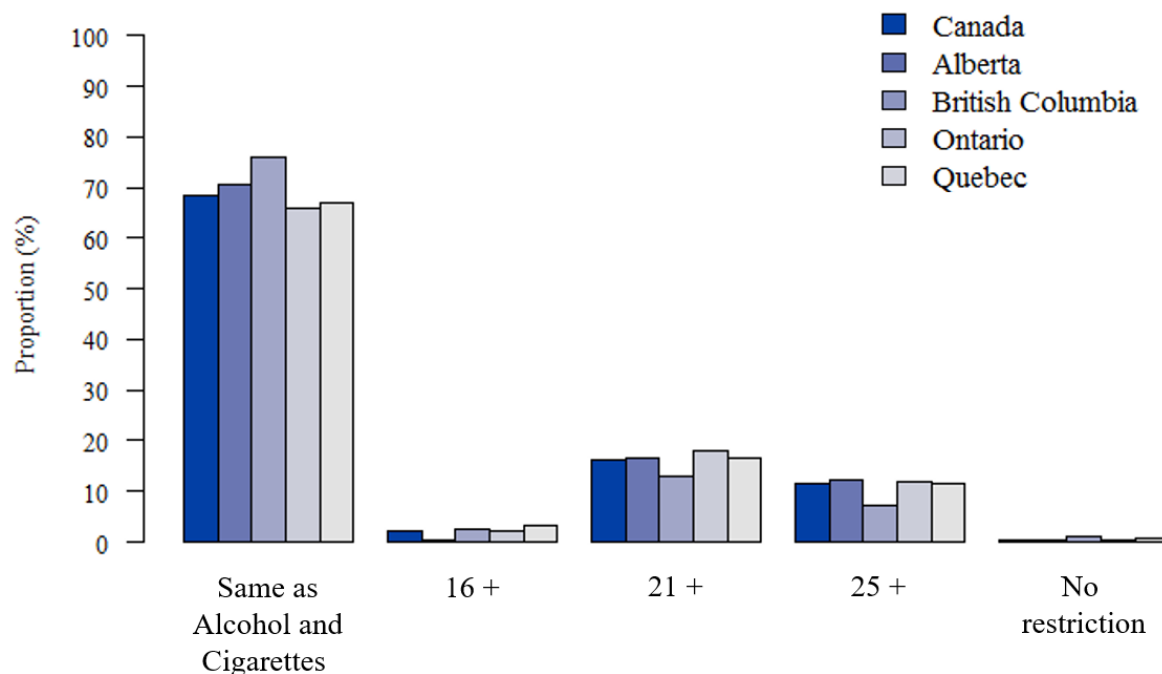


## Regulation of Purchasing

Respondents were asked about their opinion of the legal age for purchasing cannabis. 68% responded that the legal age to purchase cannabis should be the same as the legal age for purchasing alcohol and cigarettes (Figure 46

Figure 46). 16% of participants responded that the legal age for purchasing cannabis should be 21 years old and above. Provincial level data did not significantly differ from national level data on legal age for purchasing cannabis.

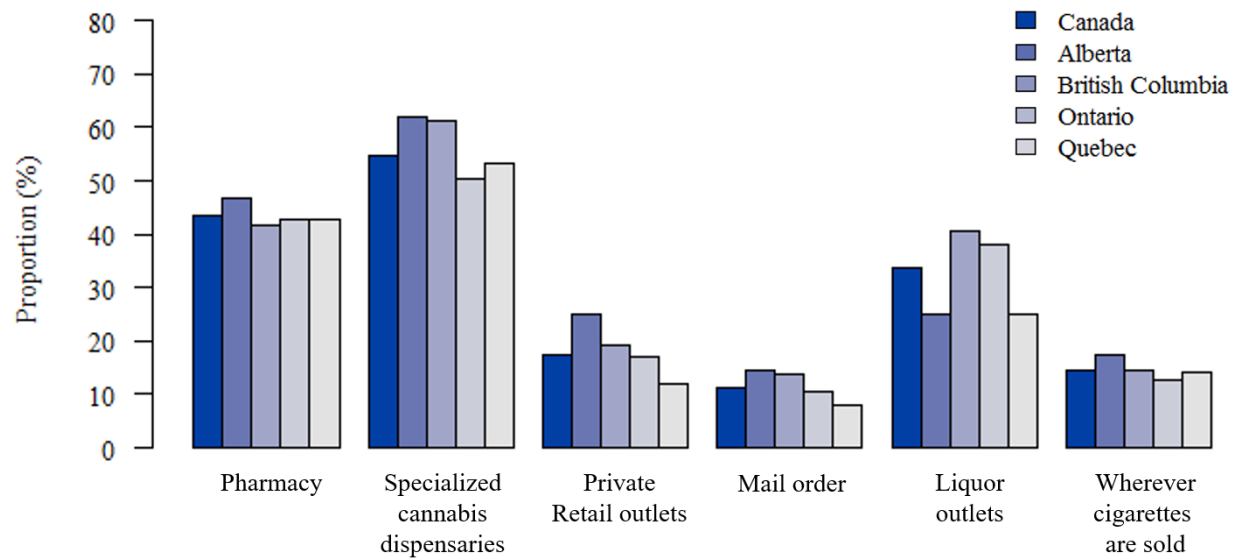
Figure 46: Canadian perspective of the legal age to purchase cannabis



Respondents' preference of cannabis sales locations were examined. Nationally, the most preferred cannabis sales locations are specialized cannabis stores (55%), pharmacy (44%), and liquor stores (34%) (Figure 47). Current cannabis users had different preferences, with seventy-one-percent preferring it to be sold in a specialized cannabis store and 19% preferring it to be sold in cigarette outlets. The least preferred sales method was mail order (11%).



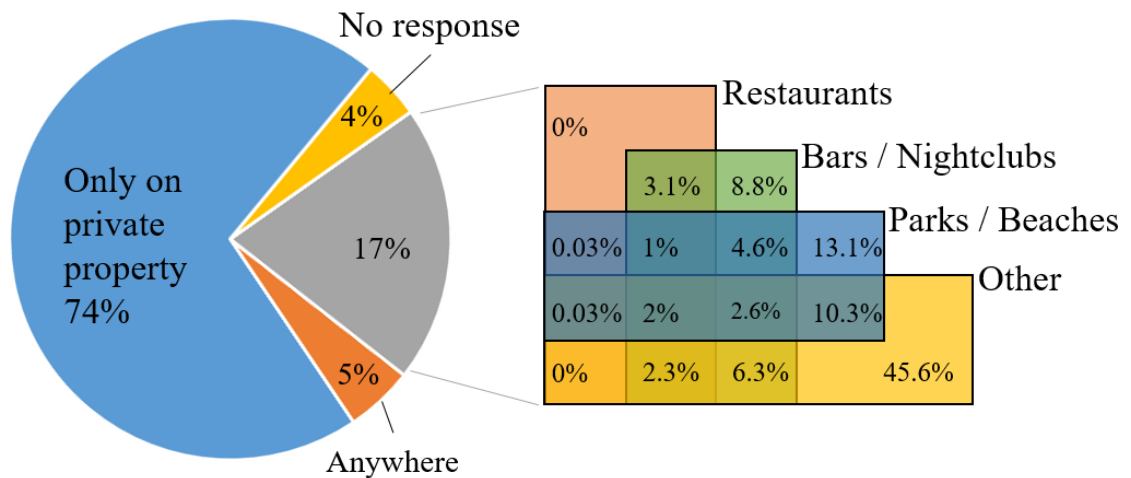
Figure 47: Canadian perspective of cannabis sales locations



### Regulation of Use

74% of Canadians think that if cannabis was legalized it should be consumed only on private property. 5% responded that users should be allowed to consume it anywhere, and 17% reported other locations such as restaurants, bars, nightclubs, parks, and beaches (Figure 48). Among those that reported other locations, 8.8% indicated only in bars and nightclubs, 3.1% indicated it should also be allowed in restaurants, 4.6% indicated beaches in addition to nightclubs and 1% indicated that cannabis consumption should be allowed in all three locations (nightclubs, restaurants and beaches). Further, 61% responded that, if cannabis were legalized, users should be able to grow a limited number of plants for personal use.

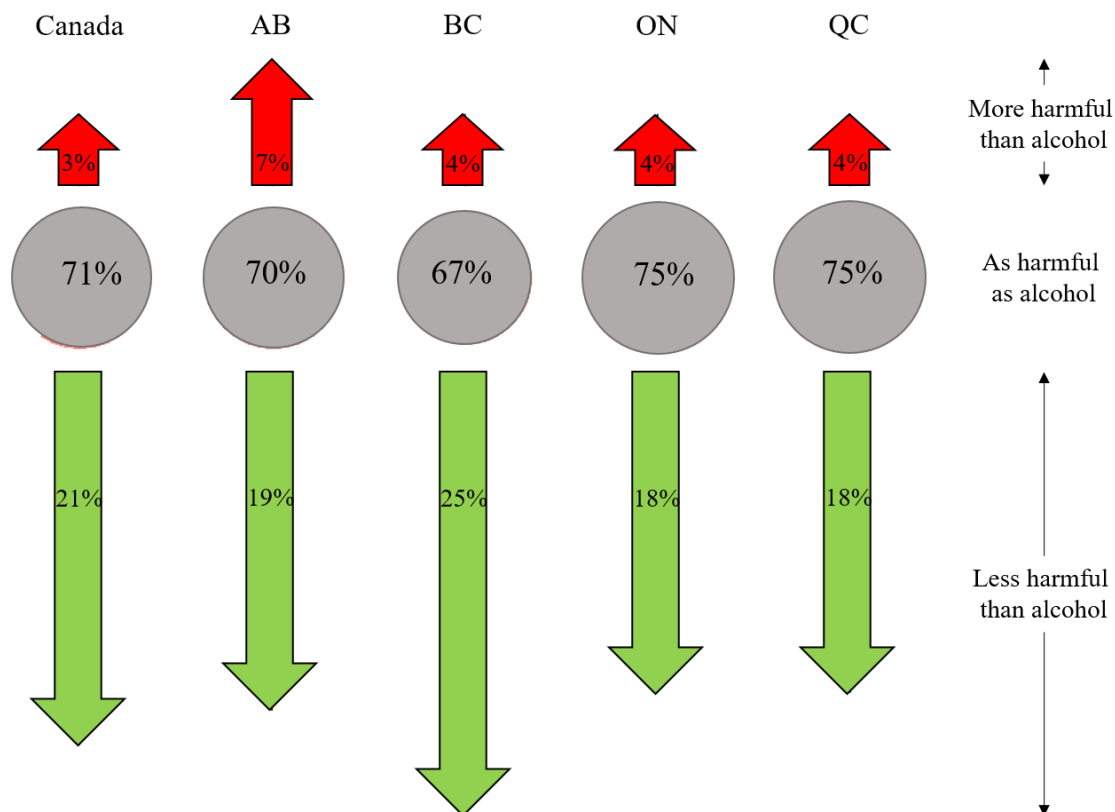
Figure 48: If cannabis was legalized, where people should be allowed to consume?



#### Driving under the influence of Cannabis

When asked about driving under the influence of cannabis, 71% responded that driving under the influence of cannabis is as harmful as driving under the influence of alcohol. 21% percent responded that they did not believe driving under the influence of cannabis was as harmful as alcohol, and 3% responded that it is more harmful than driving under the influence of alcohol. The provincial response pattern is not significantly different from the national level results (Figure 49).

Figure 49: Canadian perspective of driving under the influence of cannabis



## Conclusions

One country, four states and one jurisdiction have legalized non-medical cannabis use. The regulations around use, production, and sales varies across all places that have legalized. Legal age of consumption is 21 years in all jurisdictions except in Uruguay, where the age limit is 18 years. Public consumption is prohibited in all jurisdictions and the amount of cannabis that an individual is allowed to possess at any given time varies, range from 1 ounce (Alaska) to 8 ounces (Oregon). For non-medical cannabis, there is no taxation in Uruguay, there is also no tax in Washington D.C. since sale of non-medical cannabis is prohibited. In Washington State the tax rate is 37% at the point of sale in Oregon there is a 17% excise tax with an additional local tax up to 3%, and in Colorado there is a 15% excise tax from producers and a 10% tax on retail.

For medical cannabis, there was no information on tax rate for Washington D.C., Alaska or Uruguay, tax rate is 6.5% in Washington State, 2.9% in Colorado, and it is not taxed in Oregon.

Published literature on the impact of legalizing cannabis was of weak-moderate quality and were cohort, cross-sectional, and qualitative studies. These studies found that legalization of cannabis results in an increase in burn cases reported to the local burn center, increase in pediatric poison control cases, and increase in ED visits related to cannabis. Studies on law enforcement and impaired driving found increases in impaired driving cases, with confirmed THC and carboxy-THC. However, other than cannabis, the prevalence of alcohol and other drugs did not increase in impaired drivers. In studies on self-reported risk-factors and substance use, cannabis use was stable while there was a decrease in alcohol and cigarette use. These studies also reported lower perceived harm and increased approval of cannabis use, which were concerning to treatment providers. Overall, there is some evidence that experience with cannabis legalization may have negative repercussions with respect to: resource utilization; law enforcement and impaired driving cases; self-reported cannabis-specific risk-factors; and substance use including, but not limited to, cannabis.

A grey literature search found that after legalization, states reported that: self-reported cannabis use remained stable, alcohol and cigarette use decreased, cannabis use disorders increased, number of arrests for cannabis-related crimes decreased, number of drivers testing positive for THC increased and health care resource utilization associated with cannabis use increased.

The majority of Canadians think that cannabis is equivalent to alcohol and cigarettes in terms of use, sales and economic regulations. More than 50% of respondents prefer cannabis to be taxed similar to alcohol and cigarettes and the legal age for purchasing cannabis to be the same as the legal age for purchasing alcohol and cigarettes. Seventy-four-percent of Canadians think if cannabis was legalized, it should be consumed only in a private property and 60% of respondents agreed to allow users to grow limited number of cannabis plants for their private use. Further, more than 70% responded that driving under the influence of cannabis is similarly harmful as driving under the influence of alcohol.

Table 20: Summary of Cannabis, Alcohol and Tobacco Regulations in Jurisdictions where Cannabis is Legal

	Non-medical Cannabis Regulation	Medical Cannabis Regulation	Alcohol Regulation	Tobacco Regulation
<b>Uruguay</b>				
<b>Regulation of Sales</b>	<p><i>Control over sale:</i> Only sold at licensed pharmacies to registered individuals; adults permitted up to 10g per week from pharmacy; overseen by the Institute for Regulation and Control of Cannabis</p> <p><i>Control over growing:</i> Six licensed commercial growers allowed, allowed 6 plant maximum in personal grow-op</p> <p><i>Retail licensing:</i> Limited to pharmacies only</p> <p><i>Number of licensed retailers:</i> Approximately 40 pharmacies have registered as cannabis distributors</p> <p><i>Number of licensed cultivators:</i> 2</p> <p><i>Production estimates:</i> 2 tons per year from each licensed cultivator</p> <p><i>Sales over time:</i> N/A</p>	<p><i>Control over sale:</i> Dried cannabis may be sold from pharmacies (cannabis oil must be requested by form, and imported from the United States)</p> <p><i>Control over growing:</i> State-controlled, limited commercial production licenses permitted, medical and non-medical cannabis to be grown separately and have separate licensing programs</p> <p><i>Patient requirements:</i> Prescription from licensed physician</p> <p><i>Physician restrictions:</i> N/A</p>	<p><i>Control over sale:</i> NR</p> <p><i>Control over production:</i> A production license is required. Government produces Scotch, rum, vodka, cognac</p> <p><i>Retail licensing:</i> A sale license is required</p>	<p><i>Control over sale:</i> Ministry of Public Health</p> <p><i>Control over production:</i></p> <p><i>Retail licensing:</i> NR</p>
<b>Regulation of Use</b>	<p><i>Age for legal consumption:</i> 18+</p> <p><i>Amount allowed:</i> Six plants/household, adults permitted 40g/month (10g/week), annual cap 480g/member of a cannabis club</p> <p><i>Consumption:</i> Follows tobacco regulation. Use at work or during the work day is prohibited</p> <p><i>DUI definition:</i> Detectable THC in the body</p>	<p><i>Patient age:</i> 18+</p> <p><i>Amount allowed:</i> Not specified</p> <p><i>Consumption:</i> Same as non-medical cannabis</p>	<p><i>Age for legal consumption:</i> 18+</p> <p><i>Where can you consume:</i> Restrictions on consumption are voluntary in health care establishments, educational building, public transport, workplaces and government offices. Not allowed in parks, streets, sporting events and leisure events</p>	<p><i>Age for legal consumption:</i> Prohibits sale of tobacco products to persons under 18</p> <p><i>Where can you consume:</i> Designated Smoking Areas that exclude all enclosed public places and workplaces, public</p>

			<p><i>When can you consume:</i> Off-premise sales have hourly restrictions and are banned from midnight to 6am</p> <p><i>DUI definition:</i> 0.03% for amateur drivers (since March 2009); 0.0% BAC law in effect Jan 2016</p>	transportation, & the outdoor premises of health & educational institutions
<b>Economic Regulation</b>	<i>Taxation rate:</i> 0% - categorized as an agricultural product; no luxury item tax (like there is with cigarettes and alcohol)	<i>Taxation:</i> Unclear	<i>Taxation:</i> Excise taxes as a % of retail price:  Beer 27%, Wine (no tax), Spirits 18%	<i>Taxation: Excise tax on cigarettes: 49% of retail price</i>
<b>Alaska</b>				
<b>Regulation of Sales</b>	<p><i>Control over sale:</i> First retail licenses issued in Fall 2016, cannabis clubs in operation currently, 'Cannabis Cafes' are permitted under law but yet to open; activity overseen by the Cannabis Control Board</p> <p><i>Control over growing:</i> 6 plants/household for personal use; businesses may apply for cultivation licenses</p> <p><i>Retail licensing:</i> Candidates must meet zoning requirements, pay fees, and pass inspections before being awarded a license</p> <p><i>Number of licensed retailers:</i> 4 licensed</p> <p><i>Number of licensed cultivators:</i> 18 licensed</p> <p><i>Production estimates:</i> It is estimated that for the first year, 4 tons of cannabis will be supplied by the retail market, with this figure increasing to 13 tons by 2020</p> <p><i>Sales over time:</i> N/A</p>	<p><i>Control over sale:</i> Dispensaries that solely provide medical cannabis are not permitted, applications to use medical cannabis are through the Alaskan Division of Public Health</p> <p><i>Control over growing:</i> Up to six plants for at-home cultivation, no more than three mature at one time</p> <p><i>Patient requirements:</i> Diagnosed with cachexia, cancer, chronic pain, glaucoma, HIV/AIDS, multiple sclerosis, nausea, or a condition where one experiences seizures</p> <p><i>Physician restrictions:</i> N/A</p>	<p><i>Control over sale:</i> Alcoholic Beverage Control board oversees manufacture, possession, &amp; sale.</p> <p><i>Control over production:</i> Alcoholic Beverage Control board.</p> <p><i>Retail licensing:</i> Issuance of licenses by the ABCB to private business. License must be operated at least 30, 8hr days, each year.</p>	<p><i>Control over sale:</i> Department of Commerce, Community and Economic Development</p> <p><i>Control over production:</i> Department of Commerce, Community and Economic Development</p> <p><i>Retail licensing:</i> Department of Revenue provides 6 types of cigarette licenses (buyer-\$25/year, direct-buying retailer, cigarette distributor, manufacturer, vending machine operator, wholesale-distributor, and tobacco products only distributor- all \$50/year.)</p>

<b>Regulation of Use</b>	<p><i>Age for legal consumption:</i> 21+</p> <p><i>Amount allowed:</i> One ounce at any time</p> <p><i>Consumption:</i> Public consumption prohibited</p> <p><i>DUI definition:</i> Relies on field sobriety tests; may be ticketed for operating a vehicle with a motor, or any aircraft or watercraft with or without a motor</p>	<p><i>Patient age:</i> Any age, patients under 18 must have a parent or legal guardian to consent to the use of cannabis as treatment for the minor, and serve as the primary caregiver for the minor</p> <p><i>Amount allowed:</i> No more than one ounce of usable cannabis</p> <p><i>Consumption:</i> Public consumption prohibited, use on federal land prosecuted under federal law</p>	<p><i>Age for legal consumption:</i> 21+</p> <p><i>Where can you consume:</i> Illegal in public places other than licensed premises</p> <p><i>When can you consume:</i> Licensed businesses open 8am-5pm every day of the year except election days. Local governing bodies can limit hours of operation by ordinance</p> <p><i>DUI definition:</i> driving while under the influence of alcohol or other chemical substances, or driving with a blood or breath alcohol level of .08 or &gt;</p>	<p><i>Age for legal consumption:</i> 19+</p> <p><i>Where can you consume:</i> Designated Smoking Areas that exclude in all portions elementary and secondary schools &amp; children's day care facilities, state &amp; local government public meeting &amp; assembly rooms, private &amp; public washrooms, health care offices, institutions &amp; hospitals, and elevators. Smoking is also not allowed in food service establishments having a seating capacity of at least 50 person or grocery stores.</p>
<b>Economic Regulation</b>	<p><i>Taxation rate:</i> US\$50 per ounce on parts of the cannabis plant transferred from the cultivation facility to either a product manufacturing facility or a retail store. A rate lower than \$50 may be established for certain parts of the plant</p>	<p><i>Taxation:</i> No information available</p>	<p><i>Taxation:</i> Excise Tax Rates by Gallon:</p> <p>Liquor (&gt;21% Alcohol): \$12.80</p> <p>Wine (&lt;21% Alcohol): \$2.50</p> <p>Beer, Malt Beverages, Hard cider: \$1.07</p> <p>Approved Reduced Rate Brewery: \$.35</p>	<p><i>Taxation:</i> Excise tax on manufacture, importation, acquisition, distribution and/or sale of cigarettes is \$.10 per cigarette or \$2.00 per pack of 20.</p> <p>Excise tax on tobacco products other than cigarettes is 75% of the product's wholesale price.</p>
<b>Colorado</b>				
<b>Regulation of Sales</b> <sup>323,346-352</sup>	<p><i>Control over sale:</i> Department of Revenue oversees sale of cannabis similarly to alcohol. Only one ounce is allowed to be purchased at one time by Colorado residents</p>	<p><i>Control over sale:</i> Patients are required to obtain cannabis from dispensaries (not permitted to fill prescriptions for a Schedule I substance at a</p>	<p><i>Control over production:</i> Liquor Enforcement Division, Department of Revenue</p>	<p><i>Control over sale:</i> Tobacco Enforcement</p>

	<p><i>Control over growing:</i> Department of Revenue oversees manufacturers, cultivators, and labs. Residents over 21 are allowed to grow up to 6 plants</p> <p><i>Retail licensing:</i> City and county governments can deny licensure requests by individuals within their jurisdiction. Licensing fees are several hundred dollars.</p> <p><i>Number of licensed retailers:</i> 454</p> <p><i>Number of licensed cultivators:</i> 613</p> <p><i>Production estimates:</i> An average of 597,415 plants were cultivated each month in 2015 (medical and non-medical)</p> <p><i>Sales over time:</i> An average of 8,911 pounds of bud/flower for non-medical purposes were sold each month in 2015</p>	<p>pharmacy). Department of Revenue oversees sale of cannabis.</p> <p><i>Control over growing:</i> Patients permitted to grow up to six cannabis plants, three or fewer mature at one time</p> <p><i>Patient requirements:</i> Possession of a state-issued Medical Cannabis Registry Identification Card, recommended by a physician</p> <p><i>Physician restrictions:</i> Until 2009, physicians were only permitted to prescribe cannabis to five patients at a time, a restriction that has since been removed</p>	<p><i>Retail licensing:</i> Retailers excluding chain stores or multiple liquor licenses must first obtain license approval at local government level with an initial background investigation.</p>	<p>Unit, Department of Revenue</p> <p><i>Control over production:</i> Tobacco Enforcement Unit, Department of Revenue</p> <p><i>Retail licensing:</i> A Colorado retailer does not need a Colorado cigarette tax license if the retailer only purchases cigarettes with the stamps already affixed for sales to consumers.</p>
<b>Regulation of Use</b>	<p><i>Age for legal consumption:</i> 21+</p> <p><i>Amount allowed:</i> Purchase and possess up to one ounce</p> <p><i>Consumption:</i> Public consumption prohibited</p> <p><i>DUI definition:</i> 5ng THC/mL blood</p>	<p><i>Patient Age:</i> Any age, patients under 18 must be diagnosed by two separate doctors with a debilitating medical condition and have a parent primary caregiver to administer the medication</p> <p><i>Amount Allowed:</i> Possess up to two ounces</p> <p><i>Consumption:</i> Public consumption prohibited</p>	<p><i>Age for legal consumption:</i> 21</p> <p><i>Where can you consume:</i> All alcohol except 3.2% beer is illegal to consume in public other than a place which is licensed for that purpose.</p> <p><i>When can you consume:</i></p> <p>Off-Premises Licenses: 8am-midnight all days</p> <p>On-Premises Licenses: 7am-2am all days</p> <p><i>DUI definition:</i> Maximum BAC level 0.08%.</p> <p><i>Control over sale:</i> Liquor Enforcement Division, Department of Revenue</p>	<p><i>Age for legal consumption:</i> 18</p> <p><i>Where can you consume:</i> Private homes residences and automobiles, certain hotel rooms, any retail tobacco business, a cigar-tobacco bar, an airport smoking concession, outdoor area of any business, a non-public place of employment with three or fewer employers, private non-residential buildings on a farm/ranch, floor plan of a licensed casino.</p>



<b>Economic Regulation</b>	<i>Taxation rate:</i> 15% excise tax from cultivator to processors or retailers; 10% excise tax on retail (plus existing local or state sales tax). Local governments may impose additional retail taxes on cannabis.	<i>Taxation:</i> 2.9% state sales tax (on all goods), and any local sales tax	<i>Taxation:</i> Excise Tax Rates:  Beer and Hard Cider: 8 cents/gallon  Wine: 7.33 cents/liter  Spirituos Liquors: 60.26 cents/liter  Winery Grape/Produce Tax: 10 cents/ton	<i>Taxation:</i> Wholesalers are required to collect and remit to the Colorado Department of Revenue 4.2 cents on each cigarette sold, evidenced by affixing of stamps to cigarette packs. Retailers charge state sales tax on all retail sales of cigarettes.
<b>Oregon</b>				
<b>Regulation of Sales</b>	<p><i>Control over sale:</i> Oregon Liquor Control Commission oversees all businesses that ‘serve adults’</p> <p><i>Control over growing:</i> Oregon Liquor Control Commission oversees cultivators; up to 4 plants for personal use</p> <p><i>Retail licensing:</i> Oregon Liquor Control Commission is taking applications as of January 2016</p> <p><i>Number of licensed retailers:</i> 48</p> <p><i>Number of licensed cultivators:</i> 306</p> <p><i>Production estimates:</i> Not found</p> <p><i>Sales over time:</i> \$22,970,868 October 2015 sales (112% increase from medical sales only)</p>	<p><i>Control over sale:</i> Oregon Health Authority provides licenses to dispensaries allowing them to control sale</p> <p><i>Control over growing:</i> Up to six mature cannabis plants for home cultivation</p> <p><i>Patient requirements:</i> Diagnosis with a debilitating medical condition</p> <p><i>Physician restrictions:</i> N/A</p>	<p><i>Control over sale:</i> Oregon Liquor Control Commission</p> <p><i>Control over production:</i> Oregon Liquor Control Commission</p> <p><i>Retail licensing:</i> License Services within the Oregon Liquor Control Commission is responsible for issuing and renewing licenses to Oregon businesses involved in the manufacture, distribution, and retail sale of alcoholic beverages.</p>	<p><i>Control over sale:</i> Department of Revenue</p> <p><i>Control over production:</i> Department of Revenue</p> <p><i>Retail licensing:</i> All business, except for sole proprietorships, are required to have a federal tax identification number. There is no fee to be licensed.</p>
<b>Regulation of Use</b>	<i>Age for legal consumption:</i> 21+	<i>Patient age:</i> Any age, patients under 18 must have a parent or guardian who consents to the use of medical cannabis as	<i>Age for legal consumption:</i> 21	<i>Age for legal consumption:</i> 18

	<p><i>Amount allowed:</i> 8 ounces at home; 1 ounce on person form purchased at a retail store</p> <p><i>Consumption:</i> Public consumption prohibited</p> <p><i>DUI definition:</i> No limit on level of THC. Relies on field sobriety tests and police officer observations</p>	<p>treatment for the minor, and serve as the primary caregiver for the minor</p> <p><i>Amount allowed:</i> Not more than 24 ounces of usable cannabis</p> <p><i>Consumption:</i> N/R</p>	<p><i>Where can you consume:</i> No law against public intoxication.</p> <p><i>When can you consume:</i> 7 a.m. to 2:30 a.m. every day on licensed premises.</p> <p><i>DUI definition:</i> Motorists will fail a DUI field test if their blood alcohol reading is 0.08% or higher. For drivers under 21 years old, any amount of alcohol in the bloodstream. For new drivers the legal limit is a BAC of 0.04%.</p>	<p><i>Where can you consume:</i> Certified smoke shops and cigar bars, and up to 24% of motel/hotel rooms, and smoking of non-commercial tobacco for American Indian ceremonial purposes.</p>
<b>Economic Regulation</b>	<p><i>Taxation rate:</i> 17% excise tax; local governments may tax up to an additional 3%</p>	<p><i>Taxation:</i> Not taxed</p>	<p><i>Taxation:</i> Excise Tax Rates:</p> <p>Beer: 8 cents/gallon</p> <p>Wine (&lt;14%): 67 cents/gallon</p> <p>Spirits: \$22.73 per gallon</p>	<p><i>Taxation:</i> \$1.31 per pack of 20 cigarettes</p>
<b>Washington State</b>				
<b>Regulation of Sales</b>	<p><i>Control over sale:</i> Sale of cannabis is overseen by the Washington Liquor and Cannabis Control Board</p> <p><i>Control over growing:</i> At-home cultivation prohibited; businesses may apply for a cultivation license</p> <p><i>Retail licensing:</i> Number of businesses determined by population density; limits on number of licenses one individual holds at one time</p> <p><i>Number of licensed retailers:</i> 453</p> <p><i>Number of licensed cultivators:</i> 908</p>	<p><i>Control over sale:</i> State-licensed dispensaries no longer permitted, medical patients may access cannabis from licensed retail stores</p> <p><i>Control over growing:</i> Up to 6 plants permitted for at-home cultivation and 8 ounces of prepared cannabis from those plants</p> <p><i>Patient requirements:</i> Recommendation from a physician for use of cannabis as treatment for any debilitating condition, registering as a medical patient is voluntary</p> <p><i>Physician restrictions:</i> Must write recommendation on tamper-resistant paper</p>	<p><i>Control over sale:</i> Washington State Liquor and Cannabis Board</p> <p><i>Control over production:</i> Washington State Liquor and Cannabis Board</p> <p><i>Retail licensing:</i> An endorsement on a Business License, issued by the Washington State Department of Revenue Business Licensing Service.</p>	<p><i>Control over sale:</i> Washington State Liquor and Cannabis Board</p> <p><i>Control over production:</i> Washington Office of the Attorney General</p> <p><i>Retail licensing:</i> Issued through the Department of Revenue's Business Licensing Services, then the Liquor &amp; Cannabis Board's Enforcement Division</p>

	<p><i>Production estimates:</i> 59,394 pounds of cannabis harvested from producers (Jul 2014 – Jun 2015)</p> <p><i>Sales over time:</i> 22,654 pounds of useable cannabis sold (Jul 2014 – Jun 2015)</p>			
<b>Regulation of Use</b>	<p><i>Age for legal consumption:</i> 21+</p> <p><i>Amount allowed:</i> Adults can possess 1 ounce of cannabis, 7 grams of cannabis concentrate/extract for inhalation, 16 ounces of cannabis infused product in solid form, 72 ounces of cannabis infused product in liquid form</p> <p><i>Consumption:</i> Public consumption prohibited</p> <p><i>DUI definition:</i> 5ng THC/mL blood</p>	<p><i>Patient age:</i> 18+; if under 18, the patient may appoint a designated provider over the age of 21 who must purchase and administer the cannabis, who is authorized by the health care provider</p> <p><i>Amount allowed:</i> 48 ounces of cannabis-infused product, 3 ounces of dried cannabis, 216 ounces of cannabis-infused liquids, or 21 grams of cannabis concentrate</p> <p><i>Consumption:</i> Public consumption prohibited</p>	<p><i>Age for legal consumption:</i> 21</p> <p><i>Where can you consume:</i> Illegal in public places other than licensed premises.</p> <p><i>When can you consume:</i> Licensed premises between 6am-2am all days.</p> <p><i>DUI definition:</i> Maximum blood alcohol level 0.08%; 0.04% for commercial vehicle drives; and, 0.02% for minors (under 21).</p>	<p><i>Age for legal consumption:</i> 18</p> <p><i>Where can you consume:</i> Designated areas excluding all bars, restaurants, non-tribal casinos, private residences used to provide childcare, foster care, adult care, or similar social services, and at least 75% of sleeping quarters within a hotel. Also excludes within 25 feet of enclosed prohibited areas.</p>
<b>Economic Regulation</b>	<p><i>Taxation rate:</i> 37% tax at the point of sale</p>	<p><i>Taxation:</i> Subject to retail sales tax, which is 6.5%</p>	<p><i>Taxation:</i> Beer tax high rate (producers): \$8.08/barrel; low tax rate \$4.782 per barrel.</p> <p>Beer and Wine Tax (consumers): 9.5% state and local sales tax. Table wine 22.67 cents per liter</p> <p>Spirits (for consumers): 20.5%</p> <p>Spirits (for retailers): 13.7%</p>	<p>Taxation: Cigarette tax rate of \$30.25 for a carton of cigarettes. In addition to cigarette tax, cigarettes are also subjective to sales or use tax.</p>
<b>Washington D.C.</b>				
<b>Regulation of Sales</b>	<p><i>Control over sale:</i> Sale of cannabis is prohibited at this time</p>	<p><i>Control over sale:</i> Must be from non-governmental, not-for-profit corporations</p>	<p>Control over production: Alcoholic Beverage Regulation Administration</p>	<p><i>Control over sale:</i> Department of Health</p>

	<p><i>Control over growing:</i> 6 plants/household for personal use (Note: residents growing in federal housing projects may be subject to prosecution under federal law)</p> <p><i>Retail licensing:</i> N/A</p> <p><i>Number of licensed retailers:</i> N/A</p> <p><i>Number of licensed cultivators:</i> N/A</p> <p><i>Production estimates:</i> N/A</p> <p><i>Sales over time:</i> N/A</p>	<p><i>Control over growing:</i> Home cultivation not permitted</p> <p><i>Patient requirements:</i> Diagnosis with a debilitating condition, as recommended by a licensed physician practicing in D.C.</p> <p><i>Physician restrictions:</i> N/A</p>	<p>Retail licensing: Issued by the Alcoholic Beverage Regulation Administration</p>	<p><i>Control over production:</i> Department of Health</p> <p><i>Retail licensing:</i> Administered by the Department of Consumer and Regulatory Affairs, for the sale of cigarettes to consumers in original packages from a place of business.</p>
<b>Regulation of Use</b>	<p><i>Age for legal consumption:</i> 21+</p> <p><i>Amount allowed:</i> No more than two ounces at one time</p> <p><i>Consumption:</i> Public consumption prohibited; but consumption in private events and clubs would be permitted</p> <p><i>DUI definition:</i> Impairment of the slightest degree will qualify an individual as being impaired under the law, determined using field sobriety tests</p>	<p><i>Patient age:</i> Any age, patients under 18 must have written consent from a parent or guardian that they understand the medical conditions, risk for use, and consent to the use of cannabis as treatment for the medical condition</p> <p><i>Amount allowed:</i> No more than two ounces at one time</p> <p><i>Consumption:</i> Public consumption prohibited, consumption on federal land prohibited under federal law</p>	<p><i>Age for legal consumption:</i> 21</p> <p><i>Where can you consume:</i> Illegal in public places other than licensed premises.</p> <p><i>When can you consume:</i> Liquor can be served by a licensed business from 8am–2am on Monday - Thursday, from 8am to 3am on Friday and Saturday and 10am–2am on Sundays. The day before a federal holiday, alcohol may be served from 8am–3am. On January 1 (New Year's Eve), liquor may be served from 8am–4am. Off-premises retailers, such as grocery and other stores, may sell liquor from 9am–10pm daily.</p> <p><i>DUI definition:</i> BAC 0.07% or lower.</p> <p><i>Control over sale:</i> Alcoholic Beverage Regulation Administration</p>	<p><i>Age for legal consumption:</i> 18</p> <p><i>Where can you consume:</i> Retail tobacco stores, tobacco bars, outdoor area of a restaurant, club, brew pub, most hotel rooms, theatrical productions, establishments granted an “economic hardship waiver” by the mayor.</p>

