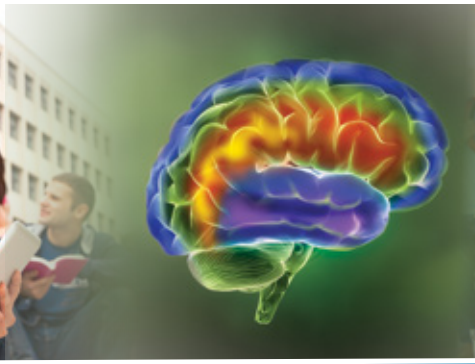
SUBSTANCE ABUSE IN CANADA 2015

The Effects of Cannabis Use **during Adolescence**



Canadian Centre
on Substance Abuse
Centre canadien **de lutte contre les toxicomanies**

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Suggested citation: George, T., & Vaccarino, F. (Eds.). (2015). *Substance abuse in Canada: The Effects of Cannabis Use during Adolescence*. Ottawa, ON: Canadian Centre on Substance Abuse.

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Ce document est également disponible en français sous le titre :
Toxicomanie au Canada : Les effets de la consommation de cannabis pendant l'adolescence.

ISBN 978-1-77178-261-6

The Effects of Cannabis Use **during Adolescence**

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Foreword

For over 25 years, the Canadian Centre on Substance Abuse (CCSA) has provided national leadership to advance solutions that will reduce the harms of alcohol and drugs on individuals and their families. Part of our unique role involves bringing people and knowledge together to effect changes in policy, practice and programs, and make a difference in the lives of Canadians. This role includes advancing knowledge and promoting research on the disease of addiction and issues around substance abuse in Canada and globally.

To this end, CCSA regularly produces reports in the *Substance Abuse in Canada* (SAIC) series; the latest, released in June 2014, was on childhood and adolescent pathways to substance use disorders. That report examined how biological, behavioural and social factors, and experiences during the early developmental years can lead to or protect against later-life substance use disorders and concurrent mental and physical health problems.

The 2014 SAIC report highlighted important questions about the connection of mental health issues, environmental factors and substance abuse in younger children and adolescents. As we are all aware, adolescence is a time of significant development and change. It is also the period when substance use most commonly begins. In Canada, the drug of choice for young people is cannabis, with almost one-quarter of 15- to 24-year-olds reporting past-year cannabis use. In fact, Canadian youth are the highest users of cannabis compared to youth in other developed countries. Of particular concern is recent research suggesting that Canada's youth do not have the knowledge they need about the risks associated with this drug to make informed decisions.

Because young people are disproportionately more likely than those in other age groups to use substances, engage in risky patterns of use and experience harms from that use, CCSA considered it vital to take a closer and more comprehensive look at exactly what effects can arise from adolescent use of this illicit drug. This examination is of particular importance given public dialogue in Canada about cannabis policy, the move towards regulation and legalization in some American states, and the use of cannabis for medical and therapeutic purposes.

The issue of cannabis use is given a great deal more attention today than even a few years ago, and mixed messages in our own country and abroad are being internalized by young people. Public debates about cannabis need to be informed by evidence. To make the evidence available is precisely the role of CCSA, an organization dedicated to finding the signal amidst the noise on complex issues like cannabis. This SAIC report provides an overview of current knowledge to help ensure that converging evidence of the effects of cannabis on the brain and behaviour is brought to bear on discussions of the issue, and to bring about changes where needed.

CCSA chose to focus on youth because young people represent the future of our country. Brain development during adolescence lays the foundation for success later in life or, conversely, for challenges in adulthood. And so, while there are many other issues involved in the larger debate about where cannabis fits in political, health and law enforcement spheres, the focus of this report is squarely on the health effects youth could experience if they use cannabis: in essence, what we know about those effects, what we don't know and what we need to focus attention on in the future, so that we can work together towards better policies, practices and programs aimed at this cohort.

So what does this report tell us about the health effects of adolescent cannabis use? First and foremost, cannabis is not a harmless drug. It can be addictive and the risk increases the earlier it is used. Early and frequent use also increases the risk of short-term cognitive impairment and under performing in school, as well as psychotic symptoms and disorders. Cannabis use significantly impairs coordination and reaction time, so it is not surprising that it is the most common illicit drug found to be involved in car accidents, including fatal ones. And although we do not know the full extent of the impact of early cannabis use on long-term cognitive ability and associated educational and occupational successes, evidence is mounting that cannabis affects the young brain in a harmful way that cannot be ignored.

All Canadians need to be made more aware of the health risks and harms outlined in this report. This knowledge must be used to communicate with youth through comprehensive, factual

and multi-faceted prevention messaging and programs that involve family members, schools and the community. Evidence-informed approaches to drug prevention — like those found in CCSA's Canadian Standards for Youth Substance Abuse Prevention — can have a significant impact on youth substance use and abuse and can contribute to the overall health and well-being of young people.

As importantly, when we harness opportunities for prevention and intervention at the earliest stages, these investments in our young people can yield long-term improvement in health and socioeconomic outcomes for both individuals and families. The evidence in this report is important for healthcare professionals, who are often the first line of defence in early screening and intervention for problematic substance use. This focus follows recommendations made by the House of Commons Standing Committee on Health earlier this year to increase the capacity of healthcare professionals in this regard.

Another key recommendation arising from the report is the need for a national research agenda in Canada aimed at improving understanding of the short- and long-term harms related to cannabis, including its relationship to the development of addiction in vulnerable population groups, such as youth. Regardless of the future of cannabis from a legal or medical perspective, we all need to ensure that we have a common and scientifically rooted understanding of how this substance interacts with the developing brain of adolescents and under what conditions — not only for their health and safety in the short term, but also considering long-term implications for them and society as a whole.

This report presents an immediate opportunity to enhance youth drug use prevention and intervention programs, as well as emerging policy frameworks, with factual information and in a fashion that has been shown to work. We know that cannabis is not a benign substance. It has clear harms and poses risks to those who use it on a regular and frequent basis, including negative health, economic and social ramifications. It is now up to readers to take the information in this report and use it to help reduce the incidence of harms associated with cannabis use among adolescents, to help young people make smarter and more informed choices about their todays and their tomorrows.

Acknowledgements

It gives me great pleasure to take this opportunity to thank the authors of the report — Dr. Joanna Henderson, Dr. Andra Smith, Dr. Tony George, Michelle Goodman, Dr. Bernard Le Foll, Dr. Kevin Gray, Dr. Aimee McCrae-Clark and Dr. Harold Kalant — for their expertise and superb work in gathering and synthesizing the vast amount of cutting-edge research discussed in this report. Special thanks to the editorial team, Drs. Tony George and Franco Vaccarino, for their exceptional editing of and contributions to the entire report, and for integrating the evidence and key messages of the individual authors. CCSA is also indebted to Dr. Amy Porath-Waller, interim director of research, who played an essential leadership role in developing this report and pulling together all the experts to bring this evidence forward. I am also happy to have the occasion once again to thank members of CCSA's Scientific Advisory Council for their expert advice and assistance with this report and the SAIC series in general. Last but not least, I would like to draw attention to the continued hard work and dedication of CCSA staff who support our research program and make possible such publications as this.

Rita Notarandrea
Chief Executive Officer (interim)
Canadian Centre on Substance Abuse

Foreword

Cannabis remains the most commonly used illegal substance in Canada. Many people have used cannabis, or know someone who has, and infer from their first-hand knowledge that cannabis is a harmless or relatively benign substance that can be used safely. "I have tried marijuana several times and nothing bad has happened to me; it is less harmful than alcohol" is an oft-heard assertion. Although the insights gained from personal knowledge can be compelling, all good scientists know that solid research evidence is not established with the casual study of a single person.

Current debates about cannabis use are rife with mere opinion and misinformation. And, to complicate the matter further, the evidence related to the possible health risks of cannabis use appears to be contradictory. How do we weigh the evidence? Is it a drug with a variety of adverse or hazardous effects or does it pose low risk to people's health? What is one to believe?

There are many websites and authorities that claim to offer accurate information about cannabis. Indeed, a simple Google search of the word cannabis yields over 60 million results. How can the average person make sense of this confusing picture?

Several researchers have engaged young people to better understand their attitudes and beliefs about cannabis — why they use it or don't use it and, more specifically, what they want to know about it (Bottorff, Johnson, Moffat, & Mulvogue, 2009; Haines, Johnson, Carter, & Arora, 2009; Haines-Saah, Moffat, Jenkins, & Johnson, 2014; Moffat, Jenkins, & Johnson, 2013). Young people are clearly interested in receiving scientifically sound information about cannabis. And we have learned that scare tactics and the provision of misinformation, even if well intended, are not helpful; they only serve to discredit the source. When information is not freely available, youth tend to rely on Internet sources to piece together information as best they can, or they rely on their often equally ill-informed peers for the information they seek.

The research evidence suggests that, more than information, young people are seeking opportunities to discuss what is known about substances such as cannabis, and the decisions they must make about various forms of substance use. To be effective, we must engage in informed and rational discussions with young people about decision making and cannabis use, and support them in their quest for understanding.

Parents, teachers, public health practitioners and many others with important relationships with youth often struggle with how to have meaningful conversations about cannabis. They too are searching for credible sources of information.

This report, *Substance Abuse in Canada: The Effects of Cannabis Use during Adolescence*, fills an important void; it summarizes the current scientific evidence related to cannabis use. The reader will receive a thorough assessment of the state of the science. What emerges is a picture of the heightened risks experienced by particular young people — including those who are very young, who smoke cannabis frequently, or who have a family history of serious mental illness. In many ways, our understanding of the effects of cannabis use is not as complete as we would like. Despite decades of research and thousands of years of use, there are many unanswered questions related to the consequences of cannabis use. We must answer these questions and we must determine the best ways to prevent or minimize the associated risks for people who choose to use the substance and for society as a whole.

Regardless of the gaps in our knowledge, it is important to clearly communicate what we do know about the risks to which young people are exposed when they use cannabis. In the concluding chapter, Dr. Harold Kalant summarizes several important ideas emphasized in this report and they are worth repeating here:

- Cannabis is not a harmless drug.
- It can be addictive, especially if use starts in adolescence.
- Early and frequent cannabis use is linked with reduced IQ, lower school performance and increased risk of dropping out.

- Cannabis use affects cognitive and motor functions, and is a safety hazard for drivers.
- Early and frequent use can alter the structure of the developing brain, including areas responsible for memory, decision making and executive functioning.
- There is a link between cannabis and mental illness.
- Some adverse effects might be irreversible, with the potential to seriously limit a young person's educational, occupational and social development.

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TERMINOLOGY NOTES

Several of the terms used in this document have specific and distinct clinical significance, but to avoid repetition have been used as equivalents. Unless otherwise noted, the definitions below are based on those provided in the fourth and fifth editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR and DSM-5, respectively) (American Psychiatric Association, 2000, 2013).

Addiction: Generally applied to patterns of heavy, compulsive use of psychoactive drugs and an inability to stop substance use, even though it is leading to severe, clinically relevant problems in multiple domains of a person's life (e.g., when such use becomes physically hazardous; causes failure to fulfill obligations at work, school or home; or creates legal, social or interpersonal problems).

Substance dependence: Also referred to as "drug or alcohol dependence," substance dependence constitutes a cluster of cognitive, behavioural and physiological symptoms indicating continued substance use despite the occurrence of severe substance-related problems. In DSM-5, the diagnosis of substance dependence has been combined with that of substance abuse (see below) and both have been replaced by the single term "substance use disorder," underscoring the fact that a substance use disorder is not synonymous with physical dependence. In DSM-5, the severity that was previously captured by the diagnostic label "substance dependence" is now captured by specifying current severity (e.g., "substance use disorder, severe").

Substance abuse: Also known as "drug or alcohol abuse," this term refers to a maladaptive pattern of substance use resulting in recurrent and significant adverse consequences. It is a pattern of use under hazardous circumstances and involves neglecting one's external obligations, legal problems and interpersonal problems. It has also been replaced by the term "substance use disorder," but is indicative of a disorder of mild severity.

Introduction

*By **Joanna Henderson, PhD**, Assistant Professor, Department of Psychiatry, University of Toronto, and Head of Research, Child, Youth and Family Program, Centre for Addiction and Mental Health*

About Substance Abuse in Canada

Since 2005, *Substance Abuse in Canada* has shone a spotlight on key contemporary issues related to substance abuse, and identified specific areas for action in both policy and practice. Each report in the series is intended for a broad audience that includes policy makers, program development personnel, researchers, educators and health professionals. Health journalists are also an important audience as they can help raise the public profile of the issues discussed and help create the impetus for change.

This sixth *Substance Abuse in Canada* report focuses on the effects of cannabis use during adolescence. After a brief introduction emphasizing the scope of the issue and why it matters to Canadians, the report presents the cognitive and behavioural effects of cannabis use in youth, looking at its impact on adolescent brain development and exploring the links between cannabis use and mental illness. The report also examines the question of whether cannabis is addictive and summarizes the interventions currently available for cannabis use disorders. Finally, the report concludes with a call to action that outlines the practical implications of the latest research on cannabis use during adolescence

This report is not meant to be a systematic review; instead, it is intended to provide a high-level, broad overview of this important health issue by integrating neuroscience with the behavioural and social context of cannabis use by youth.

THE SERIES TO NOW

The first *Substance Abuse in Canada* report, ***Current Challenges and Choices***, examined a variety of topics, including the prevention of alcohol problems, alternative sanctions for cannabis use and possession, drug-impaired driving, and the abuse and diversion of prescription medication.

The second report, ***Focus on Youth***, looked at the prevalence of substance use and its associated harms among young people, exploring the underlying neurobiology of substance use in adolescence and identifying existing gaps in youth-centric services.

The third edition, ***Concurrent Disorders***, focused on the co-occurrence of mental health and substance abuse problems, examining the interconnections between addiction and mental illness, the costs concurrent disorders place on the healthcare system, and why treating these complex cases requires new and innovative approaches.

The fourth in the series, ***Licit and Illicit Drug Use during Pregnancy***, addressed the medical and obstetrical consequences of drug abuse and dependency in pregnant women, as well as the short- and long-term effects that prenatal exposure to drugs can have on a child's development.

The fifth edition, ***Childhood and Adolescent Pathways to Substance Use Disorders***, explored influences during childhood and adolescence that can affect substance abuse later in life, as well as the implications an understanding of those influences has for prevention and treatment.

The Effects of Cannabis Use during Adolescence, the current report, reviews the effects of cannabis use during adolescence, looking specifically at the drug's impact on youth health and brain development, as well as the interventions currently available for treating cannabis use disorders.

Why it's time to take a closer look at youth cannabis use

Cannabis has always been a significant political, health and law-enforcement issue. With its recent legalization in Alaska, Colorado, Oregon, Washington and the District of Columbia, however, the debate around this illicit substance has gained considerable profile.

Across North America, the public discourse on cannabis tends to focus on sociopolitical and legal issues: assessing the economic impact of legalization or decriminalization, for instance, or determining how cannabis for medical purposes figures into the equation.

Yet as policy makers and media outlets explore the issue in greater detail, the answers to many questions are still unclear. What is the distinction between adult and adolescent use? Why is there seemingly a double standard about medical and recreational use? With new evidence, opinions and perspectives being released and discussed every day — covering a broad spectrum of considerations — the public has become increasingly confused about cannabis' status, prevalence and effects.

For teenagers, making decisions about cannabis without having the facts can have profound consequences. Adolescence is marked by significant social, psychological and physiological changes. It is a time when young people begin to develop increasingly close bonds with their peers and explore their own distinct social identities. It is also when mental health problems can start to emerge and substance use begins.

Because of the rapid changes in brain structure and function that occur during adolescence, use of cannabis during this developmental period can have negative cognitive, mental health and physical effects.

How prevalent is youth cannabis use in Canada?

Canadian youth use cannabis more than any other illicit drug and many start using it as early as late elementary school. In fact, Canadian adolescents have among the highest rates of cannabis use compared to their peers in other developed countries (UNICEF Office of Research, 2013).

According to the 2013 Canadian Tobacco, Alcohol and Drugs Survey, 22.4% of youth aged 15–19 reported past-year use of cannabis; among young adults aged 20–24, 26.2% reported past-year use. In total, youth use cannabis at a rate 2.5 times higher than adults aged 25 and older, of whom only 8.0% reported past-year cannabis use (Statistics Canada, 2015).

Other national studies have shown similar results. In the 2012–2013 Youth Smoking Survey (YSS), 19% of grade 7–12 students reported past-year cannabis use. For students in grades 7–9, past-year cannabis use rates were 3%, 7% and 15%, respectively (Health Canada, 2014). These are lower than the rates reported for alcohol (41%) and binge drinking (29%), but higher than cigarettes (14%) and other illegal drugs (6%).

At the provincial level, a series of school surveys conducted in Ontario, Quebec, New Brunswick, Nova Scotia, and Newfoundland and Labrador in 2012–2013 (see Table 1; Asbridge & Langille, 2013; Boak, Hamilton, Adlaf, & Mann, 2013; Gupta, Wang, Collette, & Pilgrim, 2013; Newfoundland and Labrador Student Drug Use Survey Working Group, 2013; Traoré et al., 2014) found that the rates of past-year cannabis use by all students in grades 7–12 ranged from 22.9% (in Quebec) to 34.7% (in Nova Scotia), with rates peaking in grade 12 (as high as 54.7% in Nova Scotia). As a point of comparison, the reported rates of past-year cigarette smoking were substantially lower than those for cannabis use (Ontario, 8.5%; New Brunswick, 14.1%; Nova Scotia, 13.2%; Newfoundland and Labrador, 16.4%).

Rates of past-year cannabis use across grades have declined significantly over the past decade in both Ontario and New Brunswick; in Nova Scotia and Newfoundland and Labrador, past-year cannabis use rates have remained relatively stable. In contrast, all four jurisdictions have seen large declines in cigarette smoking during that same time.

While the current levels of past-year cannabis use are concerning, more problematic is the high-frequency use of cannabis reported by some students. Daily or near-daily use by adolescents is associated with increased harms (Hall, 2015) and, as shown in Table 1, the rates for this type of heavy cannabis use range from 1% to 6% in the five provinces that conducted student surveys in 2012–2013.

Table 1. Rates of cannabis use among Canadian students by province, 2012–2013

	Past-year cannabis use (%)					Daily or almost daily cannabis use (%)				
	Grade					Grade				
Province	**7**	**9**	**10**	**12**	**Total**	**7**	**9**	**10**	**12**	**Total**
ON[1] (2013)	1.7	14.6	24.5	39.2*	23.0	^	^	2.0	5.1*	2.7
QC[2] (2013)	4.3	24.9	32.2	—	22.9	^	1.2	1.2	—	1.4
NB (2012)	6.0	27.0	32.0	45.0*	28.3	—	—	—	—	—
NS (2012)	7.0	32.7	39.9	54.7*	34.7	^	5.8	7.0	11.1*	6.4
NL (2012)	4.2	27.4	40.2	46.5*	30.0	0.4	3.8	8.3	8.9*	5.4

1 Estimates for Ontario are based on grades 7 through 12.
2 Estimates for Quebec are based on grades 7 through 11. Quebec asks only about daily use and not almost daily use.
^ Suppressed due to small number.
— Not asked. * Denotes significant difference between Grade 7 and Grade 12 at $p < .01$.

These surveys include only youth attending school who were able to participate. Given these limitations, the actual rates of both past-year and heavy cannabis use among Canadian youth are likely to be higher than reported.

What motivates youth to use cannabis?

Like adult cannabis users, youth report feelings of increased sociability and euphoria when using cannabis (Menghrajani, Klaue, Dubois-Arber, & Michaud, 2005). Yet youth also describe a number of other factors that motivate their cannabis use, which can be divided into five distinct categories: enhancement ("it's exciting"); social ("it helps me enjoy a party"); coping ("it helps me forget about my problems"); expansion ("it helps me understand things differently"); and conformity ("so I won't feel left out") (Green, Kavanagh, & Young, 2003; Simons, Correia, Carey, & Borsari, 1998). Recently, this list has been extended to include an additional category: routine ("I use it out of boredom") (Benschop et al., 2015).

Substantial individual variations in motives for cannabis use have been noted, as well as different motives for different episodes of use (Bonn-Miller & Zvolensky, 2009; Shrier & Scherer, 2014). In addition, different motives have been found to be related to different affective states and traits. For example, social anxiety and child maltreatment are both associated with cannabis-related problems through higher rates of use associated with coping motives (Buckner, Bonn-Miller, Zvolensky, & Schmidt, 2007; Vilhena-Churchill & Goldstein, 2014).

While motives reflect the valuing or prioritizing of particular experiences, cannabis use can also be looked at in terms of *expectancies*, which reflect an individual's beliefs about the experiences that will result from cannabis use (Cooper, 1994; Kuntsche, Wiers, Janssen, & Gmel, 2010). A number of expectancy domains have been identified, including cognitive and behavioural impairment, relaxation and tension reduction, social and sexual facilitation, perceptual and cognitive enhancement, physical effects and cravings, and overall negative effects (Schafer & Brown, 1991; Torrealday et al., 2008).

As a whole, these domains can be grouped into two broader categories: negative expectancies and positive expectancies. Adolescents who delay initiating cannabis use tend to have high negative expectancies; those who start using cannabis with greater frequency typically have high positive expectancies (Aarons, Brown, Stice, & Coe, 2001; Fulton, Krank, & Stewart, 2012; Schafer & Brown, 1991; Skenderian, Siegel, Crano, Alvaro, & Lac, 2008).

How do youth perceive cannabis use?

Canadian youth perceive cannabis use to be widespread, not just among their peers but also among adults as well. It is often described as a substance "everyone" is using "all the time." They also believe cannabis to be relatively harmless, viewing it as a more "natural" substance that is not really a drug at all (Porath-Waller, Brown, Frigon, & Clark, 2013). Evidence from the Monitoring the Future Study in the United States shows

an inverse association between the perception of the risk associated with cannabis use and past-year use among high school seniors over the past 40 years (see Figure 1).

In general, young people have a wide range of opinions about cannabis, some of which reflect inaccurate information and others reflecting conflicting messages received through the media, peers and adults. For example, some youth have expressed the belief that cannabis can prevent — or even cure — cancer. Youth have also expressed mixed beliefs about cannabis' impact on one's ability to drive, with some stating that using cannabis improves driving performance and is not as dangerous as drinking and driving (Porath-Waller et al., 2013).

What are the effects of cannabis use on youth?