<b>Economic Regulation</b>	<i>Taxation rate:</i> There is currently no tax rate as the retail sale of cannabis is prohibited in D.C. at this time	<i>Taxation:</i> No information available	<i>Taxation:</i>  Beer: \$2.79/barrel  Distilled Spirits: \$1.50/gallon  Light Wine (14% or less): \$0.30/gallon	<i>Taxation:</i> \$2.50 per pack of 20 cigarettes
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# Glossary of Terms

**Addiction** – A condition in which the body must have a drug to avoid physical and psychological withdrawal symptoms <sup>477</sup>

**Anhedonia** – Inhibited ability to experience pleasure <sup>478</sup>

**Arteritis** – Inflammation of the lining of the arteries <sup>479</sup>

**Cannabidiol (CBD)** – One of over 60 cannabinoids found in cannabis; CBD is a non-psychoactive substance <sup>480</sup>

**Cannabinoids** – a group of compounds produced by the cannabis plant <sup>481</sup>

**Cannabis** – a preparation made from the plant Cannabis sativa L which contains tetrahydrocannabinol, the primary cannabinoid responsible for psychoactive effects. Cannabis is used to refer to the plant as a whole <sup>482</sup>

**Gastroschisis** – A birth defect where a baby’s intestines are outside of the body due to a hole near the belly button <sup>483</sup>

**Marijuana** - preparation made from the plant Cannabis sativa L which contains tetrahydrocannabinol, the primary cannabinoid responsible for psychoactive effects. Marijuana is used to refer to the dried leaves of the cannabis plant <sup>482</sup>

**Metabolites** – Intermediary products of metabolic reactions <sup>484</sup>

**Second-hand smoke** – Smoke that has been exhaled from a person smoking a marijuana product, or tobacco product <sup>485</sup>

**Drug Dependence** – A state in which an organism functions normally only in the presence of a drug; manifested as a physical disturbance when the drug is removed (withdrawal) <sup>486</sup>

**THC** – Present in cannabis, this cannabinoid is responsible for psychoactive effects <sup>487</sup>

**Third-hand smoke** – Residue of smoke that remains after a burning tobacco or marijuana product has been extinguished <sup>488</sup>

**Ventricular septal defect** – A birth defect, where a hole is present in the heart which allows blood to pass between the right and left sides of the heart, and causes the heart to work harder <sup>489</sup>

**White matter** – Comprised of axons, it connects neurons in different brain regions into circuits <sup>490</sup>

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Appendix 1

Table 1: Cannabis use in Canada and across provinces by social variables (CADUMS 2012 survey data)

Variable		Canada	AB	BC	SK	MB	ON	QC	Mariti mes
Total Past 12 Month Use Prevalence		10%	11%	14%	10%	13%	9%	9%	11%
Sex	Male	14%	16%	19%	14%	15%	11%	13%	15%
	Female	7%	7%	9%	6%	11%	7%	6%	6%
Age	15-17	15%	19%	23%	18%	39%	2%	21%	25%
	18-24	22%	29%	19%	23%	30%	18%	27%	22%
	25-34	19%	11%	25%	14%	23%	20%	28%	17%
	35-64	7%	10%	12%	8%	7%	7%	4%	9%
	65+	1%	0%	3%	2%	2%	2%	0%	1%
Cultural/Rac ial Background	Caucasian	11%	12%	16%	93%	11%	10%	9%	10%
	Other (Single Background)	6%	11%	5%	16%	21%	3%	7%	17%
	Multiple	12%	0%	9%	18%	33%	9%	24%	11%
Aboriginal Status	Aboriginal	22%	16%	24%	25%	42%	0%	20%	17%
	Non-aboriginal	10%	11%	14%	9%	11%	9%	9%	10%
Educational Attainment	Less than high school	12%	12%	22%	13%	18%	7%	11%	12%
	Completed high school	11%	10%	16%	16%	15%	10%	11%	12%
	Some post- secondary	12%	12%	16%	8%	12%	11%	12%	9%
	University degree	7%	11%	7%	5%	10%	7%	2%	9%
Income	Less than \$30,000	11%	9%	15%	5%	12%	13%	8%	9%
	\$30,000-49,000	8%	17%	14%	10%	9%	8%	3%	8%
	\$50,000-79,000	13%	13%	12%	9%	20%	18%	8%	13%
	Over \$80,000	11%	12%	14%	14%	14%	8%	14%	11%
Employment Status	Full-time	11%	12%	14%	12%	13%	10%	9%	12%
	Part-time	15%	25%	18%	14%	14%	9%	21%	11%
	Unemployed	15%	16%	26%	12%	20%	13%	12%	18%
	Retired	2%	1%	5%	1%	4%	3%	0%	2%
	Homemaker	2%	5%	5%	7%	16%	0%	0%	3%
	Student	17%	15%	18%	16%	30%	12%	21%	20%
	Self-employed	14%	7%	21%	12%	4%	15%	13%	18%
	Other	15%	11%	23%	11%	31%	16%	9%	14%
Marital Status	Married/ Common-law	8%	9%	12%	6%	7%	7%	6%	7%
	Divorced/Separat ed	11%	13%	16%	17%	14%	14%	3%	9%
	Widowed	1%	1%	2%	2%	8%	0%	0%	1%
	Never married	19%	21%	21%	21%	29%	15%	20%	22%

Appendix 2

Figure 1. Flow Chart for health effects and harms systematic review



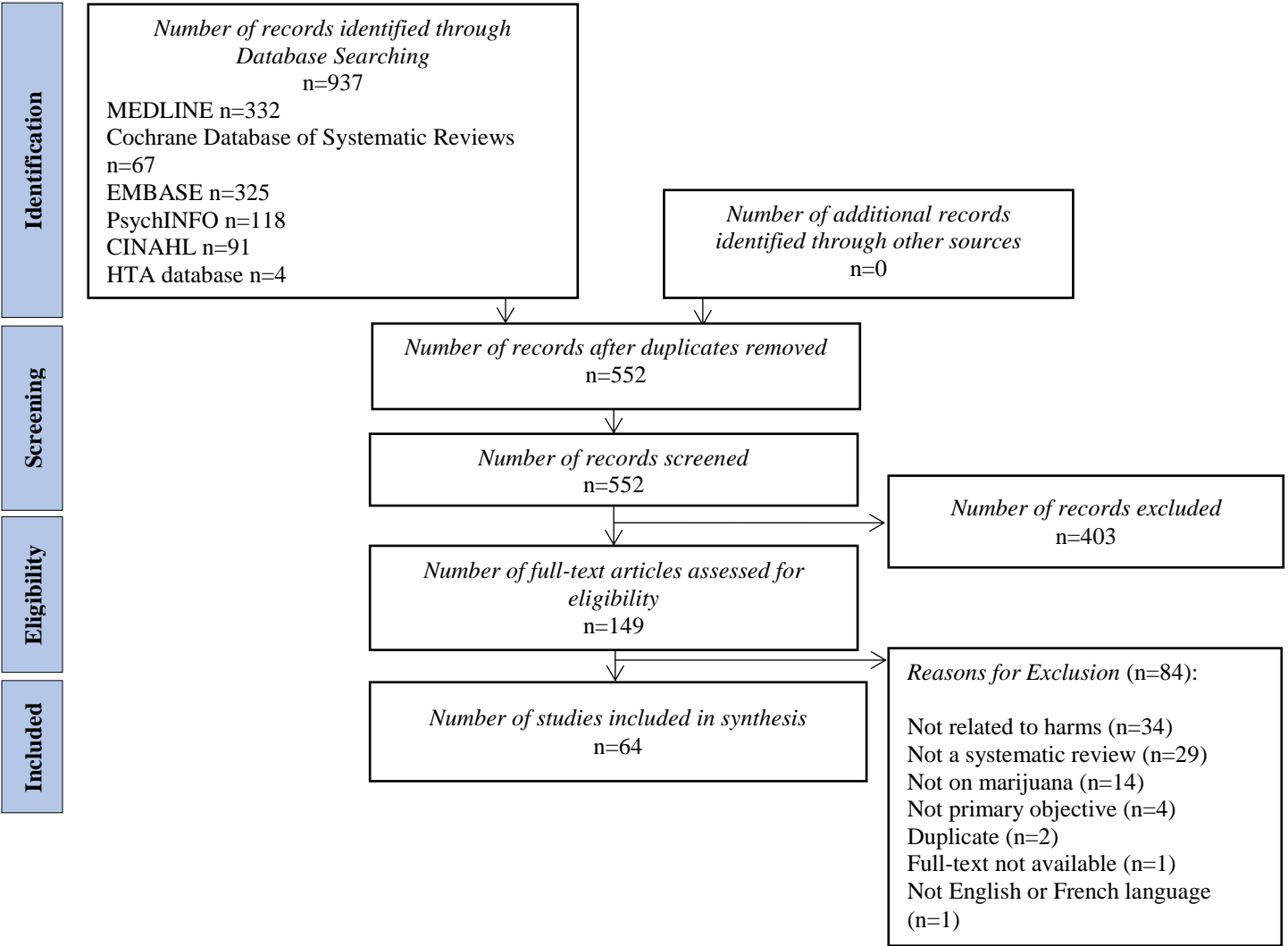


Table 1. Health effects and harms systematic review

Changes to the Brain					
Author, Year of Publication, Country	PICO	Search strategy	Studies included	Key outcomes	Quality Assessment
Arnone, 2006, United Kingdom	<i>Population:</i> general population <i>Intervention:</i> illicit substance use <i>Comparator:</i> healthy, matched controls <i>Outcome:</i> mean diffusivity, fractional anisotropy, and intervoxel coherence changes in the corpus callosum (measures of structural damage)	<i>Databases searched:</i> BNI, CancerLit, Cochrane Library, EMBASE, Medline, PsychInfo, PubMed <i>Years searched:</i> introduction of DTI until July 2006 <i>Key words used:</i> diffusion tensor imaging, magnetic resonance imaging, DTI, RMI, alcoholism, marijuana, cannabis, cocaine, ecstasy, MDMA, methamphetamine, substance misuse <i>Inclusion criteria:</i> original data; studies that addressed the question “use of DTI in substance misuse” <i>Exclusion criteria:</i> studies that did not report significant results; studies that examine areas other than the corpus callosum	<i>Number of citations identified in Search:</i> not reported  <i>Number of studies included:</i> 9  <i>Number of patients in all included studies:</i> 19	<ul style="list-style-type: none"><li>No difference in the structural integrity of cannabis users compared to non-users</li><li>Confounders not controlled for in either study</li></ul>	2/11
Batalla, 2013, Spain	<i>Population:</i> chronic adult and adolescent users <i>Intervention:</i> cannabis use <i>Comparator:</i> non-users <i>Outcome:</i> brain structure and function	<i>Databases searched:</i> EMBASE, Medline, PubMed, LILACS <i>Years searched:</i> inception until August 2012 <i>Key words used:</i> cannabis, marijuana, marihuana, delta-9-tetrahydrocannabinol, THC, cannabidiol, CBD, neuroimaging, brain imaging, computerized tomography, CT, magnetic resonance, MRI, single photon emission tomography, SPECT, functional magnetic resonance, fMRI, positron emission tomography, PET, diffusion tensor MRI, DTI-MRI, spectroscopy, MRS <i>Inclusion criteria:</i> use of structural or functional neuroimaging techniques involving chronic cannabis users; inclusion of a control group of healthy volunteers matched by age, gender, and handedness; and users that were abstinent for at least 12 hours before brain scanning <i>Exclusion criteria:</i> non-neuroimaging studies of cannabis use; neuroimaging studies that involved participants who had other neurological or psychiatric disorders, or individuals who met criteria for alcohol dependence or other substance use disorders; neuroimaging studies with recreational or naïve cannabis users	<i>Number of citations identified in Search:</i> 142  <i>Number of studies included:</i> 43  <i>Number of patients in all included studies:</i> 711	<i>Structural</i> <ul style="list-style-type: none"><li>In adults - reduced hippocampal volume and white matter integrity in chronic users, often persisting after abstinence</li><li>In adults - changes also described in amygdala, cerebellum, and frontal cortex of chronic users</li><li>Adolescent results inconclusive</li></ul> <i>Functional</i> <ul style="list-style-type: none"><li>Lower resting blood flow globally, and in cerebellum, prefrontal cortex, and striatum</li><li>No significant difference in performance between controls and users</li></ul>	6/11
Batalla, 2014, Spain	<i>Population:</i> naïve or occasional cannabis users; animals or human <i>Intervention:</i> cannabis use <i>Comparator:</i> non-users <i>Outcome:</i> acute effects of brain functioning	<i>Databases searched:</i> EMBASE, Medline, PubMed, LILACS <i>Years searched:</i> inception until June 2012 <i>Key words used:</i> <i>for humans:</i> cannabis, marijuana, delta-9-tetrahydrocannabinol, THC, cannabidiol, CBD, cannabinoid, neuroimaging, brain imaging, magnetic resonance, MRI, single photon emission tomography, SPECT, functional magnetic resonance, fMRI, positron emission tomography, PET, spectroscopy, MRS; <i>for animals:</i> animal, rat, cannabis, marijuana, delta-9-tetrahydrocannabinol, THC, cannabidiol, CBD, cannabinoid, cerebral blood flow, cerebral glucose utilization, microdialysis, electrophysiological, dopamine release, single photon emission tomography, SPECT, positron emission tomography, PET <i>Inclusion criteria:</i> use of functional neuroimaging techniques involving animals naïve to cannabinoids or naïve/occasional users; acute experimental administration of cannabinoids; same gender, age, handedness in all subjects; in vivo studies involving cannabinoid effects on blood flow, cerebral metabolism, or dopamine release <i>Exclusion criteria:</i> non-neuroimaging studies of experimental administration of cannabinoids; neuroimaging studies that involved participants who had other neurological or psychiatric disorders, or individuals with substance abuse disorders; neuroimaging studies with chronic cannabis users; in vitro	<i>Number of citations identified in Search:</i> 224  <i>Number of studies included:</i> 45  <i>Number of patients in all included studies:</i> 889	<ul style="list-style-type: none"><li>Increased cerebral blood flow to prefrontal, insular, cerebellar, and anterior cingulate regions; associated with depersonalization and increase anxiety</li><li>THC influenced learning, memory, and affect; CBD seems to have the opposite effect</li></ul>	5/11

		experiments; chronic or combined drug administration; anesthetized animals during the experimental procedure			
Colizzi, 2016, United Kingdom	<p><i>Population:</i> general human population and animals</p> <p><i>Intervention:</i> cannabis and delta-9-tetrahydrocannabinol exposure</p> <p><i>Comparator:</i> non-users</p> <p><i>Outcome:</i> glutamate functioning</p>	<p><i>Databases searched:</i> Medline, EMBASE, PsychInfo</p> <p><i>Years searched:</i> inception until October 29<sup>th</sup>, 2015</p> <p><i>Key words used:</i> cannabis, delta-9-tetrahydrocannabinol, marijuana, marihuana, tetrahydrocannabinol, dronabinol, glu*, glutamate(s), glutamine, glutamic acid</p> <p><i>Inclusion criteria:</i> human or animal studies; studies investigating the acute and/or long-term effects of cannabis use/administration or delta-9-tetrahydrocannabinol use/administration; studies measuring molecular markers related to glutamate neurotransmission including glutamate metabolites, synaptic transmission, enzyme activity, neurotransmitter release and uptake, transporters, receptors, brain neurotransmitter levels</p> <p><i>Exclusion criteria:</i> studies where cannabis or delta-9-tetrahydrocannabinol were not the intervention or exposure of interest; studies in which the neurochemical outcomes were not directly reported upon</p>	<p><i>Number of citations identified in Search:</i> 268</p> <p><i>Number of studies included:</i> 41 (5 human, 36 animal)</p> <p><i>Number of patients in all included studies:</i> 239 humans, animal not reported</p>	<ul style="list-style-type: none"> <li>Chronic cannabis use associated with decreased levels of glutamate in the cortical and subcortical areas, especially in females</li> <li>Delta-9-tetrahydrocannabinol affects glutamate release and reuptake and reduces the inhibition of glutamate</li> </ul>	7/11
Cookey, 2014, Canada	<p><i>Population:</i> cannabis users and non-users</p> <p><i>Intervention:</i> cannabis use</p> <p><i>Comparator:</i> early-phase schizophrenia without cannabis use vs. cannabis use without schizophrenia vs. concurrent cannabis use and schizophrenia</p> <p><i>Outcome:</i> white matter tissue</p>	<p><i>Databases searched:</i> Medline, EMBASE, Cochrane, PsychInfo</p> <p><i>Years searched:</i> 1994 until November 2013</p> <p><i>Key words used:</i> schizophrenia, diffusion tensor imaging, humans, cannabis or marijuana smoking, diffusion, tensor, imaging, diffusion tensor imaging, early onset, first episode, cannabis, marijuana</p> <p><i>Inclusion criteria:</i> English language; assess early phase schizophrenia relative to healthy controls; report diffusion tensor imaging, fractional anisotropy values</p> <p><i>Exclusion criteria:</i> multiple illicit drug use or heavy alcohol use; sample sizes smaller than 20</p>	<p><i>Number of citations identified in Search:</i> 65</p> <p><i>Number of studies included:</i> 18</p> <p><i>Number of patients in all included studies:</i> 725</p>	<ul style="list-style-type: none"> <li>Decreased white matter in early-phase schizophrenia without cannabis use</li> <li>Cannabis use caused additional white matter disruption, especially in adolescence</li> </ul>	5/11
James, 2013, United Kingdom	<p><i>Population:</i> adolescent cannabis users</p> <p><i>Intervention:</i> cannabis use</p> <p><i>Comparator:</i> non-users</p> <p><i>Outcome:</i> brain structure and function</p>	<p><i>Databases searched:</i> EMBASE, Medline, PubMed, PsychLIT, LILACS</p> <p><i>Years searched:</i> inception until December 2012</p> <p><i>Key words used:</i> marijuana, cannabis, delta-9-tetrahydro- cannabinol, THC, cannabidiol, CBD, neuroimaging, brain imaging, computerized tomography, CT, magnetic resonance, MRI, single photon emission tomography, SPECT, functional magnetic resonance, fMRI, positron emission tomography, PET, diffusion tensor MRI, DTI- MRI, spectroscopy, MRS.</p> <p><i>Inclusion criteria:</i> case-control design; healthy controls; participants under 19</p> <p><i>Exclusion criteria:</i> non-neuroimaging studies of cannabis use; participants older than 19; subjects with other neurological or psychiatric disorders or other substance abuse disorders</p>	<p><i>Number of citations identified in Search:</i> 141</p> <p><i>Number of studies included:</i> 24</p> <p><i>Number of patients in all included studies:</i> 450</p>	<ul style="list-style-type: none"> <li>Cannabis use associated with memory disruptions, loss of IQ, loss of inhibition, and more compensatory brain activity in adolescents</li> <li>May be associated with adolescent-onset schizophrenia due to loss of grey and white matter, but minimal evidence exists</li> </ul>	5/11
Lorenzetti, 2010, Australia	<p><i>Population:</i> chronic cannabis users</p> <p><i>Intervention:</i> chronic cannabis use</p> <p><i>Comparator:</i> non-users</p> <p><i>Outcome:</i> brain changes and psychopathological symptoms</p>	<p><i>Databases searched:</i> PubMed</p> <p><i>Years searched:</i> not reported</p> <p><i>Key words used:</i> cannabis or marijuana, MRI, computed tomography, or neuroimaging</p> <p><i>Inclusion criteria:</i> use of structural neuroimaging techniques; cannabis as the principal drug of abuse</p> <p><i>Exclusion criteria:</i> samples with any major psychopathologies; not empirical studies (review articles, case studies)</p>	<p><i>Number of citations identified in Search:</i> 154</p> <p><i>Number of studies included:</i> 13</p> <p><i>Number of patients in all included studies:</i> 285</p>	<ul style="list-style-type: none"> <li>Inconsistent findings, but abnormalities identified in the hippocampus, parahippocampus, and amygdala</li> <li>Often related to high frequency and long-term use and more likely in adolescent users</li> </ul>	3/11

Malchow, 2013, Germany	<p><i>Population:</i> schizophrenia patients</p> <p><i>Intervention:</i> cannabis use</p> <p><i>Comparator:</i> non-users</p> <p><i>Outcome:</i> brain morphology</p>	<p><i>Databases searched:</i> PubMed, We of Knowledge</p> <p><i>Years searched:</i> inception until 2012</p> <p><i>Key words used:</i> schizophrenia, psychosis, sMRI, structural imaging, cannabis, marijuana, marihuana, tetrahydrocannabinol</p> <p><i>Inclusion criteria:</i> humans; English language; neuroimaging studies examining brain structure</p> <p><i>Exclusion criteria:</i> not reported</p>	<p><i>Number of citations identified in Search:</i> 105</p> <p><i>Number of studies included:</i> 16</p> <p><i>Number of patients in all included studies:</i> 484</p>	<ul style="list-style-type: none"> <li>Weak evidence that chronic cannabis use may affect brain morphology in patients with schizophrenia and those at high-risk</li> <li>Inconclusive evidence that cannabis affects brain structure prior to schizophrenia or causes schizophrenia</li> </ul>	4/11
Martin-Santos, 2010, United Kingdom	<p><i>Population:</i> adult cannabis users</p> <p><i>Intervention:</i> cannabis use</p> <p><i>Comparator:</i> non-users</p> <p><i>Outcome:</i> brain structure and functioning</p>	<p><i>Databases searched:</i> EMBASE, Medline, PubMed, LILACS, PsychLIT, books on substance abuse neuroimaging</p> <p><i>Years searched:</i> inception until January 2009</p> <p><i>Key words used:</i> marijuana, cannabis, delta-9-tetrahydrocannabinol, THC, cannabidiol, CBD, neuroimaging, brain imaging, computerized tomography, CT, magnetic resonance, MRI, single photon emission tomography, SPECT, functional magnetic resonance, fMRI, positron emission tomography, PET, diffusion tensor MRI, DTI-MRI, spectroscopy, MRS</p> <p><i>Inclusion criteria:</i> for case-control studies: inclusion of a control group of healthy volunteers matched for age, sex, and handedness; users were abstinent for 12 hours before brain scanning; for experimental administration of cannabinoids: parallel or cross-over design; participants were abstinent for at least 1 week</p> <p><i>Exclusion criteria:</i> non-neuroimaging studies of cannabis use; neuroimaging studies involving those under 18 years of age; subjects who had other neurological or psychiatric disorders or who tested positive for drugs other than cannabis</p>	<p><i>Number of citations identified in Search:</i> 66</p> <p><i>Number of studies included:</i> 41</p> <p><i>Number of patients in all included studies:</i> 665</p>	<ul style="list-style-type: none"> <li>Lower resting global, prefrontal, and anterior cingulate cortex blood flow in cannabis users, related to impairments in time estimation, attention, working memory, cognitive flexibility, decision making and psychomotor speed</li> <li>Impaired cognitive efficiency in cannabis users compared to controls</li> <li>Changes in volume only related to chronic users</li> </ul>	5/11
Quickfall, 2006, Canada	<p><i>Population:</i> cannabis users</p> <p><i>Intervention:</i> cannabis use</p> <p><i>Comparator:</i> non-users</p> <p><i>Outcome:</i> brain structure and functioning</p>	<p><i>Databases searched:</i> Medline</p> <p><i>Years searched:</i> 1966 until February 2005</p> <p><i>Key words used:</i> cannabis, marijuana, or tetrahydrocannabinol, and computed tomography, MRI, functional MRI, single photon emission computed tomography, positron emission tomography, cerebral blood flow, or neuroimaging</p> <p><i>Inclusion criteria:</i> published in peer-reviewed journals; focus on users who were directly exposed to cannabis; employed anatomical structural or functional neuroimaging techniques</p> <p><i>Exclusion criteria:</i> animal studies; single case reports</p>	<p><i>Number of citations identified in Search:</i> 112</p> <p><i>Number of studies included:</i> 30</p> <p><i>Number of patients in all included studies:</i> 655</p>	<ul style="list-style-type: none"> <li>Smoked and infused cannabis increased global cortical activity, especially in chronic users</li> <li>Acute and chronic exposure were associated with increased activity during exposure and decreased activity during abstinence in the frontal, limbic, and cerebellar regions</li> <li>Conflicting results of the effect on the temporal lobe</li> </ul>	3/11
Rapp, 2012, Switzerland	<p><i>Population:</i> cannabis users with psychosis or at high-risk or genetic risk of psychosis</p> <p><i>Intervention:</i> cannabis uses</p> <p><i>Comparator:</i> healthy, non-users</p> <p><i>Outcome:</i> brain structure</p>	<p><i>Databases searched:</i> ISI Web of Knowledge, PubMed</p> <p><i>Years searched:</i> inception until November 2011</p> <p><i>Key words used:</i> psychosis, schizophrenia, first episode, at-risk mental state, high risk, and cannabis, marijuana, delta-9-tetrahydrocannabinol, and brain structure, neuroimaging, brain imaging, brain abnormalities, magnetic resonance, diffusion sensor MRI, post mortem, quantitative autoradiography, radiology and binding, in situ hybridization</p> <p><i>Inclusion criteria:</i> original publication in a peer reviewed journal; studying the brain of psychosis patients or individuals at risk for psychosis or individuals at genetic risk for psychosis in relation to cannabis use applying in vivo structural neuroimaging or post mortem autoradiography or in situ</p>	<p><i>Number of citations identified in Search:</i> 33</p> <p><i>Number of studies included:</i> 19</p> <p><i>Number of patients in all included studies:</i> 350</p>	<ul style="list-style-type: none"> <li>Cannabis use associated with decreased activity globally and in the cingulum, dorsolateral prefrontal cortex, and cerebellum in users with or at high risk of psychosis compared to healthy non users</li> <li>Post mortem results and studies examining white matter changes were inconclusive</li> </ul>	7/11

		hybridization techniques; included both cannabis smokers and non-smokers; described specific effects of cannabis on brain if subjects had a general substance abuse or substance dependence disorder diagnosis  <i>Exclusion criteria:</i> functional brain imaging studies			
Rocchetti, 2013, United Kingdom	<i>Population:</i> non-psychotic cannabis users  <i>Intervention:</i> cannabis use  <i>Comparator:</i> non-users  <i>Outcome:</i> brain structure	<i>Databases searched:</i> Web of Knowledge (Medline, Web of Science)  <i>Years searched:</i> inception to February 2013  <i>Key words used:</i> MRI, DTI, VBM, cannabis, neuroimaging, structural, grey matter, white matter  <i>Inclusion criteria:</i> original paper or short communication in a peer-reviewed journal; recruited cannabis-user subjects without a diagnosis of psychosis and matched controls; employed structural imaging techniques; reported sufficient data to allow meta-analytical computations  <i>Exclusion criteria:</i> subjects with a diagnosis of a psychotic disorder; overlapping samples; systematic or critical reviews; did not report enough data to be included in the meta-analysis	<i>Number of citations identified in Search:</i> not reported  <i>Number of studies included:</i> 14  <i>Number of patients in all included studies:</i> 362	<ul style="list-style-type: none"><li>• No statistically significant differences in whole brain volume between users and non-users</li><li>• Significantly decreased hippocampal volume in users</li><li>• Inconsistent results on amygdala volume due to publication bias</li></ul>	8/11
Sami, 2015, United Kingdom	<i>Population:</i> cannabis users  <i>Intervention:</i> cannabis use  <i>Comparator:</i> non-users  <i>Outcome:</i> dopamine functioning	<i>Databases searched:</i> Medline, EMBASE, PsychInfo  <i>Years searched:</i> inception until July 2014  <i>Key words used:</i> cannabidiol, cannabinoid, cannabis, CBD, THC, hashish, marijuana, tetrahydrocannabinol, endocannabinoid, dopa*, dopamine, PHNO, raclopride, fallypride, iodobenzamide, IBZM, FMT, PE21, CIT, NNC112, SCH23390, D1, D2, D3, DAT, AADC, MAO  <i>Inclusion criteria:</i> human studies; investigating acute and long-term effects of cannabinoid administration; measuring molecular markers related to dopaminergic neurotransmission including biomarkers in peripheral blood, in vivo imaging, or post mortem brain tissue  <i>Exclusion criteria:</i> studies where cannabinoid administration was not the intervention or exposure of interest; or where neurochemical outcomes were not directly reported on	<i>Number of citations identified in Search:</i> 2796  <i>Number of studies included:</i> 25  <i>Number of patients in all included studies:</i> 244	<ul style="list-style-type: none"><li>• Minimal evidence, but acute cannabis use is weakly associated with increased peripheral and striatal dopamine and decreased neocortical dopamine</li><li>• Similar results for chronic users</li><li>• Larger effects in those at genetically predisposed to or at clinical high risk of psychosis</li></ul>	6/11
Sneider, 2014, United States	<i>Population:</i> cannabis users  <i>Intervention:</i> cannabis use  <i>Comparator:</i> non-users  <i>Outcome:</i> changes in brain chemistry	<i>Databases searched:</i> PubMed, EMBASE  <i>Years searched:</i> not reported  <i>Key words used:</i> marijuana, cannabis, MRS, MRSI, proton MRS  <i>Inclusion criteria:</i> not reported  <i>Exclusion criteria:</i> neuroimaging other than MRS (MRI, CT, PET, DTI, fMRI, CBF, CBV)	<i>Number of citations identified in Search:</i> not reported  <i>Number of studies included:</i> 8  <i>Number of patients in all included studies:</i> 140	<ul style="list-style-type: none"><li>• Cannabis use associated with lower levels of N-acetyl-aspartate, myo-inositol, and choline, which are associated with lower cognitive efficiency and impulse control</li><li>• Associated with alterations in GABA levels in the frontal lobe</li></ul>	1/11
Wrege, 2014, Switzerland	<i>Population:</i> general population  <i>Intervention:</i> acute or chronic cannabis use  <i>Comparator:</i> no cannabis use  <i>Outcome:</i> impulsivity and neuroimaging	<i>Databases searched:</i> PubMed  <i>Years searched:</i> inception until 2012  <i>Key words used:</i> cannabis, cannabinoid, THC, marihuana, marijuana, impulsivity, motor control, motor inhibition, disinhibition  <i>Inclusion criteria:</i> English German or Spanish; parallel, crossover or case-control design with control group; include impulsivity measure  <i>Exclusion criteria:</i> psychiatric or neurological disorder	<i>Number of citations identified in Search:</i> 774  <i>Number of studies included:</i> 13  <i>Number of patients in all included studies:</i> 223	<ul style="list-style-type: none"><li>• Prefrontal blood flow was lower in chronic cannabis users</li><li>• Studies found increased brain metabolism during cannabis use</li><li>• Structural changes such as reduced prefrontal volume and white matter integrity differed between cannabis users in individuals who had not used cannabis</li><li>• Brain structure alterations were stronger in those who used cannabis before 16 years old</li></ul>	6/11
Cancer					
Author, Year of Publication,	PICO	Search strategy	Studies included	Key outcomes	Quality Assessment

Country					
De Carvalho, 2015, Brazil	Population: adult cannabis users  Intervention: cannabis use  Comparator: non-users  Outcome: head and neck cancer	Databases searched: the Cochrane library, PubMed, LILACS, EMBASE, BBO, Bireme SciELO  Years searched: inception to July 2015  Key words used: hashish, marijuana, bhang, ganja, hemp, C. sativa, oral, oropharyngeal, nasopharyngeal, head and neck neoplasms, neoplasm neck, cancer of the head and neck, head and neck cancer, head cancer, neck cancer, aerodigestive tract neoplasms upper, upper aerodigestive tract neoplasms  Inclusion criteria: case-control studies, cohort, or systematic reviews; allocation criteria defined for cases and controls; cases with definitive diagnosis of head and neck cancer; matched controls by at least gender  Exclusion criteria: technical articles; reports or case reports; opinion articles; review articles	Number of citations identified in Search: 3558  Number of studies included: 6  Number of patients in all included studies: 907	<ul style="list-style-type: none"><li>No association between lifetime cannabis use and risk of head and neck cancer (OR = 1.021, 95% CI = 0.912-1.143)</li></ul>	9/11
Gurney, 2015, New Zealand	Population: adult cannabis users  Intervention: cannabis use  Comparator: non-users  Outcome: testicular cancer	Databases searched: CINAHL, Cochrane library, EMBASE, Medline, ProQuest Central, ProQuest Dissertations and Theses, Scopus, Web of Science  Years searched: January 1980 until May 2015  Key words used: cannabi*, marijuana, marihuana, THC, tetrahydrocannabinol, cancer of the testi*, seminoma*, testi* cancer, testi* carcinoma, testi* germ cell tumo(u)r, testi* neoplasm, testi* tumo(u)r  Inclusion criteria: reported association between cannabis and testicular cancer; data provided were summary associations  Exclusion criteria: not reported	Number of citations identified in Search: 149  Number of studies included: 3  Number of patients in all included studies: 719	<ul style="list-style-type: none"><li>Current cannabis use, using cannabis on a weekly basis, and chronic use associated with testicular germ cell tumors</li><li>Current cannabis use: OR = 1.62 (95% CI = 1.13-2.31)</li><li>Weekly use: OR = 1.92 (95% CI = 1.35-2.72)</li><li>Chronic use (more than 10 years): OR = 1.50 (95% CI = 1.08-2.09)</li></ul>	8/11
Huang, 2015, United States	Population: cannabis users  Intervention: cannabis use  Comparator: non-users  Outcome: any cancer	Databases searched: PubMed, Medline  Years searched: inception until August 2014  Key words used: marijuana, cannabis, cancer  Inclusion criteria: epidemiologic studies investigating cannabis use that provided risk estimates for cannabis exposure  Exclusion criteria: not reported	Number of citations identified in Search: not reported  Number of studies included: 34  Number of patients in all included studies: 21,138	<ul style="list-style-type: none"><li>No association with head and neck, and lung cancer</li><li>Associated with testicular cancer</li><li>Insufficient evidence for bladder, prostate, penile, cervical and childhood cancer, but small associations exist for prostate and cervical cancer</li><li>Tends to be dose-dependent</li></ul>	5/11
Mehra, 2006, United States	Population: cannabis smokers  Intervention: cannabis smoking  Comparator: non-users, tobacco-only smokers  Outcome: lung cancer, changes to the lung that could lead to cancer, inhaled tar exposure	Databases searched: Medline, EMBASE, Psychlit  Years searched: 1966 until October 2005  Key words used: cannabis, cannabinoids, marijuana abuse, marijuana smoking, marijuana usage, neoplasms, carcinoma, pathology, smoking/pathology, tars/respiratory tract diseases, respiratory physiology, lung, respiratory tract tumor, respiratory tract infections, respiratory system  Inclusion criteria: adults (18+); humans  Exclusion criteria: letters, reviews, case series involving fewer than 10 patients; studies not involving humans or intentional smoking or lung conditions	Number of citations identified in Search: 186  Number of studies included: 19  Number of patients in all included studies: 66,349 (only the number of male participants reported)	<ul style="list-style-type: none"><li>Cannabis smoking associated with more inhaled tar exposure than tobacco smoking</li><li>More pathological lung changes in cannabis smokers compared to tobacco smokers</li><li>No association with cannabis smoking and lung cancer, despite more tar and pathological changes</li></ul>	8/11
Health Effects					
Author, Year of Publication, Country	PICO	Search strategy	Studies included	Key outcomes	Quality Assessment