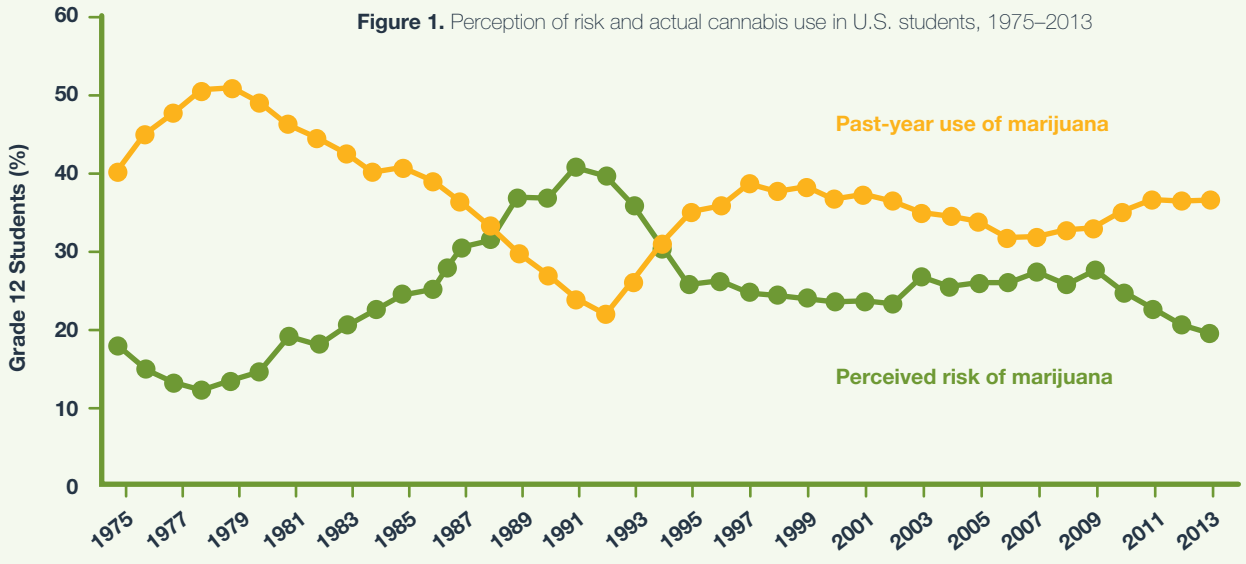
Dose, potency and cumulative exposure all contribute to the potential effects of cannabis use in youth. Of these factors, dose has been less studied due to the fact that the amount of active ingredient to which youth are exposed during each episode of use varies according to the overall substance content (i.e., proportions of cannabis and non-cannabis ingredients), the amount of active ingredient (e.g., THC, cannabidiol), the mode of administration (e.g., joints, vaporizers) and individual versus shared use.

Acute safety risks associated with cannabis use

While some people, especially inexperienced users, will experience unpleasant events such as intense anxiety, panic and psychotic symptoms when using cannabis, the risk of overdose is extremely low, even among individuals with the highest levels of use (Calabria, Degenhardt, Hall, & Lynskey, 2010; Gable, 2004). That said, cannabis use can lead to hospitalization: in 2011, approximately 1,600 hospital stays in Canada were recorded as being primarily due to a cannabinoid-related disorder (Young & Jesseman, 2014). In comparison, there were nearly 20,000 hospital stays due to alcohol-related disorders during that same time period. The duration of the hospital stay varies by age group, with youth between the ages of 15 and 24 likely to be in hospital longer than other age groups when receiving treatment for cannabinoid-related disorders.

Perhaps the most significant acute safety concern for youth is driving under the influence of cannabis. In the student surveys discussed earlier, approximately 10–20% of senior or licensed students reported driving within one hour of using cannabis — nearly identical to the rates reported for driving under the influence of alcohol (Asbridge & Langille, 2013; Boak et al., 2013; Newfoundland and Labrador Student Drug Use Survey Working Group, 2013; Gupta et al., 2013; Traoré et al, 2014; Young et al., 2011). Although evidence suggests it is not

Figure 1. Perception of risk and actual cannabis use in U.S. students, 1975–2013



Source: Volkow, Baler, Compton, & Weiss, 2014; reproduced with permission, Massachusetts Medical Society

quite as dangerous as driving under the influence of alcohol, driving under the influence of cannabis is still associated with a significantly increased risk of collision and injury; that risk climbs even higher when driving under the influence of both alcohol and cannabis (Asbridge, Hayden, & Cartwright, 2012; Hartman & Huestis, 2013; Li et al., 2012; Ramaekers, Berghaus, van Laar, & Drummer, 2004).

Short- and long-term effects of cannabis use

Also of great concern for youth are the numerous studies indicating that cannabis use can result in a number of short- and long-term physical, mental and psychosocial effects. Specifically, evidence suggests that high-frequency use — in particular, daily or near-daily use beginning in adolescence — is associated with a wide range of poor outcomes. Some studies have also suggested that these associations may have dose-response characteristics, potentially indicating a causal connection (Silins et al., 2014).

Many studies of cannabis-related outcomes, however, have lacked methodological rigor and do not provide adequate evidence regarding the direction of influence (Hall, 2014). Did the psychosocial or health problem exist before the cannabis use and increase the risk of cannabis use? Did cannabis use lead to the psychosocial or health problem? Or was there a common factor that led to both the psychosocial or health problem *and* the cannabis use? Moreover, examination of the biological indicators of the actual cannabinoid doses consumed has been lacking (Freeman, Mokrysz, & Curran, 2014), limiting the extent to which conclusions about causality can be drawn.

The following bullets overview health, mental health and psychosocial outcomes from studies where there is strong evidence of a connection between cannabis use and the variable of interest, after controlling for other potential factors, and where the causal association is plausible. (Subsequent chapters provide a more comprehensive summary and discussion of this evidence.) Unless otherwise specified, these findings are based on "regular" or "heavy" use, which is typically defined as daily or near-daily cannabis use (Hall, 2014).

- When compared to alcohol and tobacco, cannabis use has the fastest rate of transition to substance use disorder among adolescents (Ridenour, Lanza, Donny, & Clark, 2006). Youth who are regular cannabis users are more likely to use other illicit substances (Fergusson & Boden, 2008; Hurd, Michaelides, Miller, & Jutras-Aswad, 2014; Lynskey, Coffey, Degenhardt, Carlin, & Patton, 2003; Silins et al., 2014).
- The risk of dependence (i.e., lack of control over use of cannabis despite the associated harms) is approximately 9% among individuals with any lifetime cannabis use (Lopez-Quintero et al., 2011) and approximately 16% among those who initiated cannabis use during adolescence (Anthony, 2006). While most individuals who use cannabis do not become dependent, heavy cannabis use in adolescence is associated with an increased risk for dependence (Silins et al., 2014). Symptoms of tolerance and withdrawal, such as depression, insomnia, anxiety and disturbances in appetite, are reported by some cannabis users, experienced typically in the context of high-frequency, long-term use (Allsop et al., 2012; Budney, Hughes, Moore, & Vandrey, 2004).
- Regular cannabis use in adolescence is associated with experiencing psychotic symptoms, especially when there is a family or personal history of psychotic disorders (Fergusson, Horwood, & Swain-Campbell, 2003; Large, Sharma, Compton, Slade, & Nielssen, 2011; Moore et al., 2007; Zammit, Allebeck, Andreasson, Lundberg, & Lewis, 2002). Indeed, the risk of reporting psychotic symptoms or being diagnosed with schizophrenia in adulthood is doubled in individuals with regular cannabis use in adolescence (Hall, 2015; Moore et al., 2007). While the evidence is not as strong regarding other mental health issues, there are possible links between regular cannabis use in youth and increased risk for depression and suicide (Lev-Ran et al., 2013; Silins et al., 2014).

- Acute cannabis intoxication has been linked to deficits in attentional focus, information processing, motor coordination and reaction time (Hall, 2015), while long-term regular use that starts in adolescence has been found to be associated with impairments in attention, memory and verbal learning (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013; Porath-Waller, 2009; Solowij & Battisti, 2008). There is also evidence that, among long-term daily cannabis users, these deficits coalesce into declines in IQ (Meier et al., 2012), although some have challenged this finding (Rogeberg, 2013). In some contexts, the long-term cognitive impairments that result from regular cannabis use have been reversed, but this appears less likely for heavy use that begins in adolescence (Meier et al., 2012; Porath-Waller, 2009).
- As the acute effects of cannabis can impact learning and schoolwork completion, youth who use cannabis regularly are more likely to drop out of high school and, in turn, less likely to pursue post-secondary education (Fergusson & Boden, 2008; Horwood et al., 2010; Lynskey et al., 2003; Silins et al., 2014). In addition, youth who are already vulnerable to poor educational outcomes due to other factors might be more likely to use cannabis regularly and affiliate with peers who also use cannabis.

Youth might be particularly vulnerable to these negative outcomes due to the extensive structural and neurochemical changes that are taking place in the brain during adolescence, especially the ongoing development and maturation of the prefrontal cortex, which is critical to higher-order cognitive processes such as impulse control, working memory, planning, problem solving and emotional regulation (Luna, Garver, Urban, Lazar, & Sweeney, 2004; Spear, 2013).

Adolescent brain development is also affected by the endocannabinoid system. Endocannabinoids (cannabinoids naturally occurring in the body) regulate the activity of neurotransmitters like dopamine and serotonin, which in turn affect memory, coordination, appetite, pain, mood, pleasure and motivation. Cannabis use can disrupt the functioning and development of these systems (Bossong & Niesink, 2010).

Given the high rates of cannabis use by youth during this critical period of their development — as well as the multitude of cannabis-related information being released and discussed every day — it is more important than ever to review what is known, what is not known and what evidence is emerging about the effects of cannabis use during adolescence. The evidence reviewed in this report will help support efforts to reduce harm to youth by decreasing the number who use cannabis and delaying the initiation of use. By situating the relevant neuroscience in the broader behavioural and social contexts of youth cannabis use, this report aims to provide a much-needed resource for any person or institution responsible for youth policies, programs and practices pertaining to cannabis.

Chapter-by-chapter summary

Chapter 1: What are the brain and behavioural effects of cannabis use in youth?

A number of key neurodevelopment phases must occur during adolescence before the brain is fully ready for adulthood. The brain's process of pruning inefficient neurons and insulating axons optimizes it for future success, but also makes youth more vulnerable to the effects of cannabis use. The regions of the brain that undergo the most fine-tuning during the teenage years are those responsible for decision making, judgment, planning and problem solving, and these regions are potentially most susceptible to cannabis when they are not yet fully developed.

This chapter explores the role of the endocannabinoid system and how it can be hijacked by the psychoactive component of cannabis, delta-9-tetrahydrocannabinol (THC). THC induces neurotoxic changes that affect the natural process of neurodevelopment in adolescence and in turn promote physical changes in the brain's structure — effectively altering the functions responsible for emotional and cognitive performance.

The chapter then reviews recent assessments of the impact of cannabis on behaviours like cognitive functioning, academic performance, motivation, risk taking and psychomotor skills, presenting findings from both traditional neuropsychological assessments and neuroimaging technologies, such as magnetic resonance imaging. The latter allow researchers

to observe the actual changes happening to the brain's architecture (e.g., volume and health of grey and white matter) and functioning (e.g., blood flow) when exposed to THC.

Chapter 2: Is there a link between cannabis and mental health?

Several neuropsychiatric disorders and unsafe behaviours, including mental illness and substance abuse, typically begin to emerge during adolescence. Cannabis use has been found to have potentially adverse effects among those who are vulnerable to mental illness. Presenting the latest epidemiological, neurobiological and clinical evidence, this chapter looks at how cannabis use affects the development and prognosis of schizophrenia, mood and anxiety disorders, eating disorders and childhood behavioural disorders (such as attention deficit hyperactivity disorder).

Current evidence suggests cannabis use is associated with the development of psychotic symptoms and disorders, with an enhanced vulnerability to psychosis linked to disturbances in the endocannabinoid system and genetic variations in the enzymes responsible for dopamine metabolism. In contrast, the development of childhood behavioural disorders likely precedes and might lead to later cannabis use.

So does drug use induce mental illness? Or does mental illness increase risk for drug use? While there is clearly a strong relationship between mental illness and cannabis use, the direction and causal nature of that relationship is not well understood and is likely different for each type of disorder. As such, further research into the underlying mechanisms that put individuals at risk for both substance use and mental illness, including interventional and neurophysiological studies, will be essential moving forward.

Chapter 3: Is cannabis addictive?

Cannabis is the world's most widely used illicit drug, with approximately 23% of Canadian youth using it on a daily or near-daily basis during the past three months, but does it prossess the same addictive properties as other drugs of abuse? Despite the perception that it is not an addictive drug, evidence indicates cannabis use can lead to addiction: one in six of those who initiate cannabis use during adolescence will become dependent.

This chapter begins with a primer on addiction, describing how addictive substances are classified by the medical field and defining key terms like "abuse," "dependence" and "substance use disorder." It then presents the neurobiological, preclinical and clinical evidence on cannabis' addictive potential, including animal-based studies showing that THC induces self-administration behaviour in primates, as well as clinical studies exploring the symptoms of cannabis dependence and withdrawal. It also presents epidemiological evidence on the frequency of addictive states associated with cannabis, with a particular focus on how individuals transition from use to dependence and whether cannabis can actually be considered a "gateway" drug to other illicit substances. The chapter concludes by looking at the biological and environmental factors that might affect a person's vulnerability to addiction, including genetics, gender, socioeconomic status and age of initiation of use — making efforts to prevent or delay the onset of cannabis use particularly important.

Chapter 4: What interventions are available for cannabis use disorders?

The detrimental effects of cannabis use discussed in the previous chapters underscore the importance of prevention, early detection and treatment interventions targeting youth. This chapter looks at the efficacy of prevention initiatives and many emerging treatments for adolescents, including:

- Comprehensive prevention programs, which have been shown to be most effective when delivered in school-based settings;
- Screening and brief intervention tools administered by clinicians, which can help healthcare providers assess and address clinically relevant risk categories of substance use;
- Behavioural and psychotherapeutic interventions such as cognitive behavioural therapy (i.e., helping correct inaccurate or negative thinking), motivational enhancement therapy (i.e., increasing commitment to change), multidimensional family therapy (i.e., targeting inter- and intrapersonal functioning) and contingency management (i.e., providing rewards upon demonstration of desired behaviour) — all of which show promising but modest effects in reducing cannabis use; and

- Pharmacological interventions and medications targeting withdrawal symptoms, abstinence initiation and relapse prevention, as well as the treatment of co-morbid cannabis use and mental illness.

Although the development of treatments specifically for cannabis use has lagged behind advancements for other substances of abuse, an evidence base has emerged to guide the treatment of adolescents with cannabis use disorders with the strongest evidence being in support of psychosocial interventions.

Chapter 5: Cannabis and Youth — A Summary of Key Findings and Major Questions, and a Call to Action

Summarizing the key findings presented in the previous chapters, this final section of the report outlines recommendations for research topics that will help improve prevention and treatment outcomes, as well as immediate actions that can be taken to inform cannabis-related policy and help reduce the harms associated with cannabis use during adolescence.

While progress continues to be made in recognizing and understanding the causes, mechanisms and long-term effects of cannabis use in youth, many questions still need to be addressed. Future research should focus on improving our understanding of why youth use cannabis, in particular identifying the specific attitudes and values that have contributed to the high level of use by Canadian youth. Research should also focus on their patterns of use, the links between cannabis use and mental disorders such as depression and anxiety, and the efficacy of various therapeutic interventions and preventive education programs.

In addition to these longer-term projects, a number of practical measures should be implemented today to mitigate the risk posed to youth by cannabis. These include, for example, working with the healthcare sector to encourage the use of brief screening procedures for cannabis use among young patients; bringing together health and education experts to develop standardized school-based education programs; and being more systematic about the collection of cannabis-related data in all venues, from police incident reports to hospital admissions to the roadside collection of oral fluid from suspected impaired drivers.

Above all, it is urgent that the evidence reviewed in this report be seriously taken into account by governments and research agencies when important policy issues are being contemplated.

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1

What are the Brain and Behavioural Effects of Cannabis Use in Youth?

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Chapter at a Glance

- Several key neurodevelopmental phases must occur during adolescence before the brain is fully prepared to deal with the challenges associated with adulthood.
- The prefrontal cortex, which is responsible for higher-order cognitive functions like decision making and problem solving, is particularly susceptible to the effects of cannabis during these developmental phases.
- The psychoactive component of cannabis (THC) hijacks the brain's internal cannabinoid system, resulting in disrupted neural regulation and neurotoxic changes in the brain.
- Structural brain imaging suggests that cannabis users, especially early onset users, have altered grey and white matter.
- Functional brain imaging shows that cannabis has a negative impact on processes such as executive functioning, motivation and risk-taking behaviour.
- Despite the accumulating evidence, a wide range of variables such as study methodology, dosage, age of onset and other substance use limit the conclusions that can be made from the current literature.
- Teens, adults and the community at large, including policy makers, need to be further educated about the significant impact cannabis has on the developing brain.

1.1 Cannabis and the developing brain

While the brain is continually reshaping itself well into adulthood, its development shifts into high gear during the teenage years. A number of key neurodevelopmental phases must occur before the brain is fully ready to deal with the challenges of the adult world. For example, the adolescent brain undergoes a pruning phase to remove neurons that are not being used or are inefficient (Giedd, 2008). A process of myelination also takes place in which a fatty substance called myelin forms an insulating shield around the axons of neurons, increasing the speed of electrical transmission to make communication between neurons more efficient (Anderson, 2002).

Processes like pruning and myelination are essential to optimizing the brain for success during early adulthood, and their streamlining of neural development is the very thing that makes youth more vulnerable to the effects of cannabis use. The regions of the brain that undergo the most pruning, myelination and other fine-tuning are those required for higher-order cognitive processes such as decision making, judgment, emotional regulation, planning and problem solving. Key among these regions is the prefrontal cortex (Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001; Rubia et al., 2000; Sowell et al., 2003), which is most susceptible to the neurotoxic effects of cannabis when it is not yet fully developed.

Without a well-developed prefrontal cortex, a teen has to rely on other brain regions for cognition, namely the less-evolved limbic system, which is responsible for emotions. This reliance allows the "emotional" brain to control behaviour, rather than enlisting the help of the prefrontal cortex or the "thinking" brain. This control of behaviour by the emotional brain can lead to increased risk-taking behaviour, poor decision making and inferior reasoning ability.

1.1.1 The endocannabinoid system

The human brain makes its own chemicals that resemble the psychoactive component of cannabis, delta-9-tetrahydrocannabinol (THC). Two of these naturally occurring cannabinoids, anandamide and 2-arachidonoyl-glycerol (2-AG), are considered neurotransmitters because they bind to cannabinoid receptors (CB_1 and CB_2) located in the prefrontal cortex, anterior cingulate, basal ganglia, amygdala, hippocampus and cerebellum (Herkenham, Lynn, Melvin, de Costa, & Rice, 1991; Batalla et al., 2013).

This endocannabinoid system plays an important role in the maturation of the cortical neuronal networks that reach maximal levels during late adolescence. It is also involved in modulating other neurotransmitter systems such as dopamine, enhancing

brain cell growth and, ultimately, controlling brain functions such as appetite, motor activity, motivation, mood, immune system activity, reward, learning and memory (Breivogel & Sim-Selley, 2009; Gray, 2013; Pope, Mechoulam, & Parson, 2010).

The presence of endogenous cannabinoids (i.e., those occurring in the brain) has led some to suggest that cannabis use is "natural" and benign. However, when THC is taken into the brain, it targets the CB_1 receptors in much higher quantities than endogenous cannabinoids, effectively flooding the system to the point that it no longer works efficiently. This "hijacking" of the endocannabinoid system wreaks havoc on many complex neurophysiological processes, disrupting the regulatory role the system plays and inducing neurotoxic changes in brain regions rich with CB_1 receptors (Breivogel & Sim-Selley, 2009). These neurotoxic changes have been shown to dramatically affect the natural process of neurodevelopment in adolescence and, in turn, promote physical changes in the brain's structure — effectively altering the functions responsible for emotional and cognitive performance (Batalla et al., 2013).

Given that CB_1 receptors are widely dispersed throughout the brain, many different types of behaviour are affected by cannabis use, ranging from academic performance to motivation to psychomotor skills like driving. While there are many individual-level variables that make it difficult to make unequivocal assertions, through the use of both neuropsychological testing and neuroimaging technologies, the evidence is mounting that early onset cannabis use has a tremendous impact on the structure and functioning of the teenage brain and can weaken the foundation for future life success.

1.2 Behavioural Impact of Cannabis Use

Much of the research on the impact of cannabis on the developing brain has come from traditional neuropsychological testing batteries and the field of brain imaging, particularly magnetic resonance imaging (MRI) and functional MRI (fMRI). However, consistent results have been difficult to ascertain given the multifaceted nature of this type of research and the wide range of variables that must be taken into account, including the age and socioeconomic status of test participants, the number of years they have been using cannabis, frequency and quantity of use, the potency and dosage of the cannabis used, and any potential interactions between cannabis and other licit or illicit drugs. In addition, few longitudinal studies have measured behaviour before and after cannabis use in a young population, making it difficult to compare short- and long-term effects.

That said, the existing neuropsychological evidence from the few longitudinal studies indicates behavioural deficits resulting from early cannabis use, particularly in the areas of cognitive ability and academic performance (Bava, Jacobus, Thayer, & Tapert, 2013; Hatchard, Fried, Hogan, Cameron, & Smith, 2014; Meier et al., 2012; Smith, Longo, Fried, Hogan, & Cameron, 2010; Smith et al., 2011).

1.2.1 Impact on cognitive ability, IQ and executive functioning

Cognitive ability is often associated with intelligence quotient (IQ), but as IQ studies typically have several confounding variables, there have been mixed and controversial results with respect to cannabis' impact on a person's IQ.

The findings of a long-running longitudinal study in New Zealand by Meier and colleagues (2012) associated adolescence-onset heavy cannabis use with an eight-point decrease in IQ by age 38. Those losing the most IQ points were those who had started cannabis use during their teenage years. Some critics, however, suggested these results were an artifact of socioeconomic status (Rogeberg, 2013).

Another longitudinal study from the United Kingdom reported that teens who had used cannabis at least 50 times by age 15 did not show a decrease in IQ compared to prior testing conducted at age eight (Mokrysz et al., 2014). In a counter argument, Moffitt, Meier, Caspi, & Poulton (2013) refuted the challenges to their study (Meier et al., 2012) to show that their results could not be accounted for by socioeconomic status and that their results were in fact accurate. Meier has also commented on the Mokrysz study suggesting that this study was not comparable to the New Zealand study because the children were only 15 at the time of testing, meaning they would not show results similar to those of adults who had been using cannabis four or more times per week for 20 years after adolescence.

The two studies highlight the difficulties of using IQ as a measure of cognitive ability when studying the effects of cannabis on youth. Furthermore, IQ studies have historically been criticized for having limited predictive validity for life outcomes (Duckworth, Quinn, Lynam, Loeber, & Stouthamer-Loeber, 2011).

Executive functioning is a more credible predictor of future success, and refers to the group of cognitive processes involved in goal-directed behaviour such as planning, organizing, decision making, impulse control and working memory. The longitudinal study by Meier and colleagues (2012), for example, linked cannabis to a broad decline across several cognitive domains related to executive functioning, including verbal comprehension, processing speed, perceptual reasoning and memory. Continual use was associated with greater decline. Among those who started using cannabis during adolescence but eventually quit, the cognitive deficits caused by persistent use were not fully restored by cessation.