Calabria, 2010, Australia	<p><i>Population:</i> cannabis users</p> <p><i>Intervention:</i> cannabis exposure</p> <p><i>Comparator:</i> general population</p> <p><i>Outcome:</i> overall mortality</p>	<p><i>Databases searched:</i> Medline, EMBASE, PsychInfo</p> <p><i>Years searched:</i> January 1990 until January 2008</p> <p><i>Key words used:</i> cannabis, mortality, cohort, drug use</p> <p><i>Inclusion criteria:</i> human studies; mortality associated with cannabis use or dependence</p> <p><i>Exclusion criteria:</i> not focused on cannabis or mortality; review articles and case series</p>	<p><i>Number of citations identified in Search:</i> not reported</p> <p><i>Number of studies included:</i> 19</p> <p><i>Number of patients in all included studies:</i> 387,635 (cannabis use not reported)</p>	<ul style="list-style-type: none"> <li>Insufficient data to determine all-cause mortality is higher in users compared to the general population</li> <li>Heavy cannabis use associated with increased risk of poor driving</li> <li>Cannabis use associated with suicide, but minimal evidence</li> </ul>	5/11
Grotenhermen, 2010, Germany	<p><i>Population:</i> cannabis users</p> <p><i>Intervention:</i> cannabis use</p> <p><i>Comparator:</i> non-users</p> <p><i>Outcome:</i> arteritis</p>	<p><i>Databases searched:</i> PubMed, EMBASE, Web of Science</p> <p><i>Years searched:</i> inception until February 2009</p> <p><i>Key words used:</i> cannabi*, marijuana, THC, arteritis, thromboangiitis obliterans, Buerger's disease</p> <p><i>Inclusion criteria:</i> case reports, reviews, commentaries; cannabis arteritis; TAO mentioning cannabis, cannabis, cannabinoids, or THC</p> <p><i>Exclusion criteria:</i> not reported</p>	<p><i>Number of citations identified in Search:</i> not reported</p> <p><i>Number of studies included:</i> 17</p> <p><i>Number of patients in all included studies:</i> 94</p>	<ul style="list-style-type: none"> <li>Most studies had concurrent tobacco and cannabis use, so little association was found for just cannabis and arteritis</li> </ul>	4/11
Hackam, 2015, Canada	<p><i>Population:</i> cannabis users</p> <p><i>Intervention:</i> cannabis exposure</p> <p><i>Comparator:</i> non-users</p> <p><i>Outcome:</i> stroke</p>	<p><i>Databases searched:</i> Medline, EMBASE</p> <p><i>Years searched:</i> inception until November 30<sup>th</sup>, 2014</p> <p><i>Key words used:</i> cannabis, cerebrovascular disease</p> <p><i>Inclusion criteria:</i> case studies; cases underwent parenchymal imaging; humans</p> <p><i>Exclusion criteria:</i> not reported</p>	<p><i>Number of citations identified in Search:</i> 989</p> <p><i>Number of studies included:</i> 34</p> <p><i>Number of patients in all included studies:</i> 64</p>	<ul style="list-style-type: none"> <li>Cannabis exposure associated with increased risk of stroke</li> </ul>	5/11
Korantzopolous, 2008, Greece	<p><i>Population:</i> cannabis smokers</p> <p><i>Intervention:</i> cannabis smoking</p> <p><i>Comparator:</i> non-smokers</p> <p><i>Outcome:</i> atrial fibrillation</p>	<p><i>Databases searched:</i> Medline, EMBASE</p> <p><i>Years searched:</i> inception until January 2007</p> <p><i>Key words used:</i> marijuana, hashish, cannabis, atrial fibrillation, arrhythmias, tachycardia, palpitations, heart, cardiovascular</p> <p><i>Inclusion criteria:</i> not reported</p> <p><i>Exclusion criteria:</i> not reported</p>	<p><i>Number of citations identified in Search:</i> not reported</p> <p><i>Number of studies included:</i> 6</p> <p><i>Number of patients in all included studies:</i> 6</p>	<ul style="list-style-type: none"> <li>Cannabis smoking associated with atrial fibrillation, but minimal evidence exists</li> </ul>	4/11
Lindsey, 2012, United States	<p><i>Population:</i> illicit drug users</p> <p><i>Intervention:</i> illicit and prescription drug exposure</p> <p><i>Comparator:</i> illicit drugs with no concurrent prescription drugs</p> <p><i>Outcome:</i> cross-interactions of substances</p>	<p><i>Databases searched:</i> Medline, Iowa Drug Information Service, Google Scholar, International Pharmaceutical Abstracts, EBSCO Academic Search Premier</p> <p><i>Years searched:</i> inception to March 2011</p> <p><i>Key words used:</i> cocaine, marijuana, cannabis, methamphetamine, amphetamine, ecstasy, <i>N</i>-methyl-3,4-methylenedioxymethamphetamine, methylenedioxymethamphetamine, heroin, gamma-hydroxybutyrate, sodium oxybate, interaction(s), drug interactions, drug-drug interactions</p> <p><i>Inclusion criteria:</i> human clinical trials, case reports/reviews</p> <p><i>Exclusion criteria:</i> not reported</p>	<p><i>Number of citations identified in Search:</i> not reported</p> <p><i>Number of studies included:</i> not reported</p> <p><i>Number of patients in all included studies:</i> not reported</p>	<ul style="list-style-type: none"> <li>Cannabis may interact with tricyclic antidepressants, protease inhibitors, and warfarin therapy</li> <li>Most common side effects of interactions related to cardiac functioning</li> <li>May interact with other depressants (alcohol, barbiturates) but no clinical trials</li> </ul>	4/11

Reece, 2009, Australia	<i>Population:</i> chronic cannabis users <i>Intervention:</i> cannabis use <i>Comparator:</i> non-users, occasional users <i>Outcome:</i> psychiatric, respiratory, cardiovascular, bone, neurodevelopment, genotoxic, mutagenic, and oncogenic effects	<i>Databases searched:</i> Medline, PubMed, PsychInfo, Google Scholar, Scopus, ProQuest, Web of Knowledge, EbscoHost <i>Years searched:</i> not reported <i>Key words used:</i> cannabis, marijuana, marihuana, toxicity, complications, mechanisms <i>Inclusion criteria:</i> original data; describe mechanisms; published in “recent years” <i>Exclusion criteria:</i> not reported	<i>Number of citations identified in Search:</i> 5198 <i>Number of studies included:</i> not reported <i>Number of patients in all included studies:</i> not reported	<ul style="list-style-type: none"><li>Chronic cannabis use associated with worsening psychotic symptoms, violent suicides, higher anxiety, increased inflammation in lungs, and can cause cardiovascular issues</li><li>Heavy chronic use may be associated with bone loss and certain cancers</li></ul>	2/11
Schwitzer, 2015, France	<i>Population:</i> cannabis users <i>Intervention:</i> cannabis exposure <i>Comparator:</i> non-users <i>Outcome:</i> visual processing	<i>Databases searched:</i> PubMed, Google Scholar <i>Years searched:</i> inception until February 2014 <i>Key words used:</i> cannabis, cannabinoid, marijuana, THC, vision, visual processing, visual system, visual cortex, retinal processing, retina, thalamus <i>Inclusion criteria:</i> English language only; related to cannabis and vision <i>Exclusion criteria:</i> not reported	<i>Number of citations identified in Search:</i> not reported <i>Number of studies included:</i> not reported <i>Number of patients in all included studies:</i> not reported	<ul style="list-style-type: none"><li>Acute and regular cannabis use associated with increased visual disturbances, increased foveal glare, decreased retinal processing, reduction of visual symptoms, decreased activation in the secondary visual cortex, and decreased thalamic volume</li><li>Many effects residual</li><li>Also associated with improvement in some visual functioning, but no experimental evidence</li></ul>	4/11
Tetrault, 2007, United States	<i>Population:</i> adult cannabis smokers <i>Intervention:</i> acute and chronic cannabis exposure <i>Comparator:</i> non-users <i>Outcome:</i> airway response, pulmonary function or respiratory complications	<i>Databases searched:</i> Medline, PsychInfo, EMBASE <i>Years searched:</i> January 1966 until October 2005 <i>Key words used:</i> not reported <i>Inclusion criteria:</i> not reported <i>Exclusion criteria:</i> not humans; did not report results of respiratory complications or pulmonary functioning; case series with fewer than 10 subjects	<i>Number of citations identified in Search:</i> 965 <i>Number of studies included:</i> 34 <i>Number of patients in all included studies:</i> 14,183	<ul style="list-style-type: none"><li>Acute cannabis inhalation associated with bronchodilation, but not present in long-term smokers</li><li>Long-term smoking associated with increased respiratory complications such as cough, sputum production, and wheeze</li></ul>	8/11
Mental Illness					
Author, Year of Publication, Country	PICO	Search strategy	Studies included	Key outcomes	Quality Assessment
Ben Amar, 2007, Canada	<i>Population:</i> cannabis users <i>Intervention:</i> cannabis use <i>Comparator:</i> non-users <i>Outcome:</i> psychosis	<i>Databases searched:</i> PubMed, PsychInfo <i>Years searched:</i> January 1962 until June 2005 <i>Key words used:</i> cannabis or marijuana, schizophrenia or psychosis <i>Inclusion criteria:</i> longitudinal studies, reviews; addresses the causal nature of the cannabis/psychosis relationship <i>Exclusion criteria:</i> not reported	<i>Number of citations identified in Search:</i> 622 <i>Number of studies included:</i> 15 <i>Number of patients in all included studies:</i> 107,691	<ul style="list-style-type: none"><li>Cannabis use was associated with psychosis in those with a vulnerability to psychosis</li><li>Cannabis use associated with worsening of psychotic symptoms</li></ul>	3/11
Borges, 2016, Mexico	<i>Population:</i> cannabis users <i>Intervention:</i> cannabis use <i>Comparator:</i> non-users <i>Outcome:</i> suicidality	<i>Databases searched:</i> Medline, PsychInfo, Google Scholar, public-use databases <i>Years searched:</i> 1990(1995 for acute use) until February 2015 <i>Key words used:</i> cannabis, marijuana, marihuana, suicide, suicide attempt, suicide ideation, suicidal, suicidality <i>Inclusion criteria:</i> English language; original articles, critical review reports, public use data on cannabis use and suicidality	<i>Number of citations identified in Search:</i> not reported <i>Number of studies included:</i> not reported	<ul style="list-style-type: none"><li>Minimal evidence for acute cannabis use and suicidality</li><li>Any and heavy cannabis use associated with suicidality, but heterogeneity and publication bias high</li><li>Chronic cannabis use and death by suicide: OR = 2.56 (95% CI = 1.25-5.27)</li><li>Any cannabis use and suicidal ideation: OR = 1.43 (95% CI = 1.13-1.83)</li></ul>	5/11



		<i>Exclusion criteria:</i> synthetic cannabinoids	<i>Number of patients in all included studies:</i> not reported	<ul style="list-style-type: none"> <li>Heavy cannabis use and suicidal ideation: OR = 2.53 (95% CI = 1.00-6.39)</li> <li>Any cannabis use and suicide attempt: OR = 2.23 (95% CI = 1.24-4.00)</li> <li>Heavy cannabis use and suicide attempt: OR = 3.20 (95% CI = 1.72–5.94)</li> </ul>	
Crippa, 2009, United Kingdom	<i>Population:</i> cannabis users <i>Intervention:</i> cannabis use <i>Comparator:</i> non-users <i>Outcome:</i> anxiety	<i>Databases searched:</i> Medline, PsychLIT, EMBASE <i>Years searched:</i> inception until August 2008 <i>Key words used:</i> cannabis, marijuana, THC, tetrahydrocannabinol, delta-9-tetrahydrocannabinol, cannabinoids, anxiety, panic, phobia, stress <i>Inclusion criteria:</i> not reported <i>Exclusion criteria:</i> not reported	<i>Number of citations identified in Search:</i> not reported <i>Number of studies included:</i> not reported <i>Number of patients in all included studies:</i> not reported	<ul style="list-style-type: none"> <li>Frequent cannabis use associated with higher levels of anxiety compared to non-users</li> <li>Higher prevalence of anxiety disorders in chronic cannabis users than the general population; anxiety disorders may increase risk of using cannabis</li> <li>Anxiety associated with cannabis withdrawal</li> <li>No association between cannabis use and an increased risk in developing anxiety disorders</li> </ul>	4/11
Gibbs, 2015, United Kingdom	<i>Population:</i> cannabis users, those with bipolar <i>Intervention:</i> cannabis exposure <i>Comparator:</i> non-users, those without bipolar <i>Outcome:</i> manic symptoms	<i>Databases searched:</i> PsychInfo, Cochrane, Scopus, EMBASE, Medline <i>Years searched:</i> 1980 until June 2014 <i>Key words used:</i> cannabis, marijuana, delta-9-tetrahydrocannabinol, cannabinoids, cannabidiol, cannabiol, tetrahydrocannabivarin, bipolar disorder, manic depressive disorder, mania, hypomania, manic depression, dipolar spectrum, onset, trigger, induce*, course <i>Inclusion criteria:</i> prospective primary experimental, prospective, cohort, longitudinal designs; participants had bipolar I or II or described as experiencing mania; clinical and subclinical mania symptoms and episodes; English language <i>Exclusion criteria:</i> participants primarily diagnosed with a psychotic disorder; non-English	<i>Number of citations identified in Search:</i> 781 <i>Number of studies included:</i> 6 <i>Number of patients in all included studies:</i> 2,391	<ul style="list-style-type: none"> <li>Cannabis use increases the likelihood, severity or duration of manic phases in those with bipolar disorder (OR = 2.97, 95% CI = 1.80-4.90)</li> <li>Cannabis use also associated with increased risk of hypomanic symptoms in those at high risk of developing bipolar disorder</li> </ul>	9/11
Kedzior, 2014, Germany	<i>Population:</i> cannabis users <i>Intervention:</i> cannabis use <i>Comparator:</i> non-users <i>Outcome:</i> anxiety	<i>Databases searched:</i> PsychInfo, Medline <i>Years searched:</i> inception until March 2013 <i>Key words used:</i> cannabis, marijuana, marihuana, affective disorder, anxiety disorder, anxiety, misus*, abus*, depend*, harmful use, harmful usage <i>Inclusion criteria:</i> general population; anxiety diagnosis with or without cannabis use; odds ratios; cannabis use with or without anxiety <i>Exclusion criteria:</i> no data from healthy non-users; data from people seeking treatment for cannabis use disorder or other psychiatric disorders other than anxiety or depression; inadequate data	<i>Number of citations identified in Search:</i> 267 <i>Number of studies included:</i> 31 <i>Number of patients in all included studies:</i> 173,577	<ul style="list-style-type: none"> <li>Those with anxiety are more likely to use cannabis or have cannabis use disorder</li> <li>Anxiety and cannabis use: OR = 1.24 (95% CI = 1.06-1.45)</li> <li>Anxiety and cannabis use disorder: OR = 1.68 (95% CI = 1.23-2.31)</li> <li>Comorbid anxiety and cannabis use disorder may require more treatment than cannabis use disorder alone</li> </ul>	9/11
Kraan, 2016, The Netherlands	<i>Population:</i> those at ultra-high risk of psychosis <i>Intervention:</i> cannabis use <i>Comparator:</i> non-users, general population <i>Outcome:</i> psychosis	<i>Databases searched:</i> EMBASE, Medline, PsychInfo <i>Years searched:</i> 1996 until August 2015 <i>Key words used:</i> clinical high risk, attenuated positive symptoms, brief limited intermittent psychotic symptoms, genetic risk and deterioration, basic symptoms, familial high risk, prodrom*, at risk mental state, ultra high risk, attenuated psychotic symptoms, high risk, substance use, substance abuse, substance use disorder, cannabis, marijuana, tobacco, hallucinogens, cannabis misuse, risk factors, psychosis, schizophrenia, schizo*, psychoti* <i>Inclusion criteria:</i> individuals meeting ultra-high risk criteria; reported the effect of cannabis use on transition to psychosis; prospective design; English language	<i>Number of citations identified in Search:</i> 5560 <i>Number of studies included:</i> 7 <i>Number of patients in all included studies:</i> 330	<ul style="list-style-type: none"> <li>No relationship between any cannabis use and transition to psychosis in ultra-high risk individuals (OR = 1.14, 95% CI = 0.856-1.524)</li> <li>Cannabis abuse or dependence was significantly associated with transition to psychosis (OR = 1.75, 95% CI = 1.135-2.710)</li> </ul>	10/11

		<i>Exclusion criteria:</i> cannabis use not assessed separately			
Large, 2011, Australia	<i>Population:</i> substance users  <i>Intervention:</i> cannabis, alcohol, other psychoactive drugs  <i>Comparator:</i> patients with psychosis but no drug use  <i>Outcome:</i> age of onset of psychosis	<i>Databases searched:</i> CINAHL, EMBASE, Medline, PsychInfo, ISI Web of Science  <i>Years searched:</i> inception until June 2010  <i>Key words used:</i> schizophrenia, psychosis, substance, dual diagnosis, drug abuse, cannabis, alcohol, amphetamine, cocaine, age  <i>Inclusion criteria:</i> English language; reported the use of a psychoactive drug other than tobacco; compared age of onset with a control group  <i>Exclusion criteria:</i> not reported	<i>Number of citations identified in Search:</i> 1293  <i>Number of studies included:</i> 83  <i>Number of patients in all included studies:</i> 8167	<ul style="list-style-type: none"> <li>Significantly earlier age of onset of psychosis in cannabis users compared to non-users (2.70 years earlier, <math>p &lt; 0.001</math>)</li> <li>General substance use also associated with earlier age of onset</li> <li>Alcohol not associated with earlier onset</li> </ul>	9/11
Le Bec, 2009, France	<i>Population:</i> adolescents or young adults without psychosis  <i>Intervention:</i> cannabis use  <i>Comparator:</i> non-users  <i>Outcome:</i> chronic psychotic disorders	<i>Databases searched:</i> MEDLINE  <i>Years searched:</i> 1966 until June 2005  <i>Inclusion criteria:</i> human studies; prospective and longitudinal studies; objective of studies to examine causal link between cannabis use and psychosis  <i>Exclusion criteria:</i> literature reviews	<i>Number of citations identified in Search:</i> 60  <i>Number of studies included:</i> 7  <i>Number of patients in all included studies:</i> 50,275	<ul style="list-style-type: none"> <li>Statistically significant associations between cannabis use and psychosis or psychotic symptoms</li> <li>Those initially with pre-psychotic symptoms had stronger associations between cannabis and psychosis</li> <li>Many studies observed dose-response associations and cannabis use occurring before emergence of psychotic symptoms</li> </ul>	3/11
Lev-Ran, 2014, Canada	<i>Population:</i> cannabis users  <i>Intervention:</i> cannabis use  <i>Comparator:</i> non-users  <i>Outcome:</i> depression	<i>Databases searched:</i> EMBASE, Medline, PsychInfo, ISI Web of Science  <i>Years searched:</i> inception until December 2012  <i>Key words used:</i> cannabis, marijuana, marihuana, depression, depressed, depressive disorder, mood, mood disorder, affective disorder, dysthymia  <i>Inclusion criteria:</i> original paper in a peer-review journal; population-based data collected longitudinally and prospectively; cannabis use; depression was controlled at baseline; odds ratio  <i>Exclusion criteria:</i> not reported	<i>Number of citations identified in Search:</i> 4764  <i>Number of studies included:</i> 14  <i>Number of patients in all included studies:</i> 76,058	<ul style="list-style-type: none"> <li>Cannabis use associated with risk of developing depression compared to non-users</li> <li>Any cannabis use and depression: OR = 1.17 (96% CI = 1.05-1.30)</li> <li>Heavy cannabis use and depression compared to no or light use: OR = 1.62 (95% CI = 1.21-2.16)</li> </ul>	10/11
Marconi, 2016, United Kingdom	<i>Population:</i> cannabis users  <i>Intervention:</i> cannabis use  <i>Comparator:</i> non-users  <i>Outcome:</i> psychosis or psychotic symptoms	<i>Databases searched:</i> PubMed, EMBASE, PsychInfo  <i>Years searched:</i> inception until December 31 <sup>st</sup> 2013  <i>Key words used:</i> dose-response, daily use, duration, high frequency, heavy use, psychosis, schizophrenia, schizophreni*, cannab*, cannabis, marijuana, marihuana  <i>Inclusion criteria:</i> peer-reviewed; any language; cohort, cross-sectional; assessed cannabis with a dose criterion before onset of psychosis; psychosis-related outcomes  <i>Exclusion criteria:</i> subjects who had a mental illness before cannabis use; subjects at ultra-high risk; studies examining comorbidity; studies examining age of onset of psychosis; neuropsychological measures or schizoid personality traits; cannabis not measured by dose	<i>Number of citations identified in Search:</i> 571  <i>Number of studies included:</i> 16; 10 for meta-analysis  <i>Number of patients in all included studies:</i> 66,816	<ul style="list-style-type: none"> <li>Heavy cannabis use associated with a significant increase in risk of schizophrenia and other psychotic outcomes compared to non-users (OR = 3.90, 95% CI = 2.84-5.34)</li> <li>Average cannabis use also significantly associated with schizophrenia and psychotic outcomes (OR = 1.97, 95% CI = 1.68-2.31)</li> </ul>	7/11
Minozzi, 2010, Italy	<i>Population:</i> cannabis users  <i>Intervention:</i> cannabis use  <i>Comparator:</i> non-users  <i>Outcome:</i> psychosis	<i>Databases searched:</i> Medline, EMBASE, CINAHL  <i>Years searched:</i> 2000 until August 2007  <i>Key words used:</i> substance-related disorders, cannabis, marihuana, marijuana, psychosis, psychotic disorders, schizophrenia, psychotic*  <i>Inclusion criteria:</i> systematic reviews that assess cannabis and psychosis	<i>Number of citations identified in Search:</i> 41  <i>Number of studies included:</i> 5	<ul style="list-style-type: none"> <li>Consistent, significant associations between cannabis use and onset of psychotic symptoms</li> <li>Quality and methodological concerns limit the results</li> </ul>	7/11

		<i>Exclusion criteria:</i> not reported	<i>Number of patients in all included studies:</i> 265,403		
Moore, 2007, United Kingdom	<i>Population:</i> cannabis users  <i>Intervention:</i> cannabis use  <i>Comparator:</i> non-users  <i>Outcome:</i> psychotic or affective mental health outcomes	<i>Databases searched:</i> Medline, EMBASE, CINAHL, PsychInfo, ISI Wed of Knowledge, ISI Proceedings, ZETOC, BIOSIS, LILACS, MedCarib  <i>Years searched:</i> inception until September 2006  <i>Key words used:</i> psychosis, schizophrenia, affective disorder, depression, cannabis (all with synonyms not reported)  <i>Inclusion criteria:</i> population-based longitudinal or case-control nested studies; humans  <i>Exclusion criteria:</i> patients with mental illness or substance-related problems; prison populations; RCTs of medical cannabis	<i>Number of citations identified in Search:</i> 4804  <i>Number of studies included:</i> 11  <i>Number of patients in all included studies:</i> not reported	<ul style="list-style-type: none"> <li>Increased incidence of psychosis-related outcomes in those who had ever used cannabis (OR=1.41, 95% CI: 1.20-1.65)</li> <li>Heavy and earlier use increased risk</li> <li>More frequent cannabis use increased the incidence of any psychotic outcome (OR = 2.09, 95% CI = 1.54-2.84)</li> </ul>	7/11
Myles, 2016, Australia	<i>Population:</i> patients with first episode psychosis  <i>Intervention:</i> inhaled cannabis  <i>Comparator:</i> patients with first episode psychosis who do not use cannabis, patients with chronic psychosis  <i>Outcome:</i> length of time from cannabis use to psychosis	<i>Databases searched:</i> Medline, EMBASE, CINAHL, PsychInfo, ISI Web of Science  <i>Years searched:</i> October 2014 to “current”  <i>Key words used:</i> psychosis, schizophrenia, cannabis, marijuana  <i>Inclusion criteria:</i> English language; cohorts that reported on first episode psychosis; inhaled organic cannabis; could be included in a meta-analysis  <i>Exclusion criteria:</i> not first episode; subjects suffering from drug-induced or organic psychoses; subjects recruited for a clinical trial or RCT; synthetic or oral cannabinoids; cohorts that were part of a larger cohort	<i>Number of citations identified in Search:</i> 2113  <i>Number of studies included:</i> 61  <i>Number of patients in all included studies:</i> 10,762	<ul style="list-style-type: none"> <li>33.7% (95% CI = 29-38%) of subjects used cannabis prior to psychosis</li> <li>Pooled interval between first cannabis use and age of psychosis onset was 6.3 years (SMD = 1.56, 95% CI = 1.40-1.72)</li> <li>Cannabis use higher in patients with first episode psychosis compared to patients with chronic, long-term psychosis</li> </ul>	6/11
Myles, 2012, Australia	<i>Population:</i> smokers  <i>Intervention:</i> cannabis or tobacco use  <i>Comparator:</i> tobacco users compared to cannabis users  <i>Outcome:</i> age of onset of psychosis	<i>Databases searched:</i> EMBASE, Medline, PsychInfo, ISI Web of Science  <i>Years searched:</i> inception until September 2011  <i>Key words used:</i> cannabis, marijuana, tobacco, nicotine, smoking, schizophrenia, psychosis  <i>Inclusion criteria:</i> separately reported substance and non-using groups; report age of onset of psychosis; be suitable for meta-analysis  <i>Exclusion criteria:</i> bipolar, psychotic depression, substance-induced psychosis	<i>Number of citations identified in Search:</i> 589  <i>Number of studies included:</i> 38 for cannabis; 40 for tobacco  <i>Number of patients in all included studies:</i> 3199 for cannabis; 5562 for tobacco	<ul style="list-style-type: none"> <li>Tobacco not significantly associated with earlier age of onset of psychosis</li> <li>Cannabis significantly associated with earlier age of onset of schizophrenia spectrum psychosis and broad psychosis</li> <li>Age of psychosis was 32 months earlier (SMD = 0.399, 95% CI = -0.493- -0.306) for cannabis users compared to non-users</li> </ul>	10/11
Rey, 2004, Australia	<i>Population:</i> young cannabis users  <i>Intervention:</i> cannabis use  <i>Comparator:</i> non-users  <i>Outcome:</i> behavioural problems, mental disorders	<i>Databases searched:</i> Medline, Pre-Medline, PsychInfo, EMBASE, Web of Science  <i>Years searched:</i> 1994 until 2004  <i>Key words used:</i> not reported  <i>Inclusion criteria:</i> not reported  <i>Exclusion criteria:</i> not English; adults	<i>Number of citations identified in Search:</i> Not reported  <i>Number of studies included:</i> Not reported  <i>Number of patients in all included studies:</i> Not reported	<ul style="list-style-type: none"> <li>Cannabis has a low non-continuation rate</li> <li>About 10% of users have cannabis dependence; more common in those who start use young</li> <li>Data on cannabis as a gateway drug is inconclusive</li> <li>Symptoms of anxiety and depression higher in females, but results are inconclusive</li> </ul>	1/11
Ruiz-Veguilla, 2012, Spain	<i>Population:</i> patients with schizophrenia and first-episode psychosis  <i>Intervention:</i> cannabis use	<i>Databases searched:</i> BIOSIS Citation Index SM, BIOSIS Previews, the Cochrane Library, EMBASE, Inspec, ISI Proceedings, Journal Citation Reports, Medline, PsychInfo, PubMed, Web of Science  <i>Years searched:</i> inception until November 2011	<i>Number of citations identified in Search:</i> 1225  <i>Number of studies</i>	<ul style="list-style-type: none"> <li>Smoking cannabis was associated with fewer neurological soft signs in psychotic patients than non-users</li> </ul>	8/11

	<p><i>Comparator:</i> non-users</p> <p><i>Outcome:</i> neurological soft signs focused on sensory integration, motor coordination, motor sequencing, and primitive reflexes (ex. audio-visual integration, finger-nose test, gaze)</p>	<p><i>Key words used:</i> psycho, schizophre<sup>n</sup>*, first episode, neurolog* soft signs, neurolog* soft signs, movement* disorder*, NSS, sensory integrati*, motor coordinati*, motor sequenc*, primitive reflex*, audio-visual integrat*, stereognos*, graphaestes*, extinction, right-left confusion, tandem walk*, rapid alternat* movement*, finger-thumb opposition, finger-nose test, rhythm tapping, fist-ring test, rhythm tapping, fist-ring test, fist-edge-palm test, Oszeretski test, gaz*, palmo-mental, snout, grasp*, cannab*, tetrahydrocannab*, THC, marihuana, marijuana, endocannabinoid*, CBD</p> <p><i>Inclusion criteria:</i> Subjects met the clinical definition of psychosis or schizophrenia; any cannabis use; any age and gender; studies were not excluded due to any medications or comorbidities of subjects; all the studies were included irrespective of other design quality issues, and case report studies were also initially considered</p> <p><i>Exclusion criteria:</i> not reported</p>	<p><i>included:</i> 5, 2 for meta-analysis</p> <p><i>Number of patients in all included studies:</i> 172</p>		
Schoeler, 2016, United Kingdom	<p><i>Population:</i> patients with psychosis</p> <p><i>Intervention:</i> continued cannabis use</p> <p><i>Comparator:</i> non-users, patients who discontinue use</p> <p><i>Outcome:</i> relapse</p>	<p><i>Databases searched:</i> Medline</p> <p><i>Years searched:</i> inception until April 2015</p> <p><i>Key words used:</i> marijuana, marihuana, cannabis, illicit substance, outcome, hospital*, relapse, readmission, psycho*, bipolar, schizophrenia</p> <p><i>Inclusion criteria:</i> patients with pre-existing psychotic disorders; follow-up of at least 6 months</p> <p><i>Exclusion criteria:</i> continued or discontinues cannabis use could not be determined</p>	<p><i>Number of citations identified in Search:</i> 1903</p> <p><i>Number of studies included:</i> 24</p> <p><i>Number of patients in all included studies:</i> 16565</p>	<ul style="list-style-type: none"> <li>Patients who continued using cannabis had higher relapse rates than patients who discontinued use and non-users</li> <li>Patients who discontinued cannabis did not differ in relapse rate from non-users</li> </ul>	9/11
Semple, 2005, United Kingdom	<p><i>Population:</i> cannabis users</p> <p><i>Intervention:</i> cannabis use</p> <p><i>Comparator:</i> non-users</p> <p><i>Outcome:</i> schizophrenia or schizophrenia-like psychosis</p>	<p><i>Databases searched:</i> EMBASE, PsychInfo, Medline</p> <p><i>Years searched:</i> 1966 until January 2004</p> <p><i>Key words used:</i> cannabis, schizophrenia, other key words not reported</p> <p><i>Inclusion criteria:</i> original data; case-control studies; exposure to cannabis preceded schizophrenia or schizophrenia-like psychosis</p> <p><i>Exclusion criteria:</i> not reported</p>	<p><i>Number of citations identified in Search:</i> not reported</p> <p><i>Number of studies included:</i> 11, 7 in meta-analysis</p> <p><i>Number of patients in all included studies:</i> 113,802</p>	<ul style="list-style-type: none"> <li>Early use of cannabis was associated with an increased risk of psychosis (OR = 2.9, 95% CI = 2.4-3.6)</li> <li>Dose-related effect seen in individuals who used cannabis during adolescence, those who previously experience psychosis, and those at genetic high risk</li> </ul>	5/11
Szoke, 2014, France	<p><i>Population:</i> cannabis users</p> <p><i>Intervention:</i> cannabis use</p> <p><i>Comparator:</i> non-users</p> <p><i>Outcome:</i> psychometric schizotypy</p>	<p><i>Databases searched:</i> PubMed, PsychInfo</p> <p><i>Years searched:</i> inception until 2013</p> <p><i>Key words used:</i> schizot*, psychotic-like, psychosis-proneness, cannabi*, THC, marijuana</p> <p><i>Inclusion criteria:</i> humans; English-language</p> <p><i>Exclusion criteria:</i> not reported</p>	<p><i>Number of citations identified in Search:</i> 63</p> <p><i>Number of studies included:</i> 29</p> <p><i>Number of patients in all included studies:</i> 21,736</p>	<ul style="list-style-type: none"> <li>Life-time cannabis use and current cannabis use were both associated with higher schizotypy scores</li> </ul>	3/11
Van der Meer, 2012, The Netherlands	<p><i>Population:</i> those at clinical high risk for psychosis</p> <p><i>Intervention:</i> cannabis use</p> <p><i>Comparator:</i> non-users</p> <p><i>Outcome:</i> first episode psychosis</p>	<p><i>Databases searched:</i> Medline, PsychInfo, PubMed, EMBASE</p> <p><i>Years searched:</i> 1995 until October 31<sup>st</sup> 2011</p> <p><i>Key words used:</i> at risk population*, high risk, UHR, risk factor*, prodromal, prodrome, at * risk, early * symptom*, clinical* * risk, high risk population, psychosis, psychoses, psychotic, psychotic disorder*, prepsychosis, prepsychotic, schizophrenia, schizophrenic, paranoi*, delusion*, hallucination*, hallucinogen*, psychedel<sup>i</sup>?, psychodelic?, cannabis, cannabinoid*, tetrahydrocannabinol, THC, hashish,</p>	<p><i>Number of citations identified in Search:</i> 729</p> <p><i>Number of studies included:</i> 11</p> <p><i>Number of patients in all included studies:</i> 742</p>	<ul style="list-style-type: none"> <li>Inconclusive results about cannabis use and severity of symptoms at baseline, pre-psychotic symptoms, and early onset of psychosis</li> <li>Weak evidence suggesting cannabis may worsen symptoms in younger users</li> </ul>	4/11