1.2.2 Impact on academic performance

Given the adverse effects of cannabis on executive functioning, it is no surprise that academic performance — and as a result, long-term success into adulthood — can be affected negatively by cannabis use. Results from the longitudinal study by Mokrysz and colleagues (2014) showed that teens who used cannabis at least 50 times by age 15 scored an average of three percent lower on compulsory school exams at age 16 than those who did not smoke cannabis. Furthermore, after integrating data from three large, long-running studies in Australia and New Zealand, Silins and colleagues (2014) found that young adults who used cannabis daily before the age of 17 were significantly less likely to complete high school or obtain a university degree. There was also a dose-response relationship between frequency of adolescent cannabis use and all adverse young adult outcomes, strongly supporting the hypothesis that early use can indeed impact long-term success into adulthood.

1.3 Using neuroimaging to take a closer look at how cannabis affects the brain

With neuropsychological testing providing variable results that have not been unequivocally or consistently published in the literature, the field of neuroimaging — specifically, magnetic resonance imaging (MRI) — plays an increasingly important role in understanding the impact of cannabis on the developing brain.

Two main types of MRI will be discussed here: structural MRI and functional MRI. Structural MRI, which is used to view the anatomy of the brain, including the neuronal connections between brain regions, is a powerful tool for identifying the extent to which cannabis use alters the brain's grey matter and white matter. Functional MRI (fMRI) is a technique that measures changes in the brain's blood flow during cognitive tasks, providing a non-invasive window into the brain as it works.

fMRI's ability to observe and measure brain activity is more sensitive than neuropsychological testing alone. Specifically, it can identify subtle differences in brain activity even when the individuals participating in the cognitive test show similar task scores and performance, making it invaluable for demonstrating the damage early onset cannabis use can have on brain functioning.

1.3.1 What structural MRI reveals about cannabis' impact on the brain

In general, structural MRI results have demonstrated that cannabis exposure during the adolescent years has a significant negative effect on brain volume, the folding patterns of the cortex, neural connectivity and white matter integrity (Lisdahl, Wright, Medina-Kirchner, Maple, & Shollenbarger, 2014; Wrege et al., 2014).

More specifically, a number of studies have revealed differences in the volume of the hippocampus, amygdala, cerebellum, striatum, insula, temporal pole and prefrontal cortex between groups of adolescent cannabis users and non-users (Ashtari et al., 2011; Battistella et al., 2014; Churchwell, Carey, Ferrett, Stein, & Yurgelun-Todd, 2012; Cousijn et al., 2012a; Filbey et al., 2014; Gilman et al., 2014; Gruber, Dahlgren, Sagar, Gonenc, & Killgore, 2012; Medina, Schweinsburg, Cohen-Zion, Nagel, & Tapert, 2007; Medina et al., 2009; Medina, Nagel, & Tapert, 2010; McQueeny et al., 2011; Schacht, Hutchison, & Filbey, 2012).

Interestingly, some of these studies showed *increased* brain volumes in cannabis users while others showed *decreased* volumes. This bidirectional relationship between cannabis and brain volume might seem counterintuitive; however, when looked at in conjunction with reports of changes to executive functioning, mood and risk-taking behaviour, changes in brain volume are indicative of negative effects. Rather, they represent altered grey and white matter architecture suggestive of disrupted neuronal pruning and less efficient connectivity, both of which are important for healthy neurodevelopment.

Brain volume, folding and thickness

A recent study that used voxel-based morphometry (a neuroimaging analysis technique) found that the age of onset of cannabis use significantly influenced the magnitude of brain volume reductions in the medial temporal cortex, temporal pole, parahippocampal gyrus, insula and orbitofrontal cortex, and volume increases in the cerebellum between regular cannabis users and occasional users (Battistella et al., 2014). Reductions were observed in regions dense with CB_1 receptors that contribute to emotional, motivational and executive functioning abilities, which suggests that the increased volume of the cerebellum experienced by regular cannabis users was related to the developmental processes that occur in the brain during adolescence, in particular, the pruning of excess neurons. Because the cerebellum is also rich in CB_1 receptors, exposure to cannabis during early adolescence might have affected its ability to prune unnecessary synaptic connections.

A similar explanation might be applied to Gilman and colleagues' (2014) findings of a difference in three structural measurements (shape, size and density) of the nucleus accumbens when comparing cannabis users (mean of 11 joints per week with a large standard deviation of 9.61) compared to non-users. While these results have been met with criticism, they highlight the importance of using multiple structural MRI measures to identify the early effects of cannabis exposure on the brain's architecture. For example, while several regions of the brain were shown to be significantly different between the using and non-using groups, others showed a difference in only one of the three structural measures. If the other two measures were the only ones quantified, the results would have been misinterpreted — emphasizing the need for future research to focus on multimodal imaging.

Structural MRI measurements have also suggested that cannabis use has an adverse effect on the folding and thickness of the cortex (Lopez-Larson et al., 2011; Mata et al., 2010). In addition, a number of studies have used magnetic resonance spectroscopy (a technique for quantifying certain neurotransmitters and chemicals found in the brain, including glutamate, n-acetyl aspartate, creatinine, GABA and myo-inositol) to compare adolescent chronic cannabis users to non-users. Two studies conducted by Prescot and colleagues (2011; 2013), for example, have shown reduced amounts of certain chemicals in the anterior cingulate of cannabis users.

Building from the previous work of Silveri and colleagues (2011), Mashhoon and colleagues (2013) found that white matter reductions in cannabis users were localized to the thalamus. Their assertion that this effect among cannabis-dependent young men (with an average of only 5.5 years of use) might reflect an early neurochemical response to the toxicity of cannabis is suggestive of the suppression of glial cell function, which support neurons, and increased compensation efforts to maintain cellular volumes. However, further investigation is required to determine if these neuronal and glial cell variations underlie the other structural and functional anomalies observed in young cannabis users and if these neurochemical alterations could have a long-lasting impact on brain health into adulthood.

Predictive brain signatures

As most of the MRI studies cited so far have been cross-sectional in design, the antecedents of the structural differences between cannabis users and non-users are questionable. In particular, it remains unclear whether the results of these studies reflect pre-existing brain differences that lead to increased cannabis use and subsequent variations in brain development and behavioural outcomes.

The importance of this question was highlighted by Cheetham and colleagues (2012), who examined whether existing structural abnormalities in the brain were predictive of future cannabis use in adolescence. After obtaining brain images of participants at age 12 (before the onset of cannabis use) and then again at 16 (after they had commenced use), they found that the orbitofrontal cortex volume was smaller in the 12- year-olds who went on to use cannabis. Because no other brain regions were significantly predictive of this behaviour, these results suggest that the structural size of the orbitofrontal cortex, which is responsible for many aspects of behaviour, including decision making, impulse control, self-regulation and reward sensitivity, might contribute to a risk of cannabis use.

Interestingly, both left and right orbitofrontal size predicted later cannabis use. However, when controlling for other substance use, only the size of the right side remained significant. This difference highlights a methodological issue that plagues any kind of drug-related research: the use or abuse of multiple substances. As it can be difficult to find a sample of young participants who use only cannabis, the specificity of any results is limited.

Clinical Vignette

Steve

Steve is 16 years old and lives with his mother, who works three part-time jobs to make ends meet. While Steve did well in elementary school and was active in team sports, he found high school much harder and struggled to keep up. He also started to feel insecure: he didn't reach puberty when his friends did, he didn't make any of the school teams and he was intensely afraid of speaking up in class. At home, his mother wasn't often around — and when she was, she seemed stressed.

Some friends shared weed with Steve at his first high school dance. His connection to it was immediate. He felt relaxed and socially confident. Over the next few months he started to smoke up more frequently and hung out with friends who liked to do the same. Over the summer between grades 9 and 10, he smoked weed almost every day; when the new school year started he would sometimes get high at lunch. Steve noticed right away that he worried less about doing class presentations and talking in front of his peers when he was high. By the second semester of Grade 10, however, he was skipping classes to get high with friends and started to fail some courses. When one of his teachers talked to him about whether he "has what it takes" to go to university, Steve was embarrassed and agreed to switch out of courses geared toward university preparation. In the summer before Grade 11, Steve found out his father likes to smoke weed occasionally and they got high together on a camping trip.

Now, near the end of Grade 11, Steve's attendance at school is very poor and he hasn't completed many assignments. Instead, he smokes weed a few times each day and stays up late at night playing video games with friends online. His mother is constantly on his case about his use of cannabis — but Steve finds if he isn't high, he can't stop worrying about his future.

Health of white matter

Evidence of altered neuronal health following adolescent cannabis use has emerged from studies using diffusion tensor imaging (DTI), which is an MRI technique that allows for an investigation into the quality or health of the white matter tracts in the brain (Le Bihan et al., 2001). For example, DTI is able to localize changes in the axonal health of the corpus callosum (the large bundle of white matter that connects the brain's two hemispheres) that might impair communication between the left and right sides of the brain, and potentially affect a person's cognitive abilities. Several DTI studies have reported reduced white matter quality in the corpus callosum of cannabis users (Arnone et al., 2008; Ashtari, Cervellione, Cottone, Ardekani, & Kumra, 2009; Bava et al., 2009; Bava, Jacobus, Thayer, & Tapert, 2013; Gruber, Silveri, Dahlgren, & Yurgelun-Todd, 2011; Gruber, Dahlgren, Sagar, Gonenc, & Lukas, 2014; Jacobus, Squeglia, Infante, Bava, & Tapert, 2013; Zalewsky et al., 2012).

Once again, the difficulty of quantifying the impact of cannabis exclusively, without other contributing factors, comes into play. Bava and colleagues (2013) performed a longitudinal DTI study in which they imaged cannabis and alcohol users twice: once at the start of the study period and then again 18 months later. While adolescent cannabis users had attenuated white matter integrity in seven tracts throughout the brain, it was actually the use of alcohol between imaging sessions that predicted a change in structural measurements.

Other cross-sectional studies have controlled for alcohol use and observed similar disorganization of white matter structure in young cannabis users. Zalewsky and colleagues (2012) showed, using DTI, that the earlier heavy users started using cannabis, the more impaired the axonal connectivity, particularly in the hippocampus. Given that developing white matter has higher concentrations of cannabinoid receptors than the mature brain and is therefore more susceptible to the potential damage caused by cannabis, these findings suggest that delaying the age of onset might help protect the white matter microstructure.

The alteration of neuronal structure — specifically, reducing the health of the axons that are the foundation for the communication between brain regions — is paramount to cognitive challenges. This connection was highlighted most recently by Gruber and colleagues (2014) who showed that earlier cannabis use onset was related to reduced white matter health and increased impulsivity. Cannabis users were divided into early and late onset groups, with the former showing a correlation between low white matter integrity and high impulsivity, while the latter did not show this relationship.

1.3.2 What functional MRI reveals about cannabis' impact on the brain

Given the widespread impact cannabis has on grey and white matter, including connectivity, cortical thickness, density, volume and neurochemical health, and the complex relationship between these alterations and a wide range of individual-level variables, concisely synthesizing the results of structural MRI studies would be a difficult task. Using fMRI, which measures changes in the brain's blood flow, to support the findings derived from structural MRI techniques can help us better understand the impact of cannabis on brain development.

More specifically, fMRI measurements of brain activity are based on the blood oxygen level dependent effect. Increased neuronal activity and communication between brain regions requires increased blood flow, which can be observed and quantified during the performance of cognitive tasks and while at rest (i.e., when no task is being performed).

Resting-state fMRI

A study by Behan and colleagues (2013) found that chronic cannabis users showed heightened neural activity between the bilateral inferior parietal lobules and the left cerebellum when compared to non-users. These findings suggest a different pattern of connectivity or communication between parts of the brain of cannabis users. Looking specifically at younger users, Houck and colleagues (2013) performed resting-state fMRI on a group of high-risk adolescents (aged 14–18) and found that high cannabis use was correlated with increased connectivity within a fronto-temporal network. Orr and colleagues (2013), meanwhile, observed that cannabis users had increased *intra*-hemispheric frontal to cerebellum connectivity as well as decreased *inter*-hemispheric frontal to cerebellum connectivity when compared to non-users.

Similar to those of structural MRI studies, these findings have varied results due to the range of methodologies used and regions imaged by each study. Nonetheless, this differential pattern of communication between brain areas at rest suggests a significant alteration of intrinsic connectivity in cannabis users.

In another study, Cheng and colleagues (2014) used resting-state fMRI to differentiate between cannabis users and non-users on an individual basis. They found patterns of connectivity ranging from the prefrontal cortex to the cerebellum to be predictive of whether a participant was a cannabis user. In fact, based on these connectivity patterns, they were able to correctly predict cannabis use in 84–88% of participants, further emphasizing the consistency of altered functional connectivity in cannabis users.

While this one study showed a high accuracy rate in predicting brain signatures of cannabis users, it is difficult to assimilate the findings from resting-state fMRI results, as both increases and decreases have been reported in functional connectivity and blood flow, making the results seem dichotomous. Still, the imaging results provide valuable insight into the neural mechanisms that are the basis for cannabis' effect on cognition.

Task-driven fMRI

By measuring activity in the brain as a task is being performed, fMRI can be used to quantify changes in neural functioning as a result of acute administration of cannabis. Specifically, the altered blood flow observed during several types of cognitive tasks can further enhance our understanding of the neural impact of cannabis, particularly on important types of cognition that contribute to the orchestration of goal-directed behaviour.

The immediate effects of cannabis on cognition have been reported in a number of studies that used fMRI after administering cannabis or a placebo, then repeating the procedure later with the substance not administered during the first session. For example, van Hell and colleagues (2011) showed that cannabis increased blood perfusion in the anterior cingulate cortex, superior frontal cortex, insula, cerebellum and substantia nigra, while reducing perfusion in the post-central and occipital gyri. These brain regions coincide with the behavioural effects that occur following cannabis use, including an altered sense of time, euphoria, impaired psychomotor activity, and reduced attention and working memory.

Similar results were observed by Bossong and colleagues (2012), who found that, following cannabis use, performance on the Sternberg item-recognition task decreased while brain activity for low working memory loads increased. However, as the task became more difficult, a negative linear relationship between working memory load and activity was observed. Other effects noted following cannabis administration included an impact on the dorsolateral prefrontal cortex, inferior temporal gyrus, cerebellum and inferior parietal lobule. The behavioural effects mentioned above correlate with blood-flow alterations in these brain regions and also involve areas where structural differences have been observed between cannabis users and non-users.

While the van Hell and Bossong studies were interested in the brain's direct response to cannabis, others have imaged abstinent participants (Schweinsburg et al., 2010; Tapert et al., 2007) and others long-term users to compare the effects of early and later onset use. Variability in the methodology makes it difficult to consolidate these results; however, the underlying consensus from the fMRI literature is that patterns of brain activity are less efficient in cannabis users compared to non-users and the earlier the onset, the more significant the negative influence of cannabis on brain functioning (Gruber et al., 2012).

Using fMRI to assess performance on specific tasks

fMRI can be used to evaluate the performance of cannabis users in a variety of different cognitive tasks. For example, Tapert and colleagues (2007) used fMRI during a go/no go task in abstinent adolescent cannabis users to demonstrate that even after 28 days of cannabis abstinence, brain activity was significantly different between users and non-users, with users having significantly more activity in several prefrontal, parietal and occipital areas. An increase in neural activity was also detected during a go/no go task by Smith and colleagues (2011) and during a counting Stroop task by Hatchard and colleagues (2014).

Although increased neural activity might seem like a positive adaptive response, it is likely that cannabis is forcing the brain to work harder to perform the task and engaging more resources to respond accurately. This increased demand on the brain is a sign of a required or necessary compensation to perhaps overcome its altered structural integrity. Over time, the brain cannot compensate further and it gets fatigued and falters. In real-life situations (i.e., outside the imaging scanner), this compensation might be insufficient and problems with cognitive efficiency might arise (Smith et al., 2011). This is particularly problematic at a time of brain development when the

prefrontal cortex is undergoing fine-tuning and optimization for executive functioning.

Go / No Go task (tests inhibitory function)
This test involves the presentation of white letters, one at a time, on a black screen. Fifty percent of the letters are "X" and the rest are other randomly selected letters. There are two test conditions: one where participants are instructed to press a button when an X is presented and refrain from pressing for all other letters, and one where they are instructed to refrain from pressing for X and press for all other letters.

Counting Stroop task (tests conflict processing)
This test involves number words (e.g., "one," "two") and animal words (e.g., "dog," "cat") printed in white on a black background. Participants are presented with up to four identical words, one above another, and asked to report the number of words observed using the appropriate button on the response pad (e.g., index finger for one word, middle finger for two words). The test consists of 16 30-second blocks, each containing 20 groups of words.

In addition to cognitive inhibition, other behaviours that fall under the umbrella of executive functioning, including working memory, attention and visuospatial processing, have been studied with fMRI and shown to be negatively affected by cannabis use. Smith and colleagues (2010) imaged a group of young adults between 19–21 years of age from the Ottawa Prenatal Prospective Study as they performed a visuospatial 2-back working memory task. Because this longitudinal study followed participants since they were *in utero*, control for many lifestyle variables, including other drug use and prenatal drug exposure, was possible, and further socio-demographic information was available. Like the other studies mentioned above, researchers found that the youth who has smoked one or more joints per week for at least three years showed significantly more brain activity than non-users in the dorsolateral prefrontal cortex and several temporal lobe regions when completing the task.

Visuospatial 2-back task (tests working memory)
This test involves a circle presented in white on a black background at one of nine different positions on a screen. The circle is displayed in a given position for 75 milliseconds before being relocated. The task includes two conditions: a control condition where participants are asked to press a button each time the circle is in the middle of the screen, and a working memory condition where they are required to press a button each time the circle appeared in the same position it occupied two appearances before.

Other studies have shown similar results, including increased:

- Activity in prefrontal regions of male teenage cannabis users (13–19 years old) as they performed a novel working memory task (Jager, Block, Luijten, & Ramsey, 2010);
- Activation of the left superior parietal lobe in early-onset cannabis users compared to later-onset users as they performed a verbal working memory challenge (Becker, Wagner, Gouzoulis-Mayfrank, Spuentrup, & Daumann, 2010), and
- Prefrontal cortex blood flow in chronic cannabis users compared to non-users (Abdullaev, Posner, Nunnally, & Dishion, 2010).

Other fMRI studies have revealed *reduced* activity in cannabis users or abstinent users compared to non-users (De Bellis et al., 2013; Schweinsburg et al., 2008).

Although these studies all reveal altered blood flow in cannabis users, methodological differences (such as the ages of the participants and the cognitive tasks performed) significantly limit the ability to compare and synthesize the evidence. To implicate a network of functional and morphological alterations that might moderate the effects of cannabis on executive functioning, there will need to be a more concerted effort for methodological consistency, including multimodal assessment and the use of different types of fMRI data analyses.

1.4 What neuroimaging reveals about cannabis' impact on youth behaviour

Using neuroimaging to explore how cannabis affects the structure and functioning of the developing brain can also lead to important conclusions on how cannabis influences youth behaviour.

1.4.1 Impact on motivation

One way to look at the negative impact of cannabis on cognition is to examine the correlation between cannabis use in adolescence and apathy or amotivation (Lynskey & Hall, 2000). Adolescents who are less motivated typically do not perform as well in school, leading to a possible cascade effect on future achievement.

Neuroimaging has begun to uncover the mechanisms through which the motivation of cannabis users is reduced. In perhaps one of the most comprehensive MRI studies to investigate the neurobiological impact of cannabis, Filbey and colleagues (2014) incorporated DTI, voxel-based structural morphometry and resting-state fMRI to show that the orbitofrontal cortex of cannabis users had reduced grey matter volume as well as increased structural and functional connectivity. They also showed that these effects lead to neural alterations that are modulated by the age of onset and duration of use.

The orbitofrontal cortex, which is rich in CB_1 receptors, acts as a network hub for many behaviours involved in reward processing, motivation, self-awareness and decision making. It is also one of the last brain regions to complete the pruning and myelination processes, making it a significant target for the neurotoxic effects of cannabis, especially when early onset and chronic use occurs. Alterations in this region might well underlie the motivational and affective changes observed in young people who use cannabis.

Neuroimaging studies have provided valuable information on the neural underpinnings of reward processing and decision making, both of which play an important role when youth are choosing whether to use cannabis or to change how much they use. Cousijn and colleagues (2012b; 2013; 2014) have performed several studies using fMRI during gambling and working memory tasks to determine if brain activity can predict future drug use. While both heavy cannabis users and non-users demonstrated normal performance in both tasks, the former showed higher activation in core areas associated with decision making and working memory. Within the cannabis users, these brain activity patterns predicted changes in cannabis use, with more activity (i.e., working harder to perform the task) correlating with escalated cannabis use six months later. The results from the gambling task, meanwhile, suggest an alteration in processing of motivational information in heavy cannabis users and that users who are biased toward immediate rewards have a higher probability of increasing drug use.

But how does *abstinence* from cannabis affect motivation? To address this question, Jager and colleagues (2010) used a monetary incentive delay task with fMRI in abstinent, but previously frequent, cannabis users and non-using controls. Again, despite performance similarities between the two groups, the task activated different brain regions of the reward circuitry in the cannabis users, who showed augmented activity in the striatum during the anticipatory stages of both reward and non-rewarding events. This finding suggests that users, even after abstinence, might have an overly sensitive motivational response to reward.

The findings also suggest that adolescent cannabis use actually reduces the ability of the brain to disengage the motivational circuit when no reward can be obtained, strengthening the need for reinforcements (i.e., the high from using cannabis), even when facing the negative consequences of this risk-seeking behaviour. This finding might also suggest an increased vulnerability for other kinds of risk-taking behaviour that could continue into adulthood, including continued and heightened drug use.

Similar findings come from De Bellis and colleagues (2013), who used fMRI on individuals performing the decision-reward uncertainty task. Compared to the control group, abstinent users with cannabis use disorder showed augmented activity in posterior decision-making brain regions when making risky decisions, as well as attenuated activations to reward in the orbitofrontal cortex. These findings further support the role of the orbitofrontal cortex in cannabis use and its relationship to altered neurophysiology during risky behaviour, decision making and motivation.

1.4.2 Impact on driving skills

As cannabis use is associated with a potential increase in risk-taking behaviour, the probability that youth will drive while under the influence of cannabis, which brings with it a significantly increased risk of motor vehicle collisions compared to unimpaired driving, is an issue of great concern (Asbridge, Hayden, & Cartwright, 2012, Gerberich et al., 2003).

Based on recent epidemiological and laboratory evidence, the acute effects of cannabis increase the risk of motor vehicle collision by two to three times, a level of risk that increases even further when cannabis is mixed with alcohol (Hall, 2015). This increased risk is not surprising given the deleterious effects of cannabis on psychomotor functions such as balance, psychomotor speed, visual tracking and coordination (Liguori, Gatto, & Jarrett, 2002; Messinis, Kyprianidou, Malefaki, & Papathanasopoulos, 2006; Weinstein et al., 2008). While drivers who use cannabis have been shown to compensate by driving slower than normal, they typically have reduced control when there is increased task complexity, resulting in more lane weaving, slower reaction times, impaired divided attention task performance and reduced critical tracking test performance (Anderson, Rizzo, Block, Pearlson, & O'Leary, 2010; Downey et al., 2013; Hartman & Huestis, 2013; Lenne et al., 2010).