		<p>marijuana, marijuana, marijuana usage, marijuana smoking, hallucinogenic drugs, psychoactive drug, psychedelic agent*</p> <p><i>Inclusion criteria:</i> English language; contained data on the relation between cannabis use and clinical high risk status or symptomatology; first episode</p> <p><i>Exclusion criteria:</i> papers where cannabis was only analyzed as a confounder or was not analyzed separately</p>			
Zammit, 2008, United Kingdom	<p><i>Population:</i> patients with psychosis</p> <p><i>Intervention:</i> cannabis use</p> <p><i>Comparator:</i> patients with psychosis without cannabis use</p> <p><i>Outcome:</i> severity of symptoms, adherence to treatment, other adverse outcomes</p>	<p><i>Databases searched:</i> Medline, EMBASE, CINAHL, PsychInfo, ISI Web of Knowledge, ISI Proceedings, ZETOC, BIOSIS, LILACS, MedCarib</p> <p><i>Years searched:</i> inception until November 2006</p> <p><i>Key words used:</i> psychosis, schizophrenia, hallucinations, delusions, substance abuse, and unspecified synonyms</p> <p><i>Inclusion criteria:</i> longitudinal studies of people with psychosis; case-control nested studies</p> <p><i>Exclusion criteria:</i> comorbid psychosis and cannabis misuse or dependence</p>	<p><i>Number of citations identified in Search:</i> 15,303</p> <p><i>Number of studies included:</i> 13</p> <p><i>Number of patients in all included studies:</i> not specified</p>	<ul style="list-style-type: none"> <li>• Cannabis use was associated with increased relapse and rehospitalization and decreased treatment adherence</li> <li>• Inconsistent results about cannabis use and severity of symptoms</li> </ul>	9/11
Neurocognitive Effects					
Author, Year of Publication, Country	PICO	Search strategy	Studies included	Key outcomes	Quality Assessment
Broyd, 2016, Australia	<p><i>Population:</i> cannabis users</p> <p><i>Intervention:</i> cannabis exposures</p> <p><i>Comparator:</i> non-users</p> <p><i>Outcome:</i> cognitive outcomes</p>	<p><i>Databases searched:</i> PubMed, Scopus</p> <p><i>Years searched:</i> January 2004 until February 2015</p> <p><i>Key words used:</i> cannabi*, marijuana, cognit*, memory, attention*, learning, inhibit*, impuls*, reward, decision making, executive function*, information process*, performance, functional brain imaging, fMRI, event related potential, electroencephalogram, not rats or mice or review or MDMA or ecstasy or amphetamine</p> <p><i>Inclusion criteria:</i> neuropsychological or cognitive experimental tasks; regular or former cannabis users or following acute administration of cannabis; human participants</p> <p><i>Exclusion criteria:</i> cannabis is not the primary drug; trait measures of cognition; major psychopathology or neurological conditions; animals; neuroimaging, electrophysiological, or autonomic measures as the primary outcome; treatment; “real world” tasks; case studies</p>	<p><i>Number of citations identified in Search:</i> 6441</p> <p><i>Number of studies included:</i> 105</p> <p><i>Number of patients in all included studies:</i> not reported</p>	<ul style="list-style-type: none"> <li>• Impaired verbal learning and memory and psychomotor functioning in chronic and occasional users</li> <li>• Inconsistent evidence regarding working memory, attention, and executive functioning, but some evidence suggests impairment</li> <li>• Many impairments exist after abstinence</li> </ul>	4/11
Ganzer, 2016, Germany	<p><i>Population:</i> abstinent cannabis users</p> <p><i>Intervention:</i> cannabis use</p> <p><i>Comparator:</i> current users, non-users</p> <p><i>Outcome:</i> neurocognitive functioning</p>	<p><i>Databases searched:</i> EMBASE, Ovid MEDLINER, PsychInfo, PSYNDEXplus Literature</p> <p><i>Years searched:</i> 2004 until 2015</p> <p><i>Key words used:</i> cannabi*, THC, marijuana, marihuana, neuro*, cognit*, assess*, abilit*, affect*, process*, function*, impair*, residual, long-term, abstinen*, abstain*, lasting, non-acute, non-intox*, persist*</p> <p><i>Inclusion criteria:</i> clinical trials; humans</p> <p><i>Exclusion criteria:</i> subjects with a history of chronic medical and neurological illness or severe psychiatric disorder, or substance use disorder; animal studies; case reports, expertises, commentaries, books</p>	<p><i>Number of citations identified in Search:</i> 1038</p> <p><i>Number of studies included:</i> 38</p> <p><i>Number of patients in all included studies:</i> 2025</p>	<ul style="list-style-type: none"> <li>• Poorer attention, motor function, and memory and learning in abstinent users than non-users</li> <li>• Impairments in inhibition, impulsivity, and decision making in abstinent users, but inconsistent evidence</li> <li>• Highly inconsistent evidence with regards to visual spatial functioning</li> <li>• Differences in activation patterns and structural differences in the brain of abstinent users compared to controls</li> </ul>	9/11

Garfield, 2013, Australia	<p><i>Population:</i> illicit substance users</p> <p><i>Intervention:</i> substance use</p> <p><i>Comparator:</i> non-users</p> <p><i>Outcome:</i> anhedonia</p>	<p><i>Databases searched:</i> PubMed, PsychInfo, Medline</p> <p><i>Years searched:</i> not reported</p> <p><i>Key words used:</i> anhedonia, drug, substance, alcohol, nicotine, dependence, addiction, abuse</p> <p><i>Inclusion criteria:</i> human samples; lifetime history of a defined substance use disorder or long-term daily use; measured anhedonia</p> <p><i>Exclusion criteria:</i> reviews; non-substance related psychiatric disorders</p>	<p><i>Number of citations identified in Search:</i> 245</p> <p><i>Number of studies included:</i> 32, 3 on cannabis</p> <p><i>Number of patients in all included studies:</i> not reported</p>	<ul style="list-style-type: none"> <li>Those with baseline cannabis abuse reported higher levels of anhedonia than those with no baseline cannabis abuse</li> <li>Baseline anhedonia did not predict cannabis use</li> <li>Abstinence from cannabis was associated with a decrease in anhedonia</li> </ul>	3/11
Gates, 2014, Australia	<p><i>Population:</i> adult cannabis users</p> <p><i>Intervention:</i> measured cannabis</p> <p><i>Comparator:</i> non-users</p> <p><i>Outcome:</i> sleep</p>	<p><i>Databases searched:</i> EMBASE, CINAHL, Cochrane Library/EBM Reviews, Medline, PsycEXTRA</p> <p><i>Years searched:</i> inception until 2012</p> <p><i>Key words used:</i> cannabinoid/s, tetrahydrocannabinol, THC, cannabis/marijuana, sleep, sleep onset, sleep apnea, sleep treatment, sleep wake cycle, sleep deprivation, rapid eye movement (REM) sleep, non-rapid eye movement (NREM) sleep, sleep disorder, insomnia</p> <p><i>Inclusion criteria:</i> not reported</p> <p><i>Exclusion criteria:</i> review papers, posters, qualitative articles, opinion pieces, letter, editorials, case reports (n&lt;7), published abstracts</p>	<p><i>Number of citations identified in Search:</i> 2215</p> <p><i>Number of studies included:</i> 39</p> <p><i>Number of patients in all included studies:</i> 203 recreational users</p>	<ul style="list-style-type: none"> <li>No consistent effect of cannabis on sleep time</li> <li>Increased time spent in stage 2 and decreased time in slow wave sleep</li> <li>Overall results inconsistent</li> </ul>	4/11
Gonzalez, 2002, United States	<p><i>Population:</i> abstinent cannabis users</p> <p><i>Intervention:</i> cannabis use</p> <p><i>Comparator:</i> non-users, current users</p> <p><i>Outcome:</i> neurocognitive effects</p>	<p><i>Databases searched:</i> not reported</p> <p><i>Years searched:</i> not reported</p> <p><i>Key words used:</i> not reported</p> <p><i>Inclusion criteria:</i> non-acute neuropsychological effects of cannabis; humans; adults; English language</p> <p><i>Exclusion criteria:</i> not reported</p>	<p><i>Number of citations identified in Search:</i> 1014</p> <p><i>Number of studies included:</i> 40</p> <p><i>Number of patients in all included studies:</i> 741</p>	<ul style="list-style-type: none"> <li>Poorer motor performance, executive function, reaction time, learning, and verbal domains</li> <li>However, results highly inconsistent and generally poor quality</li> </ul>	5/11
Grant, 2003, United States	<p><i>Population:</i> adult, long-term cannabis users</p> <p><i>Intervention:</i> cannabis use</p> <p><i>Comparator:</i> non-users, occasional users</p> <p><i>Outcome:</i> neurocognitive performance</p>	<p><i>Databases searched:</i> Medline/HealthSTAR, PsychInfo, BioSys, Current Contents, Dissertation Abstracts international, Article First, Science Citation Index Expanded, Social Science Citation Index</p> <p><i>Years searched:</i> not reported</p> <p><i>Key words used:</i> marijuana, marijuana, tetra-hydrocannabinol, THC, cannabis, neuro*, cognitive, assessment, ability, effects, processes, impairment, cognition, drug effects</p> <p><i>Inclusion criteria:</i> includes a cannabis only group and control group; can calculate effect size; measures neuropsychological tests; reports length of abstinence</p> <p><i>Exclusion criteria:</i> not humans or adults</p>	<p><i>Number of citations identified in Search:</i> 1014</p> <p><i>Number of studies included:</i> 11 for meta-analysis</p> <p><i>Number of patients in all included studies:</i> 1032; 632 users</p>	<ul style="list-style-type: none"> <li>Inconsistent results on all measures except learning and forgetting, both of which were small</li> <li>Learning: -0.21 (99% CI = -0.39- -0.022)</li> <li>Forgetting: -0.27 (99% CI = -0.49- -0.044)</li> </ul>	4/11
Rabin, 2011, Canada	<p><i>Population:</i> patients with schizophrenia</p> <p><i>Intervention:</i> cannabis use</p> <p><i>Comparator:</i> non-users</p> <p><i>Outcome:</i> neurocognition</p>	<p><i>Databases searched:</i> PsychInfo, Medline, PubMed</p> <p><i>Years searched:</i> not reported</p> <p><i>Key words used:</i> schizophrenia, psychosis, cannabis, tetrahydrocannabinol, THC, marijuana, neuropsych*, neurocog*, cognitive impairment</p> <p><i>Inclusion criteria:</i> English language; humans; compare schizophrenia cannabis-users to a control group; could be used for meta-analysis; participants have no other concurrent drug or alcohol use disorders</p>	<p><i>Number of citations identified in Search:</i> not reported</p> <p><i>Number of studies included:</i> 8</p> <p><i>Number of patients in all included studies:</i> 942; 356 cannabis users</p>	<ul style="list-style-type: none"> <li>Higher neurocognitive functioning in cannabis users compared to non-users</li> </ul>	4/11

		<i>Exclusion criteria:</i> not reported			
Schoeler, 2016, United Kingdom	<i>Population:</i> patients with or without a psychotic disorder  <i>Intervention:</i> long-term cannabis use  <i>Comparator:</i> non-users  <i>Outcome:</i> memory function	<i>Databases searched:</i> Medline  <i>Years searched:</i> inception until June 2014  <i>Key words used:</i> neuropsych*, cognit*, memory, learning, recall, marijuana, marihuana, cannabis, THC, cannabinalol, cannabidiol  <i>Inclusion criteria:</i> not reported  <i>Exclusion criteria:</i> not reported	<i>Number of citations identified in Search:</i> not reported  <i>Number of studies included:</i> 88  <i>Number of patients in all included studies:</i> 3261 subjects with a psychotic disorder	<ul style="list-style-type: none"><li>• Cannabis use significantly impaired global memory in healthy users compared to non-users</li><li>• Cannabis use in patients with psychosis improved memory compared to non-users</li></ul>	4/11
Schreiner, 2012, United States	<i>Population:</i> chronic cannabis users, abstinent or current  <i>Intervention:</i> cannabis use  <i>Comparator:</i> non- or minimal-users  <i>Outcome:</i> neurocognitive performance	<i>Databases searched:</i> PsychInfo, PsycARTICLES, PubMed, Medline  <i>Years searched:</i> not reported  <i>Key words used:</i> marijuana, marihuana, tetra-hydrocannabinol, THC, cannabis, neuro*, cognit*, assess*, ability*, effect*, process*, impair*, residual, long-term, abstinen*, abstain*, lasting, non-acute, persist*  <i>Inclusion criteria:</i> human subjects; cannabis only users; control group of nonusers or with very limited drug experience; could be included in meta-analysis; behavioral measure of neuropsychological functioning; participants not under the influence of any substances during testing; history of other substance use or psychiatric illness addressed; the period of abstinence from cannabis before testing is reported  <i>Exclusion criteria:</i> reviews; acute effects only; brain imaging; not humans or chronic users	<i>Number of citations identified in Search:</i> not reported (~800)  <i>Number of studies included:</i> 33  <i>Number of patients in all included studies:</i> 1010 current or former users	<ul style="list-style-type: none"><li>• Cannabis use was associated with significant effects on global neurocognition</li><li>• No significant residual effects seen on abstinent users compared to non-users</li></ul>	5/11
Smith, 2014, Australia	<i>Population:</i> chronic heavy users or drug dependent  <i>Intervention:</i> chronic drug use or dependence  <i>Comparator:</i> healthy non-dependent individuals  <i>Outcome:</i> behavioral inhibition	<i>Databases searched:</i> PubMed, PsychInfo, Project Cork, DRUG, Medline, Medline in process, EMBASE, CINAHL  <i>Years searched:</i> not reported  <i>Key words used:</i> Go-NoGo, SSRT, stop-signal, response inhibition, inhibit, disinhibit, neurocognitive function, executive function, executive dysfunction, cognitive control, cognition disorders, reaction time  <i>Inclusion criteria:</i> English, compare drug dependent or chronic heavy-user group to control, report outcome on behavioural inhibition  <i>Exclusion criteria:</i> studies that delivered stop-signals at only one delay; within-subject acute effects of drugs; studies on family members of substance dependent individuals	<i>Number of citations identified in Search:</i> 265  <i>Number of studies included:</i> 97  <i>Number of patients in all included studies:</i> 6,542	<ul style="list-style-type: none"><li>• No statistically significant evidence of inhibitory deficit was observed for cannabis</li><li>• Small to medium non-statistically significant effects were observed</li></ul>	7/11
Prenatal Effects					
Author, Year of Publication, Country	PICO	Search strategy	Studies included	Key outcomes	Quality Assessment
English, 1997, Australia	<i>Population:</i> babies born to mothers using cannabis during pregnancy  <i>Intervention:</i> cannabis use during pregnancy  <i>Comparator:</i> no cannabis use during pregnancy  <i>Outcome:</i> birth weight	<i>Databases searched:</i> Medline  <i>Years searched:</i> 1966-November 1995  <i>Key words used:</i> cannabis, substance abuse, fetal-development, pregnancy complications, neonatal diseases and abnormalities, infant-newborn, birth weight  <i>Inclusion criteria:</i> cannabis use during pregnancy and birth weight  <i>Exclusion criteria:</i> commentaries, letters and abstracts	<i>Number of citations identified in Search:</i> Not reported  <i>Number of studies included:</i> 10  <i>Number of patients in all included studies:</i> 32,843	<ul style="list-style-type: none"><li>• Women who used cannabis at least four times per week had a 131g reduction in birth weight (95% CI = 52-109g)</li><li>• Birth weight increase by 62 g (95% CI = 8g-132g) among women who were infrequent users</li><li>• The pooled odds of low birthweight for any use was 1.09 (95% CI 0.94-1.27)</li></ul>	4/11

Gunn, 2016, United States	<i>Population:</i> children of women who used cannabis during pregnancy, and women who used cannabis during pregnancy  <i>Intervention:</i> cannabis use during pregnancy  <i>Comparator:</i> No cannabis use during pregnancy  <i>Outcome:</i> Maternal, fetal, perinatal and neonatal outcomes	<i>Databases searched:</i> PubMed, Medline, EMBASE, CINAHL, PsychInfo, Web of Science and Sociological Abstracts  <i>Years searched:</i> inception to April 2014  <i>Key words used:</i> cannabis, and maternal, fetal, perinatal, and neonatal outcomes; details not reported  <i>Inclusion criteria:</i> randomized controlled trials, case-control, cross sectional, and cohort studies, investigate effects of prenatal use of cannabis on maternal, fetal, perinatal and neonatal outcomes  <i>Exclusion criteria:</i> inclusion of women using other illicit drugs in addition to cannabis	<i>Number of citations identified in Search:</i> 6854  <i>Number of studies included:</i> 24  <i>Number of patients in all included studies:</i> not reported	<ul style="list-style-type: none"> <li>Women who use cannabis during pregnancy have increased odds of anemia (OR = 1.36. 95% CI = 1.10-1.69)</li> <li>Infants whose mothers used cannabis during pregnancy had decreased birthweight (OR = 1.77, 95% CI = 1.04-3.01)</li> <li>Infants whose mothers used cannabis during pregnancy were more likely to be placed in the ICU (OR = 2.02, 95% CI = 1.27-3.21)</li> </ul>	8/11
Viteri, 2015, United States	<i>Population:</i> illicit drug users  <i>Intervention:</i> maternal cannabis use during pregnancy  <i>Comparator:</i> no maternal cannabis use during pregnancy  <i>Outcome:</i> congenital anomalies, long-term implications	<i>Databases searched:</i> PubMed  <i>Years searched:</i> not reported  <i>Key words used:</i> not reported  <i>Inclusion criteria:</i> not reported  <i>Exclusion criteria:</i> not reported	<i>Number of citations identified in Search:</i> not reported  <i>Number of studies included:</i> 128 (number included on cannabis not reported)  <i>Number of patients in all included studies:</i> not reported	<ul style="list-style-type: none"> <li>Inconsistent association between teratogenicity (congenital anomalies) and cannabis. Most studies suggest a lack of teratogenicity or a small affect</li> <li>Cannabis use associated with inattention and impulsivity at 10 years old, lower IQ scores, increased errors of omission, academic underachievement (especially in spelling and reading), and increased rate of adolescent cannabis and cigarette use</li> </ul>	2/11
Williams, 2007, Scotland	<i>Population:</i> children ages 0-18 followed from birth  <i>Intervention:</i> maternal exposure to pregnancy  <i>Comparator:</i> no maternal exposure to toxins during pregnancy  <i>Outcome:</i> childhood mental health disorders	<i>Databases searched:</i> EMBASE, Medline, PsychInfo, SSCI  <i>Years searched:</i> Inception until 2005  <i>Key words used:</i> key words related to longitudinal studies, risk period, measurements, risks, children, substances, and childhood mental health; details not reported  <i>Inclusion criteria:</i> birth cohort, prospective, longitudinal, twin or prospective epidemiological studies; examine prenatal, prostrnatal and/or early childhood risk factors and association with childhood mental health disorders; children 0-18 years old followed from birth  <i>Exclusion criteria:</i> risk factors not identified as being associated with the prenatal period; the following mental disorders: organic disorder, schizophrenia, manic episode bipolar disorder, sexual dysfunction, and disorders of adult personality and behavior	<i>Number of citations identified in Search:</i> 2,968  <i>Number of studies included:</i> 100 (6 on cannabis use)  <i>Number of patients in all included studies:</i> not reported	<ul style="list-style-type: none"> <li>Cannabis use during pregnancy impacted child’s ability to maintain attention</li> <li>Children exposed to cannabis were found to have increased depressive symptoms from ages 10-12</li> </ul>	4/11
<b>Social Harms</b>					
Author, Year of Publication, Country	PICO	Search strategy	Studies included	Key outcomes	Quality Assessment
Ashbridge, 2012, Canada	<i>Population:</i> general population  <i>Intervention:</i> Cannabis use  <i>Comparator:</i> no cannabis use  <i>Outcome:</i> motor vehicle collisions	<i>Databases searched:</i> 19 databases (detailed not reported)  <i>Years searched:</i> not reported  <i>Key words used:</i> not reported  <i>Inclusion criteria:</i> controlled observational epidemiology studies focused on motor vehicle collisions  <i>Exclusion criteria:</i> experimental studies or simulations	<i>Number of citations identified in Search:</i> not reported  <i>Number of studies included:</i> 9  <i>Number of patients in all included studies:</i> not reported	<ul style="list-style-type: none"> <li>Cannabis significantly increase the risk of collisions with an odds ratio of 1.92 (95% CI = 1.35-2.73)</li> <li>Estimates were higher in case-control studies and studies of fatal collisions</li> </ul>	4/11



Macleod, 2004, United Kingdom	<p><i>Population:</i> general population aged 25 and under</p> <p><i>Intervention:</i> cannabis use</p> <p><i>Comparator:</i> no cannabis use</p> <p><i>Outcome:</i> educational attainment, use of other drugs, psychological health, antisocial behavior, other social problems</p>	<p><i>Databases searched:</i> Medline, EMBASE, CINAHL, PsychLIT, Web of Science, Lindesmith Center, DrugScopt, US National Institute on Drug Abuse and Substance Abuse and Mental Health Services Administration, and Addiction Abstracts</p> <p><i>Years searched:</i> inception until June 2003</p> <p><i>Key words used:</i> not reported</p> <p><i>Inclusion criteria:</i> prospective studies. General population, measured use of any illicit drug by individuals aged 25 or younger and looked at psychological or social harm</p> <p><i>Exclusion criteria:</i> not reported</p>	<p><i>Number of citations identified in Search:</i> not reported</p> <p><i>Number of studies included:</i> 32</p> <p><i>Number of patients in all included studies:</i> not reported</p>	<ul style="list-style-type: none"><li>• Cannabis use was consistently associated with reduced educational attainment, and use of other drugs</li><li>• Cannabis use was inconsistently associated with psychological problems (some found no association, others found increased use was associated with increase problems), and anti-social or other problematic behavior</li><li>• Cannabis used at a younger age was consistently associated with greater psychological and social problems</li></ul>	8/11

**Figure 2.** Flow Chart for second- and third-hand smoke systematic review

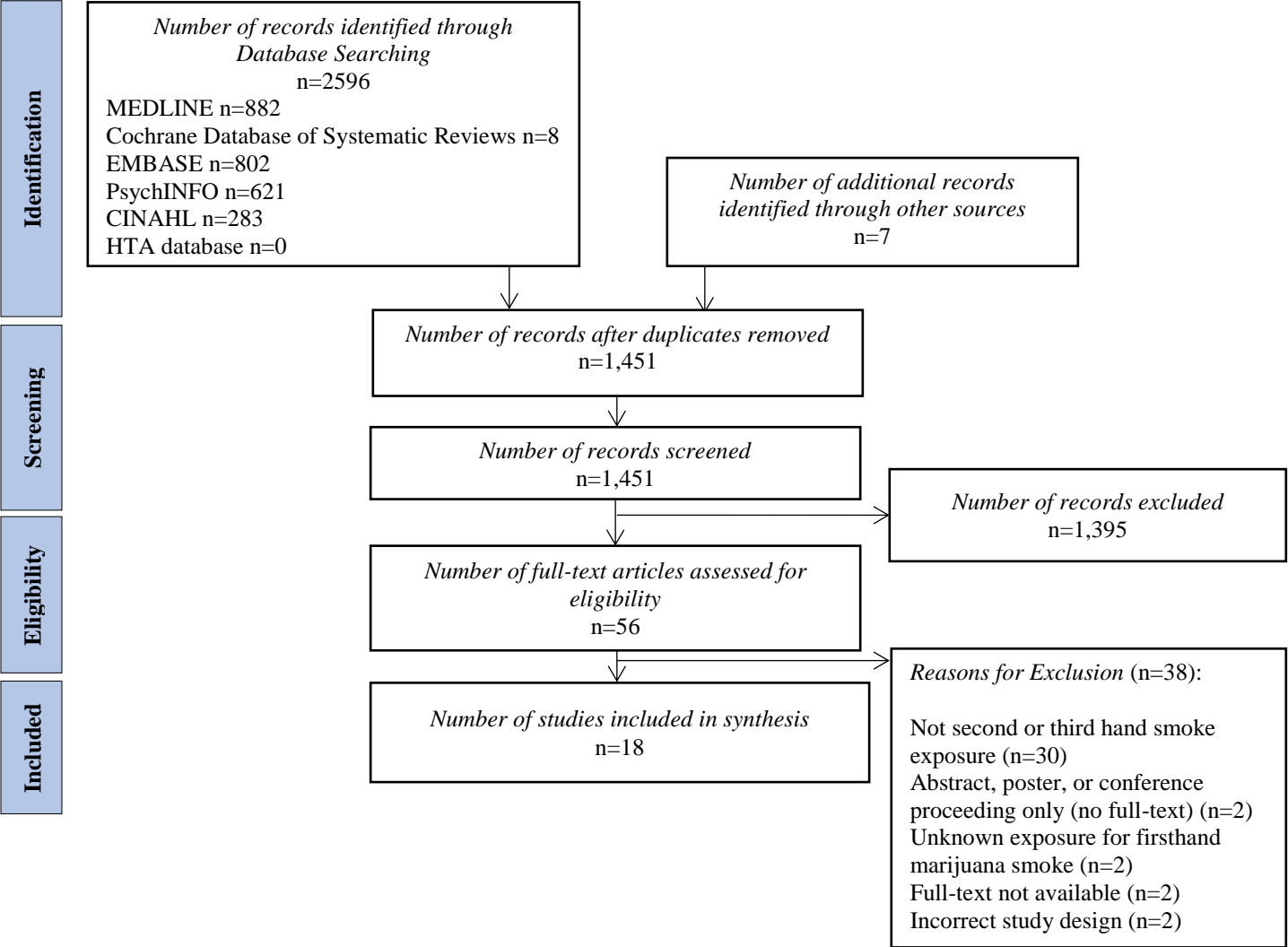


Table 2. Second- and third-hand smoke systematic review

Author, Year of Publication, Country	Intervention	Patient Selection/Testing	Outcomes	Key Findings	Quality Assessment
Cone, 2015, United States	<i>Intervention:</i> Drug-free non-smokers were exposed to cannabis smoke from individuals smoking cannabis in a controlled environment laboratory over three sessions. Unlimited cannabis was provided to smokers. <i>Multiple trials:</i> (1) 5.3% THC in unventilated environment, (2) 11.3% THC in unventilated environment, (3) 11.3% THC in ventilated environment <i>Timeline of exposure:</i> 1 hour for each session	<i>Participant Selection:</i> Not reported <i>Total number of active smokers:</i> 6 <i>Total number of non-smokers (passive smokers):</i> 6 <i>Inclusion Criteria for smokers:</i> self-reported use of cannabis at least twice per week in the past 90 days <i>Inclusion Criteria for non-smokers:</i> History of lifetime cannabis exposure but had not used cannabis or other illicit drugs in the past 6 months <i>Characteristics of Smokers:</i> Not Reported <i>Characteristics of non-Smokers:</i> Not Reported	<i>Environmental/air quality/atmospheric outcomes:</i> N/A  <i>Biological outcomes:</i> Oral fluid, whole blood  <i>Behavioral outcomes:</i> Self-report of drug effects (Drug Effects Questionnaire – visual analogue scale)	- Mean maximum THC concentration in oral fluid in non-smokers: <ul style="list-style-type: none"><li>• Session 1: 34.0 (4.9-86) ng/mL</li><li>• Session 2: 81.5 (12-308) ng/mL</li><li>• Session 3: 16.9 (1.7-75) ng/mL</li></ul> - No cannabinoid metabolites were detected in nonsmoker oral fluid specimens. - Cannabinoid metabolite concentrations in oral fluid specimens in smokers post-exposure: <ul style="list-style-type: none"><li>• Session 1: 1.248 (0.0065-3.349) ng/mL</li><li>• Session 2: 0.955 (0.105-3.173) ng/mL</li><li>• Session 3: 0.884 (0.081-3.042) ng/mL</li></ul> - Mean maximum THC and THCCOOH concentrations in whole blood specimens in nonsmokers: <ul style="list-style-type: none"><li>• Session 1: 1.4 (0.6-1.8) ng/mL THC, 1.2 (0.8-1.7) ng/mL THCCOOH</li><li>• Session 2: 3.1 (1.2-5.6) ng/mL THC, 2.5 (0-5.1) ng/mL THCCOOH</li><li>• Session 3: 0.5 (0-0.9) ng/mL THC, 0.2 (0-0.7) ng/mL THCCOOH</li></ul> - Nonsmokers reported highest drug effects after Session 2, compared to Sessions 1 and 3.	22/27
Cone, 2015, United States	<i>Intervention:</i> Drug-free non-smokers were exposed to cannabis smoke from individuals smoking cannabis in a controlled environment laboratory over three sessions. The potency and ventilation of the environment was changed between each of the sessions. <i>Multiple trials:</i> (1) 5.3% THC in unventilated environment, (2) 11.3% THC in unventilated environment, (3) 11.3% THC in ventilated environment <i>Timeline of exposure:</i> 1 hour for each session	<i>Participant Selection:</i> Participants recruited through newspaper ads, flyers posted on a university campus and around the community, and by word-of-mouth <i>Total number of active smokers:</i> 8 <i>Total number of non-smokers (passive smokers):</i> 18 <i>Inclusion Criteria for smokers:</i> self-reported use of cannabis at least two times per week during the past 90 days and did not test positive for any other illicit substances <i>Inclusion Criteria for non-smokers:</i> Healthy individuals who self-reported lifetime cannabis use but had not used cannabis or any other illicit drugs in the past 6 months. <i>Characteristics of Smokers:</i> 3 females, 5 males with an average age of 29 (SD 6) years, and an average BMI of 25.6 kg/m <sup>2</sup> <i>Characteristics of non-Smokers:</i> 9 females, 9 males with an average age of 28 (SD 7) years, and an average BMI of 24.7 kg/m <sup>2</sup>	<i>Environmental outcomes:</i> Total cannabis use (weight)  <i>Biological outcomes:</i> Urine analysis  <i>Behavioral outcomes:</i> N/A	- Total cannabis material smoked: <ul style="list-style-type: none"><li>• Session 1: 10.3 g of 5.3% THC cannabis</li><li>• Session 2: 14.4 g of 11.3% THC cannabis</li><li>• Session 3: 16.5 g of 11.3% THC cannabis</li></ul> - Non-smoker urine analysis (maximum cannabinoid metabolite concentrations): <ul style="list-style-type: none"><li>• Session 1: 11.2 ng/mL</li><li>• Session 2: 28.3 ng/mL</li><li>• Session 3: 7.5 ng/mL</li></ul> - In Session 1, participants started the experiment without goggles but many experienced eye irritation, caused by the high level of smoke in the environment. As a result, the people smoking cannabis reported that they refrained from smoking at times that they otherwise would have because they were concerned about adding more smoke to the room.	22/27
Cone, 1987, United States	<i>Intervention:</i> Individuals with drug-free urine samples were exposed to the smoke of cannabis cigarettes with 2.8% THC under double-blind conditions <i>Multiple trials:</i> 5 trials, 3 with 4 cigarettes (one ventilated, one not) and 2 with 16 cigarettes (all unventilated) <i>Timeline of exposure:</i> 1 hour each day, 6 consecutive days	<i>Participant selection:</i> Not reported <i>Total number of active smokers:</i> 0 <i>Total number of non-smokers (passive smokers):</i> 7 <i>Inclusion criteria for smokers:</i> N/A <i>Inclusion criteria for non-smokers:</i> Healthy, drug-free subjects with history of cannabis use with 14 consecutive days of cannabinoid-free urine tests; two cannabis-naïve subjects who were members of the research team <i>Characteristics of smokers:</i> N/A <i>Characteristics of non-smokers:</i> All males, average age 36 years, average weight of 74.7 kg	<i>Environmental outcomes:</i> Room-air concentrations of THC  <i>Biological outcomes:</i> Urine analysis  <i>Behavioral outcomes:</i> N/A	- Urine analysis (minimum and maximum measures of cannabinoid metabolites): <ul style="list-style-type: none"><li>• 4 cigarettes: 10.5 ng/mL to 29 ng/mL</li><li>• 16 cigarettes: 38 ng/mL to &gt;100 ng/mL</li></ul> - Room THC content at 30 minutes: <ul style="list-style-type: none"><li>• 4 cigarettes, 2 smokers, ventilated: 0.02 µg/L</li><li>• 4 cigarettes, 2 smokers, unventilated: 1.54 µg/L</li><li>• 4 cigarettes, machine, unventilated: 0.88 µg/L</li><li>• 16 cigarettes, machine, unventilated: 2.97 µg/L</li></ul> 16 cigarettes, machine, unventilated: 5.58 µg/L	20/27

Cone, 1986, United States	<p><i>Intervention:</i> Individuals with drug-free urine samples were exposed to the smoke of cannabis cigarettes with 2.8% THC under double-blind conditions</p> <p><i>Multiple trials:</i> 3 trials, one with 4 cigarettes and two with 16 cigarettes, one with five previous cannabis users and one with two cannabis-naïve subjects</p> <p><i>Timeline of exposure:</i> 1 hour each day, 6 consecutive days</p>	<p><i>Participant selection:</i> Not reported</p> <p><i>Total number of active smokers:</i> 0</p> <p><i>Total number of non-smokers (passive smokers):</i> 7</p> <p><i>Inclusion criteria for smokers:</i> N/A</p> <p><i>Inclusion criteria for non-smokers:</i> Healthy, drug-free subjects with history of cannabis use with 14 consecutive days of cannabinoid-free urine tests; two cannabis-naïve subjects</p> <p><i>Characteristics of smokers:</i> N/A</p> <p><i>Characteristics of non-smokers:</i> All males, average age 36 years, average weight of 74.7 kg</p>	<p><i>Environmental outcomes:</i> N/A</p> <p><i>Biological outcomes:</i> Urine analysis (EMIT 20, 100), whole blood analysis, pulse, blood pressure</p> <p><i>Behavioral outcomes:</i> Measured by subscales of the Addiction Research Center Inventory, a single-dose questionnaire, and a visual analog scale</p>	<p>- Physiologic effects:</p> <ul style="list-style-type: none"> <li>Changes in pulse and blood pressure were variable, and some results were significantly different from placebo</li> <li>There were no significant changes to pupillary diameter and respiration rate</li> </ul> <p>- Chemical analysis of body fluids:</p> <ul style="list-style-type: none"> <li>Four cigarettes: <math>4.6 \pm 2.2</math> positive urine tests per subject by the EMIT 20 test</li> <li>Sixteen cigarettes: <math>35.2 \pm 3.8</math> positive urine tests per subject by the EMIT 20 test</li> <li>There was a high level of between-subject variability in the positive EMIT 20 assays for the 4-cigarettes results, as one subject had 0 positive results, and another produced 12</li> <li>Blood tests were only taken from one subject (who tested negative after passive exposure to four cigarettes), and his THC levels ranged from 0.8 to 2.5 ng/mL over the course of the study</li> </ul> <p>- Behavioral effects:</p> <ul style="list-style-type: none"> <li>After exposure to smoke from both 4 and 16 cigarettes, drug responses were elevated for all scales but one. Only responses after exposure to 16 cigarettes were significant</li> <li>Responses were time-related, where effects were strongest right after smoke exposure cessation, and effects generally wore off after around 3 hours (after exposure to 16 cigarettes)</li> <li>Subjective reports from passive inhalation of the smoke from 16 cigarettes were similar to the reports from actively smoking one cannabis cigarette (2.8% THC)</li> </ul>	22/27
Cone, 1986, United States	<p><i>Intervention:</i> Individuals with drug-free urine samples were exposed to the smoke of cannabis cigarettes with 2.8% THC under double-blind conditions</p> <p><i>Multiple trials:</i> 3 trials, one with 4 cigarettes and two with 16 cigarettes, one with five previous cannabis users and one with two cannabis-naïve subjects</p> <p><i>Timeline of exposure:</i> 1 hour each day, 6 consecutive days</p>	<p><i>Participant selection:</i> Not reported</p> <p><i>Total number of active smokers:</i> 0</p> <p><i>Total number of non-smokers (passive smokers):</i> 7</p> <p><i>Inclusion criteria for smokers:</i> N/A</p> <p><i>Inclusion criteria for non-smokers:</i> Healthy, drug-free subjects with history of cannabis use with 14 consecutive days of cannabinoid-free urine tests; two cannabis-naïve subjects</p> <p><i>Characteristics of smokers:</i> N/A</p> <p><i>Characteristics of non-smokers:</i> All males, average age 36 years, average weight of 74.7 kg</p>	<p><i>Environmental outcomes:</i> N/A</p> <p><i>Biological outcomes:</i> Urine analysis (EMIT 20, EMIT 100), whole blood analysis</p> <p><i>Behavioral outcomes:</i> Subscales of the Addiction Research Center Inventory: single-dose questionnaire, visual analog scale, circular lights task, digit-symbol substitution task</p>	<p>- Physiological effects:</p> <ul style="list-style-type: none"> <li>Highly variable; supine pulse elevated after both tests but only significantly on one day of the 4-cigarette test</li> </ul> <p>- Chemical analysis of body fluids:</p> <ul style="list-style-type: none"> <li>24 hours after exposure to passive smoke from 16 cigarettes there were a large number of positive urine tests from all participants</li> <li>4 out of 5 subjects produced at least one positive urine test after exposure to four cigarettes</li> </ul> <p>- Behavioral effects:</p> <ul style="list-style-type: none"> <li>Peak effects visible immediately after cessation of exposure</li> <li>All scales except PCAG significantly different after the 16-cigarette test</li> </ul>	19/27
Herrmann, 2015, United States	<p><i>Intervention:</i> Drug-free non-smokers were exposed to cannabis smoke from individuals smoking cannabis in a controlled environment laboratory over three sessions. Unlimited cannabis was provided to smokers.</p> <p><i>Multiple trials:</i> (1) 11.3% THC in unventilated environment, (2) 11.3% THC in ventilated environment (11 air-exchanges per hour)</p> <p><i>Timeline of exposure:</i> 1 hour</p>	<p><i>Participant Selection:</i> Participants were recruited from Baltimore, MD using media advertising and word-of-mouth</p> <p><i>Total number of active smokers:</i> 7</p> <p><i>Total number of non-smokers (passive smokers):</i> 12</p> <p><i>Inclusion Criteria for smokers:</i> 18-45 years old, use cannabis at least two times per week during the past 90 days, provide urine sample that is THC positive and negative for other drugs, negative breath alcohol reading at screening and day of session, BMI 19-34kg/m<sup>2</sup>, not pregnant or nursing</p> <p><i>Inclusion Criteria for non-smokers:</i> 18-45 years old, cannabis use at least once but not during the past 6 months, provided urine sample negative for all drugs, negative breath alcohol reading at screening and session, BMI 19-34kg/m<sup>2</sup>, not pregnant or nursing</p> <p><i>Characteristics of Smokers:</i> 4 males, 3 females with an average</p>	<p><i>Environmental outcomes:</i> Total weight of cannabis smoked</p> <p><i>Biological outcomes:</i> blood, urine, saliva and hair for 8 hours after exposure, heart rate, blood pressure</p> <p><i>Behavioral outcomes:</i> Drug Effect Questionnaire, Divided attention task (DAS), digit symbol substitution task (DSST), paced auditory serial addition task (PASAT)</p>	<p>- Non-smoker blood concentration of THC:</p> <ul style="list-style-type: none"> <li>All participants had detectable cannabinoids following exposure in an unventilated environment; mean of 3.2 ng/mL at Time 0</li> <li>4 of 6 participants had detectable cannabinoids following exposure in the ventilated environment; mean of 0.7 ng/mL at Time 0</li> </ul> <p>- Non-smoker urine concentration of cannabinoid metabolites:</p> <ul style="list-style-type: none"> <li>One participant produced a positive urine sample 4 hours post-exposure in the unventilated environment using federal (U.S.) drug testing guidelines</li> <li>No participants produced positive urine samples after exposure in a ventilated environment</li> </ul>	22/27

		age of 29.4 (SD 5.8) and an average BMI of 25.6 kg/m <sup>2</sup> <i>Characteristics of non-Smokers:</i> 3 males, 3 females with an average age of 28.7 and an average BMI of 25.3 kg/m <sup>2</sup>		<ul style="list-style-type: none"> <li>- Non-smoker physiological effects: <ul style="list-style-type: none"> <li>• After the unventilated session, a statistically significant increase in heart rate was observed</li> <li>• No significant effects on blood pressure or heart rate were observed following the ventilated session</li> </ul> </li> <li>- Non-smoker subjective effects: <ul style="list-style-type: none"> <li>• Significant changes in reports of “drug effect”, “pleasant drug effect”, “tired”, and “hungry/have munchies” was observed between pre- and post-exposure in the unventilated environment, and reports of “alert” and “vigorous” were significantly lower</li> <li>• The only significant change in the ventilated environment was an increase in the reports of “hungry/have munchies”</li> </ul> </li> <li>- Non-smoker behavioral effects: <ul style="list-style-type: none"> <li>• Participants attempted significantly more patterns in the DSST in the hour after being exposed to smoke in an unventilated environment, and the number of attempted and correctly completed patterns decreased significantly as well</li> <li>• The number of DSST patterns attempted and completed correctly increased from baseline following exposure to smoke in a ventilated environment; performance on the PASAT and DAT remained unchanged</li> </ul> </li> </ul>	
Law, 1984, United Kingdom	<i>Intervention:</i> Nonsmokers were exposed to cannabis smoke (9.8% THC) in a small, unventilated room <i>Multiple trials:</i> No <i>Timeline of exposure:</i> Smokers consumed their cannabis cigarette (which took 10 to 34 minutes), and then the nonsmoking participants remained in the room for three hours	<i>Participant selection:</i> Not reported <i>Total number of active smokers:</i> 6 <i>Total number of non-smokers (passive smokers):</i> 4 <i>Inclusion criteria for smokers:</i> Not reported <i>Inclusion criteria for non-smokers:</i> Not reported <i>Characteristics of smokers:</i> Not reported <i>Characteristics of non-smokers:</i> Not reported	<i>Environmental outcomes:</i> Gas-chromatography determined environmental exposure  <i>Biological outcomes:</i> Urine analysis, whole blood analysis (using radioimmunoassay)  <i>Behavioral outcomes:</i> N/A	<ul style="list-style-type: none"> <li>- Non-smoking blood samples: <ul style="list-style-type: none"> <li>• Cannabinoids were not detected 1 to 4 hours after passive smoke inhalation</li> </ul> </li> <li>- Non-smoking urine concentration of cannabinoid metabolites: <ul style="list-style-type: none"> <li>• ‘Low amounts’ of cannabinoids were detected in passive inhaler’s urine</li> </ul> </li> <li>- Non-smoker subjective effects: <ul style="list-style-type: none"> <li>• No passive inhalers reported subjective effects</li> </ul> </li> </ul>	13/27
Maertens, 2009, Canada	<i>Intervention:</i> Tobacco and cannabis cigarettes were combusted and sidestream and mainstream smoke was passed through a filter and the condensates were tested for genotoxicity (Salmonella mutagenicity) and cytotoxicity (THC not reported) <i>Multiple trials:</i> Two trials – one at ‘standard’ smoking conditions and the other at ‘extreme’ smoking conditions; <i>Timeline of exposure:</i> Under the ‘standard’ smoking conditions each puff had a 35mL volume, 2s duration, and were taken at 60s intervals. For the ‘extreme’ conditions, each puff had a 70mL puff volume, 2s duration, and were taken at a 30s interval. Each trial lasted 20 mins	<i>Tests:</i> Neutral Red Uptake Assay (NRUA), Salmonella Mutagenicity Test (SMT), Cytokinesis Block Micronucleus Assay (CBMA) <i>Statistical analysis:</i> <ul style="list-style-type: none"> <li>• NRUA: analysis of variance for multiple cytotoxicity assessment values</li> <li>• SMT: least-squares linear regression analysis for number of revertant genes</li> <li>• CBMA: poisson regression model, Bonferroni-corrected <math>\alpha</math> level for change in the concentration effect</li> </ul>	<i>Environmental outcomes:</i> N/A  <i>Biological outcomes:</i> cytotoxicity, mutagenicity, concentration of bi-nucleoid cells  <i>Behavioral outcomes:</i> N/A	<ul style="list-style-type: none"> <li>- Cannabis appears to be more cytotoxic than tobacco in the particulate and combined particulate/gas phases, however the gas phase of cannabis appears to be less cytotoxic than tobacco</li> <li>- The particulate phase was the most cytotoxic</li> <li>- Unlike tobacco, none of the cannabis samples elicited a positive detection of a frameshift mutation when metabolic activation was withheld.</li> <li>- Mutagenicity analysis shows that cannabis smoke is more mutagenic than tobacco smoke</li> <li>- Cytokinesis block micronucleus assay shows that cannabis smoke is more cytostatic as well, as there was an increase in micronucleus frequency when exposed to cannabis smoke</li> </ul>	18/27
Maertens, 2013, Canada	<i>Intervention:</i> Tobacco and cannabis cigarettes were combusted and mainstream smoke was passed through a filter and the smoke condensates were collected (THC not reported) <i>Multiple trials:</i> One trial was conducted with tobacco and the other with cannabis <i>Timeline of exposure:</i> Conditions were crafted to resemble cannabis smoking behavior (with a 70mL puff volume, a duration of 2s, at intervals of 30s)	<i>Tests:</i> Lactate dehydrogenase (LDH) assay, XTT assay, Microarray hybridization (MH) <i>Statistical analysis:</i> <ul style="list-style-type: none"> <li>• LDH: determines cytotoxicity</li> <li>• XTT: determines cytotoxicity</li> <li>• MH: to determine gene expression – followed Agilent’s protocol</li> </ul>	<i>Environmental outcomes:</i> N/A  <i>Biological outcomes:</i> cytotoxicity, RNA extractions, microarray hybridization  <i>Behavioral outcomes:</i> N/A	<ul style="list-style-type: none"> <li>- Cell toxicity was highest in cannabis smoke concentrates after a 6 µg/mL threshold, and cell response was ~3 times greater than that observed for tobacco smoke</li> <li>- Cannabis smoke consistently caused more significant changes in gene expression when compared to tobacco smoke, both after 6 hours of exposure, and after 4 hours of recovery time from exposure.</li> <li>- The benchmark dose of cannabis smoke required to alter KEGG pathways is much lower than that required for tobacco smoke, indicating that cannabis smoke is more potent than tobacco smoke</li> </ul>	17/27

Moir, 2007, Canada	<i>Intervention:</i> Combustion of cannabis cigarettes in a controlled environment and systematic comparison of the contents of both mainstream and side stream cannabis and tobacco smoke <i>Multiple trials:</i> No <i>Timeline of exposure:</i> N/A	<i>Tests:</i> Borgwaldt 20 port rotary smoking machine, or Cerulean 20 port linear smoking machine <i>Smoking practice:</i> Two kinds: ‘ISO’: 35mL, 2 sec duration, 60 sec interval; ‘Extreme’: 70mL, 2 sec duration, 30 sec interval <i>Sample collection:</i> Not reported	<i>Environmental outcomes:</i> Quantify content of mainstream and side stream cannabis and tobacco smoke  <i>Biological outcomes:</i> N/A  <i>Behavioral outcomes:</i> N/A	- Total particulate matter increased 2.4 times under extreme smoking practice compared to ISO smoking practice - Ammonia was found in mainstream cannabis smoke at 20 times the amount found in tobacco mainstream smoke, and hydrogen cyanide was found in significantly higher amounts in cannabis smoke when compared to tobacco smoke - Arsenic and lead were absent from cannabis smoke (which agrees with the certificate of analysis provided by the grower) *Note: authors found nicotine in cannabis smoke samples, indicating a possibility of cross-contamination between samples.	16/27
Moore, 2011, United States	<i>Intervention:</i> Passive exposure to cannabis in a Dutch “coffee shop” <i>Multiple trials:</i> 2 trials in 2 different coffee shops, with varying numbers of active smokers (varying % THC) <i>Timeline of exposure:</i> 3 hours in each shop	<i>Participant selection:</i> Volunteers, selection strategy not reported <i>Total number of active smokers:</i> 16 in Trial 1, 6 in Trial 2 <i>Total number of non-smokers (passive smokers):</i> 10 <i>Inclusion criteria for smokers:</i> Any active smoker in the coffee shop during the 3-hour exposure timeline <i>Inclusion criteria for non-smokers:</i> Healthy non-cannabis smokers <i>Characteristics of smokers:</i> Not reported <i>Characteristics of non-smokers:</i> 5 males, average age 22.8 years, weight 84 kg, height 1.9 m, BMI 233; 5 females, average age 23.8 years, weight 62.4 kg, height 1.71 m, BMI 21.2	<i>Environmental outcomes:</i> Air cannabinoid content (Quantisal collection device)  <i>Biological outcomes:</i> Oral fluid (Quantisal collection device)  <i>Behavioral outcomes:</i> N/A	- Air cannabinoid THC content: <ul style="list-style-type: none"><li>• Pad 1 (Trial 1): 290 ng/mL</li><li>• Pad 2 (Trial 2): 212 ng/mL</li><li>• Pad 3 (Trial 3): 216 ng/mL</li></ul> - Oral fluid THC levels after 3 hours of exposure (minimum and maximum): <ul style="list-style-type: none"><li>• Trial 1: 1.6-5.3 ng/mL</li><li>• Trial 2: 2.3-17 ng/mL</li></ul>	19/27
Morland, 1985, Norway	<i>Intervention:</i> Subjects were exposed to cannabis and hashish smoke in a small, unventilated car <i>Multiple trials:</i> First trial with hashish (1.5% THC), second trial with cannabis (1.5% THC) <i>Timeline of exposure:</i> 30 mins	<i>Participant selection:</i> Volunteers, selection strategy not reported <i>Total number of active smokers:</i> 5 <i>Total number of non-smokers (passive smokers):</i> 10 <i>Inclusion criteria for smokers:</i> Not reported <i>Inclusion criteria for non-smokers:</i> Healthy, cannabis naïve individuals <i>Characteristics of smokers:</i> Not reported <i>Characteristics of non-smokers:</i> 7 males, 3 females “... of normal weight in relation to their height, age, and sex.”	<i>Environmental outcomes:</i> N/A  <i>Biological outcomes:</i> Blood cannabinoid levels (RIA), urine analysis (EMIT)  <i>Behavioral outcomes:</i> N/A	- Blood concentrations of THC immediately after exposure: <ul style="list-style-type: none"><li>• After exposure to hashish: 1.1-1.4 ng/mL</li><li>• After exposure to cannabis: 3.5-6.2 ng/mL</li></ul> - Blood concentrations of THC 2.5 hours after exposure: <ul style="list-style-type: none"><li>• After exposure to hashish: 0 ng/mL</li><li>• After exposure to cannabis: 0.3 ng/mL</li></ul> - Urine concentration of cannabinoid metabolites: <ul style="list-style-type: none"><li>• After exposure to hashish: one participant tested positive (&gt;20ng/mL) twice between 4 and 24 hours after exposure</li></ul> After exposure to cannabis: On Day 2 (~24 hours after exposure) range was 14-30 ng/mL	16/27
Mule, 1988, United States	<i>Intervention:</i> In the first part of this experiment, smokers were asked to smoke cannabis as they usually do and observed. In the second part, non-smokers were exposed to four cannabis cigarettes (27 mg THC) in an unventilated room <i>Multiple trials:</i> No <i>Timeline of exposure:</i> 1 hr	<i>Participant selection:</i> Not reported <i>Total number of active smokers:</i> 8 <i>Total number of non-smokers (passive smokers):</i> 3 <i>Inclusion criteria for smokers:</i> Occasional (1 cig/week) or moderate (1-3 cigs/week) smokers, <i>Inclusion criteria for non-smokers:</i> Not reported <i>Characteristics of smokers:</i> All male, 5’9”-6’1” tall, weighed between 154-175 lbs, and were 21-27 years old <i>Characteristics of non-smokers:</i> Not reported	<i>Environmental outcomes:</i> N/A  <i>Biological outcomes:</i> Urine analysis (EMIT)  <i>Behavioral outcomes:</i> N/A	- Urine concentrations of cannabinoid metabolites (20-24 hours post exposure) All three samples tested at >6 ng/mL, less than the sensitivity of the EMIT assay so true values are unknown	18/27
Niedbala, 2005, United States	<i>Intervention:</i> Participants were placed in severe secondhand smoke conditions in an unventilated van for 1 hour <i>Multiple trials:</i> Two trials, each with four smokers and four passive inhalers. Trial 1 5.4% THC, and Trial 2 10.4% THC. <i>Timeline of exposure:</i> Smokers finished their cigarettes within 20 mins, and participants remained inside of the van for 60 mins	<i>Participant selection:</i> Volunteers, does not state recruitment strategy <i>Total number of active smokers:</i> 8 (2 groups of 4) <i>Total number of non-smokers (passive smokers):</i> 8 (2 groups of 4) <i>Inclusion criteria for smokers:</i> Healthy, Caucasian males who reported infrequent cannabis use in the past <i>Inclusion criteria for non-smokers:</i> Healthy, Caucasian males who tested as cannabis-free prior to the study based on oral fluid, urine tests, and self-report data <i>Characteristics of smokers:</i> 18 to 24 years of age for both groups <i>Characteristics of non-smokers:</i> 34 to 50 years old for the first group, and 25 to 50 years old for the second group	<i>Environmental outcomes:</i> Intercept collector pads  <i>Biological outcomes:</i> Oral fluid, urine analysis  <i>Behavioral outcomes:</i> N/A	- Intercept devices (environmental THC): <ul style="list-style-type: none"><li>• THC concentrations got as high as 14 ng/mL (range from 3 to 14 ng-mL) over the 45 minutes that participants spent in the environment</li></ul> - Oral fluid analysis: <ul style="list-style-type: none"><li>• All participants screened positive at the 3 ng/mL cutoff</li><li>• At Time 0, the average THC concentration in oral fluid was 5.3 ng/mL (SEM: 4.7-5.9 ng/mL)</li></ul> - Urine concentration of cannabinoid metabolites: <ul style="list-style-type: none"><li>• All subjects tested negative at the 15ng/mL cutoff for THCCOOH, although levels of THCCOOH could be detected post-exposure</li></ul>	16/27



				<ul style="list-style-type: none"> <li>• Trial 1: mean peak THCCOOH concentrations were 11.2 ng/mL (<math>\pm 2</math> ng/mL) at 6 to 8 hours post-exposure</li> <li>• Trial 2: mean peak THCCOOH concentrations were 8.42 ng/mL at 4-8 hours</li> </ul>	
Niedbala, 2004, United States	<p><i>Intervention:</i> Participants sat in a sealed room, smokers consumed one cannabis cigarette each with an approximate THC level of 1.75%</p> <p><i>Multiple trials:</i> No</p> <p><i>Timeline of exposure:</i> The smoking period lasted approximately 20 minutes, and all participants remained in the room for 4 hours</p>	<p><i>Participant selection:</i> Volunteers, does not state recruitment strategy</p> <p><i>Total number of active smokers:</i> 5</p> <p><i>Total number of non-smokers (passive smokers):</i> 4</p> <p><i>Inclusion criteria for smokers:</i> Healthy, caucasian males who reported prior infrequent use of cannabis</p> <p><i>Inclusion criteria for non-smokers:</i> Healthy, caucasian males who tested as cannabis-free prior to the start of the study</p> <p><i>Characteristics of smokers:</i> 21 to 25 years old</p> <p><i>Characteristics of non-smokers:</i> 37 to 49 years old</p>	<p><i>Environmental outcomes:</i> Air sample</p> <p><i>Biological outcomes:</i> Oral fluid analysis, urine analysis</p> <p><i>Behavioral outcomes:</i> N/A</p>	<ul style="list-style-type: none"> <li>- Air sample analysis: <ul style="list-style-type: none"> <li>• Highest THC concentrations in the air were found in sample taken during smoking (0.19 <math>\mu</math>g/mL)</li> </ul> </li> <li>- Non-smoker oral fluid: <ul style="list-style-type: none"> <li>• Peak measures of THC in oral fluid were taken 20 minutes after exposure, with a mean of 13.4 ng/mL (<math>\pm 3.9</math> ng/mL)</li> </ul> </li> <li>- Non-smoker urine concentrations of cannabinoid metabolites: <ul style="list-style-type: none"> <li>• All passive smokers produced negative urine samples by the cutoffs used in this study (50 ng/mL and 15 ng/mL)</li> <li>• One participant had traces of THCCOOH in their urine after ~6 hours (3.4 ng/mL)</li> </ul> </li> </ul>	15/27
Perez-Reyes, 1983, United States	<p><i>Intervention:</i> Four subjects smoked cannabis cigarettes in the presence of two non-smokers in both a room (Trials 1 &amp; 3) and a car (Trial 2), biological samples were taken and compared between smoking and non-smoking groups.</p> <p><i>Multiple trials:</i> Three; Trial 1 with two cigarettes with 2.5 and 2.8% THC, Trial 2 with two cigarettes with 2.8% THC, and Trial 3 with four cigarettes with 2.8% THC</p> <p><i>Timeline of exposure:</i> Trial 1: 1 hr, Trial 2: 1 hr, Trial 3: 1 hr for 3 consecutive days</p>	<p><i>Participant selection:</i> Not reported</p> <p><i>Total number of active smokers:</i> 6</p> <p><i>Total number of non-smokers (passive smokers):</i> 6</p> <p><i>Inclusion criteria for smokers:</i> Experienced cannabis users</p> <p><i>Inclusion criteria for non-smokers:</i> Cannabis-naïve subjects</p> <p><i>Characteristics of smokers:</i> Three males, three females; “...healthy and of normal weight and height in relation to their age and sex.”</p> <p><i>Characteristics of non-smokers:</i> Three males, three females; “...healthy and of normal weight and height in relation to their age and sex.”</p>	<p><i>Environmental outcomes:</i> THC presence in air</p> <p><i>Biological outcomes:</i> Urine analysis (EMIT), blood samples</p> <p><i>Behavioral outcomes:</i> N/A</p>	<p>Urine analysis (minimum and maximum measures of cannabinoid metabolites):</p> <ul style="list-style-type: none"> <li>• Trial 1: &lt;20 ng/mL sensitivity</li> <li>• Trial 2: All but one sample &lt;20 ng/mL, which was “slightly above” 20 ng/mL</li> </ul> <p>Trial 3: One sample (over 3 days of exposure) registered at “slightly above 20 ng/mL”, the rest were &lt;20 ng/mL</p>	16/27
Rohrich, 2010, Germany	<p><i>Intervention:</i> Individuals were exposed to cannabis smoke in a Dutch “coffee shop with ventilation (% THC not available)</p> <p><i>Multiple trials:</i> No</p> <p><i>Timeline of exposure:</i> 3 hrs</p>	<p><i>Participant selection:</i></p> <p><i>Total number of active smokers:</i> 8 to 25 at one time</p> <p><i>Total number of non-smokers (passive smokers):</i> 8</p> <p><i>Inclusion criteria for smokers:</i> Active smoker in the coffee shop at the time</p> <p><i>Inclusion criteria for non-smokers:</i> No history of cannabis use, and no contact with cannabis in the month proceeding the experiment</p> <p><i>Characteristics of smokers:</i> Not reported</p> <p><i>Characteristics of non-smokers:</i> 4 male, 4 female</p>	<p><i>Environmental outcomes:</i> N/A</p> <p><i>Biological outcomes:</i> Blood testing (Inspec), urine analysis (GC-MS)</p> <p><i>Behavioral outcomes:</i> N/A</p>	<p>Blood concentrations of THC:</p> <ul style="list-style-type: none"> <li>• 1.5 hrs post-exposure: 0.5-0.7 ng/mL</li> <li>• 3.5 hrs post-exposure: 0.4-0.7 ng/mL</li> <li>• 6 hrs post-exposure: None detected</li> </ul> <p>Urine concentrations of cannabinoid metabolites (THCCOOH):</p> <ul style="list-style-type: none"> <li>• 1.5 hrs post-exposure: 0.3 ng/mL</li> <li>• 3.5 hrs post-exposure: 0.8 ng/mL</li> <li>• 6 hrs post-exposure: 0.5 ng/mL</li> </ul> <p>14 hrs post-exposure: 0.3 ng/mL</p>	15/27
Zeidenberg, 1977, United States	<p><i>Intervention:</i> A number of heavy cannabis smokers consumed cannabis around a placebo smoker in a locked ward (THC level not reported)</p> <p><i>Multiple trials:</i> No</p> <p><i>Timeline of exposure:</i> 3 weeks</p>	<p><i>Participant selection:</i> Not reported</p> <p><i>Total number of active smokers:</i> 5</p> <p><i>Total number of non-smokers (passive smokers):</i> 1</p> <p><i>Inclusion criteria for smokers:</i> Not reported</p> <p><i>Inclusion criteria for non-smokers:</i> Not reported</p> <p><i>Characteristics of smokers:</i> Not reported</p> <p><i>Characteristics of non-smokers:</i> Not reported</p>	<p><i>Environmental outcomes:</i> N/A</p> <p><i>Biological outcomes:</i> Urine analysis</p> <p><i>Behavioral outcomes:</i> Subjective reporting, physical exam</p>	<ul style="list-style-type: none"> <li>- Urine concentration of cannabinoid metabolites: <ul style="list-style-type: none"> <li>• The participant tested positive for THC for 25 days, including 11 days after cessation of exposure</li> <li>• The peak amount of THC found in the participants’ system was two weeks after his first exposure (150 ng/mL)</li> </ul> </li> <li>- Subjective and physiological effects: <ul style="list-style-type: none"> <li>• The participant reported dizziness, nausea and was found to display symptoms of tachycardia and conjunctivitis</li> </ul> </li> </ul>	14/27

**Table 3.** Perceptions of harms of non-medical cannabis use on physical health, by province

<b>Cigarettes</b>	<b>Less harmful</b>	<b>Similar harm</b>	<b>More harmful</b>	<b>Don't know</b>
Canada	11.8%	57.5%	29.7%	0.9%
Alberta	15.3%	60.9%	23.8%	0%
British Columbia	10.0%	55.8%	32.6%	1.6%
Ontario	9.5%	55.2%	34.7%	0.7%
Quebec	15.0%	60.3%	23.0%	1.7%
<b>Alcohol</b>	<b>Less harmful</b>	<b>Similar harm</b>	<b>More harmful</b>	<b>Don't know</b>
Canada	21.6%	55.8%	21.8%	0.9%
Alberta	28.7%	45.8%	25.5%	0%
British Columbia	20.5%	55.9%	23.2%	0.5%
Ontario	19.9%	56.6%	22.1%	1.4%
Quebec	23.3%	57.3%	18.3%	1.1%
<b>Prescription drugs</b>	<b>Less harmful</b>	<b>Similar harm</b>	<b>More harmful</b>	<b>Don't know</b>
Canada	8.0%	39.1%	51.0%	1.9%
Alberta	14.1%	34.8%	51.0%	0%
British Columbia	5.2%	36.9%	54.0%	3.8%
Ontario	5.0%	35.5%	58.0%	1.4%
Quebec	9.1%	50.7%	37.5%	2.8%
<b>Other illicit drugs</b>	<b>Less harmful</b>	<b>Similar harm</b>	<b>More harmful</b>	<b>Don't know</b>
Canada	11.8%	12.8%	74.9%	0.5%
Alberta	16.5%	15.1%	68.4%	0%
British Columbia	11.0%	10.0%	78.0%	0.9%
Ontario	6.8%	14.5%	77.8%	0.9%
Quebec	15.8%	12.1%	62.0%	0%

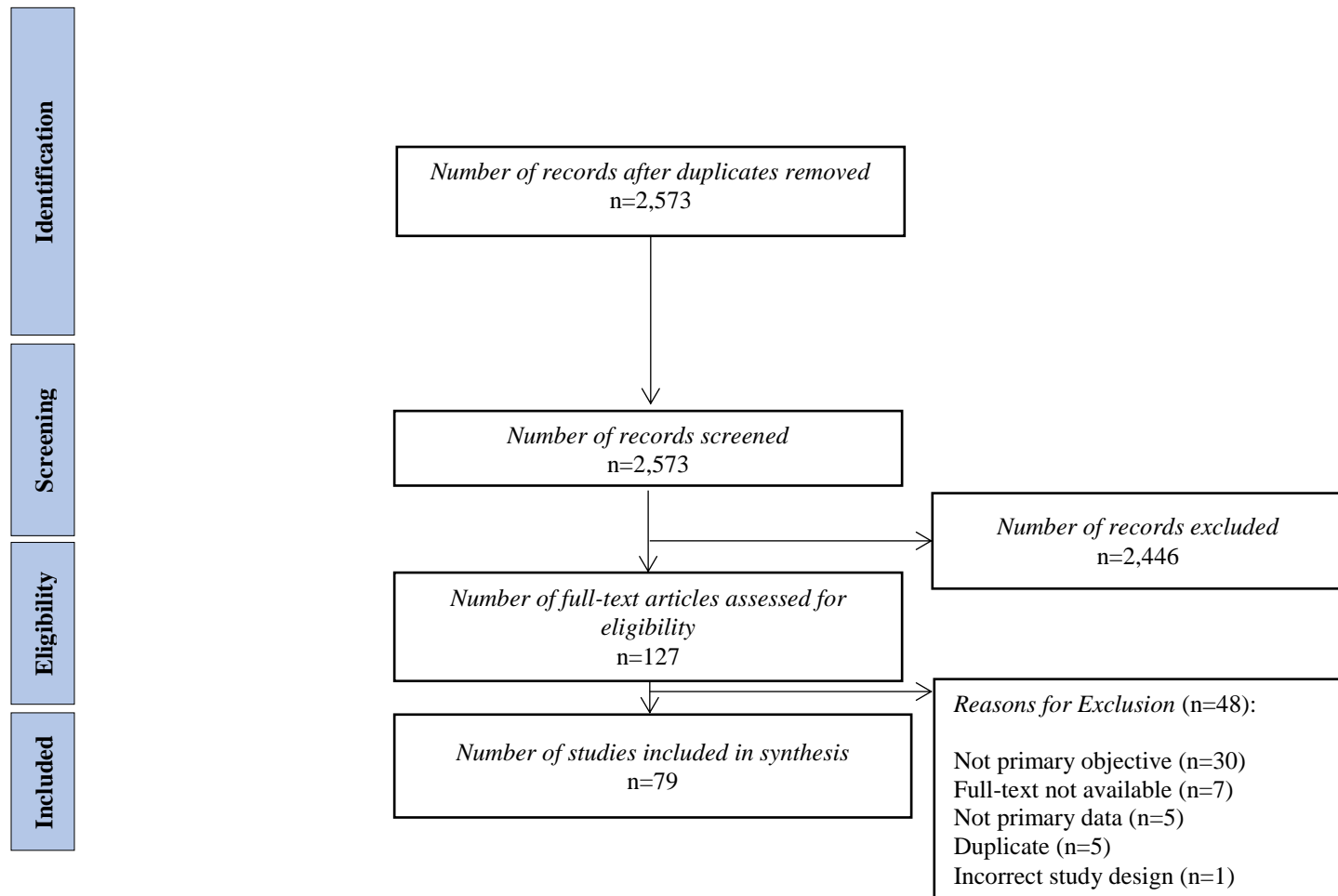
**Table 2.** Perceptions of harms of non-medical cannabis use on mental health, by province

<b>Cigarettes</b>	<b>Less harmful</b>	<b>Similar harm</b>	<b>More harmful</b>	<b>Don't know</b>
Canada	34.4%	41.0%	22.8%	1.9%
Alberta	28.7%	44.9%	26.4%	0%
British Columbia	42.9%	41.7%	13.0%	2.3%
Ontario	33.3%	41.2%	22.4%	3.1%
Quebec	34.6%	40.8%	22.9%	1.7%
<b>Alcohol</b>	<b>Less harmful</b>	<b>Similar harm</b>	<b>More harmful</b>	<b>Don't know</b>
Canada	18.9%	60.8%	18.9%	1.4%
Alberta	24.8%	56.9%	16.8%	1.4%
British Columbia	19.9%	54.8%	23.9%	1.4%
Ontario	16.0%	59.4%	23.1%	1.5%
Quebec	19.4%	66.3%	12.5%	1.8%



<b>Prescription drugs</b>	<b>Less harmful</b>	<b>Similar harm</b>	<b>More harmful</b>	<b>Don't know</b>
Canada	6.7%	43.4%	47.6%	2.2%
Alberta	8.7%	48.2%	40.8%	2.3%
British Columbia	8.8%	37.4%	50.4%	3.4%
Ontario	5.9%	38.8%	53.3%	2.0%
Quebec	5.5%	51.3%	41.4%	1.9%
<b>Other illicit drugs</b>	<b>Less harmful</b>	<b>Similar harm</b>	<b>More harmful</b>	<b>Don't know</b>
Canada	12.7%	17.8%	59.0%	0.5%
Alberta	22.6%	16.1%	60.4%	0.9%
British Columbia	14.7%	13.8%	71.0%	0.4%
Ontario	7.5%	20.1%	71.4%	1.0%
Quebec	13.5%	17.8%	68.6%	0%

**Figure 1.** Flow Chart for gateway systematic review



## APPENDIX 3

Figure 1: Flow Chart of Systematic Review Process

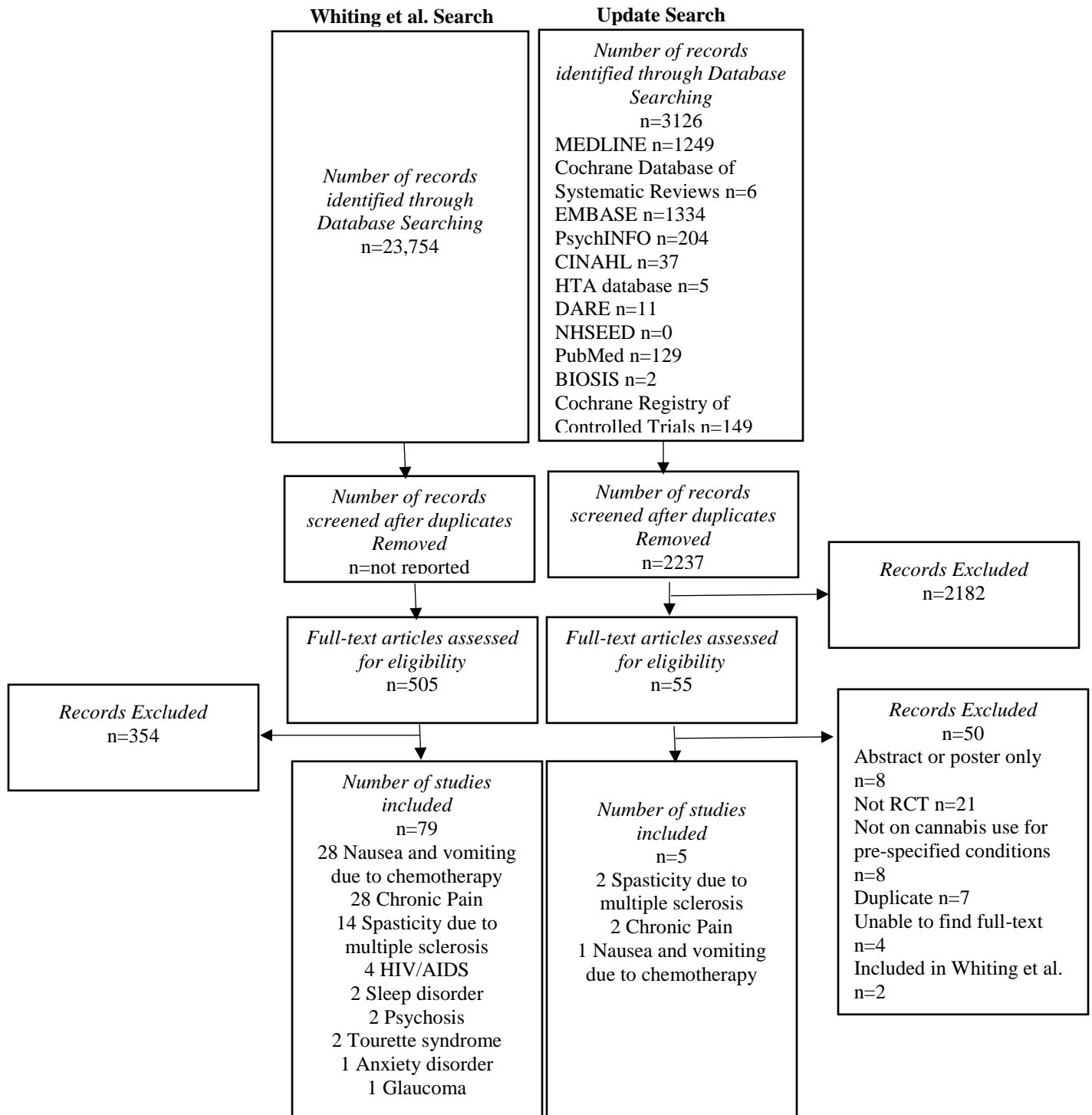


Figure 2: Trials by intervention and method of administration

	Total trials	Number of trials by method of administration
<b>Synthetic</b>		
<b>Nabilone</b>	21	Capsules (oral): 21
<b>Dronabinol</b>	15	Capsules (oral): 15
<b>Levonantradol</b>	6	Capsules (oral): 1
		Intramuscular: 5
<b>Ajulemic Acid</b>	1	Capsules (oral): 1
<b>Not synthetic</b>		
<b>THC</b>	26	Capsule (oral): 12
		Smoked: 8
		Oromucosal Spray: 6
<b>Nabiximols (Sativex)</b>	22	Oromucosal spray: 22
<b>CBD</b>	5	Capsule (oral): 3
		Oromucosal Spray: 2
<b>THC/CBD</b>	4	Capsule (oral): 4
<b>Cannabis</b>	3	Vaporized: 2
		Smoked: 1
<b>ECB-002A</b>	1	Tablet (oral): 1
<b>Total trials</b>	104	