This effect has been supported with fMRI research into the impact of cannabis on the motor network, namely the cingulo-cerebellar circuitry (Lopez-Larson et al., 2012). The cerebellum is involved in motor control, while the cingulate gyrus is the cognitive–attentional component of the motor network. Activity in this circuitry was found to be altered (in fact, reduced) in adolescent cannabis users compared to non-users during a simple finger-tapping task. This relationship between activity in the cingulo-cerebellar circuitry and lifetime quantity of cannabis use accentuates the negative effect cannabis has on motor functioning, including driving skill. Because of this negative effect on driving, jurisdictions that have recently legalized cannabis use need to institute strict driving regulations pertaining to cannabis-related impairment.

In Washington, a state that legalized cannabis in 2013, Couper and Peterson (2014) looked at whether the legislative changes had affected the prevalence of cannabis in the state's suspected impaired-driving cases. They found an increase from 19.1% to 24.9% for THC and from 27.9% to 40% for carboxy-THC (a metabolite of THC) in the blood of drivers suspected of impaired driving. A similar study was performed in Colorado using the Fatality Analysis Reporting System, which allows for the comparison of the proportion of drivers involved in fatal crashes who were cannabis-positive to those who were alcohol-impaired (Salomonsen-Sautel, Min, Sakai, Thurstone, & Hopfer, 2014). Since 2009, when medical marijuana became commercially available in the state, there has been an increase in the proportion of drivers who were cannabis-positive, but no such increase in alcohol-related crashes. When compared to other states that had not commercialized medical cannabis, Colorado showed an increased proportion of drivers in fatal crashes who were cannabis-positive.

1.5 Conclusions and implications

The dynamic neurodevelopment that occurs during adolescence is instrumental in creating an optimized brain that will help propel teens into a prosperous adulthood. By hijacking the neurodevelopment process, cannabis significantly affects cognition, academic achievement, motivation, risk-taking behaviour and psychomotor skills.

The most consistent finding from both structural and functional MRI studies has been a negative effect of cannabis on the structure and functioning of the anterior cingulate, cerebellum and prefrontal cortex (specifically, the orbitofrontal cortex). These brain regions are critical for executive functioning, decision making, response inhibition and the ability to carry out goal-directed behaviour, all of which are necessary for long-term success into adulthood.

While the results emerging from the latest neuroimaging studies align well with each other, further research that can better control for many different variables (including other drug use, age of onset of use and dosage) and can incorporate multivariate outcome measures and techniques (including a mix of neuroimaging and neuropsychological assessments) is required. Until then, the high incidence of cannabis use in youth and the mounting evidence of its disruption of brain development must be taken seriously by teenagers, their parents, healthcare professionals and policy makers across the country, as it is a critical societal issue with implications that cannot be minimized or ignored.

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2

Is There a Link Between Cannabis and Mental Illness?

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Chapter at a Glance

- High rates of substance use disorders have been observed among individuals living with mental illness.
- This co-morbidity has a negative impact on the prognosis and course of illness of all psychiatric disorders, especially when cannabis use is initiated during adolescence.
- Current evidence suggests a strong relationship between cannabis use and psychosis; however, the role of adolescent cannabis use in the onset of depression, anxiety, eating disorders and childhood behavioural disorders is less understood.
- Further research using multidisciplinary approaches will be needed to develop a greater understanding of the underlying relationship between cannabis use and mental illness.

2.1 Introduction

Adolescence is a critical period of psychosocial and physiological development — and is also the time when several neuropsychiatric disorders and unsafe behaviours, including mental illness and substance abuse, typically begin to emerge.

In this context, it is important to recognize that cannabis use has potentially adverse effects among those who are vulnerable to mental illness, including teens. For example, we know that cannabis use leads to an earlier onset of psychotic symptoms (Veen et al., 2004) and is a major risk factor for developing schizophrenia (Semple, McIntosh, & Lawrie, 2005). Cannabis use has also been shown to worsen symptoms of mood and anxiety disorders (Degenhardt, Hall, & Lynskey, 2003), eating disorders (Ross & Ivis, 1999) and childhood behavioural disorders (Fergusson & Boden, 2008).

While there is a strong relationship between mental illness and substance use, the underlying reasons why are still largely unknown. Does drug use induce mental illness? Or does mental illness increase risk for drug use? While researchers have traditionally attempted to answer this question through epidemiological methods (i.e., by uncovering the pattern of substance use in association with the onset of symptoms), *causality* cannot be determined in this way. Because of this limitation, researchers have turned to interventional and neurophysiological studies to uncover the underlying links between adolescent cannabis use and the development of mental illness.

2.2 The endocannabinoid system and the development of psychiatric disorders

As discussed in the previous chapter, the primary psychoactive component in cannabis, delta-9-tetrahydrocannabinol (THC), hijacks the endocannabinoid system by targeting the cannabinoid type 1 (CB_1) receptor in much higher quantities than the cannabinoids produced naturally by the brain. With such a vast pattern of expression, CB_1 receptors are implicated in many neurological functions, including emotional regulation, motor control, cognition, memory, reward and addiction (Herkenham, 1991). The presence of exogenous cannabinoids such as THC likely interferes with the regulatory role of the endocannabinoid system, potentially leading to long-lasting consequences for adult brain functioning.

Aberrant endocannabinoid functioning may be directly associated with the development of several psychiatric disorders and may account for cannabis' deleterious effect on the course of these disorders. For example, cannabis users with

schizophrenia or depression have lower levels of anandamide (one of the naturally occurring cannabinoids) compared to non-users (Hill & Gorzalka, 2005; Leweke et al., 2007). Post-mortem studies have also revealed a decrease in CB_1 receptor density in people with depression, with contrasting density increases in those with schizophrenia (Ceccarini et al., 2013).

While these findings suggest that aberrant endocannabinoid system functioning might contribute to the development of co-morbid cannabis dependence and mental illness, inconsistencies in the research highlight the need for continued investigation.

2.3 Cannabis' link to schizophrenia

Individuals with schizophrenia report severe psychotic symptoms and often experience substantial social disability, a loss of motivation, disturbed behaviour and cognitive deficits. While the notion of a cannabis–psychosis link has been around for decades, the potential causal relationship between these two disorders is still being debated. However, the current epidemiological and neurobiological research suggests that individuals with a predisposition to schizophrenia might be more vulnerable to the psychosis-inducing effects of THC.

2.3.1 Epidemiological evidence

Some of the most compelling evidence outlining the association between cannabis use and the onset of psychosis originates from longitudinal studies. One of the first studies on this topic followed 50,465 Swedish adolescents over the course of 15 years, with investigators finding that individuals who used cannabis on more than 50 occasions by age 18 were six times more likely to develop schizophrenia than those who did not use cannabis (Andréasson, Engström, Allebeck, & Rydberg, 1987). This increased risk for schizophrenia held true even when controlling for concomitant mental illnesses and social background, and persisted in a follow-up study conducted 27 years later (Konings, Henquet, Maharajah, Hutchinson, & Van Os, 2008), thus demonstrating that cannabis represents an independent risk factor for the development of schizophrenia.

These findings have been replicated in longitudinal studies around the world, with both Henquet and colleagues (2005) and Arseneault and colleagues (2002) associating adolescent cannabis use with a greater probability of reporting psychotic symptoms later in life. Importantly, a number of studies have shown that this risk of developing schizophrenia is increased dose-dependently with increasing cannabis consumption (Henquet et al., 2005; Zammit, Allebeck, Andréasson, Lundberg, & Lewis, 2002).

More recently, Di Forti and colleagues (2015) suggested that regular use of cannabis with high levels of THC and low levels of cannabidiol (often referred to as "skunk") substantially increases the risk of developing schizophrenia. Specifically, they compared cannabis use in first-episode cases of psychosis to matched controls with higher than average rates of psychoses and cannabis use. While both groups showed equally high rates of lifetime cannabis use, the first-episode cases were three to five times more likely to report daily skunk use, and this association persisted after statistical adjustment for confounders.

While these studies clearly provide evidence for the *association* between cannabis use and schizophrenia, they do not provide definitive answers regarding the direction of this relationship.

2.3.2 Neurobiological evidence

Neurobiological studies employing genetic, neurophysiological and neuroimaging-based approaches suggest the existence of common underlying factors associated with a vulnerability to both cannabis use and schizophrenia. In particular, the current evidence proposes that the detrimental effects of cannabis use on schizophrenia might be linked to disturbances in endocannabinoid signalling and genetic variants associated with cannabinoid-type genes.

Research focusing on the cannabinoid receptor gene (CNR1) suggests that variations in this gene may influence the development of concurrent cannabis use and schizophrenia (Kohn & Lerer, 2005; Zhang et al., 2004). Furthermore, studies have found that individuals with schizophrenia who possess a specific type of CNR1 gene and use cannabis heavily show greater deficits in white matter volume and cognitive functioning compared to non-heavy users (Ho, Wassink, Ziebell, & Andreasen, 2011). It follows that these CNR1 gene variants might predispose people to engage in heavy cannabis use and likely worsen already aberrant cognitive functioning.

These findings have led some researchers to consider the "endocannabinoid hypothesis of schizophrenia" (Muller-Vahl & Emrich, 2008), which implicates this system in the interaction

between adolescent exposure to cannabis and an enhanced vulnerability to psychosis. However, contradictory reports have found no significant differences in the CB_1 receptors of cannabis users and non-users — and that cannabis may not have an effect on cannabinoid receptor density in those with schizophrenia (Deng, Han, & Huang, 2007; Koethe et al., 2007). While disturbances in the endocannabinoid system could represent one potential risk factor for co-morbid cannabis use among individuals with schizophrenia, the conflicting evidence highlights the need for further research.

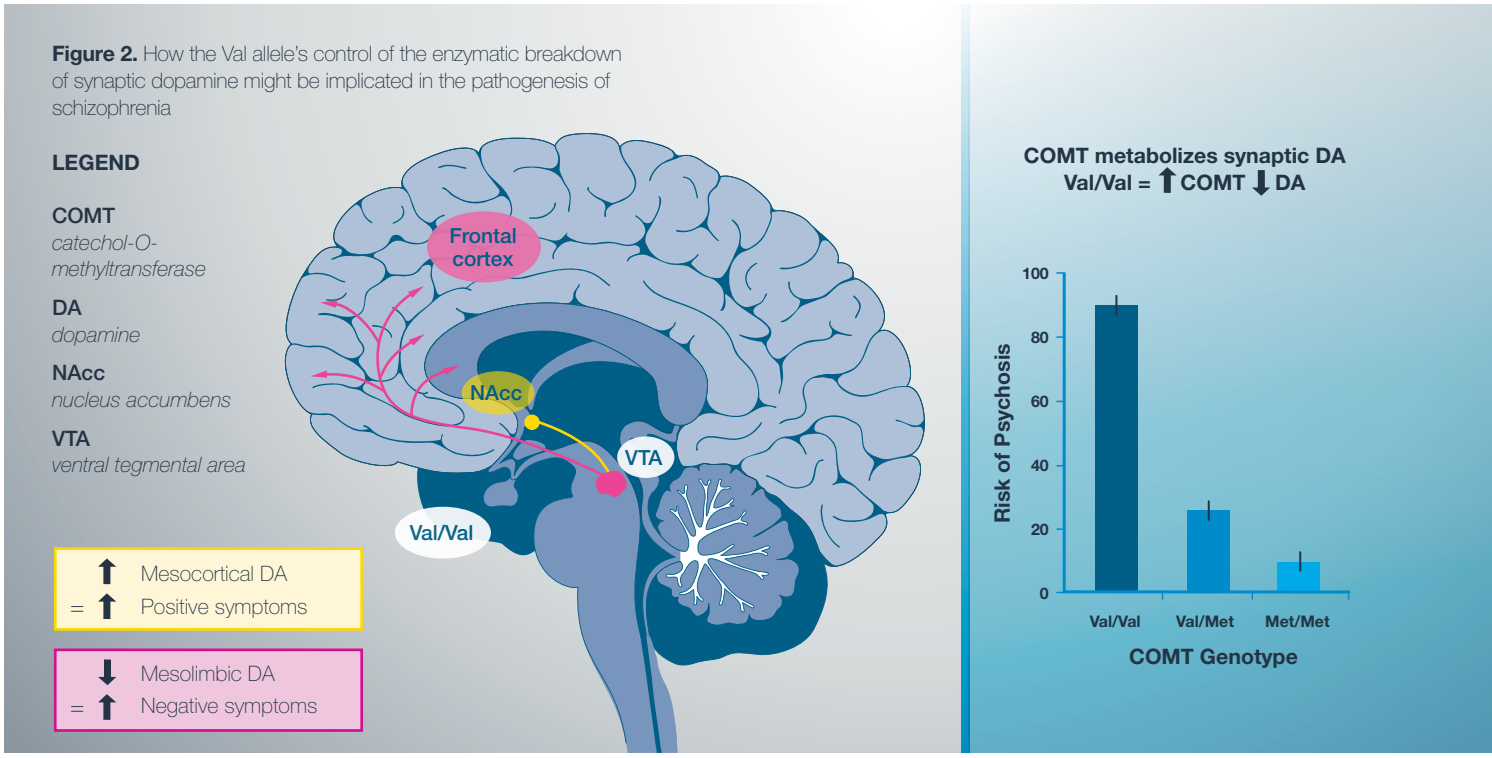
Dopamine

Dopamine pathways of the mesolimbic systems in the brain normally mediate rewarding and reinforcing processes, and these pathways are altered by drugs of abuse such as cannabis (THC) (Blum et al., 2012).

Genetic studies could provide further insight into the potential common vulnerability connecting cannabis use and schizophrenia. Given their role in both schizophrenia (Mackay et al., 1982) and addiction (Di Chiara & Imperato, 1988), genetic variants that influence dopamine have been implicated in the pathophysiology of this co-morbidity. Of specific interest is the gene for catechol-O-methyltransferase (COMT), an enzyme responsible for the metabolism of synaptic dopamine (i.e., lowering the availability of dopamine in the brain). The COMT gene is coded for by two alleles: the Met and Val alleles. (An allele is one of two or more alternative forms of a gene that arise by mutation and are found at the same position on a specific chromosome.) As illustrated in Figure 2, the combination of these alleles can influence an individual's mental health:

- Individuals who have two Met alleles show a substantial decrease in COMT enzymatic activity, leading to increased dopamine levels;
- Individuals who have two Val alleles show enhanced COMT activity, leading to decreased dopamine levels; and
- Individuals who have one of each allele show intermediate COMT activity and dopamine levels.

Figure 2. How the Val allele's control of the enzymatic breakdown of synaptic dopamine might be implicated in the pathogenesis of schizophrenia



Source for image of brain: Guzman, 2015; adapted with permission from Dr. F. Guzman
Source for graph: Caspi et al., 2005; adapted with permission from Elsevier

Several studies have uncovered an increased risk of developing schizophrenia or psychosis in individuals who have two Val alleles and are exposed to cannabis at an early age (Caspi et al., 2005; Henquet et al., 2006). However, other studies have been unable to replicate this finding (Zammit et al., 2007), suggesting there are likely several genes working together and not simply one genetic variant contributing to these disorders. COMT and the endocannabinoid system represent just two examples of the neurobiological underpinnings of cannabis use and schizophrenia; there are many additional lines of research exploring this co-morbidity (Rabin, Goodman, George, & Barr, 2014).

2.3.3 Potential mechanisms by which cannabis increases risk for schizophrenia

If cannabis use does lead to schizophrenia, it would follow that the incidence of schizophrenia would increase in parallel to the increasing rate of cannabis consumption. While several longitudinal studies have found that cannabis use has increased dramatically in recent decades, there is no clear evidence that psychosis rates in the general population have also increased (Degenhardt et al., 2003; Hickman, Vickerman, Macleod, Kirkbride, & Jones, 2007).

More recent neurobiological studies suggest there are distinct features that enhance risk, with researchers looking specifically at the shared neural pathways influencing the onset and maintenance of cannabis use among individuals with schizophrenia. Disturbances in the endocannabinoid system, aberrant neurophysiological functioning and genetic variations are just some of the areas being examined. It has been suggested that these factors precede the onset of concurrent cannabis use in individuals with schizophrenia and are influenced by both schizophrenia and cannabis use. From this diverse and somewhat conflicting body of evidence, what appears to be consistent is that among individuals with a predisposition for schizophrenia, cannabis consumption exacerbates symptoms and worsens the overall course of the illness.

2.4 Cannabis' link to mood and anxiety disorders

Compared to psychosis, much less attention has been given to the relationship between cannabis use and mood and anxiety disorders. However, given the increasing rates of suicide among adolescents (Skinner & McFaull, 2012) and evidence suggesting that both drug abuse and depression contribute to suicidal risk (Beautrais, 2000), further research on this co-morbidity is necessary. In addition, while the current research often combines mood and anxiety disorders given their overlapping characteristics and frequent co-occurrence, future research should look at these disorders separately as the risks associated with each and their underlying connections to cannabis use might not be the same.

2.4.1 Depression

There is a growing body of evidence suggesting that problematic cannabis use and mood disorders often co-occur.

Epidemiological evidence

Several longitudinal studies have revealed an increased risk of depression in cannabis users compared to those who have never tried cannabis, and that the level of risk increases with earlier initiation and more frequent use (Brook, Brook, Zhang, Cohen, & Whiteman, 2002; Ferguson, Horwood, & Swain-Campbell, 2002; Patton et al., 2002; Rey, Sawyer, Raphael, Patton, & Lynskey, 2002). Cannabis use has also been shown to lead to an increased risk of suicidal thoughts and attempts (Pedersen, 2008), especially among young females (Wilcox, Conner, & Caine, 2004).

At the same time, several cohort studies have found the association between cannabis use and depression is diminished when confounding variables like concomitant drug use, education level, marital status and other demographic characteristics are taken into consideration (Green & Ritter, 2000; Rowe, Fleming, Barry, Manwell, & Kropp, 1995). Additionally, a number of studies were unable to find that adolescent onset depression predicted later cannabis use or dependence (Hofstra, Van Der Ende, & Verhulst, 2002; Kandel & Chen, 2000; Patton et al., 2002).

While explanations of the association between these two disorders are inconsistent, epidemiological evidence suggests the direction of risk stems from cannabis use to depression and not the reverse.

Neurobiological evidence

Less is known about the neurobiological underpinnings of cannabis use and depression, with much of the evidence coming from pre-clinical research. However, researchers have begun to investigate this relationship using neuroimaging and post-mortem analysis.

In line with evidence on the cannabis–psychosis link, the endocannabinoid system could also contribute to co-morbid cannabis use and depression. It has been suggested that decreased endocannabinoid activity might contribute to the anhedonia, anxiety, decreased pain tolerance, chronic pain and decreased serotonergic activity often seen in individuals with depression (Ashton & Moore, 2011). Supporting this notion is the fact that rimonabant, an antagonist drug that binds to the CB_1 receptor and blocks it from producing its normal response, has been shown to induce symptoms of depression and anxiety (Moreira & Crippa, 2009). Finally, post-mortem studies in individuals with major depression have revealed a decrease in CB_1 receptor density, indicating aberrant endocannabinoid signalling (Koethe et al., 2007).

Agonist and antagonist drugs

For drugs that are site-specific, actions initiated can be agonist, antagonist or a combination of both. Agonists initiate activity in the cell; antagonists act in the opposite way, blocking cellular activity.

While this research is preliminary, findings do suggest disruptions in the endocannabinoid system may underlie a greater vulnerability to depression and concurrent cannabis use. Moving forward, this field would benefit from multidisciplinary methodologies that incorporate clinical trials, neuroimaging, brain stimulation and genetics.

2.4.2 Bipolar disorder

Due to its overlapping features with depression and schizophrenia, research into the effects of adolescent cannabis use on the onset and clinical course of bipolar disorder has revealed similar findings to these other disorders. However, less is known about its co-occurrence with cannabis use, especially among adolescents.

Epidemiological evidence

A few epidemiological studies beginning in adolescence and traversing the lifespan of participants have demonstrated that concurrent cannabis use and bipolar disorder is associated with a greater length of affective episodes and number of manic episodes, more rapid cycling, an increase in overall disability and more severe prognosis (Agrawal, Nurnberger, & Lynskey, 2011; Baethge et al., 2005; Lev-Ran, Le Foll, McKenzie, George, & Rehm, 2013; Strakowski et al., 2007). Furthermore, Lagerberg and colleagues (2014) found a significant dose–response relationship between cannabis use and age of onset of bipolar symptoms, even after controlling for confounding factors such as gender, bipolar subtype, and family history of substance use and psychiatric illness. Similar to the research on schizophrenia, the association between cannabis use and the earlier onset of bipolar disorder suggests a potential role of cannabis use in the initial progression of this disorder in vulnerable individuals.

Neurobiological evidence

There is limited research examining the potential underlying neurobiological mechanisms that connect cannabis use to bipolar disorder. One neuroimaging study by Bitter and colleagues (2014) found that adolescents with concurrent bipolar disorder who used cannabis did not show the same pattern of over-activation in brain regions associated with emotional processing seen consistently in those with bipolar disorder alone. This unexpected finding has led researchers to suggest that individuals with concurrent bipolar disorder and cannabis use may actually represent a unique subset of patients with bipolar disorder — and highlights the need for further research.

2.4.3 Anxiety disorders

Like mood disorders, research has shown that frequent cannabis users report higher levels of anxiety than infrequent users. However, the relationship between concurrent anxiety disorders and cannabis use has proven to be more complex than first assumed.

Epidemiological evidence

Several studies have found that adolescent cannabis dependence is associated with increased rates of psychological distress and anxiety (Dorard, Berthoz, Phan, Corcos, & Bungener, 2008), as well as an increased risk of panic attacks and panic disorders (Zvolensky et al., 2009). Furthermore, the severity of anxiety symptoms has been shown to correlate with greater levels of cannabis consumption (Clough et al., 2006). In a cohort study that followed 3,229 young adults from birth to age 21, researchers found those who used cannabis before they turned 15 and continued to use until age 21 were more likely to report symptoms of anxiety disorders, even after controlling for confounding factors (Hayatbakhsh et al., 2007).

Researchers have also considered the possibility that anxiety might lead to increased cannabis use. Specifically, social anxiety and post-traumatic stress disorder (PTSD) pose unique risks for the onset of problematic cannabis use among adolescents and young adults:

- In a longitudinal cohort study conducted over 14 years, Buckner and colleagues (2008) found that those who met criteria for a social anxiety disorder upon study entry were 6.5 times more likely to demonstrate cannabis dependence, but not abuse, at follow-up. This relationship remained significant after controlling for potential confounding variables such as gender, depression and other anxiety disorders.
- While few studies have systematically studied the relationship between PTSD and cannabis use, the increasing prevalence of this co-morbidity has given rise to increased research interest. One study examined this co-morbidity longitudinally in the adolescent offspring of adult males with and without a lifetime history of substance use disorders (Cornelius et al., 2010). Of these participants, 31 were diagnosed with PTSD and 161 were diagnosed with cannabis use disorder. Results revealed that PTSD contributed to the development of cannabis use disorder beyond the familial risk of substance use disorders.