Table 1: Medical Cannabis Review Update: Characteristics of included studies

Author, Year	Country	RCT design	N	Duration	Patient Details	Intervention	Comparator	Risk of Bias
<i>Multiple Sclerosis</i>								
Ball, 2015	UK	Parallel group	498 (329 active)	3 years	Ages 18-65, primary or secondary progressive MS, 4.0-6.5 EDSS* score, showed signs of disease progression over the past year	Dronabinol (Marinol®; Oral $\Delta^9$ - THC), max. 28 mg/day	Placebo (Vegetable oil pills)	Unclear
Leocani, 2015	Italy	Cross-over	34	10 weeks	Age 18 and older, diagnosed with progressive primary or secondary MS at least 12 months prior, relapse-free for at least 3 months, EDSS score between 3.0 and 6.5, moderate to severe spasticity on the modified Ashworth scale, test drug-free at beginning of study, stable dose of anti-spasticity medical for at least 2 months	Nabiximol (Sativex®; $\Delta^9$ - THC and CBD), participants began with one spray/day and increased by one spray for subsequent days during the titration period (2 weeks) before stable treatment period (2 weeks)	Placebo, not reported	High/Unclear
<i>Chronic Pain</i>								
de Vries, 2016	The Netherlands	Cross-over	24	2 days	Age over 18, diagnosed with chronic pancreatitis, had experienced chronic abdominal pain for the past 3 months, pain on the numeric rating scale at $\geq 3$	ECP002A (Namisol®; Oral $\Delta^9$ - THC), 8mg/day, simultaneously with diazepam (placebo)	Active placebo (diazepam), 5mg/day for non-opioid group, 10mg/day for opioid group	High
Wilsey, 2016	US	Cross-over	42	3 8-hour exposure sessions, separated by at least 3 days	Ages 19-70, diagnosed with pathology of the spinal cord due to either trauma or disease, pain intensity greater than or equal to 4/10, no symptoms of depression	Inhaled vaporized cannabis at 2.9% and 6.7% levels of THC content	Placebo cannabis, containing a small percentage of THC	High
<i>Nausea due to Chemotherapy</i>								
Cote, 2016	Canada	Parallel group	56 (29 active)	7 weeks	Ages 18-80, diagnoses of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and/or larynx, treated with radiotherapy or radiochemotherapy (either alone or postoperatively), no other cancer diagnosis in past 5 years	Nabilone (Cesamet®), 0.5 mg/day for Week 1, 2 doses of 0.5mg/day for Week 2, adjusted dose up to 4.0 mg/day for Week 3 until end of treatments)	Placebo, appearance identical to nabilone	High

\*EDSS: Expanded Disability Status Scale

# Appendix 4

Figure 1

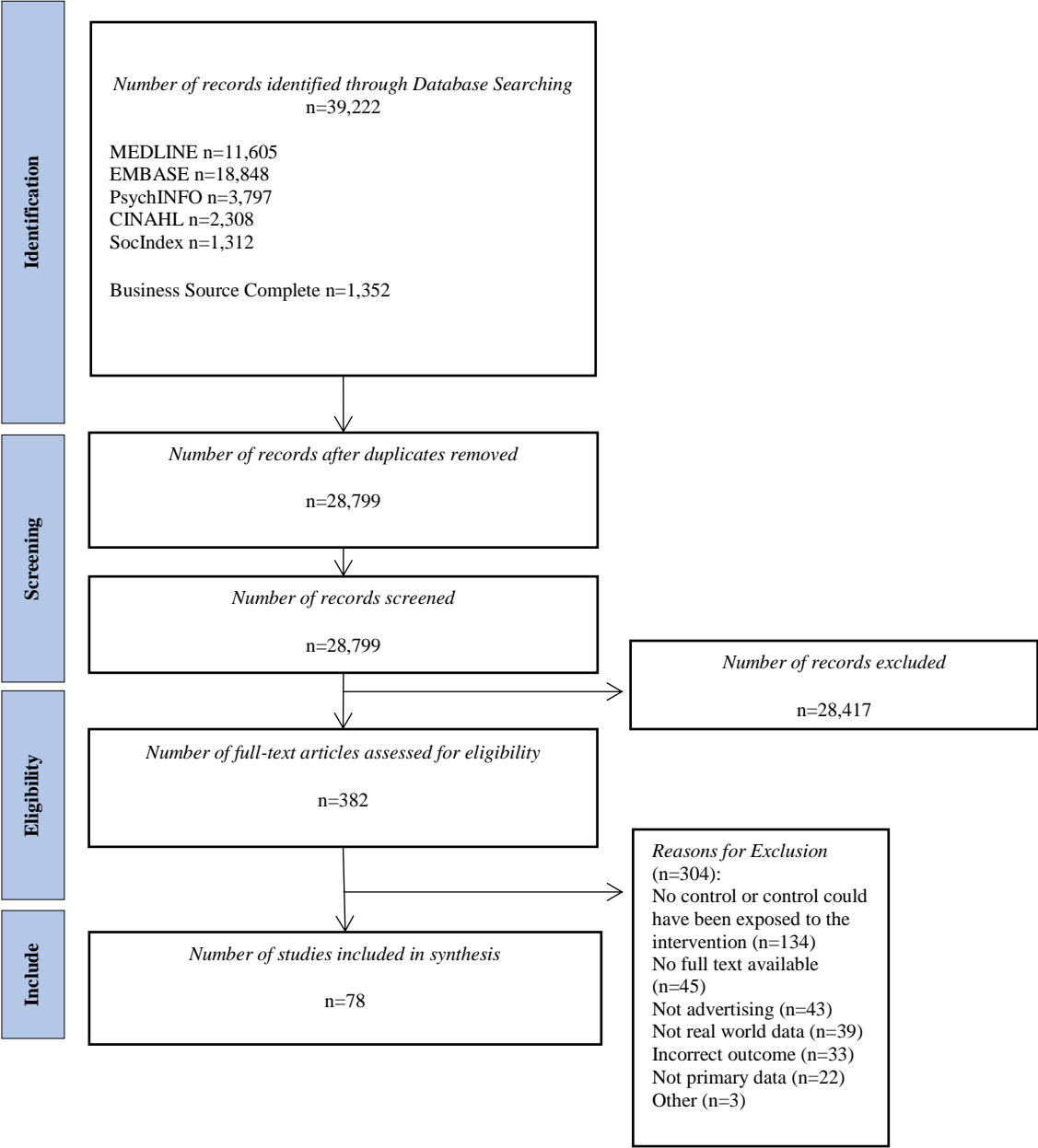


Table 1. Information on included studies

Author, Year, Country	Population	Substance type	Intervention	List of advertisements used in intervention group(s)?	Description of participants	Follow-up time	Outcomes	Funder
Barber <sup>248</sup> , 1989, Australia	General population	Alcohol	Exposure to either TV advertisements aimed at reducing drinking plus a letter, just the TV advertisements, no letter or advertisements, or just the letter	(1) TV advertisements (2) Letter alerting participants about the campaign (did not say what the message of the campaign was)	<i>Control Group/baseline:</i> no advertisement + letter: n=25; no advertisement or letter: n=24  <i>Intervention Group/follow-up:</i> advertisement + letter: n=25; advertisement with no letter: n=22	Baseline interviews occurred 12 months prior to the campaign; post-test interviews occurred 3 weeks post-campaign	<ul style="list-style-type: none"> <li>For those in the advertisement + letter group, there was an overall reduction in alcohol drinking, which was significant (p=0.05)</li> <li>No significant difference between the advertising only group and the groups without advertisements</li> </ul>	Queensland Department of Health through a grant provided by Australia's National Campaign Against Drug Abuse
Barber <sup>290</sup> , 1990, Australia	General population	Legal and illegal drugs (not specified)	Media campaign to inform the public of the dangers of both legal and illegal drugs	(1) TV (2) Print media	<i>Control Group/baseline:</i> 538 interviewed about drug-related attitudes pre-campaign; 509 considered "control" post-media campaign	First survey conducted April 1986, immediately prior to media campaign. Second interview was done 13 weeks later.	<ul style="list-style-type: none"> <li>No effect on smoking and non-significant effect on drinking</li> <li>Treatment group smokers: 40.7% decreased to 39.3%</li> <li>Control group smokers: 39.3%</li> </ul>	Not reported

					that did not have a previous interview  <i>Intervention Group/follow-up:</i> 410 re-interviewed post-campaign		<ul style="list-style-type: none"> <li>• Treatment group alcohol: 82.2% to 80.75%</li> <li>• Control group alcohol: 81.2%</li> </ul>	
Baskerville <sup>298</sup> , 2015, Canada	General population	Tobacco	Graphic labels and warnings	Graphic labels	<i>Control Group/baseline:</i> n=1,128  <i>Intervention Group/follow-up:</i> n=3,511	New callers to quitlines July to December 2012, post-introduction of new labels; pre-label period occurred during the same months of 2011	<ul style="list-style-type: none"> <li>• Increased number of new calls from 1,182 to 3,671</li> </ul>	CIHR
Borland <sup>295</sup> , 1997, Australia	General population	Tobacco	Graphic warnings	Content labelling	<i>Control Group/baseline:</i> n=510  <i>Intervention Group/follow-up:</i> n=512 new respondents; n=243	Baseline survey occurred in December 1994; follow-up survey occurred May 1995	<ul style="list-style-type: none"> <li>• 11% of those surveyed pre-implementation had quit</li> <li>• 38% made an unsuccessful attempt</li> <li>• Consumption was reduced from 22.0% to 20.5% (p&lt;0.05)</li> </ul>	Australian Commonwealth Department of human services and health



					original respondents			
Borland <sup>251</sup> , 2003, Australia	General population	Tobacco	Mass media campaign	2001 National tobacco campaign, graphic TV ads	<i>Control Group/baseline:</i> 1,000 survey respondents  <i>Intervention Group/follow-up:</i> 1,000 respondents	Two weeks	<ul style="list-style-type: none"> <li>33% progressed through at least 1 stage of quitting</li> <li>5% had quit at follow-up</li> </ul>	GlaxoSmithKline, Australian Commonwealth Department of human services and health
Boyd <sup>256</sup> , 1998, US	African American	Tobacco	Mass advertising campaign	Targeted mass media interventions developed specifically for African Americans  (1) TV (2) radio	<i>Control Group/baseline:</i> 4 regional cancer Intervention Sites regional quitlines in 11 states  <i>Intervention Group/follow-up:</i> 4 regional cancer Intervention Sites regional quitlines in 11 states	Pre-campaign: April to August 1994; post-campaign: August 1994 to July 1995; campaign occurred during August to September of 1994 and April to May 1995	<ul style="list-style-type: none"> <li>Higher call volume of African American smokers (<math>p &lt; 0.008</math>) in experimental communities</li> <li>Calls per week from African American smokers increased from 1.9 per week to 86 and 40 calls during waves 1 and 2 of the media campaign</li> </ul>	National Cancer Institute
Brown <sup>254</sup> , 2014, UK	General population	Tobacco	National smoking cessation campaign	Mass quit campaign, including:  (1) Digital	<i>Control:</i> 2007 to 2011 (excluding October): $n = 24,258$ ; October 2007 to 2011:	Monthly survey between 2007 and 2012 on quit attempts; “Stoptober”	<ul style="list-style-type: none"> <li>Quit attempts were higher in October 2012 than the rest of 2012</li> </ul>	Not reported

				(2) Mailed quitting pack (3) Digital tools (4) Text messaging	n=2,378; 2012 (excluding October): n=4,497  <i>Intervention Group/follow-up:</i> October 2012: n=433	occurred October 2012 (considered intervention)	<ul style="list-style-type: none"> <li>Odds of attempting to quit in October 2012 compared to other months 2007-2011: OR = 1.79 (95% CI: 1.20-2.68)</li> <li>Odds of attempting to quit in October 2012 compared to the rest of 2012: OR = 1.50 (95% CI: 1.05-2.15)</li> </ul>	
Campion <sup>255</sup> , 1994, UK	Pregnant women	Tobacco	Mass media campaign targeted at women 15-24	(1) Print advertisements placed in newspapers and tabloids for 10 days (2) Publicity campaign	<i>Control Group/baseline:</i> n=625  <i>Intervention Group/follow-up:</i> n=607	Baseline: 2 weeks before campaign  Results survey 2 weeks after campaign	<ul style="list-style-type: none"> <li>Quitline calls from pregnant women increased from 0% pre-campaign to 14% during the campaign</li> <li>No significant changes in prevalence of smoking behaviour</li> </ul>	Not reported
Chang <sup>303</sup> , 2011, Taiwan	General Population	Tobacco	Graphic warning labels on packages and introduced a smoke free law	Taiwan Tobacco Hazards Prevention Amendment Act was introduced in 2009. Six graphic warnings with one of six pictures with tobacco related hazards (smoking	<i>Control Group/baseline:</i> Pre-law; n= 1074  <i>Intervention Group/follow-up:</i> Post-law; n=1094	First wave of surveys conducted in July 2008, 6 months before the amended act.  Second wave of surveys	<ul style="list-style-type: none"> <li>General smokers quit motivations: 24.4% to 67.4%</li> <li>Thoughts about quitting among smokers due to the warning labels: 30.2% to 42.5% post-law</li> <li>Thoughts about quitting in response</li> </ul>	Bureau of Health Promotion, Department of Health

				and second hand smoke).		conducted in March 2009, 3 months after implementation of graphic health warnings and the smoke-free law.	to the new act: 51.7% <ul style="list-style-type: none"> <li>Quitting thoughts among females: 18% to 47.5%; and males: 31.6% to 52%</li> <li>Thoughts about quitting among smokers not exposed to household second hand smoke: 21% to 56.9%; smokers not exposed to second hand spoke in the workplace: 27.7% to 52.2%</li> </ul>	
Chang <sup>304</sup> , 2014, Taiwan	General population	Tobacco	Government act to reduce smoking	Includes both an increase in tobacco taxes combined with smoke free policies and graphic health warnings	<i>Control Group/baseline:</i> Pre-act 2007: n=16,588  <i>Intervention Group/follow-up:</i> Post-act 2010: n=16,295	Act put into place in 2009; follow-up occurred 1 year after the act was introduced	<ul style="list-style-type: none"> <li>40.9% of active smokers attempted to quit at least once</li> <li>7.9% of active smokers stopped smoking for at least 3 months</li> <li>Quit attempts increased from 39.4% to 42.9% (p=0.029)</li> <li>Individuals who had not smoked for at least 3 months increased from</li> </ul>	Not reported

							7.1% to 8.9% (p=0.029)	
Clapp <sup>312</sup> , 2003, US	2 residence halls on a university campus	Alcohol	Pre-test to ask students about their alcohol use and two intervention groups. Group 1 received a correction campaign for a 6-week period. Group 2 received an address book with information on alcohol laws	Group 1 intervention included:  (1) Posters (2) Stickers (3) Bookmarks (4) Notepads Group 2: each student received an address book that contained alcohol related laws and policies.	<i>Control Group/baseline:</i> Pretest: comparison hall: 41.7%; experimental hall: 59.3%  <i>Intervention Group/follow-up:</i> comparison all: 33.6%; experimental hall: 60.8%  Total n in experimental hall=396  Total n in comparison hall=645	Intervention took place for 6 weeks	<ul style="list-style-type: none"> <li>• Drinking behaviour in both halls increased over time</li> <li>• Experimental hall: 4 to 4.1 drinks</li> <li>• Comparison hall: 3.7 to 4.4 drinks</li> <li>• Heavy drinking also increased from 2.7 to 2.9 and 2.7 to 3.3 for the experimental and comparison group respectively</li> <li>• Mean number of days drinking increased from 5.9 to 6.9 per 28 days for the experimental group but decreased from 6.3 to 5.4 per 28 days for the comparison group</li> </ul>	Not reported
Coady <sup>257</sup> , 2013, US	General population	Tobacco	Policy implemented to place warning signs in tobacco retailer's	Signs were placed in the checkout area	<i>Control Group/baseline:</i> n=504	9 months following the distribution of signage	<ul style="list-style-type: none"> <li>• Smokers who thought about quitting increased from 31% to 43% (p=0.02)</li> <li>• There was no difference in</li> </ul>	NYC Department of Health

			checkout locations		<i>Intervention Group/follow-up:</i> n=503		<p>helping quitters stay smoke free (p=0.55)</p> <ul style="list-style-type: none"> <li>Impact of signs in changing smoker's minds about purchasing cigarettes achieved only borderline significance (15% to 8%, p=0.05)</li> </ul>	
Dixon <sup>247</sup> , 2015, Australia	General population	Alcohol	Campaign to increase knowledge of the link between alcohol and cancer	<p>Mass media campaign included:</p> <ol style="list-style-type: none"> <li>(1) TV ads</li> <li>(2) Print ads</li> <li>(3) Community posters</li> <li>(4) Web-based information</li> <li>(5) Unpaid media strategies.</li> </ol>	<p><i>Control Group/baseline:</i> n=136</p> <p><i>Intervention Group/follow-up:</i> wave 1: n=206; wave 2: n=155</p>	<p>Baseline: one month prior to wave 1.</p> <p>Follow-up: One month after waves I and II of the campaign</p>	<ul style="list-style-type: none"> <li>Approximately 50% of women felt motivated to reduce consumption</li> <li>Women who consume more than 2 drinks per day are more likely to reduce their alcohol intake than those who drink less</li> </ul>	Government of Western Australia through the Western Australia Drug and Alcohol Office
Duke <sup>258</sup> , 2015, US	General population	Tobacco	Education campaign to reduce smoking	<ol style="list-style-type: none"> <li>(1) Television ads</li> <li>(2) Radio</li> <li>(3) Print</li> <li>(4) Billboard</li> <li>(5) Transit</li> <li>(6) Web</li> </ol> <p>In both Spanish and English</p>	<p><i>Control Group/baseline:</i> n=4108 KP and n=8049 SSI smokers; total n=12,157</p> <p><i>Intervention Group/follow-up:</i> n=3051 KP and</p>	3 months	<ul style="list-style-type: none"> <li>Intention to quit in the next 30 days increased from 15.4% to 18.9%, p&lt;0.05</li> <li>Intention to quit within 6 months increased from 36.9% to 40.1%, p&lt;0.05</li> </ul>	Centers for Disease Control and Prevention

					n=2190 SSI; total n= 5241			
Durkin <sup>297</sup> , 2016, Australia	General population	Tobacco	Legislation to reduce smoking rates	Introduction of plain package to reduce the attractiveness and appeal of tobacco products	<i>Control Group/baseline:</i> n=8597  <i>Intervention Group/follow-up:</i> 6,775; further restricted 1,288 to eliminate the tax increase (occurred Dec. 1, 2013) from the impacts of packaging	9 April 2012 to 30 March 2014, original survey was conducted; follow-up occurred 1 month after the survey	<ul style="list-style-type: none"> <li>Participants who were followed-up in the early transition period had greater increases in rates of stopping smoking (OR=1.51, 95% CI: 1.08-2.10) and had higher quit attempt rates (OR=1.43, 95% CI: 1.00-2.03)</li> <li>Following up later in the transition showed greater increases in intentions to quit (OR=1.42, 95% CI: 1.06-1.92)</li> <li>Those followed up in the first year showed higher quit attempt rates (OR=1.52, 95% CI: 1.01-2.30)</li> </ul>	Funding from the Australian Government Department of Health and Ageing.
Dwyer <sup>266</sup> , 1986, Australia	General population	Tobacco	Media Campaign to reduce smoking	Media based using advertisements on television and radio. Campaign occurred between June 1983	<i>Before and after Surveys:</i>  <i>Control Group/baseline:</i> Pre-campaign survey: Total:	Pre-campaign survey occurred May-June 1983; post-campaign survey occurred	From the before and after surveys: <ul style="list-style-type: none"> <li>Both men and women from Sydney showed a decreased in the</li> </ul>	Minister of Health Department

				and November 1983	<p>n=9132; Sydney: n=3978; the rest of Australia: n=5154.</p> <p><i>Intervention Group/follow-up: Post-campaign survey: Total: n=8369; Sydney: n=4051; the rest of Australia: n=4318</i></p> <p><i>From individuals who participated in the before-after surveys: a cohort of n=900 from Sydney and n=600 from Melbourne</i></p> <p><i>Follow-up: n=949</i></p>	during the same months in 1984	<p>average number of cigarettes smoked (-0.6% and -1.3%)</p> <ul style="list-style-type: none"> <li>• There was an increase in the average number smoked among the men in the rest of Australia (0.2%)</li> <li>• There was a decrease amongst other Australian women (-0.8%)</li> </ul> <p>From the cohort study:</p> <ul style="list-style-type: none"> <li>• 3.4% decrease in the reported smoking prevalence in Sydney and 0.8% increase in Melbourne</li> </ul>	
Etter <sup>270</sup> , 2005, Switzerland	General population	Tobacco	Poster on the effects of second hand smoke	Placed on 460 large billboards in the streets and on seven tramways throughout Geneva for a 2-week period. 6000 smaller	<p><i>Control Group/baseline: Before campaign (April 18 – May 21, 2001) in both Geneva (n=853)</i></p>	1 month	<ul style="list-style-type: none"> <li>• 13% of smokers before stated they ‘often’ or ‘very often’ smoked while children were present compared to</li> </ul>	Swiss National Science Foundation and Geneva Health Administration

				posters were mailed to schools, leisure centers, kindergartens, pediatric clinics, obstetrics clinic and pharmacies	and Neuchâtel (n=1180).  <i>Intervention Group/follow-up:</i> Same people were interviewed after campaign (June 6-July 31, 2001); Geneva (n=834) and Neuchâtel (n=1121)		6% after the campaign (p<0.001) <ul style="list-style-type: none"> <li>• In the Neuchâtel group before was 18 and 10% after (p=0.005)</li> <li>• There was no significant difference between the two districts in change before and after the campaign (p=0.29)</li> <li>• Intention to quit before the campaign on a mean scale between 1-100 was 48 before the campaign and 47.5 after (p=0.869)</li> </ul>	
Farrelly <sup>273</sup> , 2005, US	General population	Tobacco	Mass media campaign to discourage use tobacco use among US youth	Hard hitting television advertisement that demoralizes smoking	<i>Control Group/baseline:</i> Grade 8: n=approx. 18,000; Grade 10: n=approx. 17,000; Grade 12: n=approx. 16,000  <i>Intervention Group/follow-up:</i>	3 years of survey data 1999-2002. Campaign was launched in February 2000	<ul style="list-style-type: none"> <li>• Decline in smoking prevalence from 25.3% to 18% between 1999 and 2002</li> <li>• Among all grades combined there was a 36% decrease</li> <li>• Biggest decline in grade 8 (45%) and the lowest in grade 12 (27%)</li> </ul>	American Legacy Foundation



					Estimated the campaign exposure impact and will examine this impact within the surveys. Can't find the numbers		<ul style="list-style-type: none"> <li>Before the campaign there was a 3.2% decline in prevalence compared with 6.8% after the campaign launch</li> <li>22% (95% CI=8.2%, 35.6%) of total decline in attributable to the campaign</li> </ul>	
Farrelly <sup>274</sup> , 2009, US	General population	Tobacco	Mass media campaign to discourage use tobacco use among US youth	Truth commercials on select TV networks and programs with high teen viewership (FOX, UPN, WB)	<i>Control Group/baseline:</i> n=8,984; aged 12-17  <i>Intervention Group/follow-up:</i> n=8,984	Longitudinal study interviewed annually between 1997-2004. Campaign occurred between 2000-2002	<ul style="list-style-type: none"> <li>Exposure to the campaign decreases risk of smoking initiation (p=0.001)</li> <li>Increased campaign exposure (10,000 gross rating points) represents a corresponding 20% decrease in the risk of smoking</li> </ul>	National Cancer Institute
Flynn <sup>275</sup> , 1997, US	School children grades 5 to 7	Tobacco	Mass media and school interventions of high risk young people	Intervention over 4 years in a matched pair:  (1) one community receiving school program only (2) the other both the school	<i>Control Group/baseline:</i> grades 4-6; n=5,454  <i>Intervention Group/follow-up:</i> Grades 8-10 and	2 years	High risk samples <ul style="list-style-type: none"> <li>By grades 8-10 smoking prevalence: media-school group: 3.4% to 20.9%; school only: 3.9% to 26.3%</li> </ul>	National Cancer Institute

				program (three to four lessons per year delivered by classroom teachers) and mass marketing (television and radio spots)	10-12; higher risk n=1250 and lower risk n=1468		<ul style="list-style-type: none"><li>• By grades 10-12: media-school: 28.6%; school only: 35.9%</li><li>• At a 2-year follow-up survey: 7.3% difference in weekly smoking favoring the media-school group</li></ul> Lower risk samples <ul style="list-style-type: none"><li>• By grade 8-10 smoking prevalence: media-school: 7.5%; school only: 13.0%</li><li>• By grades 10-12: media-school: 15.9%; school only: 20.2%</li><li>• At the 2-year follow-up: 4.3% difference favoring the media-school group was observed.</li></ul> Combined samples of both the higher and lower risk samples <ul style="list-style-type: none"><li>• 6.5% difference in favor of the media-school group</li></ul>	
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Flynn <sup>276</sup> , 1994, US	School children grades 4 to 6	Tobacco	Mass media and school program interventions to prevent smoking	Surveys, saliva samples, self- reports	<p><i>Control Group/baseline:</i> n=5458; Grades 4 to 6. One group received mass media and school intervention: n=4670. Those in two matched communities only received the school interventions</p> <p><i>Intervention Group/follow-up:</i> Same participants in n=4307 complete follow-up sample and n=1939 full- exposure sample; Grades 10 to 12</p>	4 -year cohort study	<ul style="list-style-type: none"> <li>Students exposed to media-school interventions were at lower risk for weekly smoking than those receiving only the school intervention (OR=0.62, 95% CI- 0.49, 0.78)</li> <li>Effects of the combined interventions lasted for 2 years after the completion of the study</li> </ul>	National Cancer Institute
Gagne <sup>268</sup> , 2007, Canada	General population	Tobacco	A 2005 British Columbia Ministry of Health Smoking Cessation Mass Media campaign	<p>A two-part mass media campaign:</p> <p>(1) Posters (2) Television (3) Radio</p> <p>to target 20-30- year-old blue collar workers in British</p>	<p><i>Control Group/baseline:</i> Pre-campaign June to December 2004.</p> <p><i>Intervention Group/follow-up:</i> Post-campaign</p>	3 months: part 1: early 2005; part 2: early 2006, both lasting 4 weeks	<ul style="list-style-type: none"> <li>Smoking prevalence in BC: - 0.2 percentage points; rest of Canada: +1.8 percentage points during the last half of 2004 (p=-0.44)</li> <li>Long term trends show a decline in</li> </ul>	Not reported

				Columbia about support program available to encourage quitting	March to June 2005.  British Columbia: n=1,682  Rest of Canada: n=17,387		prevalence in BC (0.9) and the rest of Canada (1.1) (p=0.51) Daily consumption: <ul style="list-style-type: none"><li>• BC: declined by 1.18; rest of Canada: increased by 0.74 cigarettes over the period before and after the campaign; not statically significant</li><li>• Increased prevalence in Canada (0.023; p=0.08), with no deviation in BC (0.003; p=0.86).</li><li>• For smokers: there was a downward trend of quantity of cigarettes smoked for rest of Canada (0.65; p&lt; 0.01) but not for BC residents (-0.10; p=0.72)</li><li>• There was a significant reduction in average daily consumption of</li></ul>	
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							non-target population (-2.23; p=0.10)	
Galduroz <sup>243</sup> , 2007, Brazil	General population	Tobacco	Law to ban cigarette advertising introduced in 2000	Advertising banned from all forms of media	<i>Control Group/baseline:</i> 1997; n=15,501  <i>Intervention Group/follow-up:</i> 2004; n=21,712	4 years after the advertising ban	<ul style="list-style-type: none"> <li>Statistically significant reduction in lifetime use in 7 of the 10 cities</li> <li>Recife and Rio de Janeiro saw no significant decrease in lifetime use for both genders</li> </ul>	<ul style="list-style-type: none"> <li>National Anti-Drug Secretary</li> </ul>
Gibson <sup>259</sup> , 2014, US	General population	Tobacco	Mass media campaign to curb tobacco use	(1) TV radio (2) Transit and convenience store ads  Message: it is easier to quit with help	<i>Control Group/baseline:</i> n=498 pre-campaign (December 2010)  <i>Intervention Group/follow-up:</i> 16 smaller monthly samples during the campaign (n=2,856); a second interview was conducted 3 months post-campaign (n=877)	Campaign aired from December 2010 through March 2012	<ul style="list-style-type: none"> <li>No behavioural outcomes or intentions significantly increased during the campaign</li> <li>Quit attempts significantly increased (OR=1.06; p&lt;0.05)</li> <li>Quit attempts with help increased with exposure to campaign (OR=0.99; p=0.65)</li> </ul>	Department of Public Health from the National Cancer Institute

Gravely <sup>299</sup> , 2016, Canada	General population	Tobacco	Health warning labels to decrease smoking	Larger graphic health warning labels	<i>Control Group/baseline:</i>  Pre-policy in 2008/9 (n=1,379)  <i>Intervention Group/follow-up:</i>  Post-policy in 2010/11 (n=1,411)	Data collected between October 2008 and February 2009,  2009/2010 enhancement of HWLs, followed by data collection between October 2010 and January 2011	<ul style="list-style-type: none"> <li>• Health warnings made you think about quitting somewhat/a lot: 20.6% pre-policy and 31.3% post-policy (OR=1.76, 95% CI: 1.34-2.29, p&lt;0.001)</li> <li>• Health warnings stopped you from having a cigarette many times: 1.9% pre-policy and 6.1% post-policy (OR=3.42, 95% CI: 1.77-6.59, p&lt;0.001)</li> <li>• Percentage of quitters who reported that HWLs led them to quit smoking was 23.5% at the pre-policy survey and 38.7% at the post-policy survey.</li> </ul>	Canadian International Development Research Centre, US National Cancer Institute, and Canadian Institutes of Health Research
Green <sup>300</sup> , 2014, Canada	General population	Tobacco	Pictorial health warnings to decrease smoking	Pictorial health warnings on cigarette packages	<i>Control Group/baseline:</i>  Wave 1 (n=598)	October 2009 implementation  3 waves of data: Wave 1 in 2009 (six months	<ul style="list-style-type: none"> <li>• From wave 1 to wave 2, more smokers considering quitting: 13.5% to 26.6% (OR=2.69,</li> </ul>	International Development  Research Centre (Waves 1 and 2),

					<i>Intervention Group/follow-up:</i> Wave 2 (n=601) and Wave 3 (n=558) Respondents lost to attrition were replaced in subsequent waves	prior to the implementation of PHWs), waves 2 and 3 conducted 10-12 months and 20-21 months, post-implementation	95% CI: 1.75-4.15, p<0.001) <ul style="list-style-type: none"> <li>From wave 1 to wave 2, smokers had 66% greater odds of reporting forgoing a cigarette “at least once in a while” because of the warnings (OR=1.66, 95% CI: 1.10-2.52, p=0.051)</li> <li>Non-statistically significant declines in warning label effectiveness indicators between waves 2 and 3</li> </ul>	and partial funding from the Bloomberg Global Initiative-International Union Against Tuberculosis and Lung Disease (Wave 3), and the World Lung Foundation (Wave 3)
Grube <sup>250</sup> , 1997, US	Youth (minors)	Alcohol	Campaign to decrease underage alcohol sales	(1) Enforcement of underage sale laws (2) Responsible beverage service training (3) Media advocacy campaign (increase awareness among owners and managers of	<i>Control Group/baseline:</i> Three matched comparison communities (pretest: 241; post-test: 243)  <i>Intervention Group/follow-up:</i> Three experimental	Pre-test conducted in October 1995 before comprehensive interventions were in place, post-test conducted approximately 10 months after	<ul style="list-style-type: none"> <li>Logistic regression analyses showed that sales to apparent minors were significantly reduced in the experimental sites at post-test than at the pre-test (p&lt;0.001)</li> <li>Outlets in comparison community were</li> </ul>	Center for Substance Abuse Prevention and National Institute on Alcohol Abuse and Alcoholism

				the enforcement efforts) (4) Media news coverage of enforcement activities, television news coverage	communities located in California and South Carolina (pretest: 238; post-test: 227)	in April-May 1996	about 1.9 times more likely to sell to a buyer than were outlets in the experimental community (p<0.02)	
Hafstad <sup>271</sup> , 1997, Norway	Adolescents aged 14 and 15	Tobacco	Campaign to prevent smoking	Mass media: (1) TV (2) Cinema advertisement (3) Newspapers (4) Posters to all schools and youth organizations	<i>Control Group/baseline:</i>  Control county (n=5,439)  <i>Intervention Group/follow-up:</i>  Intervention county (n=4,898)	Intervention county completed baseline & evaluation survey in 1992, followed by two evaluation surveys in 1993 and 1994, and final post campaign survey in 1995  Control county completed baseline survey in 1992 and final post campaign survey in 1995	<ul style="list-style-type: none"> <li>Overall increase in the proportion of daily smokers from 1992 to 1995 in the intervention county was significantly lower than in the control county among girls (8.6% versus 12.4%, respectively)</li> <li>Among boys, the net increase was 6.8% versus 10.5%, which was not statistically significant</li> <li>No significant decrease in the proportion of non-smokers between intervention and control county for girls (-13.2 versus</li> </ul>	Norwegian Women's Public Health Association



							-14.2) and boys (-10.1 versus -12.5)	
Halkjelsvik <sup>237</sup> , 2013, Norway	General	Tobacco	Campaign to decrease smoking	Mass media (1) TV commercials (2) YouTube, Facebook (3) Web-based newspapers (4) Printed ads in magazines/newspapers	<i>Control Group/baseline:</i>  Pre-campaign (n=2,543)  <i>Intervention Group/follow-up:</i>  Post-campaign (n=2,543)	Survey completed 3 weeks before (December 2011) and 3 weeks after (February 2012) the 2012 7-week national media campaign	<ul style="list-style-type: none"> <li>• The effect of campaign exposure on change from daily smoker to non-smoker: OR=1.604, (95% CI: 0.882-2.915; p=0.128)</li> <li>• The effect of campaign exposure on change from daily smoker to occasional smoker: OR=1.504 (95% CI: 0.889-2.544)</li> <li>• No effect of campaign exposure on baseline occasional smokers (p=0.575)</li> <li>• No effects on number of cigarettes per day, likelihood to quit or reduce smoking</li> <li>• Small but statistically significant effects were found on motivation to quit (p&lt;0.01)</li> </ul>	Norwegian Directorate of Health