It has been suggested that individuals with social anxiety and PTSD use cannabis primarily to reduce anxiety. Thus, cannabis dependence stems from the belief that this substance aids in coping with the negative emotional states associated with anxiety disorders. Greer and colleagues (2014), for instance, found that individuals seeking treatment for PTSD reduced their anxiety scores (as measured on the Clinician-Administered PTSD Scale) by up to 75% when using medical cannabis. This finding suggests a more complex relationship between cannabis and anxiety, such that anxiety might either be enhanced or reduced following cannabis consumption. As there are likely a number of factors, both biological and environmental, that give rise to this bidirectional relationship, further research is needed.

Clinical evidence

Cannabis has been used for its anxiety-reducing properties for centuries, but only recently have researchers investigated its therapeutic properties using laboratory-based methodologies.

While most research has targeted THC, cannabidiol has been shown to possess psychological effects that are opposite to those of THC (Zuardi, 2008). This awareness has led researchers to start investigating the role of the endocannabinoid system and cannabidiol in the treatment of anxiety disorders. For example, studies have shown that individuals with social anxiety disorders who were given cannabidiol showed reduced symptoms of anxiety, cognitive impairment and negative self-assessment during a simulated public speaking test compared to a control group given a placebo (Bergamaschi et al., 2011). Additionally, clinical research suggests that acute administration of low-dose CB_1 receptor agonists produces anxiety-inhibiting effects. The administration of dronabinol, for instance, has been shown to significantly reduce symptoms of trichotillomania, an impulse-control disorder associated with repetitive and compulsive hair-pulling (Grant, Odlaug, Chamberlain, & Kim, 2011).

Neurobiological evidence

Although epidemiological and clinical evidence suggests a relationship between cannabis use and anxiety, the direction and causal nature of this co-morbidity remains unclear. Employing more diverse methodologies with a focus on potential neurobiological vulnerabilities underlying these disorders may provide a novel perspective. However, there is currently limited research on this topic in humans.

Studies have implicated the aberrant functioning of the endocannabinoid system in an individual's susceptibility to the anxiety-inducing properties of cannabis. For example, it has been reported that cannabis use increases anxiety through dysregulation of anandamide, an endogenous cannabinoid, especially among individuals vulnerable to developing anxiety (Witkin, Tzavara, & Nomikos, 2005). Similar to research conducted on the potential genetic determinants underlying the co-morbidity of cannabis use and schizophrenia, researchers have identified variations in the CNR1 gene as a plausible candidate for the development of an anxiety disorder. One study investigated gene–gene interactions between the CNR1 gene and regions of the serotonin transporter gene (SLC6A4), finding that aberrant serotonergic and endocannabinoid system functioning may increase a person's vulnerability to anxiety (Lazary et al., 2009). While this finding proposes a promising neurobiological link between the endocannabinoid system and anxiety, further research is needed to better understand the relationship.

Clinical Vignette

Melinda

Melinda, a 24-year-old female, recently dropped out of college and is close to being kicked out of her parent's house. She was diagnosed with schizophrenia at age 21, five years after first trying cannabis. In the beginning, she smoked up only on weekends with her friends, but this quickly progressed to daily use and she now smokes weed several times throughout the day.

Although Melinda has now experienced a psychotic episode and been hospitalized after a period of heavy cannabis use, she still believes cannabis does not negatively affect her life. She has tried to quit several times but says her friends and older brother, who also smoke, make it too hard to abstain. After being placed on academic probation for showing up to class high and falling behind on her work, Melinda decided to drop out of college. In response, her parents have threatened to kick her out of the house if she does not quit cannabis. Now, Melinda is beginning to feel hopeless and depressed — and wonders if there is any way out.

2.4.4 Potential mechanisms by which cannabis increases risk for mood and anxiety disorders

While it is clear that cannabis use commonly occurs in individuals who report symptoms of depression and anxiety, it is less clear as to why these disorders commonly co-occur. It was once believed that the presence of these disorders put adolescents at risk for cannabis use later in life as a means to self-medicate and alleviate symptoms associated with medication side effects and their disorder (Musty & Kaback, 1995; Wittchen et al., 2007). However, longitudinal research has found that self-medication cannot adequately account for the pattern of cannabis use among youth with depression, anxiety or bipolar disorder (Degenhardt et al., 2003; Strakowski, McElroy, Keck, & West, 1996).

Recent research has turned its focus on the common underlying causal factors or "third variables" that might predispose individuals to both substance use and mental illness. Unfortunately, the factors that govern the behavioural outcomes of cannabis use in individuals with mood and anxiety disorders are still largely unknown, yet they are thought to include both biological and environmental considerations (Lynskey et al., 2004). Evidence supporting this hypothesis indicates that environmental factors such as social disadvantage and family dysfunction are more common among individuals who meet criteria for problematic substance use, as well as depressive disorder (Warner, Mufson & Weissman, 1995).

In terms of the neurobiological links between cannabis use and mood and anxiety disorders, the influence of cannabis on the hypothalamic–pituitary–adrenal (HPA) axis represents a potential mechanism underlying this co-morbidity. As a key component of the neuroendocrine system, the HPA axis modulates reactions to stress, including the emotional response. Dysregulation of this system has been implicated in mood and anxiety disorders. Interestingly, the HPA axis is regulated by the endocannabinoid system; it therefore follows that cannabis use activates the neuroendocrine stress response via the HPA axis (Steiner & Wotjak, 2008).

2.5 Cannabis' link to eating disorders

Eating disorders are the leading cause of morbidity and mortality among adolescents, with a lifetime prevalence of 0.9% for anorexia nervosa and 1.5% for bulimia nervosa among women (Hudson, Hiripi, Pope, & Kessler, 2007). The association between substance use disorders and eating disorders has been well studied, with a lifetime prevalence ranging from 25% to 50% depending on the disorder (Mann et al., 2014). Few studies, however, have focused on the effects of cannabis specifically on the course of eating disorders.

2.5.1 Epidemiological evidence

Research has consistently demonstrated that adolescents with anorexia nervosa use tobacco, alcohol and cannabis less frequently than grade- and sex-matched comparison populations (Stock, Goldberg, Corbett, & Katzman, 2002). In contrast, those with bulimia nervosa use these substances at rates similar to or greater than the general population (Ross & Ivis, 1999). Given that cannabis use increases appetite, it follows that cannabis is one of the most commonly abused illicit drugs among binge eaters. In their examination of the reasons why adolescents with eating disorders choose to use different drugs, Stock and colleagues (2002) found that bulimic females were most likely to use cannabis to relax or release anger. Anorexic females, on the other hand, were likely not to use cannabis because they considered it too bad for their health or against their personal beliefs.

2.5.2 Potential mechanisms by which cannabis increases risk for eating disorders

Like mood and anxiety disorders, the direction and causal nature of the relationship between eating disorders and cannabis use is not well understood. Researchers have suggested that impulsive behaviours might link these two disorders. Specifically, those who exhibit bulimic symptoms and abuse substances also demonstrate increased rates of attempted suicide, theft and risky sexual behaviours (Wiederman & Pryor, 1996).

An important biological link between cannabis use and eating disorders lies within the endocannabinoid system, which plays a key role in the regulation of food intake and energy metabolism. In fact, rimonabant, a CB_1 antagonist, was once considered for the management of obesity and has been shown to decrease

body weight and alleviate symptoms of metabolic syndrome (Horcajadas, 2007). It is likely that the interaction between environmental and biological factors leads to the use of cannabis among adolescents with eating disorders. However, further research is necessary.

2.6 Cannabis' link to childhood behavioural disorders

With the initiation of cannabis use occurring at younger ages than before, researchers have now begun to investigate its effects on a wide range of childhood disorders. However, there is little research investigating the effects of cannabis use specifically on childhood *behavioural* disorders such as attention deficit hyperactivity disorder (ADHD), conduct disorder (CD) and oppositional defiant disorder (ODD). While this field of research is complicated by the prevalence of co-morbid mental illness within childhood disorders (Szatmari, Offord, & Boyle, 1989), among all childhood behavioural disorders, high rates of substance use are apparent starting in early adolescence.

2.6.1 Epidemiological evidence

August and colleagues (2006) sought to evaluate adolescent drug use in a large sample of children who have ADHD with and without externalizing behaviours (primarily ODD). They found that the ADHD-externalizing group showed a significantly higher frequency of substance use (especially cannabis use) compared to the healthy controls and the ADHD-only groups, which suggests the relationship between ADHD and cannabis use might be driven by externalizing behaviours. This finding is consistent with previous research examining the relationship between cannabis use and CD (Heron et al., 2013). However, conflicting research has found that even after controlling for conduct problems, ADHD predicted later substance use problems with hyperactivity and impulsivity rather than inattention driving this relationship (Elkin, McGue, & Iacono, 2007).

Externalizing and internalizing behaviours
Externalizing behaviours are characterized by high levels of impulsive risk taking and aggression, while internalizing behaviours are characterized by either anxiety or depression. Both types of behaviours represent the two most common developmental pathways to substance abuse disorders.

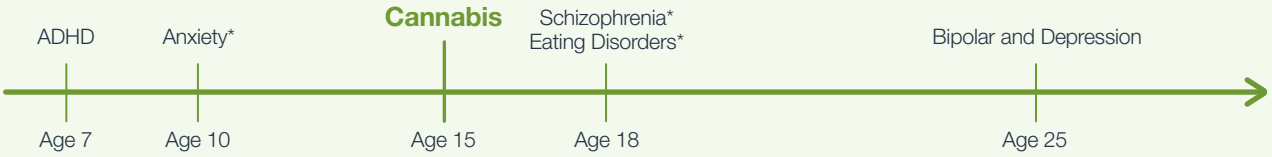
Finally, several studies looking at the interaction between ADHD and CD on substance use disorders found that individuals who presented with the most severe symptomatology were at the highest risk of substance use, especially cannabis use (Flory, Milich, Lynam, Leukefeld, & Clayton, 2003; Molina, Smith, & Pelham, 1999).

2.6.2 Potential mechanisms by which cannabis increases risk for childhood behavioural disorders

As shown in Figure 3, unlike schizophrenia and mood disorders, childhood behavioural disorders are similar to anxiety in that they manifest before the onset of cannabis use (Applegate et al., 1997; Bellivier et al., 2003; DeLisi et al., 1994; Keeton, Kolos, & Walkup 2009; Monshouwer, Smit, De Graaf, Van Os, & Volleberg 2005; Stice, Marti, & Rohde 2013). Therefore, it is likely that these behavioural childhood disorders influence cannabis use and not the other way around (Crowley, Macdonald, Whitmore & Mikulich, 1998).

So what factors associated with childhood behavioural disorders might lead to the onset of cannabis use? One of the most evident factors appears to be impulsivity, which is a key component shared between ADHD, CD and substance use problems (American Psychiatric Association, 2013; Moeller & Dougherty, 2002). Furthermore, aberrant executive functioning and developmental delays associated with poor decision

Figure 3. Average age of onset of symptoms or diagnosis of several mental illnesses compared to the average age of onset of cannabis use



LEGEND: Anxiety: Average age of adult onset is 31 | **Schizophrenia:** Average age of onset for females is 25
Eating disorders: Average age of onset ranges from 16 to 20

making represent another core feature of ADHD that likely plays a role in the onset of substance use (Tamm et al., 2013). Thus, it is possible that the negative impact of ADHD on neurocognitive function might make these individuals more vulnerable to cannabis use, giving rise to a distinctive co-morbidity profile.

2.7 Conclusions and implications

Fergusson and Horwood (1997) suggested three potential relationships between substance use disorders and mental illness:

- A shared vulnerability;
- Prior cannabis use predicting the onset of a mental illness; or
- Mental illness leading to later cannabis use.

While the current evidence clearly outlines an analogous, detrimental course for both mental illness and substance abuse, cannabis use has been shown to have differential relationships on each type of psychiatric disorder. Thus there is no undisputable support for any one of these hypotheses.

What then does the data suggest? Researchers have proposed a common underlying neurobiological vulnerability to both cannabis use and schizophrenia (Rabin et al., 2014). For individuals who are genetically vulnerable to schizophrenia, cannabis use can lead to an earlier onset of symptoms and worsening prognosis (Veen et al., 2004). In contrast, the evidence suggests that childhood behavioural disorders likely precede and might lead to the use of cannabis (Crowley et al., 1998). Additionally, it remains unclear whether the association between cannabis use and mood and anxiety disorders is due to an increased rate of depression and anxiety among cannabis users, or an increased rate of cannabis consumption among those with depression or anxiety. Similarly, the direction and causal nature of the relationship between eating disorders and cannabis use is not well understood.

These differential effects could be partly due to the average age of onset of each psychiatric disorder compared to the onset of cannabis use. Ultimately, what can be drawn from these findings is that while the link between cannabis use and mental illness varies across diagnoses — and regardless of whether cannabis use predicts mental illness or vice versa — cannabis use during adolescence has clear negative consequences.

As cannabis is the most commonly abused illicit drug worldwide, including among treatment-seeking individuals, many patients and clinicians are unaware of or downplay the potential harmful effects of this drug (McGee, Williams, Poulton, & Moffitt, 2000). Moreover, there is a deficit of research on effective treatment options specifically for individuals with mental illness and co-morbid cannabis dependence.

Given the commonality of neurobiological and environmental factors underlying mental illness and substance use, the simplest approach to improving mental health outcomes would be to reduce cannabis use in these individuals. As the age of first cannabis use is progressively decreasing, targeting health education and other preventative measures toward adolescents would be especially beneficial. Finally, addressing the misperception that cannabis use is safe, instead of focusing on the longer-term detrimental consequences for mental health in young people, could prove to be more successful in modifying cannabis use (McGee et al., 2000). Early interventions to reduce the harms of cannabis use in people at risk for mental illness may also mitigate the progression to more complex co-morbid presentations such as polysubstance use.

Continued research into the effects of cannabis use on mental illness will be needed to generate evidence-based treatment approaches and address public health implications. Moving forward, it will be especially important to address the methodological discrepancies that have led to conflicting published findings. For example, the groups of study participants discussed in this chapter included both community-based and clinical samples, poly-drug users and individuals with varying levels of cannabis dependence and mental illness severity.

Because these methodological limitations are inherent to epidemiological studies, a multidisciplinary approach that includes neurobiological research into the mechanisms linking cannabis use to mental illnesses (including genetic, pharmacological, brain stimulation and neuroimaging studies) will be needed to bridge knowledge gaps and catalyze future exploration of intervention strategies. Funding is needed to bring together researchers from numerous fields for more intense investigation and to accelerate progress in understanding and treating co-morbid cannabis use disorders and mental illness.

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3

Is Cannabis Addictive?

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Chapter at a Glance

- The general public perceives cannabis to be less addictive than other drugs of abuse. In reality, it has a significant addictive potential — in the same range as alcohol.
- Approximately 5 to 9% of those who use cannabis will develop dependence, and this rate increases to about 17% for those who start using during adolescence.
- The risk of developing cannabis dependence is related to multiple biological and environmental factors such as genetics and age of initiation of use.
- Individuals who stop using cannabis can experience symptoms of withdrawal.
- Better knowledge of the factors that facilitate the transition from cannabis use to dependence could help reduce the risk of addiction and have clinical implications for cannabis-related treatment and intervention.

3.1 Introduction

As mentioned in this report's introductory chapter, there is a growing perception among youth that cannabis is relatively harmless. This perception was countered in Chapters 1 and 2, which outlined the many ways in which cannabis in fact has a profound negative impact on brain development, behaviour and mental health.

But is cannabis an addictive substance? More specifically, does delta-9-tetrahydrocannabinol (THC), the main psychoactive component of cannabis that acts on the cannabinoid receptors in the brain, produce the same addictive properties as other drugs of abuse?

Cannabis is the world's most widely used illicit drug (United Nations Office on Drugs and Crime, 2012), with approximately 11% of Canadians aged 15 and older using cannabis at least once in the past year (Statistics Canada, 2015). Cannabis use is generally more prevalent among youth in Canada, with 22.4% of teens aged 15–19 and 26.2% of young adults aged 20–24 reporting past-year use in the 2013 Canadian Tobacco, Alcohol and Drugs Survey (CTADS).

Looking particularly at "heavy" or "regular" cannabis use, which is defined as daily or near-daily use (Hall & Pacula, 2010), the 2013 CTADS found that approximately 23% of Canadian youth and 30% of young adults who used cannabis in the past three months reported using it daily or almost daily (Statistics Canada, 2015). Evidence from around the world has shown this kind of regular use can lead to cannabis dependence, which can lead, in turn, to serious physical, psychological and social problems. In the Netherlands, for example, a study of high-risk young adults reporting heavy use found that nearly 40% developed cannabis dependence (van der Pol et al., 2013). Closer to home, findings from the 2012 Canadian Community Health Survey revealed that more than 5% of young Canadians between the ages of 15 and 24 met the criteria for cannabis abuse or dependence (Pearson, Janz, & Ali, 2013).

3.2 What is addiction?

Before exploring the frequency of addictive states associated with cannabis use, it is useful to explain what we mean by an "addictive substance," as the estimate of prevalence depends on how addiction is defined and measured.

3.2.1 Classifications of addiction

The two main classifications of addiction currently used in the medical field are the *International Statistical Classification of Diseases and Related Health Problems* (10th revision; ICD-10) and the *Diagnostic and Statistical Manual of Mental Disorder* (5th edition; DSM-5).

Developed by the World Health Organization (2010), the ICD-10 lists addictive disorders under its "mental and behavioural disorders due to psychoactive substance use" category. It also distinguishes between "harmful use" and "dependence syndrome" as follows:

- **Harmful use** is defined as a pattern of psychoactive substance use that causes physical or mental damage.
- **Dependence syndrome** is defined as a cluster of behavioural, cognitive and physiological phenomena that develop after repeated use and typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance and, in some cases, a physical withdrawal state.

The American Psychiatric Association (2013), which developed the DSM classification, now uses the term "substance use disorder" and has identified four broad categories of symptoms: *impaired control, social impairment, risky use and pharmacological criteria (including tolerance and withdrawal).*

The previous version of the DSM (DSM-IV-TR; American Psychiatric Association, 2000) listed addictive disorders under separate "abuse" and "dependence" categories:

- **Abuse** was defined as repeated instances of use under hazardous conditions; repeated, clinically meaningful impairment in social, occupational or educational functioning; or legal problems related to substance use.
- **Dependence** was defined as increased tolerance, compulsive use, impaired control and continued use despite the physical and psychological problems caused or exacerbated by substance use.

The DSM-5, however, unified these two classifications within a single "substance use disorder" continuum. As a result, studies that have artificially separated the two into different categories might ultimately underestimate the risk of addiction related to cannabis by focusing primarily on dependence when abuse might be more common (Hasin & Grant, 2004; Saha, Harford, Goldstein, Kerridge, & Hasin, 2012).

It is important to note that tolerance and withdrawal, both of which are perceived as classical manifestations of dependence, are not necessarily present in individuals who have developed a substance use disorder. Rather, they are manifestations of physical dependence. Tolerance reflects a markedly diminished effect with continued use of the same amount of cannabis, which can lead users to increase the dose and consume greater amounts of the drug. Similarly, cannabis withdrawal, which is slower to develop after cessation of exposure than tobacco withdrawal, can lead to the re-initiation of use to offset the unpleasant symptoms associated with discontinued use.

Diagnostic criteria for cannabis use disorder

The DSM-5 defines "cannabis use disorder" as "a problematic pattern of use leading to clinically significant impairment or distress." The DSM-5 diagnostic criteria for the disorder include:

- Using more cannabis than intended and trying unsuccessfully to control use;
- Spending a significant amount of time obtaining and using cannabis or recovering from its effects;
- Experiencing a strong desire or urge to use cannabis;
- Failing to fulfill major obligations at work, home or school because of cannabis use;
- Giving up or reducing important social, occupational or recreational activities because of cannabis use;
- Continuing use despite recurring social, physical or psychological problems caused by cannabis;
- Using cannabis in physically hazardous situations;
- Increasing tolerance to cannabis' effects; and
- Developing withdrawal symptoms.

(American Psychiatric Association, 2013)

3.2.2 Factors affecting the study of addiction

Research into the addictive properties of cannabis is made challenging due to the many different ways the drug can be consumed, including being smoked, eaten or inhaled using

vaporizers. In addition, multiple strains of cannabis are being produced and used, with the concentration of THC in these rising steadily over the past 30 years (see Figure 4; Volkow, Baler, Compton, & Weiss, 2014). In the United States, the average potency of cannabis seized by law enforcement officials has climbed from 3.5% in 1985 to 13.2% in 2012 (Office of National Drug Control Policy, 2013).

In most epidemiological studies, the concentration of THC in cannabis is not known or assessed (Hall, 2015). This gap means that as the potency of cannabis continues to increase, some historical findings might no longer be relevant to predicting the effects of cannabis on contemporary users, including the risk for addiction.

3.3 Neurobiological and preclinical studies on the addictive potential of cannabis

When exploring the addictive potential of cannabis, the key is to determine if THC presents the typical features associated with other drugs of abuse. The subjective effects of drugs can be studied using various procedures, with animal models available to study the cardinal features of drug dependence (Le Foll & Goldberg, 2005). For example, withdrawal can be studied by exposing animals chronically to a substance of choice and subsequently removing this substance or administering an antagonist (i.e., a substance that prevents the drugs from having an effect) to precipitate withdrawal. Several reviews have covered the impact of cannabinoid drugs on these models (Justinova, Goldberg, Heishman, & Tanda, 2005; Oleson & Cheer, 2012; Panlilio, Justinova, & Goldberg, 2010).

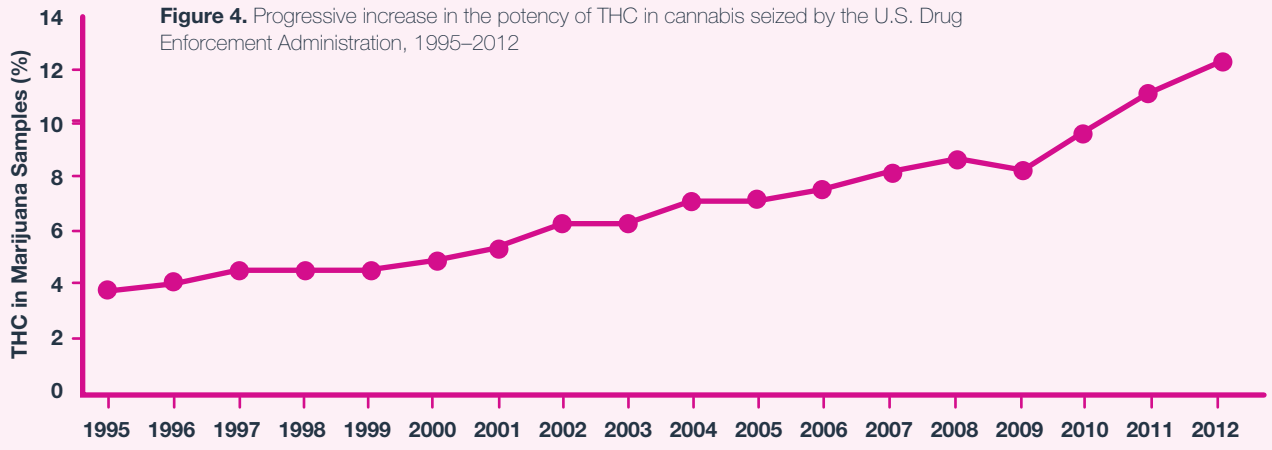

Figure 4. Progressive increase in the potency of THC in cannabis seized by the U.S. Drug Enforcement Administration, 1995–2012

Source: Volkow, Baler, Compton, & Weiss, 2014; reproduced with permission, Massachusetts Medical Society

Various factors can contribute to the prevalence of substance use and substance use disorders, including a substance's legal status and public perception regarding its effects on health and development. This variety of factors makes it important to study the addictive properties of substances in models that are not sensitive to those factors, such as preclinical models in the laboratory. Doing so makes it possible to attribute any addictive factors directly to the substance rather than to the context in which it is consumed.

In the drug discrimination paradigm, one behavioural response, such as pressing a lever, gets associated with the effects induced by a cannabinoid drug while a different behavioural response gets associated with the effects induced by a placebo. Findings from this procedure have established that animals can be trained to discriminate THC (Jarbe & Henriksson, 1974; Kubena & Barry, 1972) and that the subjective effects induced by THC are primarily mediated by the brain's CB_1 receptors (Jarbe, Gifford, & Makriyannis, 2010).

3.3.1 Intravenous drug self-administration paradigm

The "gold standard" paradigm in the field of addiction is the intravenous drug self-administration paradigm. In this procedure, an animal can choose to directly self-administer a drug such as THC by pressing a lever. There is good concordance between animals choosing to self-administer drugs and the addictive potential of those drugs in humans (Panlilio & Goldberg, 2007).

An important finding obtained using this paradigm was the demonstration of THC's ability to induce self-administration behaviour in squirrel monkeys (Tanda, Munzar, & Goldberg, 2000). Although the first demonstration was performed in psychostimulant-trained primates, subsequent work showed self-administration behaviour could also be obtained in drug-naïve primates (Justinova, Tanda, Redhi, & Goldberg, 2003). In addition, after the animals were trained, it was possible to extinguish their drug-seeking behaviour by removing access to the drug and the stimuli present during the initial training. Subsequent reintroduction of a small dose of THC or presentation of drug-associated cues reinstated the drug-seeking behaviour, demonstrating a classical model of relapse (Justinova et al., 2013).

In parallel, neurobiological studies have shown that THC can stimulate the activity of dopamine neurons and elevate dopamine levels in the brain's reward circuit, the nucleus accumbens (Chen et al., 1990; Diana, Melis, & Gessa, 1998). Dopamine increases in the nucleus accumbens are triggered by all drugs of abuse and thought to be a critical component of their addictive nature. Studies performed in animals have shown that THC can produce reward through stimulation of the ventral tegmental and nucleus accumbens (Zangen, Solinas, Ikemoto, Goldberg, & Wise, 2006).

Of note, some researchers have been successful at obtaining self-administrating behaviour in rodents using a synthetic CB_1/CB_2 agonist called WIN55,212-2 (Fadda et al., 2006; Lecca, Cacciapaglia, Valentini, & Di Chiara, 2006). However, a reliable model of intravenous THC self-administration in rodents has not yet been demonstrated. This gap might be due to the fact that THC is only a *partial* agonist of CB_1 and CB_2 receptors, which would explain its weaker reinforcing effects relative to WIN55,212-2 (Pertwee, 2008).

3.4 Clinical studies on the addictive potential of cannabis

One of the main features of all drugs of abuse is their ability to elevate dopamine in the reward circuit of the brain. The latest neuroimaging techniques have now made it possible to measure this elevation of dopamine in the human brain. Recent studies suggest the administration of THC might elevate dopamine in a similar fashion but with less potency than typical drugs of abuse such as psychostimulants (Volkow, Wang, Fowler, Tomasi, & Telang, 2011). While elevated dopamine levels typically cause users of cannabis to rate the experience as pleasant, a factor that may contribute to recreational use (Green, Kavanagh, & Young, 2003; Miller et al., 1977), cannabis use can also produce opposite effects such as dysphoria and anxiety (Johns, 2001).

3.4.1 Symptoms of cannabis dependence

Some researchers have explored the types of symptoms described by individuals who develop dependence to cannabis. Among a representative population of young adults (mean age 20.7 years) in an Australian longitudinal cohort study, 7% met the DSM-IV criteria for cannabis dependence (Coffey et al., 2002). Within this group of individuals who were cannabis-dependent:

- 91% experienced persistent desire for cannabis;
- 84% reported unintentional use of cannabis;
- 74% experienced symptoms of withdrawal;
- 74% reported spending excessive time obtaining and using cannabis;
- 63% reported continued use of cannabis despite experiencing health problems;
- 21% experienced tolerance; and
- 18% experienced negative social consequences as a result of their use.

Interestingly, the combination of withdrawal, persistent desire and unintentional use was reported by 57% of those individuals who were dependent on cannabis.

Research has also shown that the severity of symptoms associated with cannabis dependence increases among the treatment-seeking population. A recent clinical trial conducted by Mason and colleagues (2012), which involved treatment-

seeking outpatients between the ages of 18 and 65 years, found that those diagnosed with cannabis dependence reported the following symptoms:

- 98% reported the desire to quit using cannabis;
- 98% experienced withdrawal;
- 94% experienced tolerance;
- 92% reported increased use of cannabis;
- 84% reported continued use of cannabis despite experiencing health problems;
- 72% said that cannabis interfered in life tasks; and
- 62% reported spending excessive time obtaining and using cannabis.

3.4.2 Symptoms of cannabis withdrawal

It has been established that a withdrawal syndrome develops upon the cessation of exposure to cannabis (Budney & Hughes, 2006). The primary symptoms of withdrawal are behavioural and emotional, including irritability, sleeping difficulties, dysphoria, craving and anxiety; there are also symptoms associated with changes in appetite and weight loss (Budney, Hughes, Moore, & Vandrey, 2004).

Although withdrawal symptoms might contribute to the continuation of drug use to alleviate the discomfort associated with withdrawal, the relationship between withdrawal and drug-seeking behaviour remains unclear. In clinical trials, THC has been shown to be effective in decreasing the intensity of withdrawal symptoms that occur following cessation of cannabis exposure, but ineffective at helping subjects quit cannabis use altogether (Budney, Vandrey, Hughes, Moore, & Bahrenburg, 2007; Haney et al., 2004; 2008; Hart, Haney, Ward, Fischman, & Foltin, 2002).

3.5 Epidemiological studies on the addictive potential of cannabis

While providing precise estimates of the addictive potential of any given drug is complicated, the results from several epidemiological studies in the United States have allowed for the determination of some addictive potentials.

Using data collected in the early 1990s through the National Comorbidity Survey, Anthony and colleagues (1994) estimated that 4.2% of the representative sample of people aged 15–54 qualified for a lifetime diagnosis of cannabis dependence. In examining the transition from cannabis use to dependence, an estimated 46.3% of the sample had used cannabis at least once; of these users, 9.1% had developed cannabis dependence. The lifetime risk of developing dependence was found to be much higher among youth aged 15–24 (15.3%) and among males (12% compared to 5.5% for females). Notably, the lifetime risk of developing cannabis dependence among those who had ever used cannabis was found to be lower than that estimated for tobacco (32%), heroin (23%), cocaine (17%), alcohol (15%) and stimulants (11%).

Upon analyzing data from the 1991–1992 National Longitudinal Alcohol Epidemiological Survey (NLAES) and the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), both of which are large, nationally representative surveys of the U.S. population aged 18 and older, Compton and colleagues (2004) found that past-year cannabis abuse was more common than cannabis dependence. In the NLAES, the past-year prevalence of cannabis abuse was 0.9% and dependence was 0.3%. Similarly, in the NESARC, past-year cannabis abuse was reported by 1.1% and dependence by 0.4% of the sample. Whether individuals have ever been exposed to cannabis is an important consideration for such studies, as those who do not have previous experience with the drug are not at risk of subsequent development of addiction.

Consistent with findings reported by Anthony and colleagues (1994), similar estimates of cannabis dependence have been reported more recently by Lopez-Quintero and colleagues (2011) using data from the 2004–2005 NESARC. Specifically, they noted that 8.9% of cannabis users would become dependent according to DSM-IV criteria at some point in their life, with half of the cases of cannabis dependence being observed approximately five years after onset of use.

Similarly, data from the 1992 NLAES revealed that one-third of past-year cannabis users exhibited cannabis abuse or dependence. The prevalence estimates of past-year cannabis abuse and dependence among cannabis users were 23.1% and 6.3%, respectively (Grant & Pickering, 1998). Note that these estimates differ from those reported above by Compton and colleagues (2004) as this study reported prevalence estimates among past-year cannabis users, whereas Compton et al. based their estimates on the general population.

A recent analysis of NESARC data estimated that among subjects with lifetime exposure to cannabis, 7% of males and 5.3% of females would qualify for a diagnosis of cannabis dependence in their lifetime (Lev-Ran, Le Strat, Imtiaz, Rehm, & Le Foll, 2013). In addition, it was found that among those who had ever been exposed to cannabis, 47.4% of males and 32.5% of females would develop cannabis use disorder at some point in their life. These results clearly indicate that a very large percentage of cannabis users will engage in a risky pattern of use, with the majority abusing the substance at some point and only a small minority ultimately developing dependence. Overall, if we focus on the dependence criteria, it is currently estimated that around 5 to 9% of users will develop dependence (Lev-Ran, Le Strat, Imtiaz, Rehm, & Le Foll, 2013; Volkow, Baler, Compton, & Weiss, 2014).

3.6 Cannabis as a "gateway" drug

One of the risks previously associated with cannabis use was that it might predispose an individual to subsequent illicit drug use; that is, act as a "gateway drug" to other substances. Early studies on this hypothesis found high rates of cannabis use prior to the use of other illicit drugs among people who used cannabis in combination with other drugs (Fergusson & Horwood, 2000; Kandel, Yamaguchi, & Chen, 1992). Later studies suggested that regular or heavy cannabis use can lead to increased risk of using a variety of other illicit drugs (Fergusson, Boden, & Horwood, 2006; Secades-Villa, Garcia-Rodriguez, Jin, Wang, & Blanco, 2015). Multiple studies around the world also support the existence of developmental stages and sequences in drug use that were first proposed in the 1970s (Kandel, 1975).

Childhood and adolescent pathways to substance use disorders

While no one factor can predict later-life substance abuse, there are certain risk factors and behaviours that should trigger a closer look at how to build resiliency and put in place protective factors for youth.

Substance Abuse in Canada: Childhood and Adolescent Pathways to Substance Use Disorders (Leyton & Stewart, 2014) explains how childhood and adolescence are times when prevention efforts can have the most impact, particularly if they consider the child's stage of development.

The issue of cannabis being a gateway drug is much more complex, however, as multiple confounding factors suggest a person's drug use trajectory might not be linked to previous exposure to cannabis. Instead, subsequent drug choice might be due to the independent characteristics that led the individual to be at risk for using illicit drugs in the first place.

Recent laboratory studies have produced some interesting findings. Animal studies suggest nicotine is more effective than THC in producing a gateway effect (Levine et al., 2011; Solinas, Panlilio, & Goldberg, 2004). The evidence is more mixed with regard to pre-exposure to THC, which has been shown to decrease cocaine-seeking behaviour in rats (Panlilio, Solinas, Matthews, & Goldberg, 2007), have no effect on the reinforcing efficacy of heroin (Solinas et al., 2004) and, in some cases, increase nicotine self-administration (Panlilio, Zanettini, Barnes, Solinas, & Goldberg, 2013). Taken together, these findings do not support a strong impact of THC acting as a gateway drug. (It should be noted, however, that these studies were performed with the chemical component THC and not cannabis itself.)

The likelihood of initiating the use of tobacco or other licit drugs before using illicit drugs is much greater than the opposite process. One recent study found that first initiating tobacco was 17.6 times more likely than first initiating cannabis (Mayet, Legleye, Chau, & Falissard, 2011). There are also reports showing progression from "soft" to "hard" drugs in 75–80% of cases (depending on the study sample), while a hard-to-soft progression is seen in only 20–25% of cases (George & Moselhy, 2005; Tarter, Vanyukov, Kirisci, Reynolds, & Clark, 2006). Although we cannot exclude the presence of a gateway effect following cannabis exposure, there is evidence suggesting that such a phenomenon might be much more limited than the neurobiological impact of nicotine pre-exposure.

3.7 Factors affecting vulnerability to cannabis addiction

Multiple factors have been shown to modulate an individual's vulnerability to addiction to cannabis. Some are biological, such as the person's genetic background, while others are environmental.

Verweij and colleagues (2010) conducted a meta-analysis of studies examining the vulnerability of twins to cannabis use initiation and problematic cannabis use. With respect to cannabis use initiation, the proportion of total variance in the

Clinical Vignette

Chris

Chris is a 24-year-old male who has developed cannabis use disorder. In high school, Chris was bullied and had few close friends. His parents are divorced, with his father described as highly dogmatic and cold, and his mother being more accepting, as well as a regular cannabis smoker. He began smoking weed causally when he first entered university to help address his worries, cope with traumatic memories and regulate his negative emotions. He found it helped him relax after busy days and deal with his low mood, anxiety and interpersonal conflict.

Chris had a falling out with his father during university, which worsened his mood issues. His cannabis consumption increased after this major depressive episode, leading to procrastination and decreased motivation, financial difficulties, and limited professional and academic progress. Still, he was fully aware of the negative consequences of his cannabis use and was dismayed by the fact that he was using it more frequently. When he tried to stop, however, he worried excessively and had extreme difficulties sleeping. In addition, he found that he was using cannabis simply to maintain a "neutral state" — in other words, to keep from experiencing withdrawal rather than to provide a positive experience. Chris has since been diagnosed with cannabis use disorder and is now receiving treatment.

His major uses for cannabis informed the focus of his treatment: establishing good sleep hygiene; developing behavioural and cognitive coping strategies for negative mood, excessive worry and unpleasant memories; assertiveness training for dealing with interpersonal conflict and refusing cannabis; and exposure to creative pursuits with stimulus control (e.g., scheduled creative activities without the availability of weed). Through treatment, Chris acknowledged his dependence on cannabis. Today, he is committed to addressing the challenges he faces on regular basis.

study subjects accounted for by genetic factors was 48% in males and 40% in females. Shared environmental factors (something both twins were exposed to, such as time with parents) accounted for 25% of the variation in males and 39% in females, while unshared environmental factors (something unique to each twin, like separate social circles) accounted for 27% of the variation in males and 21% in females. For problematic cannabis use, the proportion of total variance accounted for by genetic factors was 51% in males and 59% in females, shared environmental factors accounted for 20% in males and 15% in females, and unshared environmental factors accounted for 29% in males and 26% in females. Thus, it can be concluded that approximately half of the vulnerability for both cannabis use initiation and problematic cannabis use is genetically driven.

It is unclear, however, how genetic factors modulate the vulnerability to cannabis addiction. It has been reported that a person's initial response at first exposure to cannabis is a strong determinant of subsequent development of addiction (Fergusson, Horwood, Lynskey, & Madden, 2003; Le Strat et al., 2009). As described in Chapter 2, there are studies suggesting that some genetic factors (such as COMT gene variants) might predispose those with them to the risk of developing psychosis following cannabis exposure (Caspi et al., 2005; Di Forti et al., 2012; van Winkel, 2011). Because it has been proposed that the brain's dopamine response might contribute to this cannabis–psychosis link, it is plausible that similar gene variants could influence the addictive potential of cannabis. For example, genes could increase the rewarding effects of cannabis, attenuate some of its aversive effects or create underlying medical issues such as mental illness that affect the addictive risk. However, such genes have not yet been identified and there could be multiple mechanisms that mediate such a biologically driven phenomenon.

3.7.1 Risk factors for the development of cannabis dependence

How individuals differ in their risk of developing cannabis dependence has been studied through large epidemiological studies performed in the general population. Using aggregated data from the 1991–1993 National Household Survey on Drug Abuse (NHSDA), Kandel and colleagues (1997) reported that the proportion of past-year users who are dependent according to DSM-IV criteria was higher for marijuana (8.2%) as compared to alcohol (5.2%). This study also reported that among adults, males were more at risk of developing cannabis dependence than females. For both genders combined, the highest rates of past-year cannabis dependence occurred between the ages of 18–25, with adolescent girls aged 12–17 found to be particularly vulnerable. The prevalence of dependence declined strongly with age, while ethnicity was found to have limited influence on the risk of dependence.

Using data from the 2000–2001 NHSDA, Chen and colleagues (2005) assessed the factors associated with the development of dependence among a group of recent onset cannabis users. The factors associated with excess risk of developing dependence included the onset of cannabis use before late adolescence, low socioeconomic status and the use of other drugs, including tobacco and alcohol, before using cannabis. Similarly, when examining the adolescent precursors of young adult cannabis dependence in a representative sample of secondary students in Victoria, Australia, Coffey and colleagues (2003) identified several independent risk factors, including being male, regular cannabis use, persistent anti-social behaviour and persistent cigarette smoking.

Fergusson and colleagues (2003) examined the linkages between early subjective responses to cannabis use and the later development of cannabis dependence using data from New Zealand's 21-year longitudinal Christchurch Health and Development Study (CHDS). Findings showed that positive responses to cannabis use prior to age 16 were associated with a much greater likelihood of developing cannabis dependence. Youth who reported experiencing five positive responses to cannabis were 28.5 times more likely to become dependent than those who did not experience any positive responses, an association that held even after controlling for potentially confounding factors such as the extent of cannabis use prior to age 16. Negative reactions to cannabis, meanwhile, were found to be unrelated to subsequent dependence.

Using data from France's Susceptibility Addiction Gene Environment (SAGE) study, Le Strat and colleagues (2009) found that the initial subjective positive effects of first cannabis exposure were associated, depending on dose, with the development of cannabis dependence at ages 18–21. Young adults who reported five positive effects from their first cannabis consumption were 28.7 times more likely to develop lifetime

cannabis dependence than those who reported no positive effects, with this association remaining significant even when controlling for individual and familial variables. Together, those two studies suggest that the biological factors that mediate this initially pleasurable response might be a strong contributor to addiction and dependence risk.

3.7.2 Cannabis dependence in high-risk users

Studies examining the predictors of cannabis dependence in the general population generally include a minority of heavy, high-risk users. These studies are generally limited to predicting the transition from non-dependent to dependent use, and subsequently fail to detect the risk factors in the high-risk population of cannabis users. In an attempt to define these risk factors, Swift and colleagues (2000) conducted a one-year longitudinal study of a sample of heavy, long-term cannabis users in Australia. They concluded that cannabis use and dependence are fairly stable among long-term users, finding that the quantity of cannabis used and the severity of the dependence symptoms at baseline were the primary predictors of those who would maintain dependence over time.

More recently, van der Pol and colleagues (2013) aimed to identify the predictors of the transition from non-dependent frequent cannabis use to DSM-IV cannabis dependence by following a sample of high-risk, frequent users aged 18–30 who were not yet dependent. Their findings revealed a number of independent predictors of cannabis dependence, including living alone, using cannabis as a coping mechanism, the number and type of recent negative life events (e.g., major financial problems), and the number and type of cannabis use disorder symptoms (e.g., impaired control over use).

3.8 Conclusions and implications

Despite the public perception that cannabis is not an addictive drug, evidence from both animal and clinical studies clearly indicates that cannabis use can lead to addiction. In fact, approximately 5 to 9% of cannabis users will develop dependence at some point in their life, and that number increases to about one in six (or 17%) among those who start using cannabis during adolescence.

Epidemiological studies have revealed that certain biological and environmental factors are strong contributors to the risk of developing cannabis dependence, including gender, risk-taking behaviours and socioeconomic status. Such factors are certainly less amenable to intervention than others; however, it will be important to use this information to help detect those who might be particularly vulnerable to becoming dependent. With the age of initiation being an especially critical factor, efforts to delay the onset of cannabis use will ultimately help reduce the risk of experiencing harms and subsequent addiction.

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4

What Interventions Are Available for Cannabis Use Disorders?

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Chapter at a Glance

- Treatment of adolescent cannabis use disorders is an active area of research.
- Comprehensive, school-based prevention programs have been shown to have some efficacy for reducing cannabis use; data on the delivery of preventative interventions in non-school settings are less available.
- Emerging evidence demonstrates that screening tools can be used in primary care and other settings to screen for substance use that warrants clinical intervention, including cannabis use.
- Cognitive behavioural therapy, motivational enhancement therapy, multidimensional family therapy and contingency management have all been shown to have some efficacy in reducing cannabis use.
- Medications have been evaluated targeting reduction of cannabis withdrawal symptoms, abstinence initiation and relapse prevention, and for the treatment of cannabis use and co-morbid psychiatric disorders. However, there are no approved medications for treating either withdrawal or dependence as of yet.
- Alternative delivery methods, including technology-based approaches, might be useful for expanding cannabis treatment accessibility and acceptance among adolescents.

4.1 Introduction

The multiple detrimental effects of early-initiation cannabis use, as described in the preceding chapters — impaired cognitive functioning, poorer educational outcomes, adverse mental health outcomes and an increased likelihood of developing dependence — underscore the importance of prevention, early detection and treatment interventions targeting youth.

Although the development of treatments specifically for cannabis use has lagged behind advancements for other substances of abuse, an evidence base is now emerging to guide the treatment of adolescents with cannabis use disorders. Current research is looking at interventions ranging from prevention programs to psychosocial and pharmacological treatments. There is also a significant interest in using alternative delivery methods such as mobile- and computer-based approaches to expand cannabis treatment accessibility and acceptance among teenagers.

Given the relative dearth of prevention and treatment interventions focusing on adolescent cannabis use disorder, this review will also incorporate and interpret evidence provided by research focused on adolescent substance use disorders, not necessarily specific to cannabis, and adult cannabis use disorder.

4.2 Prevention programs

If effective, interventions designed to prevent, delay or reduce cannabis use in youth can have a significant impact on individual outcomes and public health. School-based prevention programs have been widely implemented to target adolescent cannabis and other drug use. A recent meta-analysis of school-based prevention programs' effectiveness at reducing cannabis use (Porath-Waller, Beasley, & Beirness, 2010) found the most effective programs incorporated elements from multiple prevention models, had a longer duration, were facilitated by non-teachers and targeted high school students rather than middle school students. Overall, the reviewers found school-based programs had a 27.9% success rate at reducing adolescent cannabis use. A systematic review by Lemstra and colleagues (2010) evaluating long-term (i.e., one year or longer) school-based cannabis prevention programs found a mean reduction of seven days of cannabis use per month among adolescents participating in programs that combined drug education with the development of drug-refusal, self-management and social skills.

Data on the delivery of prevention interventions in non-school settings are less available. A Cochrane review conducted by Gates and colleagues (2006) was unable to draw firm conclusions on the benefits of non-school-based interventions

due to a dearth of studies available and the methodological differences between the studies. From the limited data, it has been suggested that motivational and family-based interventions might reduce self-reported cannabis use (Walton et al., 2014). In addition, a recent primary care trial comparing brief interventions delivered by therapist with those delivered by computer showed that computer-delivered intervention can prevent and reduce subsequent cannabis use in cannabis-naïve adolescents (Walton et al., 2014).

Prevention approaches studied to date have tended to focus on those with universal or inclusive reach rather than those targeting specific high-risk populations. In general, school and primary care settings are considered to be the optimal locations for the delivery of broad prevention strategies. Further work is needed to test targeted prevention strategies for high-risk youth.