Hallgren <sup>311</sup> , 2013, Sweden	Youth	Alcohol	Interventions to decrease alcohol usage	(1) Information and media advocacy (2) Social and emotional training (3) Availability of police (4) Media reports (5) Motivational interviewing	<i>Control Group/baseline:</i>  Six control communities (n=4,155)  <i>Intervention Group/follow-up:</i>  Six trial communities (n=4,015)	Trial from 2003-2007  Self-reported questionnaire in May of each year (except 2005)	<ul style="list-style-type: none"> <li>• Trial interventions had no measurable impact on youth drinking</li> <li>• All young people reported reductions in binge drinking over time, with no differences overall between the trial and control communities</li> <li>• Among year 9 females, binge drinking reduced by 20% (p&lt;0.001) in the trial communities compared to 10% in the control communities (p&lt;0.05)</li> <li>• Increase in alcohol-related hospital admissions between 2003 and 2007, but no significant group differences over time</li> </ul>	Karolinska Institutet, Swedish Council  For Working Life and Social Research, Swedish National Institute for Public Health
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Hammond <sup>308</sup> ,  2007,  Canada	Adult smokers	Tobacco	Campaign to reduce smoking	Health warning on cigarette packages	<p><i>Control Group/baseline:</i> Pre-implementation of new packages:  Canada (n=3,687)  United States (n=4,273)  Australia (n=3,381)  UK (n=3,634)</p> <p><i>Intervention Group/follow-up:</i>  Post-implementation of new packages:  UK (n=3,634)</p>	<p>Surveys conducted between 2002 and 2005, 2 months before and at three time points (6, 18, and 32 months) following implementation of new package warnings in UK (2003 warnings enhanced to meet minimum Framework Convention on Tobacco Control standard)</p>	<ul style="list-style-type: none"> <li>At Wave 2, UK smokers were significantly more likely to report that the health warnings had deterred them from having a cigarette (12.4%) compared to US (10.1%, <math>p&lt;0.01</math>) and Australian smokers (9.7%, <math>p&lt;0.001</math>).</li> <li>Canadian smokers were significantly more likely to report stopping from smoking a cigarette as a result of warnings (14.5% vs 10.3%, <math>p=0.007</math>), and warnings had led them to think about quitting (44.7% vs 37.8% , <math>p=0.07</math>) compared to the UK at wave 4</li> </ul>	<p>National Cancer Institute of the United States, the Roswell</p> <p>Park Transdisciplinary Tobacco Use Research Center, Robert Wood Johnson Foundation,</p> <p>Canadian Institutes of Health Research,</p> <p>National Health and Medical Research Council of Australia, Cancer Research UK, and Canadian</p> <p>Tobacco Control Research Initiative, Centre for Behavioural Research and</p> <p>Program Evaluation, National Cancer</p>
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								Institute of Canada/  Canadian Cancer Society
Hankin <sup>293</sup> , 1998, US	African- American pregnant women	Alcohol	Legislation to deter drinking in pregnancy	Alcohol beverage warning label	<p><i>Control Group/baseline:</i> Pre-legislation (September 7,1986 to November 17,1989): n=7,604 approx.</p> <p><i>Intervention Group/follow-up:</i>  Post-legislation (November 18, 1989 to May 31, 1995): n=13,523 approx.</p>	Drinking during pregnancy before the warning label was implemented (September 7, 1986 – November 17, 1989) and afterwards (November 18, 1989 – May 31, 1995)	<ul style="list-style-type: none"> <li>• Decline in drinking began eight months after the implementation of the alcohol warning label</li> <li>• Drinking increased in 1992 as unemployment rates rose and declined again in 1993 as unemployment declined</li> <li>• Decline in in-pregnancy drinking started a downward trend eight months after the label law went into effect (p&lt;0.01)</li> <li>• Label had a significant, modest impact on drinking</li> </ul>	National Institute on Alcohol Abuse and Alcoholism

Hantula <sup>288</sup> , 1993, US	Adults in smoking section of large urban hospital's fast-food cafeteria	Tobacco	Campaign to reduce smoking	Mass media for Smokeout campaign  (1) Posters (2) Smoking cessation materials (3) News releases (4) Information booth	<i>Control Group/baseline:</i>  pre-campaign observation          <i>Intervention Group/follow-up:</i> post-campaign observation	Data collected between October 1987 and January 1988, baseline observations made one month prior, follow-up two weeks after, three weeks, and two months after the Smokeout	<ul style="list-style-type: none"> <li>Smokers: mean of 16.5 people observed smoking during baseline, 8 during the Smokeout, and 15.89 after the Smokeout</li> <li>Non-smokers: mean of 55 people who were not smoking during baseline, 36 during the Smokeout, and 51.52 after the Smokeout</li> </ul>	Not reported
Harris <sup>253</sup> , 2016, Scotland	Patients with seropositive rheumatoid arthritis	Tobacco	Campaign to reduce smoking	Rheumatoid arthritis and smoking awareness materials.       Mass media (1) Posters (2) Postcards (3) Press release to national newspapers and radio stations	<i>Control Group/baseline:</i>  pre-campaign (n=320)          <i>Intervention Group/follow-up:</i> post-campaign (n=380)	Campaign launched in Fife, Scotland in 2011  (unknown timeline)	<ul style="list-style-type: none"> <li>6% more smokers in the post-campaign group were planning to quit and 8% more were concerned and thinking about stopping following the campaign.</li> <li>13/75 smokers who had cut down since the campaign had been influenced by the new information</li> </ul>	Grant from Pfizer

Hernandez <sup>314</sup> , 2012, Netherlands	General	Prescription drugs (SSRI)	Regulatory banning of SSRI use in pediatrics and young adults	Scientific and media attention of regulatory warnings	<p><i>Control Group/baseline:</i></p> <p>Control periods (January 2000 to December 2002; January 2005 to December 2006; January 2009 to December 2009)</p> <p><i>Intervention Group/follow-up:</i></p> <p>Intense media coverage of regulatory warnings (January 2003 to December 2004; January 2007 to December 2008)</p>	Trends of SSRI use between January 2000 and January 2010 in the Netherlands and the United Kingdom	<p>Netherlands</p> <ul style="list-style-type: none"> <li>SSRI use increased from 16.7 in January 2000 to 27.9 defined daily doses (DDDs)/1000/day in July 2010</li> <li>SSRI use in pediatrics, adolescents, and adults modestly decreased after the first period of media coverage and then recovered</li> </ul> <p>United Kingdom</p> <ul style="list-style-type: none"> <li>SSRI use doubled from 24.7 in January 2000 to 50.1 DDDs/1000/day in December 2009</li> <li>SSRI use showed no negative trends during this period</li> </ul>	Dutch Top Institute Pharma
Hersey <sup>277</sup> , 2003, US	Youth (12 to 24 year olds)	Tobacco	Campaign to reduce smoking	Mass media (State-funded “Truth” counter-industry media campaign)	<p><i>Control Group/baseline:</i></p> <p>All states but California, Florida,</p>	Survey conducted between December 6, 1999 and February 6,	<ul style="list-style-type: none"> <li>Results of hypothesized model that counter-industry state residence, mediated by</li> </ul>	American Legacy Foundation

					<p>and Massachusetts (n=5,499)</p> <p><i>Intervention Group/follow-up:</i></p> <p>Three states with major counter-industry media campaigns (California, Florida, and Massachusetts) (n=1,376)</p>	<p>2000 prior to the launch of the national truth campaign but in states that had campaigns on the air for over a year</p>	<p>negative industry beliefs and attitudes, exhibited a significant association with smoking status over and above the influence of cigarette price and other program components (p&lt;0.01)</p>	
<p>Hersey <sup>289</sup>, 2005, US</p>	<p>Youth (12 to 17 year olds)</p>	<p>Tobacco</p>	<p>Campaign to reduce smoking</p>	<p>Mass media (State-funded “Truth” counter-industry media campaign)</p>	<p><i>Control Group/baseline:</i></p> <p>8 months before campaign launch (n=3,439)</p> <p><i>Intervention Group/follow-up:</i></p> <p>8 months after campaign launch (n=6,233) and 15 months after campaign launch (n=6,792)</p>	<p>Three Legacy Media Tracking Surveys between December 1999 and February 2000 before launch, fall 2000 and spring 2001, roughly 8 and 15 months after campaign launch</p>	<ul style="list-style-type: none"> <li>Models provided support for a social inoculation effect, negative industry attitudes were associated with lower receptivity to pro-tobacco advertising and with less progression along a continuum of smoking intentions and behaviour (p&lt;0.05)</li> </ul>	<p>American Legacy Foundation</p>

Hersey <sup>278</sup> , 2005, US	Youth (12 to 17 year olds)	Tobacco	Campaign to reduce smoking	Mass media (State- funded “Truth” counter-industry media campaign)	<p><i>Control Group/baseline:</i></p> <ul style="list-style-type: none"> <li>States with long funded counter- industry campaigns (California, Florida, Massachusetts)</li> <li>Other states</li> </ul> <p><i>Intervention Group/follow-up:</i></p> <p>States with more recently funded counter-industry campaigns (Indiana, Minnesota, Mississippi, and New Jersey)</p> <p><i>Total from control and intervention groups:</i></p> <p>Period 1: n=3,424</p> <p>Period 2: n=12,967</p>	<p>Campaign launched in 2000</p> <p>Period 1 (November 1999-January 2000) before the launch, period 2 (autumn 2000 to spring 2001), period 3 (spring 2002 to autumn 2002)</p>	<ul style="list-style-type: none"> <li>Newer and established campaign states had significantly greater declines in current smoking from 1999 to 2002 of 55% (from 12.3% to 5.5%) and 47% (15% to 7.9%)</li> <li>Remaining states had decline of 25% (from 12.5% to 9.4%)</li> <li>Rate of decrease in campaign states (established plus newer) was roughly twice that of other states (52.6% versus 24.9%; p&lt;0.05)</li> <li>Odds of being a current smoker were reduced significantly faster in states with counter-industry media campaign than in states without these campaigns</li> </ul>	American Legacy Foundation
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					Period 3: n=10,855		<ul style="list-style-type: none"> <li>Negative perceptions about the tobacco industry showed an increasingly stronger relationship with smoking status in campaign states</li> <li>Within campaign states, youth with more negative perceptions of the tobacco industry had 14% lower odds of being current smokers in 1999 (<math>p&lt;0.05</math>). By 2002, their odds were 26% lower (<math>p&lt;0.05</math>). The rate of change was similar in established and newer campaign states</li> </ul>	
Heydari <sup>302</sup> , 2011, Iran	General population	Tobacco	Law to reduce smoking	Graphic Health Warning Labels	<i>Control Group/baseline:</i> in First phase (fall 2008) before warning labels (n=1,731)	Data were collected in 2 phases: fall 2008 and summer 2009 (9 months after the	<ul style="list-style-type: none"> <li>33.3% stated they may cut down on smoking due to this law (before implementation)</li> <li>Decreased consumption of</li> </ul>	Tobacco Prevention and Control Research Center, NRITLD, Shaheed Beheshti

					<i>Intervention Group/follow-up:</i> Second phase (summer 2009) 9 months after the implementation of the law (n=1,590)	implementation of the new law)	cigarettes occurred in 7.6% of smokers (p=0.86) <ul style="list-style-type: none"> <li>• This decrease in smoking rate was greater in males, older age, and those with low nicotine dependence</li> </ul>	University of Medical Sciences
Hitchman <sup>301</sup> ,  2014,  Canada	General population	Tobacco	Guidelines to decrease smoking	Rotation of health warnings to prevent wear out	<i>Control Group/baseline:</i> Beginning of study period in 2002 (Canada: n=2,157; US: n=2,060)  <i>Intervention Group/follow-up:</i> Time series for waves 2 through 8 (until 2011) (Canada: n=3,152; US: n=4,352)	Data was collected in 8 waves of survey data (2002 to 2011). Baseline occurred in Wave 1 (2002) .	<ul style="list-style-type: none"> <li>• Significant decrease in smokers reporting of thinking about quitting due to health warnings (overtime) in Canada but not significant decrease in the US</li> <li>• Decline of reports of smokers foregoing cigarettes due to health warnings in Canada. No decline in the US.</li> <li>• No significant decrease in reports of forgoing a cigarette between Wave 8 versus Wave 1 in either country.</li> </ul>	Canadian Institutes for Health Research, Robert Wood Johnson Foundation, Cancer Research UK, Commonwealth Department of Health and Aging, Canadian Tobacco Control Research Initiative, National Health and Medical Research Council of Australia, U.S. National Cancer Institute, Ontario Institute for Cancer Research, Ontario Institute for Cancer Research, Canadian Institutes

								of Health Research Doctoral Research Award, National Institutes of Health Training Grant
Hu <sup>279</sup> , 1995, US	General	Tobacco	Campaign to reduce smoking	(1) Taxation on cigarettes (multiple increases over multiple years) (2) Anti-smoking media campaign (paid advertising on television, radio, print, outdoor campaign)	<i>Control Group/baseline:</i> <ul style="list-style-type: none"> <li>• Tax: Beginning of time period in 1980</li> <li>• Media Campaign: before second quarter in 1990</li> </ul> <i>Intervention Group/follow-up:</i> <ul style="list-style-type: none"> <li>• Tax: Time series for sequential years until 1992</li> <li>• Media Campaign: after third quarter in 1990 until end of 1992</li> </ul>	Quarterly cigarette sales data from 1980 until 1992	Tax increase <ul style="list-style-type: none"> <li>• \$0.25 increase in tax lead to a decrease in 819 million packs sold, or 27.3 packs per capita</li> </ul> Media Campaign <ul style="list-style-type: none"> <li>• Reduced sales by 232 million packs or 7.7 packs per capita</li> </ul> Combined <ul style="list-style-type: none"> <li>• 1.56 billion fewer packs sold (significant decrease; p&lt;0.01)</li> </ul>	Cigarette and Tobacco Surtax Fund of the State of California through the Tobacco-Related Disease Research Program of the University of California

Huang <sup>260</sup> , 2015, US	General population of smokers	Tobacco	Campaign to reduce smoking	Tips From Former Smokers campaign (March 4 to June 23 2013) – focus on television and internet advertisements (three Tips advertisements on health risks of amputation, blindness, and heart attack)	<i>Control Group/baseline:</i> US Adult smokers before the 2013 campaign (n=1,404)  <i>Intervention Group/follow-up:</i> Adult smokers after the 2013 campaign (n=1,401)	Baseline occurred January 18 to February 3 2013 (wave 1) the follow-up survey from May 17 to June 9 2013 which overlapped with the campaign (March 4 to June 23 2013)	Quit Attempts <ul style="list-style-type: none"> <li>• Significant increase in quit intentions in the next 6 months for those who recalled seeing at least 1 advertisement (35% versus 46%)</li> <li>• Results were not significant in adjusted model</li> </ul> Called Quitline <ul style="list-style-type: none"> <li>• Significant increase in calls to quitline from those who recalled seeing at least 1 advertisement (3% versus 9%)</li> <li>• Recall of Tips advertisements, in bivariate model, led to increased calls to quitline (8% versus 3%, OR= 2.28; 95%CI: 1.61-3.24)</li> </ul>	U.S. National Cancer Institute, and FDA Center for Tobacco Products
Huang <sup>246</sup> , 2013,	Adolescents (13 to 15 year olds)	Tobacco	Policies to reduce smoking	(1) Smoke-free policy (2) Advertisement ban	<i>Control Group/baseline:</i> Before 2009 policy implementation;	Five waves of survey data in 2004, 2006,	<ul style="list-style-type: none"> <li>• Significant upward trend in smoking before</li> </ul>	Not reported

Taiwan				(3) Pictorial warning (4) Price increase	from 2004 to 2008 (data in 2004, 2006, and 2008; approx. 23,000 per wave)  <i>Intervention Group/follow-up:</i> After 2009 policy implementation (data in 2010 and 2011; approx. 23,000 per wave)	2008, 2010, and 2011	implementation in 2008 (p=0.003) <ul style="list-style-type: none"> <li>Significant decline in smoking prevalence of parental smoking after 2009 law implementation (p=0.03) (56.2% in 2004 to 49.5% in 2011)</li> <li>Reduction in the prevalence of smoking more than one cigarette per day and smokers who had smoked more than 100 cigarettes were not significant</li> </ul>	
Huang <sup>309</sup> , 2014, Canada	General	Tobacco	Campaign to reduce smoking	(1) Graphic warning labels (2000)	<i>Control Group/baseline:</i> US (1994-2009)  <i>Intervention Group/follow-up:</i> Canada (1991-2009)	Survey data was collected for Canada from 1991 to 2009 and US from 1994 to 2009. Baseline were the years prior to 2000 and follow-up after introduction of graphic warning	<ul style="list-style-type: none"> <li>Graphic warning labels significantly decreased smoking prevalence by 2.87-4.68 percentage points in Canada, a relative reduction between 12.1% to 19.6%</li> <li>This was 33-53 times larger than FDA's estimates of</li> </ul>	US National Cancer Institute, Canadian Institute of Health Research and the Robert Wood Johnson Foundation

						labels (2000-2009)	a 0.08 percentage point reduction.	
Hurd <sup>261</sup> , 2007, US	General population	Tobacco	Campaign to reduce smoking	Promotion of 800-QUIT-NOW (a nationwide quit number) in a month-long ABC series “Quit to Live: Fighting Lung Cancer” at the end of 16 tobacco-related news stories	<i>Control Group/baseline:</i> 61,845 total calls  <i>Intervention Group/follow-up:</i> 38,908 calls	Baseline occurred from November 2004 to October 2005 with follow up occurring 1 month after promotion in November, until December 2005	<ul style="list-style-type: none"> <li>• 29,942 overall call volume in November 2005 during the ABC campaign compared to 9,723 in October</li> <li>• Decrease to 8,966 in December after the promotion ended</li> </ul>	National Cancer Institute, National Institute of Health
Hyland <sup>280</sup> , 2006, US	General population of smokers	Tobacco	State-sponsored anti-tobacco advertising	Television advertising exposure	<i>Control Group/baseline:</i> Individuals part of a trial (1988 to 1993), current smokers aged 25-64 years who lived in communities located in California, Iowa, Massachusetts, New Mexico, New Jersey, New York, North Carolina, Oregon, Washington (n=12,435)	Baseline is from those smokers who participated in the Community Intervention Trial for Smoking Cessation between 1988 and 1993. Follow up in 2001.	<ul style="list-style-type: none"> <li>• Among 2,061 smokers in 1999 and 2000, 12.0% had quit by the 2001 survey</li> <li>• The relative risk for quitting was estimated to be 10% higher (0.98–1.24) for increased exposure to state anti-tobacco advertising between 1999 and 2000</li> <li>• For those who were more exposed to media the association was larger and</li> </ul>	National Cancer Institute’s State and Community Tobacco Control Interventions Research Initiative

					<i>Intervention Group/follow-up:</i> Survey follow-up in 2001 of US cohort participants merged with television advertising exposure data (n=2,061)		statistically significant (RR = 1.19; 95% CI: 1.03–1.38; p=0.017) with no association among those who reported lower levels of increasing anti- tobacco information	
Jasek <sup>262</sup> , 2014, US	General population (light smoker-targeted)	Tobacco	Campaign to reduce smoking specifically targeted to light-smokers	Anti-tobacco media campaigns paired with time-limited nicotine replacement therapy (NRT). Giveaway occurred in the spring and the campaign aired around New Year	<i>Control Group/baseline:</i> Weekly service contacts from October 1 2010 to January 31 2011  <i>Intervention Group/follow-up:</i> Weekly service contacts from October 1 2011 to January 31 2012 and October 1 2012 to January 31 2013	Data collected between October 1 2011 and January 31 2012 (campaign), compared with the same time in the previous and subsequent year. Follow up also occurred approximately 6 weeks after campaign ended (March 2012)	<ul style="list-style-type: none"> <li>• The proportion of light smokers requesting cessation services increased 50% (from 13% to 20%)</li> <li>• Contacts for the 20-day period when the campaign aired totaled 21 228, an increase of more than 400% over the same calendar period during the preceding and subsequent years</li> </ul>	New York City Department of Health and Mental Hygiene and Centers for Disease Control and Prevention

Jenkins <sup>281</sup> , 1997, US	Vietnamese American Men	Tobacco	Campaign to reduce smoking	Vietnamese- language media, health education materials, and activities targeting physicians, youth and business (2- year media-led campaign)	<i>Control Group/baseline:</i> Houston (Pretest: n=1,581; Post-test: n=1,209)  <i>Intervention Group/follow-up:</i> San Francisco (Pretest: n=1,133; Post-test: n=1,202)	Baseline occurred in 1990 for Houston and San Francisco. Follow up occurred in both cities in 1992.	<ul style="list-style-type: none"> <li>Increased odds of quitting (OR= 1.65; 95%CI: 1.27-2.15) in San Francisco than Houston (p=0.017)</li> <li>Significantly increase rate of quitting during prior 2 years (Pre-test: 7.2%; Post-test: 10.2%) [p ≤ 0.01]</li> <li>Post-test smoking rate in San Francisco was significantly lower than the rate in Houston (p=0.004)</li> </ul>	Cigarette and Tobacco Surtax Fund of the State of California through the Tobacco Control Section
Johnson <sup>291</sup> , 2011, US	General	Prescription drugs	Campaign to reduce prescription overdose deaths	Media campaign and print materials, bookmarks, patient information cards, and posters. Also TV spot, news releases, media advisories, interviews (May 2008 to May 2009) with slogan of “Use Only As Direct”	<i>Control Group/baseline:</i> Pre-campaign (2000 to 2008)  (n=413)  <i>Intervention Group/follow-up:</i>  Post-campaign (2009) (n=410)	Baseline data was collected from 2000 to 2008 with follow-up occurring approximately 1 year after campaign initiated.	<ul style="list-style-type: none"> <li>In 2008, there was a 14.0% reduction in the number of unintentional, opioid-related drug overdose deaths, from 301 deaths in 2007 to 259 in 2008</li> <li>This remained relatively stable during 2009 at 265 unintentional, opioid-related deaths</li> </ul>	Utah Labor Commission, Legislative Appropriation, Workers Compensation Fund of Utah, University of Utah Research Center for Excellence in Public Health Informatics, Utah Division of Substance Abuse



					Sample was extrapolated to represent entire population of the state			and Mental Health, Utah commission of Criminal and Juvenile Justice.
Kandra <sup>282</sup> , 2013, US	Youth (Age 11 to 17)	Tobacco	Campaign to reduce smoking	Advertisements launched April 2004	<p><i>Control Group/baseline:</i> Before campaign in spring 2004 (637)</p> <p><i>Intervention Group/follow-up:</i> After campaign in fall 2004 (604 of the 637) then winter 2009 (1,154)</p>	Baseline data collected in the Spring of 2004 with follow up occurring in the Fall of 2004 and Winter of 2009.	<ul style="list-style-type: none"> <li>In 2009, awareness of advertisements was associated with decreased odds of current smoking and experimenting with cigarettes</li> </ul> <p>High-sensation-seeking youth:</p> <ul style="list-style-type: none"> <li>With awareness of the advertisement: decreased odds of smoking experimentation (OR= 0.50, 95%CI = 0.26–0.98)</li> <li>Significant relationship between awareness of the advertisements and current smoking (p &lt; 0.01).</li> </ul> <p>Low-sensation-seeking</p>	NC Health and Wellness Trust Fund Commission

							youth: <ul style="list-style-type: none"> <li>No significant relationship existed between awareness of the advertisements and current smoking</li> </ul>	
Katz <sup>313</sup> , 2008, Canada	Children, adolescents, and young adults	Antidepressants	Campaign to decrease prescription of antidepressants to children and adolescents	Health Canada warning	<p><i>Control Group/baseline:</i> Pre-warning (April 1 1995 to March 31 2004; approx. 411 children, 1526 adolescents, and 3,370 young adults per year)</p> <p><i>Intervention Group/follow-up:</i> Post-warning (April 1 2004 to March 31 2006; approx. 411 children, 1526 adolescents, and 3,370 young adults per year)</p>	Baseline occurred 9 years (April 1 1995 to March 31 2004) before the warning with follow-up occurring 2 years (April 1 2004 to March 31 2006) after the warning	<ul style="list-style-type: none"> <li>Rate of antidepressant prescriptions decreased among children and adolescents (RR: 0.86; 95% CI: 0.81–0.91) and young adults (RR: 0.90, 95% CI: 0.86–0.93).</li> <li>The change in rates of use of SSRIs (other than fluoxetine) was significantly greater among the children and adolescents than among young adults (<math>p &lt; 0.001</math>)</li> <li>Ambulatory visits because of depression decreased among children and</li> </ul>	Health Sciences Centre Foundation, Canada Research Chair Award, and Canadian Institutes for Health Research New Investigator Award

							<p>adolescents (RR: 0.90, 95% CI: 0.85–0.96) and young adults (RR: 0.91, 95% CI: 0.87–0.96)</p> <ul style="list-style-type: none"> <li>• The rate of completed suicides among children and adolescents rose significantly after the warning (RR: 1.25, 95% CI: 1.08–1.44; annual rate per 1000 = 0.04 before and 0.15 after the warning)</li> <li>• No change in the rate of completed suicides among young adults (RR: 1.01, 95% CI: 0.93–1.10)</li> </ul>	
Klein <sup>283</sup> , 2005, US	Youths/Teens	Tobacco	Campaign to reduce smoking	Media Campaign in January 2001 for teens to utilize website (GottaQuit.com) through television, radio, billboards, and city busses	<p><i>Control Group/baseline:</i> Pre-campaign (n=418)</p> <p><i>Intervention Group/follow-up:</i> Post-campaign (n=259)</p>	Baseline occurred in 2000 before implementation and follow-up at 1 year after implementation of campaign	<ul style="list-style-type: none"> <li>• Self-reported tobacco use was comparable between the pre-campaign and post-campaign (p=0.575)</li> <li>• Post-campaign smokers were more likely to report they have tried to quit</li> </ul>	Monroe County Health Department

							smoking than pre-campaign	
Kozlowski <sup>284</sup> , 2000, US	General population	Tobacco	MASS campaign to counter-market light (low-tar) cigarettes	TV ads	<i>Control Group/baseline:</i>  Continental US (n=500)  <i>Intervention Group/follow-up:</i>  Massachusetts (n=501)	Campaign ran in spring and fall of 1994 and again in winter 1998. Dates of data collection not reported	<ul style="list-style-type: none"> <li>Compared with the US, MASS smoked marginally fewer cigarettes each day (p&lt;0.06)</li> <li>Lower-tar smokers were less likely to be smoking in 5 years after having seen the ad</li> </ul>	Massachusetts Department of Public Health
Kypri <sup>249</sup> , 2005, New Zealand	Youth	Alcohol	Campaign to reduce alcohol-related harm by discouraging inappropriate supply of alcohol by adults in the South Island of New Zealand	Mass media (1) Newspaper (2) Radio (3) Print media	<i>Control Group/baseline:</i> Survey of youth (n=474) (YAS I)  Baseline group of parents (PAS 1) (n=756)  <i>Intervention Group/follow-up:</i> Survey of youth (n=474) (YAS II)	Baseline surveys (YAS I and PAS I) in July 2001. Follow-up surveys in Oct 2001	<ul style="list-style-type: none"> <li>Levels of binge drinking decreased in all three districts after intervention</li> <li>Unsupervised drinking decreased in the two intervention groups compared to the comparison group, though this result was not statistically significant</li> </ul>	Not reported

					Follow-up group of parents (PAS II) (n=164)			
Langley <sup>238</sup> , 2014, UK	General population	Tobacco	Suspension ("freeze") of tobacco control mass media campaigns in England in April 2010	Mass Media (suspension)	<i>Control Group/baseline:</i> Monthly calls to quit line before intervention  <i>Intervention Group/follow-up:</i> Monthly calls to quit line after intervention	Baseline measurement collected up to April 2010, campaign began April 2010, follow-up measurement from April 2010 to September 2011	<ul style="list-style-type: none"> <li>Quit line calls and website visits fell by 65% (95% CI: 43-79) and 34% (95% CI: 11-50) respectively</li> <li>Requests for literature decreased by 98% (95% CI: 96-99) after the freeze</li> </ul>	National Prevention Research Initiative
Laugesen <sup>245</sup> , 2000, New Zealand	General Population	Tobacco	New Zealand's tobacco control programme	Ban on advertising tobacco products, and addition of health warnings	<i>Control Group:</i> Volume of sales prior to ban  <i>Intervention Group:</i>  Volume of sales after ban	Tobacco control program began in 1985. New Zealand census gave smoking prevalence data for 1976, 1981 and 1996.	<ul style="list-style-type: none"> <li>Change in smoking prevalence in adults: -17% (from 30%-25%)</li> <li>Change in prevalence in youth: -20% (from 35%-28%)</li> <li>In Maori adults: -17% (from 56% in 1981 to 46% in 1996)</li> </ul>	New Zealand Federal Government

Leung <sup>310</sup> , 2016, Hong Kong	General Population	Tobacco	Smoke-free legislation and warning labels on cigarette packs in Hong Kong in Jan 2007	Graphic and text health warnings on cigarette packs	<i>Control Group/baseline:</i>  Survey prior to change in cigarette packages (n=3740)  <i>Intervention Group/follow-up:</i>  Survey after change in cigarette packages (n=2958)	Baseline survey in 2005, legislation and warning labels implemented in Jan 2007, follow-up survey in 2008.	<ul style="list-style-type: none"> <li>Proportion of hardcore smokers (daily smokers, smoking history of &gt;6 years, no quit attempts, no intent to quit and average of at least 11 cigarettes per day) among current daily smokers increased from 22.5% (95% CI: 21.1-23.8%) in 2005 to 28.3% (95% CI: 26.7- 29.9%) in 2008</li> <li>Prevalence of hardcore smoking increased in all age groups after implementation</li> <li>This intervention did not decrease the rate of hardcore smokers</li> </ul>	Health and Health Services Research Fund
Li <sup>242</sup> , 2013, Australia	General Population	Tobacco	Point of sale marketing restrictions in the UK and the US	Tobacco displays (ban)	<i>Control Group/baseline:</i>  UK and the US (no ban)	Marketing restrictions in the UK and US began in 2006 and initial survey data taken in 2006, final survey	<ul style="list-style-type: none"> <li>Compared with smokers in Canada, smokers in the US (AOR=3.26, P&lt;0.001) and UK (AOR= 2.49, P&lt;0.001) were more likely to buy</li> </ul>	National Cancer Institute at the National Institutes of Health of the United States

					<i>Intervention Group/follow-up:</i>  Australia and Canada (ban)	data taken in 2010	unplanned cigarettes because of exposure to cigarette displays <ul style="list-style-type: none"> <li>Smokers with POS display ban were less likely to purchase non-usual brand of cigarettes; Canada (AOR=0.58, P&lt;.001) and Australia (AOR=0.71, P&lt;0.05)</li> </ul>	
Li <sup>305</sup> , 2015, Australia	General Population	Tobacco	Different cigarette package warnings in Australia, Canada and the UK	Cigarette package warnings	Sample size for each of the three countries was initially around 2000 at each survey wave, with replenishment sampling from the same sampling frame used to maintain sample size across waves.	Data collected at each wave of the ITC 4 country survey. Baseline data collected in late 2002, final data collected in early 2012. During this 10-year period the three countries introduced various types of cigarette warnings	<ul style="list-style-type: none"> <li>In the period 2-5 years' post-implementation, the Canadian warnings were responded to with individuals being more likely to forgo cigarettes than the UK ones (p&lt;0.001) with response levels in all three countries declining at similar rates</li> </ul>	National Cancer Institute at the National Institutes of Health of the United States

Li <sup>267</sup> , 2012, Australia	General population	Tobacco	Point Of Sale anti-smoking warnings in Australia, Canada, the UK and the US	POS anti-smoking warnings	<p><i>Control Group/baseline:</i> Survey data from Australia, Canada, the UK and US prior to intervention</p> <p><i>Intervention Group/follow-up:</i> Survey data from Australia, Canada, the UK and US after intervention (n= 21 613 adult smokers who completed at least one of the seven waves)</p>	Data collected at each wave of the ITC 4 country survey. Baseline data collected in 2002, final data collected in 2008.	<ul style="list-style-type: none"> <li>There was a significant positive association between reported exposure to point of sale warnings and interest in quitting (OR=1.139, p&lt;0.01) and prospective quit attempts (OR=1.216 P&lt;0.001)</li> </ul>	National Cancer Institute of the United States
Makowsky <sup>240</sup> , 1991, Canada	General population	Alcohol	Lifting advertising ban	Advertising ban	<p><i>Control Group/baseline:</i> Saskatchewan: 78 data points</p> <p><i>Intervention Group/follow-up:</i> New Brunswick: 72 data points</p>	Ban lifted Oct 3 1983, data measured April 1981-1987, change in legislation occurred in month 33	<ul style="list-style-type: none"> <li>There was no impact on wine or total alcohol sales from lifting the ban on alcohol advertising</li> <li>The sales of beer increased and the sales of spirits decreased after the legislation change</li> </ul>	Not reported



					collected at 4 week intervals			
McAfee <sup>263</sup> , 2013, US	General	Tobacco	Campaign “Tips from Former Smokers”	Mass media (1) TV (2) Billboards (3) Internet (4) Radio (5) Print advertisement	<i>Control Group/baseline:</i>  n=5,271  <i>Intervention Group/follow-up:</i>  n=5,271	3 months  (campaign started March 2012 and follow-up done between June 11-July 5)	<ul style="list-style-type: none"> <li>Quit attempts among smokers rose from 31.1% at baseline to 34.8% at follow-up, a 12% relative increase</li> <li>Prevalence of abstinence at follow-up among smokers who made a quit attempt was 13.4%</li> </ul>	Not reported
McVey <sup>272</sup> , 2000, UK	General	Tobacco	Campaign to reduce smoking	(1) TV (2) Mass media	<i>Control Group/baseline:</i> 1,494 at baseline, 1,046 at 6-month follow-up, and 764 at 18-month follow-up  <i>Intervention Group/follow-up:</i> (1) Participants exposed to TV advertising only (3,000 at baseline, and 1,754 at 18- month follow-up)	Baseline measurement was take October 1992, campaign began December 1992 and follow-up data was recorded until May 1994	<ul style="list-style-type: none"> <li>Pooled OR for not smoking in the TV ad only group compared to control: 1.53 (95% CI: 1.02-2.29)</li> <li>Pooled OR for not smoking in the mass media group compared to control: 1.67 (95% CI: 1.0-2.8)</li> <li>Pooled OR comparing the TV only and mass media campaign: 1.15 (OR= 0.74-1.78) indicating no</li> </ul>	Health Education Authority for England

					(2) Participants exposed to mass media campaign (974 at baseline, and 578 at 18 month follow-up)		<p>difference between the effectiveness of the two campaigns</p> <ul style="list-style-type: none"> <li>The ad campaign would reduce smoking prevalence by approximately 1.2%</li> </ul>	
Miller <sup>296</sup> , 2009, Australia	General	Tobacco	Graphic cigarette pack warnings	Package warnings and mass media	<p><i>Control Group/baseline:</i> Calls to quit line prior to intervention</p> <p><i>Intervention Group/follow-up:</i> Calls to quit line after intervention</p>	<p>24 months, 36 months</p> <p>(data measured starting 2004, 2006 year of introduction, 2007 data also measured)</p>	<ul style="list-style-type: none"> <li>Two years prior to campaign, the Quit line received 81,490 calls, and 84,442 calls in the year prior</li> <li>There were 40% more calls in the year of the campaign, compared to the year after</li> <li>There was no increase in the number of first time callers in the year of the campaign compared to the year before</li> </ul>	Cancer Council South Australia
Miller <sup>307</sup> , 2011, Australia	General population	Tobacco	Graphic health warnings on cigarette packets	Graphic health warnings	<p><i>Control Group/baseline:</i>  Survey of representative</p>	<p>Baseline survey conducted in Sept-Nov 2005</p> <p>GHWs implemented in</p>	<ul style="list-style-type: none"> <li>At follow-up, 19.5% of participants had quit smoking</li> <li>Significantly higher mean baseline</li> </ul>	Grant funding from the South Australian government

					population prior to warnings (n=587)  <i>Intervention Group/follow-up:</i> Survey after implementation of warnings (n=158)	2006 and follow-up survey done in Aug 2006	intention to quit (F(1,150)=11.52; p=0.01) among those that went onto quit at follow-up than among those who were still smoking at the time of follow-up	
Mudde <sup>285</sup> , 1999, US	General Population	Tobacco	National Mass Media Campaign	Mass media (1) television shows & clinic (2) Quitline (3) Local group programs (4) Comprehensive publicity program)	<i>Control Group: Random sample prior to intervention (n=1,338)</i>  <i>Intervention Group: Same sample after intervention (n=918)</i>	Intervention group interviewed in Dec 1990 before the campaign, in April 1991 as a post-test after the campaign, and at a 10-month follow-up.	<ul style="list-style-type: none"> <li>• There was a dose-response relation between exposure and quitting</li> <li>• Follow-up point prevalence abstinence rate attributable to the campaign was estimated at 4.5% after control for test effects and secular trends</li> </ul>	Dutch Smoking and Health Foundation, Dutch Cancer Foundation
Qin <sup>252</sup> , 2014, China	General population in China	Tobacco	Anti-tobacco television advertisement campaign in China	TV advertising	<i>Control Group/baseline:</i>  Participants recruited through street interception prior to campaign (n=1142)	Campaign advertisements aired during January and February 2010. No dates recorded for baseline and follow-up surveys but data	<ul style="list-style-type: none"> <li>• Among smokers who had seen the advertisement, 51.9% made an attempt to quit smoking</li> <li>• Participants who reported seeing the advertisement were more likely not to</li> </ul>	World Lung Foundation and World Health Organization, and the Jiangsu Provincial Center for Disease Control and Prevention