4.3 Screening, brief intervention and referral to treatment

Screening for substance misuse should be part of routine healthcare practice for all adolescent patients. A number of self-report and clinician-administered screening tools have been evaluated for use with adolescents, most commonly in primary care settings (Mitchell, Gryczynski, O'Grady, & Schwartz, 2013). Some protocols have included brief intervention strategies and referral to more intensive treatments when indicated. Together these approaches are commonly referred to as screening, brief intervention and referral to treatment (SBIRT).

4.3.1 Screening tools

The CAGE questionnaire, which is often used as a screener for problematic substance use in adults, is not very effective when used with adolescents. Instead, tools such as the CRAFFT questionnaire and the Brief Screener for Tobacco, Alcohol and other Drugs (BSTAD) have been shown to be better suited to youth (Kelly, Gryczynski, Mitchell, O'Grady, & Schwartz, 2014; Knight, Sherritt, Harris, Gates, & Chang, 2002).

CAGE Questionnaire

Named after key word in four questions:

- Have you felt the need to **cut** down on your drinking or drug use?
- Have people **annoyed** you by criticizing your drinking or drug use?
- Have you ever felt bad or **guilty** about your drinking or drug use?
- Have you ever needed an **eye** opener the first thing in the morning to steady your nerves or get rid of a hangover?

CRAFFT assesses a number of potential indicators of substance-related risks and impairments by asking patients the following questions:

- **C:** Have you ever ridden in a **car** driven by someone, including yourself, who was "high" or had been using alcohol or drugs?
- **R:** Do you ever use alcohol or drugs to **relax**, feel better about yourself, or fit in?
- **A:** Do you ever use alcohol or drugs while you are by yourself, **alone**?
- **F:** Do you ever **forget** things you did while using alcohol or drugs?
- **F:** Do your family or **friends** ever tell you that you should cut down on your drinking or drug use?
- **T:** Have you ever gotten into **trouble** while you were using alcohol or drugs?

The advantages of CRAFFT include its ease of use as a mnemonic and its assessment of high-risk, substance-related factors. It leaves out tobacco use, however, and lacks an assessment of substance use quantity. BSTAD, on the other hand, does include tobacco use as well as a detailed assessment of the frequency of use of each substance, but does not include some aspects of substance-related risk. As well, it assesses both patient and peer or friend substance use, with additional questions regarding the quantity of substances used in the past year.

One possible method for combining the attributes of these screening tools is a staged screening process, beginning with brief questions about the use of any substances in the past year, followed by a more detailed assessment of the quantity and associated risks of each substance identified. This staged approach was found to be effective in a recent trial among adolescents presenting for routine outpatient care (Levy et al., 2014). A single screening question on past-year frequency of use for eight categories of commonly used substances was followed by a substance-associated risk assessment derived partly from the CRAFFT questionnaire. Delivered electronically, this approach was deemed valid in assessing clinically relevant risk categories of adolescent substance use.

4.3.2 Brief interventions

With recent advances in screening methods, significant attention has been given to the development of brief interventions that can address problematic substance use revealed during the screening process. The goal of this type of treatment is to provide practical, low-burden interventions with an understanding that the patient may not be highly motivated or invested in behaviour change (i.e., "non-treatment seeking" or "pre-contemplative").

Project CHAT

Project CHAT is a brief (15–20 minute) motivational interviewing intervention focused on assessing a patient's motivation to change, enhancing motivation for change and making plans for change.

Adolescent Cannabis Check-Up

The Adolescent Cannabis Check-Up is a two-session intervention consisting of an initial assessment interview and follow-up structured feedback and skills session provided in a motivational interviewing style.

High-risk adolescents assessed in a primary care setting who received a brief motivational intervention called Project CHAT demonstrated improvements in a number of cannabis-related measures when compared to a control group receiving usual care (D'Amico, Miles, Stern, & Meredith, 2008). Recent Australian and Dutch controlled trials have also supported a brief two-session motivational enhancement intervention known as the Adolescent Cannabis Check-Up (ACCU) for non-treatment-seeking adolescent heavy cannabis users (de Gee, Verdurmen, Bransen, de Jonge, & Schippers, 2014; Martin & Copeland, 2008). Mixed outcomes, though, were derived from two controlled trials of a single-session motivational enhancement intervention (McCambridge & Strang, 2004; McCambridge, Slym, & Strang, 2008). Finally, among adolescents presenting to pediatric emergency services who screened positive for recent cannabis use, those receiving a series of brief interventions demonstrated superior substance-related outcomes when compared to those who did not receive the interventions (Bernstein et al., 2009).

4.3.3 Referral to treatment

Referral to treatment is often indicated in cases with significant cannabis use frequency and associated impairments. An array of interventions might be necessary based on the severity and risks involved. As such, healthcare providers should be aware of their own limitations in capacity and expertise, as well as the appropriate threshold at which referral to treatment is preferred over brief intervention.

4.4 Behavioural and psychotherapeutic interventions

Treatment is warranted when an adolescent develops a pattern of problematic cannabis use (e.g., when it interferes with academic, occupational, family or social roles). The intensity and modality of the treatment will depend on the frequency and quantity of use, as well as the severity of role impairments.

Psychotherapeutic approaches have been the most extensively studied for the treatment of cannabis use disorders in adolescents. The majority of evidence involves the use of the following treatment strategies:

- **Cognitive behavioural therapy (CBT):** A form of psychotherapy based on the premise that cognition can influence emotions and behaviours. CBT interventions help individuals identify and correct inaccurate or negative thinking so they can respond to challenging situations more effectively.
- **Motivational enhancement therapy (MET):** A client-centred but directive therapeutic style intended to increase an individual's commitment to change and reduce resistance to treatment. Key components of MET include expressing empathy, developing discrepancies, avoiding argumentation and supporting self-efficacy.

- **Multidimensional family therapy (MDFT):** A multisystem approach targeting the adolescent's intrapersonal and interpersonal functioning, the parent's intrapersonal and interpersonal functioning, parent–adolescent interactional functioning, and family members' interactions with sources of influence outside the family (e.g., schools, justice system).
- **Contingency management (CM):** A behavioural treatment that provides rewards or reinforcers upon demonstration of a desired behaviour (e.g., vouchers provided contingent upon confirmation of a "clean" urine drug screen).

4.4.1 Cannabis Youth Treatment Study

The largest psychotherapy trial to date is the Cannabis Youth Treatment Study (Dennis et al., 2004), which included 600 adolescent cannabis users randomized to five treatment interventions:

- Five sessions that included two MET sessions and three CBT sessions;
- Twelve sessions that included two MET sessions and 10 CBT sessions;
- The family support network approach, a multi-component treatment that includes parent education groups, therapeutic home visits and case management in addition to 12 sessions of MET and CBT;
- The adolescent community reinforcement approach, which consists of 10 individual sessions and four sessions with caregivers to educate them on how to support the adolescent's abstinence; or
- Twelve to 15 MDFT sessions.

The treatments ranged in duration from six to 14 weeks, with the outcomes repeatedly assessed over a one-year follow-up period. No one treatment approach was found to be superior in terms of days of abstinence or dependence problems, with all interventions demonstrating significant improvements in abstinence and the percentage of adolescents in recovery. Overall, the percentage of no cannabis use in the past month increased from 4% at baseline to 34% at end of treatment. Similarly, days of use were reduced by 36% from baseline to end of treatment.

4.4.2 Teen Marijuana Check-Up

Brief MET interventions have been further evaluated in adolescents with cannabis use disorders. For example, the Teen Marijuana Check-Up (TMCU) is a brief MET intervention intended to elicit voluntary self-assessment of cannabis use (Swan et al., 2008). An initial clinical trial assessed outcomes in adolescents randomized to either the TMCU intervention or an assessment control condition. Significantly reduced cannabis use was observed in both groups at a three-month follow-up; however, no between-group differences were observed (Walker et al., 2006). In a recent follow-up trial with 310 adolescent cannabis users, the TMCU was compared to one group who received drug education and another whose treatment was delayed (Walker et al., 2011). Both treatment groups demonstrated a greater reduction in use and negative consequences than those in the delayed treatment control. The TMCU group had greater reduction in use but not negative consequences compared to the educational feedback control group.

4.4.3 Multidimensional family therapy

To evaluate the potential of outpatient, family-based approaches in treating cannabis use disorders, Liddle and colleagues (2008) compared MDFT to a CBT intervention in drug-using adolescents with predominant cannabis use. Both the MDFT and CBT treatments resulted in significant decreases in cannabis use, with some indication that MDFT produced more sustained treatment effects. Another recent randomized trial conducted in the Netherlands also compared MDFT to CBT in adolescent cannabis users. Similar to the Cannabis Youth Treatment Study, the researchers found that while both groups demonstrated a reduction in use, neither treatment method was superior (Hendriks, van der Schee, & Blanken, 2011).

4.4.4 Contingency management

In the treatment of substance use disorders, CM works by providing a potent reinforcer contingent on participants meeting specified success criteria; for example, abstinence from drug use as measured by a "clean" urine drug screen (Higgins et al., 1991). The key features of CM include frequent opportunities to earn access to reinforcement (i.e., multiple urine drug screens); immediate access to opportunities to earn reinforcements (e.g., money, vouchers) following the occurrence of the target

behaviour; access to reinforcers of "perceived" appreciable value (even if their actual value is not high); constant or escalating schedule of reinforcement (i.e., successive occurrences of the target behaviour yields more opportunities for reinforcement); and resetting of the reinforcement schedule for failing to meet a minimum response criterion.

Carroll and colleagues (2006) compared the use of MET/CBT with CM, MET/CBT without CM, individual drug counselling with CM and individual drug counselling without CM in cannabis-dependent young adults referred by the criminal justice system. A significant effect of CM on treatment retention and cannabis-free urine specimens was observed, with the combination of MET/CBT and CM shown to be more effective than the other three interventions. In a subsequent study by Stanger and colleagues (2009), 69 adolescent cannabis abusers were randomized to receive either individualized MET/CBT plus CM or individualized MET/CBT without CM. While the group receiving CM had greater mean weeks of continuous abstinence when compared to the control group, there were no substantive differences between the two treatment groups.

Taken together, these findings suggest that psychotherapeutic approaches have some efficacy in reducing cannabis use. However, the effects are often modest and might not be sustained over the long-term. Contingency management is one strategy that may augment treatment response.

4.5 Pharmacological interventions

Optimizing patient outcomes will ultimately require the development of new treatment approaches for cannabis use disorders. One potential avenue worth exploring is the role of pharmacological interventions, either targeting withdrawal symptoms in early cannabis abstinence or as complements to psychosocial treatments in abstinence initiation or relapse prevention (Hart, 2005; Vandrey & Haney, 2009). Medications might also play a role in the treatment of individuals with co-morbid cannabis dependence and other psychiatric disorders.

4.5.1 Treatment of cannabis withdrawal

As discussed in Chapter 3, a valid and reliable cannabis withdrawal syndrome has been documented in both controlled laboratory and clinical evaluations (Budney & Hughes, 2006), with the common symptoms associated with withdrawal, including irritability, anxiety, restlessness, appetite changes and sleep disturbances. A number of studies have been conducted evaluating the potential use of medications to treat cannabis withdrawal on the presumption that withdrawal symptoms could contribute to difficulty achieving or maintaining abstinence. Classes of medication that have been studied include antidepressants (Haney et al., 2001; Haney, Hart, Ward, & Foltin, 2003; Penetar, Looby, Ryan, Maywalt, & Lukas, 2012), cannabinoid agonists (Budney, Vandrey, Hughes, Moore, & Bahrenburg, 2007; Haney et al., 2004; 2008), mood stabilizers (Haney et al., 2004; Johnston et al., 2014), antipsychotics (Cooper et al., 2013), sedative hypnotics (Vandrey, Smith, McCann, Budney, & Curran, 2011) and adrenergic agonists (Haney et al., 2008).

From these studies, it was found that the majority of medications either did not improve or, in some cases, worsened cannabis withdrawal symptoms. However, promising findings have been reported with the cannabinoid agonist dronabinol (Budney et al., 2007; Haney et al., 2004; 2008), the sedative hypnotic zolpidem (Vandrey et al., 2011), and the combination of dronabinol and the adrenergic agonist lofexidine (Haney et al., 2008). It should be noted, however, that these positive findings have not yet been translated into improved clinical outcomes. Further, although participants in these trials were largely young adults, adolescents were not the target population.

4.5.2 Treatment of cannabis use disorders

As with other dependencies, pharmacotherapy clinical trials for cannabis use disorders generally incorporate other treatment modalities such as CBT, MET and CM. The inclusion of a behavioural platform has several advantages, including alleviating ethical concerns of providing a placebo or non-proven pharmacotherapy intervention, as all patients receive some form of psychosocial counselling (Carroll, Kosten, & Rounsaville, 2004). Medications evaluated for cannabis disorder treatment have included antidepressants (Carpenter, McDowell, Brooks, Cheng, & Levin, 2009; Weinstein et al., 2014), mood stabilizers (Levin et al., 2004) and agonist therapy (Levin et al., 2011), as well as agents targeting other specific neurotransmitters thought to be involved in cannabis addiction (Gray et al., 2012; Mason et al., 2012; McRae-Clark et al., 2009).

Clinical Vignette
Sam

Sam began smoking cannabis at age 13 after being introduced to it by older friends. He liked the feeling it gave him and how it helped him socially, so he gradually increased his use. At age 16, Sam was suspended from school after being caught with cannabis. His mother convinced the administrators not to contact the police, assuring them she would have Sam medically evaluated by their family pediatrician.

The pediatrician interviewed Sam and his mother separately. During her interview, Sam's mother said she was disappointed in Sam, but remarked that cannabis "isn't a big deal these days." She emphasized that she and Sam have a very open relationship, and she would know if there were any significant problems. She asked if the doctor could sign a form for the school to confirm that Sam was seen and treated.

During his interview, Sam appeared irritated and was slow to engage, but eventually began to describe his cannabis use and note that "pretty much everybody smokes weed, especially the kids I want to hang out with." The pediatrician recommended that Sam receive counselling for his substance use.

Sam and his mother visited the pediatrician again the following semester, this time to request an evaluation for ADHD due to concerns about Sam's declining grades and inability to focus during class. Sam admitted that he never followed through with the counselling and continued to smoke cannabis, usually in the morning before arriving at school. He also mentioned that he was smoking alone more often, as opposed to only in social settings. Sam admits that his grades have slipped, but insists he is "getting by." He reports feeling that school "isn't really my thing anyway."

Drawing on the principles of motivational enhancement therapy, the pediatrician talked to Sam about balancing the risks and benefits of cannabis use. Although he was initially reluctant, Sam agreed to work on reducing his cannabis use. Together, Sam, his mother and the pediatrician developed a treatment plan that included monitoring, engagement in structured social activities and family-delivered rewards for desired behaviours (e.g., access to the family car with a clean urine test). Sam returned for weekly visits, where the pediatrician provided intervention based on the principles of cognitive behavioural therapy (e.g., drug-refusal skills). As a result, Sam gradually reduced and eventually stopped using cannabis completely. The pediatrician now assists Sam with the skills needed to prevent relapse.

Similar to the investigations into medications for cannabis withdrawal treatment, the majority of these trials did not target adolescent cannabis users and have not yielded positive findings. While there is speculation about potential treatment roles for novel agonist compounds (including nabilone, an oral formulation of tetrahydrocannabinol; and nabiximols, an oromucosal mouth formulation of tetrahydrocannabinol and cannabidiol), no clinical trials of these medications have been conducted for cannabis use disorder in any age group.

To date, the most promising medication for the treatment of cannabis use disorders is N-acetylcysteine (NAC), a prodrug (inactive substance that is converted to a drug within the body by the action of enzymes or other chemicals) of the naturally occurring amino acid cysteine. NAC administration has been shown to increase the release of glutamate via stimulation of the cystine-glutamate exchanger, which becomes dysregulated after chronic drug use. By normalizing this exchange process, NAC has been shown to reduce the reinstatement of drug-seeking behaviour in animal models across multiple substances. An open-label trial of NAC in cannabis users aged 18–21 demonstrated reductions in self-reported cannabis use and cannabis craving (Gray, Watson, Carpenter, & Larowe, 2010). A follow-up, placebo-controlled study showed that NAC, when paired with brief counselling and CM to promote abstinence, doubled the odds of cannabis-dependent adolescents providing clean urine cannabinoid tests during treatment (Gray et al., 2012).

4.5.3 Treatment of co-morbid cannabis use and psychiatric disorders

As reviewed in Chapter 2, there are established links between cannabis use and the poor prognosis of mental illness. However, improved substance abuse outcomes have been reported in adults receiving pharmacological treatment of co-occurring psychiatric disorders (Brady, Sonne, Anton, & Ballenger, 1995; Kranzler et al., 1994; Nunes et al., 1998). Looking specifically at cannabis use, data from the U.S. National Comorbidity Survey found that 90% of cannabis-dependent individuals had a lifetime psychiatric disorder. Given that only 55% of individuals who were non-dependent experienced some form of mental illness, these findings indicate that psychiatric co-morbidity commonly occurs among individuals using cannabis (Agosti, Nunes, & Levin, 2002). Unfortunately, a limited number of studies have evaluated the potential of the pharmacological treatment of cannabis use disorders in adolescents with other psychiatric diagnoses.

While one study showed that the antidepressant fluoxetine significantly reduces cannabis use in adults who are depressed and dependent on alcohol (Cornelius et al., 1999), more recent trials in adolescents and young adults with co-morbid major depression and cannabis use disorders did not find a significant effect of fluoxetine on cannabis-related outcomes (Cornelius et al., 2010; Findling et al., 2009; Riggs et al., 2007). This lack of effect might have been attributable to the strong psychosocial platforms used.

A placebo-controlled, randomized trial that combined CBT with the administration of atomoxetine for attention deficit hyperactivity disorder (ADHD) in adolescents with substance use disorders also did not find any group differences in ADHD or substance use outcomes (Thurstone, Riggs, Salomonsen-Sautel, & Mikulich-Gilbertson, 2010). A similarly designed but larger trial of osmotic release methylphenidate also did not yield between-group differences in primary ADHD or substance use outcomes, though the osmotic release methylphenidate group had more clean urine drug tests and improved parent-reported ADHD symptoms compared to the placebo group (Riggs et al., 2011). Trials of pemoline (Riggs, Hall, Mikulich-Gilbertson, Lohman, & Kayser, 2004) and the methylphenidate spherical drug-absorption system (Szobot et al., 2008) found that active medication produced superior ADHD outcomes than the placebo but no between-group differences in substance use outcomes.

4.6 Emerging approaches to treatment

While promising advances have been made in the treatment evidence base, a number of novel approaches are also being explored for further development. One such approach is the incorporation of mobile communications technology, which offers potential benefits in both accessibility and acceptability while also potentially providing "in-the-moment" interventions in high-risk situations for cannabis use (Shrier, Rhoads, Fredette, & Burke, 2013). Internet and computer-based interventions have also shown some promise (Tait, Spijkerman, & Riper,

2013) — and translating these kinds of interventions to mobile communications devices could yield further improvements in real-world outcomes.

Another direction being looked at is the combination of multiple potentially synergistic treatment modalities (e.g., pharmacotherapy combined with psychosocial treatment) to enhance and optimize treatment outcomes (Carroll et al., 2004; 2012). However, little work has been done in this regard with adolescent cannabis users and the findings to date in adults have been mixed.

4.7 Conclusions and implications

Cannabis use disorders are prevalent in adolescents and clinicians should use evidence-based interventions in their treatment. To date, the strongest evidence supports the use of psychosocial interventions such as cognitive behavioural, motivational enhancement and contingency management therapies. Data on the benefits of pharmacological treatments are less available. Prevention efforts to prevent, delay or reduce cannabis use among adolescents are also critical. Future research will explore alternative delivery methods for interventions, such as mobile- and computer-based approaches, which might be useful for expanding cannabis treatment accessibility and acceptance among adolescents.

While work is needed to further develop and refine prevention and treatment approaches, a number of currently available effective interventions may be used to reduce the considerable clinical and public health burden of cannabis-associated adverse outcomes in youth. Clinicians are strongly urged to use evidence-based approaches to address adolescent cannabis use.

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5

Cannabis and Youth — A Summary of Key Findings and Major Questions, and a Call to Action

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Chapter at a Glance

- The high rate of cannabis use by Canadian youth cannot be explained by biological differences between them and the youth of other countries. It is essential to study how their high level of use is influenced by the prevalent values, attitudes and expectations of Canadian society as a whole about cannabis and other drugs.
- In Canada, as in most western societies, the 15- to 24-year-old segment of the population has much higher use of cannabis than those aged 25 and over. At the same time, youth have relatively high levels of alcohol use, but much lower use of tobacco. There is a need to study motivational factors that are specific for cannabis and for youth, and the effect of individual differences in those factors.
- Canadian youth lack knowledge and have misconceptions about the effects of cannabis that contribute to favourable attitudes towards its use.
- School-based preventive education programs vary in content and efficacy. The best programs not only provide sound factual knowledge, but also attempt to change attitudes and expectations about cannabis use and its consequences. There is room for improvement of results for even the best programs.
- Peer group influences on youth views and behaviour about cannabis might be more potent than family and school influences.
- Adolescents are more sensitive than adults to the adverse effects of regular heavy use of cannabis, including cognitive impairment, dependence, poor psychosocial development, impaired school and work performance, drug-related psychiatric illness, and generally poorer treatment outcomes.
- There is a need for research on improved pharmacological and psychosocial treatment methods, and follow-up studies of their long-term efficacy.

5.1 Introduction

This report deals with the effects of cannabis on the health, psychological and social functioning, and maturation of young users. It does not deal with medical uses of cannabis or with debates about the legal status of non-medical use. The many, varied reasons for producing a report on cannabis and Canadian youth have been set out in the preceding chapters. The main reasons can be summarized:

- The 15–25 year age group has the highest rate of commencing use of cannabis in the Canadian population, and Canadian youth have the highest percentage of users in the developed world;
- Youth have the highest vulnerability to more serious adverse effects of cannabis use;
- Among heavy regular users, youth have generally poorer treatment outcomes than adults;
- Among those starting regular use at the youngest ages, some of the adverse effects may be irreversible;
- These effects can seriously limit the educational, occupational and social development of the affected individuals; and
- Youth have widespread misinformation and misperceptions about cannabis use that contribute to their motives for use and their vulnerability to adverse effects.

Given our present knowledge of these problems, it is important to reduce the harm to youth by decreasing the numbers of users and delaying the start of use to a later age. The report therefore emphasizes the need to develop and implement effective programs of preventive education, and to improve our understanding of why youth use cannabis, their patterns of use and the efficacy of different therapeutic interventions. These needs suggest a range of research questions that it is possible and desirable to explore. However, given the limited resources available for research on the spectrum of health problems, it is necessary to focus efforts on solving a more limited range of the most serious problems in order to reduce cannabis-related harms. The following discussion attempts to identify the most pressing research questions. It may stimulate others to draw up their own priority lists, and that in turn may stimulate a valuable range of other research activities and practical interventions.