					<i>Intervention Group/follow-up:</i> Participants recruited through street interception after campaign (n=1164)	were collected before and after the campaign.	intend to give cigarettes in the future than those who reported not seeing the advertisement (38.7% vs 27.5%, P<0.001)	
Quinn <sup>244</sup> , 2011, Ireland	General	Tobacco	Removing point of sale tobacco promotional displays	Point of sales displays	<i>Control Group/baseline:</i> Sales of cigarettes prior to intervention  <i>Intervention Group/follow-up:</i> Sales of cigarettes after intervention	Baseline measurement collected from 2006 to July 2009, law banning point of sales promotional displays began July 2009, and follow-up data collected from July 2009 to April 2010	<ul style="list-style-type: none"> <li>No trends in sales data were observed before and after ban of point of sales promotional displays</li> <li>There was no statistically significant difference before and after implementation of the ban</li> </ul>	Office of Tobacco Control Ireland, Cancer Research UK, the Irish Cancer Society, and ASH New Zealand
Richardson <sup>264</sup> , 2010, US	Youth	Tobacco	Exposure to “Truth” campaign	TV ads	<i>Control Group/baseline:</i> Data collected prior to intervention by random from Legacy Media Tracking Survey (LMTS) which uses	Baseline measurement collected December 1999, campaign launched in 2000, follow-up data collected	<ul style="list-style-type: none"> <li>Awareness of campaign and intention to not smoke in the next year was correlated (OR=1.43) but not statistically significant (p=0.37)</li> </ul>	Not reported

					<p>random digit dialing to reach young adults aged 18-24 (n=NR)</p> <p><i>Intervention Group/follow-up:</i> Data collected after intervention by random from Legacy Media Tracking Survey (LMTS) which uses random digit dialing to reach young adults aged 18-24 (n=NR)</p>	from 2000 to January 2004	<ul style="list-style-type: none"> <li>Awareness of campaign and intention to quit smoking was correlated (OR=1.31) and not statistically significant (p=0.06)</li> </ul>	
Saffer <sup>241</sup> , 2002, US	General	Alcohol	Advertising bans in 20 OECD countries	Advertising ban	<p><i>Control Group/baseline:</i> Country data prior to implementation of advertising bans</p> <p><i>Intervention Group/follow-up:</i> Country data after implementation of advertising bans</p>	Time series of data between 1970 (which is first year OECD estimates purchasing power parities)-1995, but baseline and follow-up data collected at various times	<ul style="list-style-type: none"> <li>Bans can reduce consumption by 5-8%</li> </ul>	National Institute on Alcohol Abuse and Alcoholism

						depending on country.		
Scammon <sup>294</sup> , 1991, US	General	Alcohol	Warnings on alcoholic beverages	Health Warnings	<p><i>Control Group/baseline:</i> Statewide representative sample from Utah prior to intervention (n=minimum 400 households)</p> <p><i>Intervention Group/follow-up:</i> Statewide representative sample from Utah after intervention, who were exposed and not exposed to the warnings (Mormons, and general population)</p>	Baseline data was collected in April, July and October of 1989 prior to intervention. Campaign began November 1989. Follow-up data collected in January, April and July of 1990.	<ul style="list-style-type: none"> <li>46.8% of the general population reported drinking alcohol two or more days per month before the campaign, compared to 49.9% after the campaign</li> </ul>	University of Utah Research Committee and the Utah State Division of Substance Abuse
Secker-Walker <sup>286</sup> , 1997, US	Youth	Tobacco	Exposure to mass media campaign to prevent smoking	Mass media (1) TV (2) Radio	<p><i>Control Group/baseline:</i> One community in Montana and one in northeastern United States received</p>	Data collected, and campaign run from 1984 to 1991	<ul style="list-style-type: none"> <li>Weekly smoking in control communities was 25.9% compared to weekly smoking in intervention</li> </ul>	Supported by NIH grants CA38395 and CA22435

					only a school program (n=2851)		communities which was 20.4% <ul style="list-style-type: none"> <li>Approximately 128 fewer students smoked in the intervention community compared to the control communities</li> </ul>	
Slater <sup>292</sup> , 2011, US	Youth	Cannabis	Two media campaigns to reduce adolescent cannabis use in 20 US communities	Be your own influence campaign - in-school and community mass media  Above the Influence Campaign – TV advertising	<i>Control Group/baseline:</i> Communities not exposed to “Be your own influence” campaign, but exposed to “Above the Influence” campaign (10 communities)  <i>Intervention Group/follow-up:</i> Communities exposed to both	Baseline data collected in the fall and spring of two school years (grade 7 and 8), and follow-up data collected in the fall and spring of the next school year (Grade 9)	<ul style="list-style-type: none"> <li>Those who were exposed to Above the Influence campaign were less likely (OR=3.85, p&lt;0.005) to use cannabis compared to those not exposed</li> <li>Community-level “Be Your Own Influence” campaign lowered the risk of using cannabis at the last measurement</li> <li>School-level “Be Your Own Influence”</li> </ul>	National Institute on Drug Abuse

					campaigns (10 communities)		campaign did not affect cannabis use at the last measurement	
Smith <sup>269</sup> , 2009, Canada	General	Tobacco	“Let’s take it outside” social marketing and community engagement campaign to reduce children’s exposure to tobacco smoke at home	Mass media (1) TV (2) Radio (3) Newspaper advertisements	<i>Control Group/baseline:</i> random digit dialing sampled from Cape Breton Island (pre-campaign n=620, post-campaign n=452)  <i>Intervention Group/follow-up:</i> random digit dialing sampled from Prince Edward Island (pre-campaign n=515, post-campaign n=592)	Baseline measurements were taken in control and intervention groups in 2002, campaign was implemented in the fall of 2002, and follow-up data was collected in 2003	<ul style="list-style-type: none"> <li>• There was no difference in the change towards smoke free homes between the control and intervention sites</li> <li>• Thus urge caution in respect to strategies used to evaluate social marketing campaigns, such as attention to knowledge and attitudes but not behaviour, and failure to utilize control sites</li> </ul>	Canadian Institute for Health Research, the Prince Edward Island Health Research Programme, Canadian Tobacco Control Research Initiative, Health Canada, Sociobehavioural Cancer Network of the National Cancer Institute of Canada
Solomon <sup>287</sup> , 2009, US	Youth	Tobacco	3 year mass media campaign to reduce smoking	Mass media (1) TV (2) Radio campaign	<i>Control Group/baseline:</i> Two media markets in South Carolina, Florida, Texas and Wisconsin were not exposed to	Baseline data collected between 1 and 6 months prior to campaign, campaign began in January 2002, follow-up	<ul style="list-style-type: none"> <li>• 30-day smoking rates increased in both control and intervention groups during 3-year follow-up (p&lt;0.01)</li> <li>• The rate of youth smoking one or</li> </ul>	Grant P01 CA82708 from the National Cancer Institute



					<p>campaign (n=1,043)</p> <p><i>Intervention Group/follow-up:</i> Two media markets in South Carolina, Florida, Texas and Wisconsin were exposed to campaign  (n=987)</p>	<p>data collected annually for three years</p>	<p>more cigarette in the past 30 days was lower in the intervention group than the control group (p=0.04)</p> <ul style="list-style-type: none"> <li>• Quit rate from baseline to last follow-up was 16% in intervention group and 12.8% in control group</li> <li>• Of those who had smoked at baseline, 59.4% resumed in the experimental condition compared to 66.1% in the control group</li> </ul>	
Vallone <sup>265</sup> , 2011, US	Racial/ethnic and educational subgroups	Tobacco	National smoking cessation campaign	Mass media  (1) TV (2) Radio (3) Internet	<p><i>Control Group/baseline:</i> n=5,616</p> <p><i>Intervention Group/follow-up:</i> n=4,067</p>	<p>Baseline data collected between February and April 2008, campaign was implemented in April 2008, and follow-up data collected between August and October 2008</p>	<ul style="list-style-type: none"> <li>• Awareness of campaign was correlated with intention to quit among non- Hispanic black respondents only (p=0.001)</li> </ul>	Not reported

White <sup>306</sup> , 2008, Australia	Youth	Tobacco	Health warning labels	Warning labels	<p><i>Control Group/baseline:</i> Survey of schools prior to intervention (16 schools, n=2432)</p> <p><i>Intervention Group/follow-up:</i> Survey of schools after intervention (25 schools, n=2050)</p>	Baseline data collected in 2005, packages changed in March of 2006, follow-up data collected in 2006 6 months after the introduction	<ul style="list-style-type: none"> <li>• Average number of cigarettes consumed per week prior to intervention was 28.9 compared to 22.1 after (p=0.037)</li> <li>• 44% were classified as never smoked and not susceptible at baseline, and 50% were classified as never smoked and not susceptible after the intervention (p=0.030)</li> </ul>	Cancer Council Victoria and Winifred and John Webster charitable trust
Wilcox <sup>239</sup> , 1985, US	General	Alcohol	Ban	Restrictions on advertising price of alcohol	<p><i>Control Group/baseline:</i> Sales data in Lower Michigan prior to ban on advertising prices</p> <p><i>Intervention Group/follow-up:</i> Sales data in Lower Michigan after ban on advertising prices</p>	<p>Data was collected in 3 periods: 1) during a restricted period between May 1981-February 1982,</p> <p>2) during a no restriction period between March 1982-May 1983, and</p> <p>3) during a restriction period June</p>	<ul style="list-style-type: none"> <li>• Price advertising did not have a significant impact on sales of alcoholic beverages</li> </ul>	Not reported

						1983-April 1984		
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## Appendix 5

### Search Strategy for Economic Regulation

#### Medline, Embase, PsychInfo and NHSEED

1. Cannabis/ae, de, pd, po, to [Adverse Effects, Drug Effects, Pharmacology, Poisoning, Toxicity]
2. exp Marijuana Abuse/
3. (bhang or bhangs or bhangstar or cannabutter or cannabis\* or doobie\* or ganga or gangas or ganja or ganjas or grass or hash\* or hashish\* or hemp or hemsps or honeycomb or mary jane\* or marihuana\* or marijuana\* or moon rock or pot or reefer\* or roach\* or shatter or weed).tw.
4. 1 or 2 or 3
5. "Costs and Cost Analysis"/
6. exp models, economic/
7. markov chains/
8. Quality-Adjusted Life Years/ or choice behavior/
9. (economic evaluation\* or cost benefit\* or cost effective\* or cost utilit\* or cost minimization or cost or costs or costing or (economic adj5 model\*) or economics).tw.
10. 6 or 7 or 8 or 9
11. ((Washington State) or Colorado or Alaska or Oregon or (District of Columbia) or (Washington DC) or Uruguay).tw.
12. Exp Washington/ or Colorado/ or Alaska/ or Oregon/ or District of Columbia/ or Uruguay/
13. 11 or 12
14. 4 and 10 and 12

#### Econlit

((bhang or marijuana or cannabis or bhangs or bhangstar or cannabutter or cannabis\* or doobie\* or ganga or gangas or ganja or ganjas or grass or hash\* or hashish\* or hemp or hemsps or honeycomb or mary jane\* or marihuana\* or marijuana\* or moon rock or pot or reefer\* or roach\* or shatter or weed)).tx.

And

((Washington State) or Colorado or Alaska or Oregon or (District of Columbia) or (Washington DC) or Uruguay).tx.

Figure 1: Flow chart for experience with economic regulation for cannabis

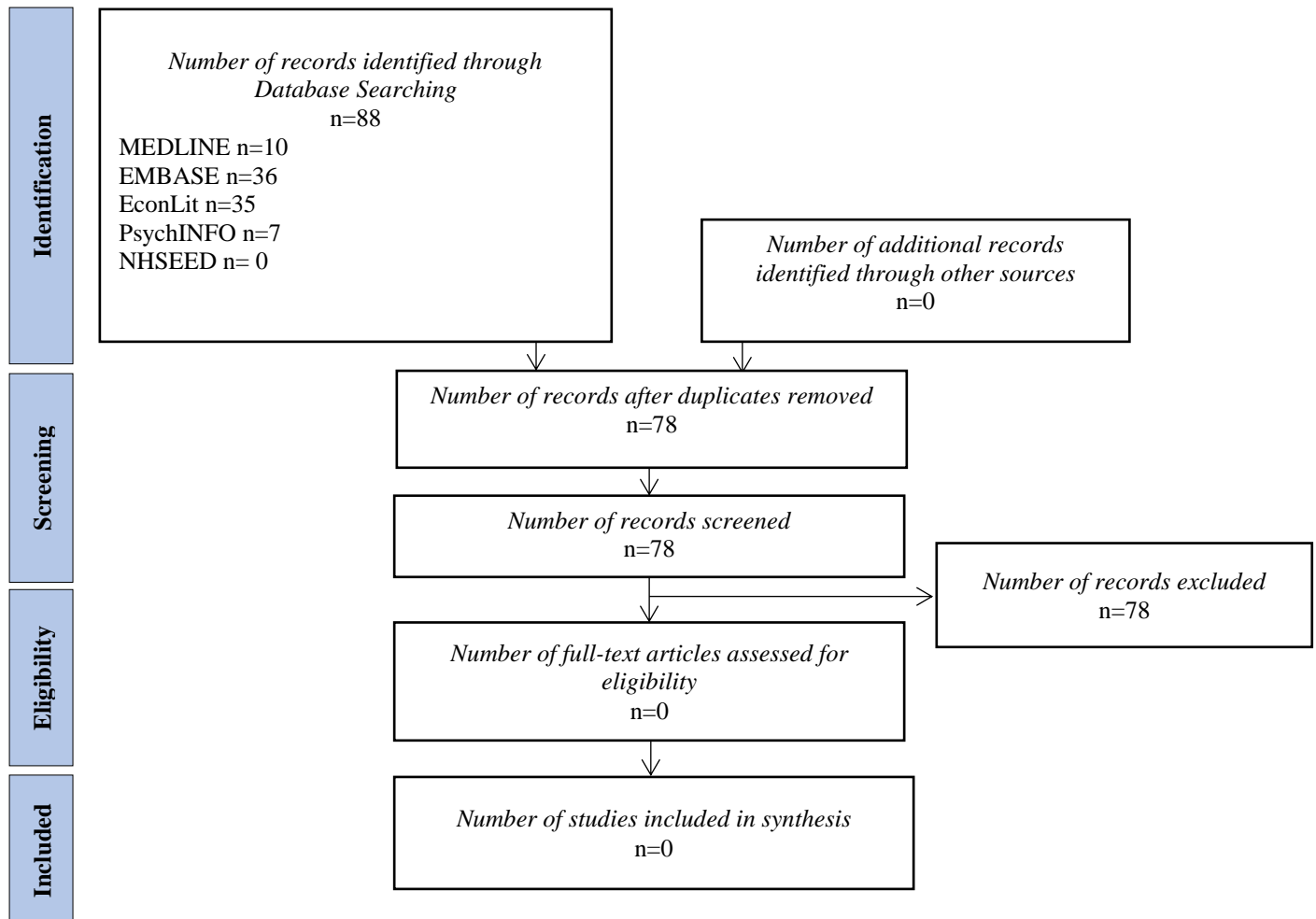
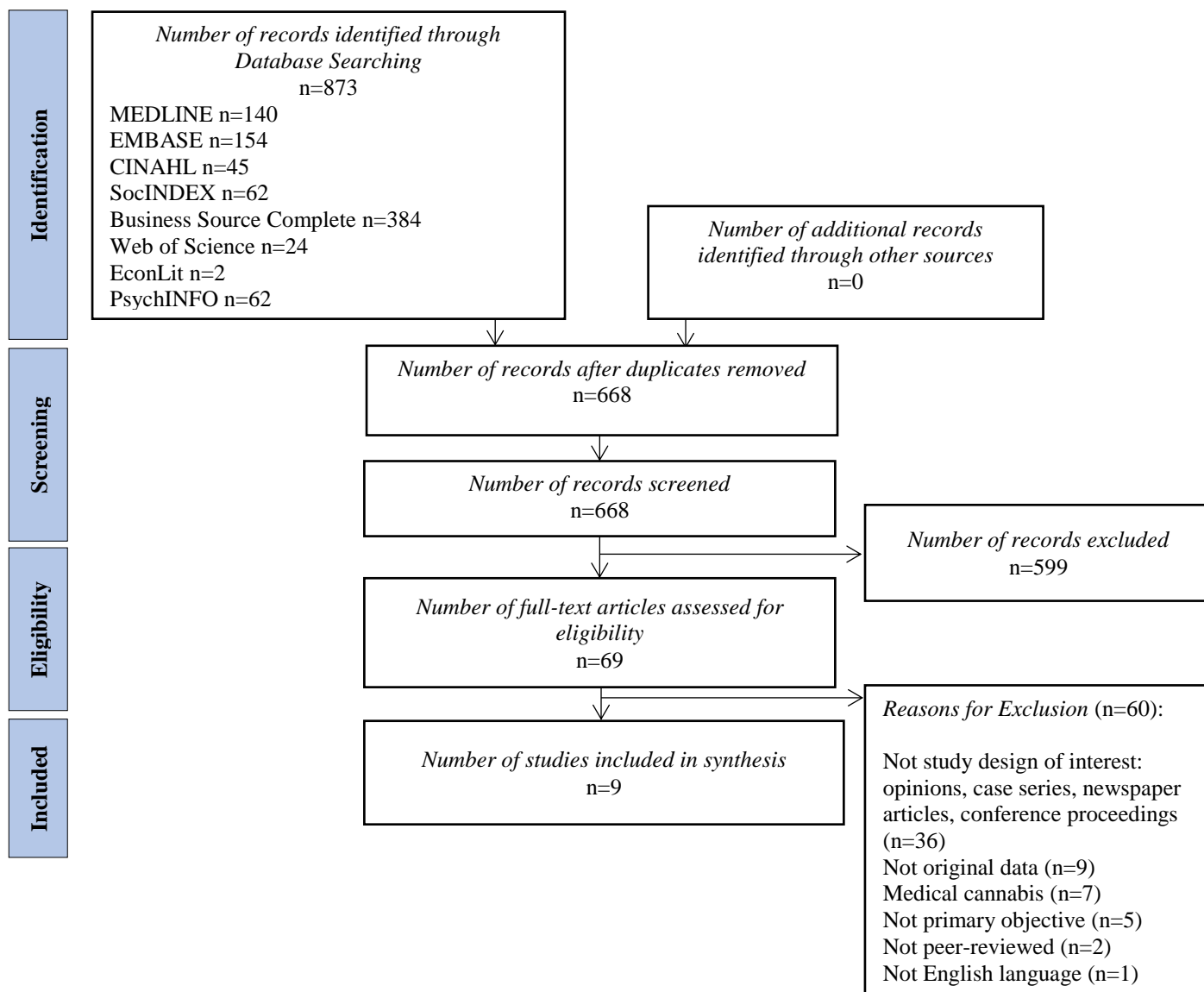


Figure 2: Flow Chart for experience with cannabis legalization systematic review



**Table 1.** Experience with cannabis legalization systematic review

Author, Year of Publication	Objective	Study Design	Participant Selection / Data Collection	Outcomes Assessed	Participant Characteristics	Key Findings	Conclusion	Quality Assessment
Colorado, USA								
Bell et al., <sup>460</sup>  2015	“To characterize hydrocarbon burns associated with BHO manufacture in Colorado.”	Cross-sectional study of medical records	<i>Participant Selection/data collection:</i> Data on hydrocarbon burns were collected through the American Burn Association’s National Burn Repository referred to the University of Colorado Burn Center  <i>Date of data collection:</i> January 1, 2008 - August 31, 2014	<ul style="list-style-type: none"><li>• Prevalence of hydrocarbon burns associated with cannabis use</li><li>• Clinical characteristics of hydrocarbon burns associated with cannabis use</li></ul>	<ul style="list-style-type: none"><li>• 29 patients with BHO burns</li><li>• 72.4% were Caucasian</li><li>• 89.7% were male</li><li>• Median age of 26 (range: 15-58)</li></ul>	<ul style="list-style-type: none"><li>• 31 visits for hydrocarbon burns associated with cannabis use reported: 0 cases prior to legalization, 19 cases during the three years where cannabis was legalized and 12 in the 8 months after legalization</li><li>• 93% were flash burns from explosions in enclosed spaces</li><li>• Median body surface involved: 10%</li><li>• Median length of stay: 10 days</li><li>• 96% were upper extremity burns and 68% were head or neck burns</li><li>• 21% required intubation</li></ul>	“Cannabis policy liberalization in Colorado has been associated with an unanticipated problem of increasing hydrocarbon flash burns due to BHO production.”	18/27
Kim et al., <sup>456</sup>  2016	“To determine whether the rates of emergency department (ED) visits related to cannabis use have increased disproportionately among out-of-state residents, as compared with	Cross-sectional study of medical records	<i>Participant Selection/data collection:</i> Urban academic hospital in Aurora, Colorado  <i>Date of data collection:</i> 2012-2014	<ul style="list-style-type: none"><li>• Rates of visits with ICD-9 codes for cannabis use adjusted for the volume of annual visits</li></ul>	<ul style="list-style-type: none"><li>• 2,603 total residents (2,469 Colorado residents; 118 out-of-state residents)</li><li>• 12% between 18-21 years</li><li>• 65% were male</li><li>• 46% white, 39% black, 16% other</li><li>• Reason for visit: 27% gastrointestinal; 26% psychiatric;</li></ul>	<b>Hospital Admissions Data</b> <ul style="list-style-type: none"><li>• Rate of ED visits related to cannabis use<ul style="list-style-type: none"><li>▪ Among out-of-state residents doubled from 85 per 10,000 visits in 2013 to 168 per 10,000 visits in 2014 (rate ratio=1.98, p=0.001)</li><li>▪ Among Colorado residents did not significantly change with 106 per 10,000 visits in 2013 to 112 per 10,000 visits in 2013 (rate ratio=1.05, p=0.26)</li></ul></li></ul>	“ED visits related to cannabis use appear to be increasing more rapidly among out-of-state residents than among	17/27

	Colorado residents.”				16% cardiopulmonary • 56% admitted and 44% discharged	• Rates did not significantly change between 2012 and 2013 among either residents  <b>State-wide Data</b>  • Rate of ED visits related to cannabis use <ul style="list-style-type: none"> <li>Among out-of-state residents rose from 78 per 10,000 visits in 2012 to 112 per 10,000 visits in 2013 to 163 per 10,000 visits in 2013 (p&lt;0.001 for both comparisons)</li> <li>Among Colorado residents rose from 61 to 70 to 86 to 101, respectively, per 10,000 visits (p&lt;0.001 for all comparisons)</li> </ul>	Colorado residents.”	
Sobesky et al., <sup>459</sup>  2016	“The aim of this study was to explore the experiences of adolescent substance misuse treatment providers within the context of legal cannabis use in one state in the United States.”	Qualitative interviews using grounded theory	<i>Participant Selection/data collection:</i> Adolescent substance misuse treatment providers (areas of psychologist, social work, counselling) with at least two years of clinical practice in Colorado before January 1, 2014  <i>Date of data collection:</i> Not Reported	• To explain the experience of adolescent substance misuse treatment providers within a context of legal cannabis use in the United States	• 11 participants • 7 female and 4 male • Average age of 44.5 years • Six white, three African American, one Latino, and one mixed race • Mean of 10.23 years of clinical work	• Seven core concepts related to cannabis use and decriminalization: normalizing, increasing access, rising addiction potential, link to opioids and other drugs, complicating substance treatment, diversity issues, and responding to change • Legalization has contributed to the continuing normalization of cannabis, validation of its consumption, and greater access to a host of new and more potent THC products by adolescents • Providers were concerned about the impact of cannabis laws on adolescent health, feeling overwhelmed due to an increased treatment need both in quantity and acuity of adolescent patients	“Results support the need to expand access to a wider range of substance misuse treatment options for adolescents and to further our understanding of the impact on this population of the cannabis laws.”	6/27



Urfer et al., <sup>461</sup>  2014	“In this study, the results of testing of whole blood samples collected from drivers in suspected DUI/D cases in Colorado during the period of January 2011 to February 2014 were analyzed.”	Toxicology testing on whole blood collected by Colorado law enforcement agencies in the course of suspected DUI of alcohol and drug investigations	<p><i>Participant Selection/data collection:</i> DUI/D law enforcement cases where whole blood samples were submitted to ChemaTox</p> <p><i>Date of data collection:</i> January 2011 - February 2014</p>	<ul style="list-style-type: none"> <li>• Number/rate of law enforcement samples submitted</li> <li>• Number of requests for drug test versus alcohol testing</li> </ul>	<ul style="list-style-type: none"> <li>• 12,082 DUI/D law enforcement cases were submitted to ChemaTox for testing</li> <li>• 87% male</li> <li>• Median age was 24 years</li> </ul>	<ul style="list-style-type: none"> <li>• The percentage of law enforcement cases with requests for cannabis screening for all years was 35%, increasing from 28% in 2011 to 37% in 2013</li> <li>• The positivity rate of cannabis screens overall was 62% with no significant change over the time frame examined</li> <li>• The percentage of positive cannabis screens in which THC was confirmed positive at or above 2 ng/mL increased significantly from 28% in 2011 to 65% in 2013</li> <li>• In THC-positive cases, most common single additional drug class was alcohol (n=612), after alcohol the most common drugs were methamphetamine, cocaine, and benzodiazepines</li> </ul>	Data illustrate a statistically significant increase in cannabis screen that result in positive THC confirmations.	18/27
Wang et al., <sup>453</sup>  2016	“To compare the incidence of pediatric cannabis exposures evaluated at a children’s hospital and regional poison center (RPC) in Colorado before and after non-medical Cannabis legalization and to compare population rate trends of RPC cases for cannabis exposures with	Retrospective cohort study	<p><i>Participant Selection/data collection:</i> Patients 0 to 9 years of age evaluated at the hospital’s emergency department, urgent care centers, or inpatient unit and poison control cases from Colorado for single-substance cannabis exposures</p> <p><i>Date of data collection:</i> January 1, 2009 - December 31, 2015</p>	<ul style="list-style-type: none"> <li>• Cannabis exposure visits and RPC cases</li> <li>• Cannabis source and type</li> <li>• Clinical effects</li> <li>• Scenarios</li> <li>• Disposition</li> <li>• Length of stay</li> </ul>	<ul style="list-style-type: none"> <li>• 81 patients evaluated at the children’s hospital and Colorado’s RPC received 163 cannabis exposure cases</li> <li>• Median age of hospital visits was 2.4 years</li> <li>• 60% were male</li> <li>• Median age of RPC cannabis exposures was 2 years</li> <li>• 8% were male</li> </ul>	<ul style="list-style-type: none"> <li>• The number of cannabis exposure visits per 1,000 ED visits for ingestion increased 2 years after legalization compared to 2 years before legalization (4.3 before and 6.4 after per 1,000 visits) (p=0.19)</li> <li>• Cannabis visits per 100,000 population increase after legalization (2.3) compared to before (1.2) (p&lt;0.001)</li> <li>• 65% of patients were observed in the ED or UC, 21% were admitted to an inpatient ward unit, and 15% were admitted to ICU</li> <li>• The annual number of cannabis exposure poison control cases increased more than 5-fold, from 9 in 2009 to 47 in 2015</li> <li>• Colorado had an average increase in poison control cases of 34% (p&lt; .001) per year while the remainder of the United States had an increase of 19% (p&lt;.001)</li> <li>• Most children had either no (28%) or minor effects (46%)</li> </ul>	“The number of children’s hospital visits and RPC case rates for cannabis exposures increased between the 2 years prior to and the 2 years after legalization.”	21/27

	the rest of the United States.”							
<b>Washington, USA</b>								
Couper et al, <sup>454</sup>  2014	“The aim of this study was to assess the effect of cannabis legalization on the prevalence of cannabis in suspected impaired driving cases. The prevalence of both active THC and its metabolite	Review of blood toxicology results over a 5 year period	<i>Participant Selection/data collection:</i> Blood toxicology results from all suspected impaired driving cases submitted by law enforcement offices from Washington State	<ul style="list-style-type: none"> <li>• Total number of impaired driving cases received for testing</li> <li>• Cases positive for carboxy-THC and THC</li> <li>• THC blood concentrations</li> <li>• Prevalence of alcohol and other drugs in driving cases</li> </ul>	<ul style="list-style-type: none"> <li>• 25,719 cases between 2009 and 2013</li> <li>• 77-81% were male</li> <li>• Median age of 25 (2009-2012) and 26 (2013)</li> <li>• Range of age from 13-85</li> </ul>	<ul style="list-style-type: none"> <li>• The number of suspected impaired driving cases submitted to the laboratory for testing increases slightly every year, from 4,809 cases in 2009 and 5,468 cases in 2013</li> <li>• Percentage of cases testing positive for THC and carboxy-THC were relatively consistent for the 4 years prior to cannabis legalization (2009–2012), with an average yearly percentage of 19.1 and 27.9% testing positive for THC and carboxy-THC, respectively. In the year following legalization (2013), the percentage of cases testing positive increased to 24.9% for THC and 40.0% for carboxy-THC (5.8 and 12.1% percentage point increase, respectively)</li> <li>• In 2013, there was an increase in the combined use of cannabis and either alcohol and/or drugs,</li> </ul>	“Prevalence of alcohol and the majority of other drugs in this same population of suspected impaired drivers submitted for testing did not change during this same 5-year period—	18/27

	carboxy-THC detected in such cases pre-legalization was compared with the prevalence post-legalization.”		<i>Date of data collection:</i> 2009 - 2013			<p>with 60% of cannabis cases testing positive for another substance compared with 51–54% in the previous 4 years</p> <ul style="list-style-type: none"> <li>• An average of 56% of cases were at or &gt;5 ng/mL over the 5-year period.</li> </ul>	cannabis was the only drug to show such an increase in frequency.”	
Fleming et al, <sup>458</sup>  2015	Assess whether associations between cannabis use and cannabis-specific risk factors have weakened over time and examine whether decreases in alcohol and cigarette use can account for the lack of expected increase in cannabis use prevalence.	Survey data from 10th-grade of 2000 to 2014	<p><i>Participant Selection/data collection:</i> biennial Washington State Healthy Youth Survey of 10th graders</p> <p><i>Date of data collection:</i> 2000 - 2014</p>	<ul style="list-style-type: none"> <li>• Cannabis use</li> <li>• Cannabis specific risk factors</li> <li>• Alcohol and cigarette use</li> <li>• Perceived harm of regular cannabis use</li> </ul>	<ul style="list-style-type: none"> <li>• 30,365 students</li> <li>• Year-specific samples ranged from 2,507 to 4,660</li> <li>• 2000: 71% non-Hispanic white</li> <li>• 2014: 57% non-Hispanic white</li> </ul>	<ul style="list-style-type: none"> <li>• Prevalence of low perceived harm of cannabis use rose between 2000 and 2002, plateaued through 2006, then rose steadily through 2014</li> <li>• Any and frequent cannabis use prevalence declined between 2000 and 2004. Any cannabis use rebounded to previous levels in 2010 but then declined slightly through 2014. Frequent use remained relatively stable since 2006.</li> <li>• Youth and community attitudes increased in prevalence in recent years and diverged from the stable or downward trend in cannabis use.</li> <li>• Prevalence of any alcohol use declined from 2000 to 2002, increased slightly in 2006, and then declined steadily to 2014. Any cigarette use declined steadily throughout the study period.</li> <li>• The association between low perceived harm and frequent use grew stronger over time (adjusted odds ratio of 10.69 in 2000 and 18.13 in 2014)</li> <li>• The decreases in alcohol and cigarette use at least partially account for the lack of increases in cannabis use</li> </ul>	Decreases in prevalence of alcohol and cigarette use largely accounted for stability in cannabis use during a period when cannabis risk factors increased (low perceived harm, youth favorable attitudes about use, and perceived community attitudes favorable to use)	17/27

Kosterman et al, <sup>457</sup>  2016	To examine parents' reactions to cannabis legalization and changes in attitudes and behaviours over time	Longitudinal survey with 15 waves of data	<p><i>Participant Selection/data collection:</i> parents in Washington State participating in Seattle Social Development Project who had face-to-face contact with their child (age 19 or younger) at least once a month</p> <p><i>Date of data collection:</i> 1985 - 2014</p>	<ul style="list-style-type: none"> <li>Assessing parents' understanding of the law at age 39</li> <li>Assessing parents' approval and perceived harm of adult and adolescent use</li> <li>Parents' cannabis use was assessed beginning when they were age 10</li> <li>Parents' cannabis-related communication and behaviour with their children</li> </ul>	<ul style="list-style-type: none"> <li>395 parents</li> <li>44% male</li> <li>45% European American, 27% African-American, 22% Asian American, and 5% Native American</li> <li>Actively parented 2.74 children on average, average child age of 9.82</li> </ul>	<ul style="list-style-type: none"> <li>32% of parents incorrectly believed the legal age of nonmedical cannabis use to be 18</li> <li>Significant increase in approval of adult cannabis use (1% at age 13 to 25% at age 19 to 52% at age 39) and decrease in perceived harm of regular use (lowest prevalence at only 65% at age 39)</li> <li>Wide opposition to teen use and use around one's children</li> <li>Substantial increases in frequency of use and cannabis use disorder among parents who used</li> </ul>	Key results showed that many parents were unclear about some basic components of the new law. Approval of adult cannabis use in 2014 was at its highest and perceived harm of regular use was at its lowest in the 29-year history of the SSDP study.	14/27
Mason et al, <sup>455</sup>  2016	"To explore the prevalence of cannabis and other substance use in 2 cohorts of adolescents who experienced the nonmedical cannabis law change in Washington	Self-reported survey data	<p><i>Participant Selection/data collection:</i> 8th graders enrolled in targeted Tacoma, Washington public schools and recruited in 2 consecutive annual cohorts</p> <p><i>Date of data collection:</i> 1985 - 2014</p>	<ul style="list-style-type: none"> <li>Lifetime and past-month cannabis, cigarette and alcohol use</li> </ul>	<ul style="list-style-type: none"> <li>238 students (second cohort experienced the Washington State nonmedical cannabis law change, first cohort did not)</li> <li>48% female</li> <li>Over 70% of students who received free or reduced-price school lunch in the 2010-2011 school year</li> </ul>	<ul style="list-style-type: none"> <li>13% of the 8th grade students reported ever using cannabis at baseline</li> <li>Cohort differences in likelihood of cannabis use were significantly different from those for cigarette and alcohol use at follow-up</li> <li>Cannabis use was higher in second cohort than the first cohort but the difference was not statistically significant (11.8% versus 6.8%, respectively, <math>p&gt;0.05</math>)</li> <li>Rates of cigarette and alcohol use were slightly lower in the second cohort than in the first cohort</li> </ul>	Cannabis use was more prevalent among teens shortly after the transition from medical cannabis legalization only to medical and nonmedical cannabis	18/27

	State at different ages.”				<ul style="list-style-type: none"><li>• 35% Caucasian, 21% African American, 17% Hispanic</li><li>• Mean age at enrollment was 13.37 years</li></ul>		legalization, although not statistically significant.  Findings provide some evidence of substitution effects.	
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