In addition, this chapter proposes a number of measures that can be taken now — on the basis of existing knowledge — to mitigate the risks posed to youth by cannabis, and to inform policy and practice so as to eliminate some of the harms resulting from society's past attitudes and responses to cannabis.

5.2 Increased understanding of cannabis use among Canadian youth

That Canadian youth have the highest prevalence of cannabis use among the 28 countries compared in the UNICEF report (2013) indicates that the reasons for use are not restricted to youth per se. There is no evidence that Canadian youth differ biologically from youth in other countries in ways that would predispose them to greater use of cannabis. Past year use by 15-year-olds in Canada was 28%, compared to less than 10% in Germany, Finland, Norway and Sweden. Somewhat surprisingly, a survey of youth in a working-class district of Santiago, Chile, found considerably lower rates of cannabis use than among Canadian youth (Delva et al,. 2014), despite the higher prevalence of low socioeconomic status, family problems and other factors generally considered to be risk factors for use (von Sydow, Lieb, Pfister, Höfler, & Wittchen, 2002; Lemstra et al., 2008, 2009). In the Chilean sample, at age 14 only 3.7% had used once or twice in the past year, and 0.4% had used 40 times or more; at age 16 the corresponding figures were 8.1% and 1.9%.

These figures suggest strongly that the values, traditions and social attitudes of a given population, including views about alcohol and other substances, affect the behaviour of youth in that population just as they do for older age groups. To understand the high use of cannabis by Canadian youth, **it is important to compare the prevalent values, attitudes and expectations of Canadian society with those of a range of other countries in relation to drug use in general and cannabis in particular**. Such information could be important in indicating where efforts should be directed to decrease use by Canadian youth.

Nevertheless, within most western societies with a relatively high standard of living, cannabis use is more common among adolescents and young adults than among older age groups (Table 2). It is necessary to identify what factors give rise to this difference. The Introduction to this report examines this question in detail, but some of the motives discussed there are not specific either to youth or to cannabis. For example, use for coping with emotional and other problems, conformity with the actual or perceived norms of one's peers, and relief of boredom have also been recognized as motivating factors for the use of alcohol, tobacco and other drugs by adults as well as youth (e.g., Enman, Zhang, & Unterwald, 2014; Rothe, 2005; Schry & White, 2013; Yeh, Chen, & Sim, 1995). **We need to look for reasons that are more selective for youth and for cannabis, as well as determine how those reasons evolve during the course of growing involvement of young people with cannabis. There is a need for longitudinal studies of changing patterns of attitudes, expectations, motivations and values, as young adolescents become regular users**.

Table 2. Recent data on past-year cannabis use by Canadians in different age groups

CADUMS 2012		CTADS 2013		
Age group	% users	Age group	% users	Age at start
15–24	20	15–19	22	15.1
25+	8	20–24	26	16.6
		25+	8	18.3

(Health Canada, 2013, Statistics Canada, 2015)

As pointed out in the Introduction, adolescence is a time of increasing independence from family, development of closer social links with peers, and exploration of new social identities. It is also a time of questioning and challenging the authority of elders and other authority figures, of high enthusiasm combined with limited experience and knowledge, and of relative freedom from the responsibilities of adulthood. This combination of characteristics was clearly demonstrated in the 1960s and '70s in the adoption of cannabis as the drug of youth, as opposed to alcohol, the drug of the older generations, and the deliberate defiance of police and other authorities by openly smoking cannabis in large groups in public places.

The distinction between the drug preferences of youth and adults is no longer as sharp as in the 1970s, and combined use of both cannabis and alcohol is reflected in the growing frequency of motor vehicle accidents involving young drivers under the influence of both substances (Beasley, Beirness, & Porath-Waller, 2011; Terry-McElrath, O'Malley, & Johnston, 2014). However, the distinction is still evident in some ways in the large decrease of tobacco smoking by youth, who nevertheless find no inconsistency in smoking cannabis. **A second important area of research is more detailed analysis of motivations for cannabis use that are specific to youth**. The findings of such research could be

helpful in designing preventive programs aimed at decreasing the recruitment of young people to cannabis use. Preventive measures should be directed toward the specific causal factors operating in youth.

A closely related research challenge arises from the fact that individual users differ from one another as to which motivational factors predominate in their initiation of use. It would be useful **to see if there is a correlation between different principal causal factors and different outcomes**; that is, to determine whether different causes predict early cessation of use, continuation of occasional light and harmless use, or heavy, prolonged use leading to major adverse effects. If such a correlation is found, it would have important prognostic significance that could lead to selective direction of therapeutic intervention to those who require it most.

In addition to these longer-term research projects, **the early detection of potentially harmful use of cannabis could be improved by working with Canadian associations of healthcare professionals to encourage physicians to administer screening and early detection questionnaires to all adolescents and young adults (ages 15–25 years) who come for non-emergency treatment or routine examination**.

The medical uses of marijuana and the regulatory systems created for managing such use are not within the scope of the present report. However, one aspect of those systems that is germane to the subject of cannabis and youth is the role of "medical marijuana" as a source of the material used by youth for non-medical purposes. The illicit market is generally assumed to be the source of the cannabis for Canadian youth. However, studies in the United States have shown a significant amount of diversion of marijuana from state medical marijuana programs to non-medical use by adolescents (Thurstone, Lieberman, & Schmiege, 2011). There is no reliable information about such diversion in Canada, but there have been instances of preparations made by licensed producers under the *Marihuana for Medical Purposes Regulations* (MMPR) that were packaged and promoted in ways that would appeal to youth. **Three practical steps should be taken immediately to prevent or reduce diversion from this source:**

1. Enforce the regulations that forbid packaging marijuana for medical purposes in any way other than the plain wrappers intended by the MMPR.
2. Inform physicians that marijuana should not be prescribed for children or adolescents, other than with the possible exception of low-delta-9-tetrahydrocannabinol (THC), high-cannabidiol (CBD) preparations that are currently being investigated for treatment of certain forms of childhood epilepsy, and possibly for treatment of inflammatory illnesses.
3. Alter the MMPR by setting maximum permissible THC concentrations and minimum CBD:THC ratios that are in accord with the best available knowledge concerning therapeutic efficacy.

5.3 Comprehensive preventive education efforts

Much research has been devoted to evaluating preventive education programs differing in objectives, complexity, duration and educational methodology. It has been claimed that preventive education programs have a benefit-cost ratio of 18:1, meaning that an expenditure of $1 in delivering the program produces a savings of $18 in health and social costs of drug use (Kim, Coletti, Crutchfield, Williams, & Hepler, 1995; Miller & Hendrie, 2008). However, cost-benefit analyses suffer from the inherent theoretical weakness of having to assign a monetary value to every cost and every benefit, even when these are of a subjective nature not normally conceived and expressed in monetary terms. In addition, most of these analyses have grouped all drug use together, so that the large reduction in tobacco smoking would tend to outweigh the contribution of cannabis use to the cost-benefit assessment. It is therefore more meaningful to assess the ability of programs to delay or reduce the onset of use of each drug separately.

The two major approaches in preventive programs have been (1) to increase accurate factual knowledge about cannabis and its effects among adolescents in particular, and (2) to change their beliefs and expectations about cannabis, and their attitudes toward its use. These approaches are discussed by both Henderson (Introduction) and McRae-Clark and Gray (Chapter 4). Both aspects are of practical importance. The Monitoring the Future project in the United States (Keyes et al., 2011) has found that marijuana use by high school students is inversely related to attitudes (approval vs. disapproval) towards use and to beliefs about its effects (harmfulness vs. harmlessness and pleasure). Such attitudes are determined strongly by birth cohort effects rather than by individual attitudes. The authors

interpret this finding as evidence that adolescents are more strongly influenced by their peers' views than by those of family or other influence groups.

Porath-Waller and colleagues (2013) have documented a series of erroneous beliefs held by Canadian adolescents about the actions and effects of cannabis, and have noted that youth with poor communication with their families are more likely to use cannabis. The latter point appears to agree with the suggestion by Keyes et al. **It is therefore important to learn how to change the beliefs and attitudes of significant numbers of adolescents, who can then influence their peers in a self-propelling change of drug use among the whole same-age cohort**.

A large proportion of programs designed for this purpose have been school-based. Porath-Waller and colleagues (2010) conducted a meta-analysis of high-quality studies to determine which features of school programs are associated with superior outcomes in their ability to prevent or deter initiation of cannabis use. The findings are reviewed in detail in Chapter 4, and only two points will be commented on here. The first is that school programs with elements drawn from multiple models, and longer and more intensive programs, had a greater success than single-model and shorter programs, in terms of lower numbers of students who had initiated cannabis use by the time of the follow-up. The most effective programs were 28% more effective than control conditions of the ordinary curriculum with no cannabis program.

This result appears similar to the reported results of a computer-based brief intervention (CBI) administered to 12- to 18-year-old American youth who had not yet begun to use cannabis. The intervention was given during visits to urban primary medical care clinics, and the results were followed up at three, six and 12 months (Walton et al., 2014). At the one-year recall, 16.8% of those who received the CBI reported any use of cannabis during the year, compared to 20.9% of those who received the same intervention from treatment personnel (TBI), and 24.2% of the control group (no intervention). The CBI reduced the initiation of use by about 30% relative to the controls, while the TBI reduced it by 13%.

A somewhat similar study by Harris and colleagues (2012) used a computer-based screening program followed by brief advice from a therapist. The study compared the changes in alcohol use and cannabis use in groups of American and Czech adolescents (mean age about 15 years, range 12–18) with and without this program. At the one-year follow-up, in the American sample alcohol was used by 29.3% of the test group vs. 37.5% in the controls, which represents a 22% reduction of users in the test group relative to the control group. In the Czech group the corresponding reduction in cannabis use was 41% (17% of users in the test group vs. 28.5% in the control group).

If these results are generalizable, it appears that quite different prevention approaches — the long, intensive, multi-component school program on the one hand, and the CBI on the other — produce comparable results. Two possible explanations come to mind. One is that the same individuals would benefit from either type of program because they are either undecided or disinclined to use cannabis, and any type of prevention program gives them enough support and encouragement to enable them to refrain from using cannabis. The other possible explanation is that different groups of adolescents, of roughly equal numbers, benefit from the different types of program. Another useful research objective, therefore, is **to study responders and non-responders to each type of program to determine what characteristics in the user predict success with a given type of preventive education program**. If there are different responsive groups for the different programs, the total preventive result could be considerably improved by differentially directing adolescents to the appropriate programs. On the other hand, if the same students benefit from either type of program, it might be sufficient to replace the long school program with computer-based screening and brief intervention carried out in schools rather than in primary care medical centres. The CBI program probably represents a considerable saving of personnel time and resources relative to the long, intensive, multi-component programs. Either exclusive use of the CBI in the one case or correctly assigning students to their individually appropriate type in the other case would mean a more efficient and economical use of resources, as well as an improved total result.

The second point arising from the Porath-Waller et al. review (2010) is that better results in school-based programs were obtained when outsiders rather than teachers directed the sessions. This finding is troublesome because it appears to suggest that such programs impose demands on the teachers that they are potentially not qualified to meet. The review suggests various possible explanations, but the question has evidently not been explored systematically. **Qualitative research involving students and teachers would be a useful way to begin identifying the potential factors underlying this relationship**.

In addition to the proposed longer-term research, **two immediate measures based on present knowledge could improve the efficacy of school-based preventive education programs:**

1. A conference of health and education experts from federal and provincial government agencies could be convened to standardize school-based education programs by selecting two of the best programs—a long multi-component program and a brief computer-based program—assign schools to one or the other in all parts of the country, and provide standard training sessions for those who are to deliver the programs. In addition to improving the programs as now taught, this measure would make it possible to begin gathering data to evaluate studies included in the research agenda set out above.
2. Set up a register of experts from agencies outside the school system who would administer the standardized programs in the designated schools to take advantage of the greater credence afforded them by students.

5.4 More research and better data on adverse effects to inform policy, practice and programs

Most knowledge of adverse effects of cannabis was gathered in earlier years when even the most potent preparations of cannabis had THC contents of less than 10%, whereas contents of 15–25% or more are now encountered, and extracts and oils with contents of 50% and more are increasingly being used. Since adverse effects are largely dose-related, **it is important to re-examine frequencies, patterns and severity of adverse effects, such as those discussed below, at present levels of cannabis potency**.

5.4.1 Driving accidents

Henderson (Introduction) points out that adverse acute effects of cannabis in youth are not numerically a major concern with the exception of impaired driving skills and resulting increase in the numbers of cannabis-impaired young drivers involved in motor vehicle accidents, injuries and fatalities. This topic is already the subject of a considerable amount of research effort (e.g., Beasley et al., 2011; Boak, Hamilton, Adlaf, & Mann, 2013; Terry-McElrath et al., 2014), which will undoubtedly continue as further data accumulate after the legalization of cannabis in various states and countries (e.g., Salomonsen-Sautel, Min, Sakai, Thurstone, & Hopfer, 2014). The evidence is reviewed in detail by Smith in Chapter 1.

However, one of the reasons for the increase in frequency of adolescents and young adults driving under the influence of cannabis is the knowledge that there is at present no roadside test for identifying the presence of cannabis in the driver that is comparable to the breath tests for alcohol. **Two practical steps towards correcting this situation could be taken immediately**:

1. Convene a meeting of federal and provincial government experts in highway safety to explore starting a large-scale program to evaluate roadside oral fluid collection from impaired, erratic and speeding drivers suspected of being under the influence of cannabis and rapid, laboratory-based quantitative analysis of the samples for cannabinoids.
2. Make the commencement of this program widely known to youth by announcing it in all schools. Depending on the quality and usefulness of the results of the evaluation phase, this collection and analysis could be incorporated into the highway traffic code.

5.4.2 Long-lasting cognitive impairment

The special vulnerability of adolescents to adverse effects of chronic cannabis use on cognitive functions has been reported by many investigators (Jager & Ramsey, 2008), together with its resulting impairment of educational achievement (Horwood et al., 2010; Homel, Thompson, & Leadbeater, 2014; Silins et al., 2014) and career options. Attention to this vulnerability has been greatly heightened by the report of long-lasting and possibly permanent reductions of cognitive functioning, as reflected in reduction of IQ (Meier et al., 2012). Adolescents

who began using cannabis at an early age and continued using it regularly experienced an impairment of brain maturation. The impairment especially affected maturation of neuronal pathways serving "executive functions" such as learning, memory, problem solving, assessment of alternative courses of action and impulse control.

The data analysed by Meier et al. came from a study of a birth cohort of over 1,000 children born in a one-year period in Dunedin, New Zealand, whose physical and mental health, education and psychosocial development were followed through regular recall interviews and examinations from birth to age 38. The finding of long-lasting cognitive impairment is potentially one of the most important considerations with respect to legalizing non-medical use of cannabis. It has been challenged on scientific grounds by proponents of legalization, and given great credence by opponents of legalization. It is important to be able to reach a secure conclusion as to its validity, so the Meier et al. paper, considered in detail in Chapter 1, deserves additional attention here.

Mokrysz and colleagues (2014) in an abstract in conference proceedings reported that in an English birth cohort study of 2,612 participants tested at ages 8 and 15 years, those who had started using cannabis in the interval and had used it at least 100 times had a decline of 3.71 IQ units relative to the non-users. However, when the results were controlled for the effects of sex, socioeconomic status, maternal factors, mental health and other drug use, the cannabis effect was attenuated, although the authors do not say whether it was no longer significant. There are problems with this study that the abstract does not explain or deal with. An alcohol effect remained significant despite these controls, but only in the moderate users and not in the heaviest users. No information is given about the age at which cannabis use began or the duration of use preceding the retests at 15 years of age, so it is not possible to tell whether this study is comparable to the Dunedin study.

A criticism of the Meier et al. paper by Rogeborg (2013) is based on the assumption that cannabis use is more common among children of low socioeconomic status (SES) families and the argument that low SES *per se* is capable of explaining the findings of Meier et al. The reasoning is that low SES children sort themselves into groups with other low SES children, which reduces their cognitive development by impairing educational history and intellectual stimulus. Rogeborg entered the Dunedin data on SES into a simulation model with hypothetical values for the influence of SES and education on the IQ, and concluded that they are capable of reproducing the differences shown in the Meier paper without invoking any causal role for cannabis. However, Moffitt and colleagues (2013) showed that cannabis use in the Dunedin study was not confined to children of low SES families, but was distributed across all SES levels. They then reanalysed the data from only those children of middle class SES, so as to minimize any influence of SES variation, and still found the same results as in their original analysis. They therefore reject the Rogeborg interpretation.

Finally, two earlier longitudinal studies that did not find long-lasting cognitive loss in cannabis users are not really relevant because they did not examine the same questions under the same conditions as the Dunedin study. Lyketsos, Garrett, Liang and Anthony (1999) carried out a study of a general population sample in East Baltimore that began in 1981 and re-examined the subjects in 1982 and 1993–1996. The primary purpose of the study was to examine age-related decline in cognitive function as measured by the Mini Mental State Examination (MMSE), but they also gathered data on the effects of a number of other factors, including alcohol and cannabis use. Subjects were divided by age into five groups: 18–30, 31–40, 41–50, 51–60 and 61–65 years. Only the 61–65 year olds showed a clinically significant decline in MMSE score between 1982 and 1993–1996. Subdivision of the age groups by levels of cannabis use showed no significant differences in decline between never, light and heavy users. However, this study is also not comparable to the Dunedin study for the following reasons:

1. More than half of the 3,401 original subjects were lost to the final follow-up, and there was no way of knowing whether the lost group differed from the follow-up group with respect to cannabis use;
2. No drug tests were done to confirm the self-reports concerning cannabis use;
3. The MMSE is not a sensitive test, and might have underestimated the cognitive declines; and
4. The youngest age group was significantly older than the most vulnerable subjects in the Dunedin study.

In addition, no data were collected on the age of starting cannabis use, and its duration and heaviness of exposure.

The other study, by Fried, Watkinson, James and Gray (2002), compared the IQ scores at ages 9–12 years, before the start of cannabis use, and again at ages 17–20 years, in four groups of subjects related to level of cannabis use: 37 non-users, 9 light current users, 15 heavy current users, and 9 former users abstinent for at least three months. The heavy current users showed a significantly lower IQ than they had shown at age 9–12, whereas the other three groups showed gains in IQ score. The fact that the former users showed a gain led to the conclusion that acute toxicity due to current heavy use impairs cognitive function, but does not cause any lasting effects. The authors urged caution in interpreting their findings because of the small numbers of subjects. Additional reasons for caution are that no data were given concerning the age at which use of cannabis started, and the "non-user" group was defined in a way that included light occasional users who had not used any cannabis during the previous two weeks.

In summary, the criticisms of the Meier et al. paper do not appear to be valid, yet it is true that it is a single study that has not been replicated. Because of the important role of effects on adolescent users in the debate about cannabis legalization, **it is important that an independent replication of the Dunedin study be undertaken in a Canadian or North American context**. Such a complex and large-scale longitudinal study cannot be undertaken lightly or inexpensively. It will require a long-term commitment of funding, and might have to be undertaken concurrently in more than one centre to achieve the necessary cohort size and number of researchers. Its importance for policy purposes is sufficiently great to warrant a major effort to make it possible.

5.4.3 Mental health

As reviewed by Goodman and George in Chapter 2, the relation between cannabis use and various mental health problems is complex and poorly understood. The precipitation of clinical symptoms of schizophrenia by cannabis in those with a genetic predisposition has been clearly demonstrated, but there has been little research on whether psychosis precipitated by cannabis use has a different clinical symptom pattern and course from psychosis originating without cannabis use.

Schizophrenic patients also have a recognized tendency to increase their use not only of cannabis, but also of alcohol, tobacco and possibly other psychoactive substances (Drake & Brunette, 1998; Rabin, Goodman, George, & Barr, 2014), perhaps as a form of intuitive self-medication for relief of their symptoms. This increase adds to the difficulty of distinguishing between cannabis use as a cause, a consequence or a co-occurrence with psychosis. It has also given rise to claims by advocates of cannabis use that it is therapeutically useful in treatment of mental disorders, one of the misconceptions about cannabis found by Porath-Waller et al. (2013) in their study of Canadian youth. **It is important, both for purposes of preventive education and for improved treatment of patients with co-morbidity, to continue both clinical and basic neurobiological studies of the temporal and mechanistic links between cannabis use and mental disturbances**.

The links between cannabis use and depression are less clear than those with psychosis. Earlier evidence reviewed by Degenhardt, Hall and Lynskey (2003) and more recent evidence reviewed by Goodman and George make clear that the link between cannabis and depression is complex, and there are numerous reasons why it is difficult to interpret. No association has been found between occasional light use of cannabis and depression, but many cross-sectional epidemiological studies have shown that heavy cannabis use and depression are frequently found together. It is still uncertain, however, to what extent cannabis use causes depression, depression causes cannabis use, or other factors cause both depression and cannabis use. Major methodological problems in the study of cannabis use and depression include lack of attention to the relation between level of cannabis use and severity of depression, failure to use standard diagnostic criteria to distinguish between temporary lowering of mood and full clinical depression, and lack of precision about the temporal relations between the drug use and the onset of depression.

Despite the mood elevation experienced by recreational users of small amounts of cannabis, the medical use of cannabis has often produced dysphoria leading to refusal to continue treatment. However, depression does not appear to be an acute overdose effect, comparable to the acute toxic psychosis produced by high-dose cannabis. A number of longitudinal

studies analyzed by Silins and colleagues (2014) have shown that early regular use of cannabis during adolescence is associated with greater risk of depression in early adulthood, whereas early experience of depression is not a predictor of later problematic use of cannabis. Though a number of possible confounders were ruled out by Silins et al., it is impossible to prove whether pharmacological the actions of cannabis initiate neuronal mechanisms leading directly to depression, or the effects of heavy cannabis use lead to social, educational and economic disturbances that are the proximal causes of the depression.

There is a need for more rigorously planned longitudinal studies of the link between cannabis and depression, as well as functional neurobiological imaging studies to explain the nature and mechanism of the link between heavy cannabis use and clinical depression and depressive phenomena.

A third important link of cannabis use and mental health is with anxiety disorders, including post-traumatic stress disorder. As reviewed by Goodman and George, cannabis has a long history of use as a sedative-anxiolytic agent, yet cannabis use by adolescents is often followed by anxiety. Contemporary research is consistent with both these observations. The endocannabinoid anandamide, which acts on the same CB_1 receptors in the brain as the plant cannabinoid THC, has an anti-anxiety effect (Gunduz-Cinar, Hill, McEwen, & Holmes, 2013). Yet the synthetic cannabinoid "Spice," which acts strongly at the same receptors, commonly produces anxiety (Spaderna, Addy, & D'Souza, 2013). The increasing use by youth of high-potency cannabis preparations with high THC and low CBD content has been followed by greater frequency of anxiety disorder (Copeland, Rooke, & Swift, 2013). The plant cannabinoid CBD, which partially blocks the action of THC at the CB_1 receptor, is currently being explored as an anti-anxiety agent, as well as for its possible anti-depression and anti-psychotic actions (Campos, Moreira, Gomes, Del Bel, & Guimaräes, 2012).

One possible explanation for these apparently contradictory findings is the fact that dose–effect curves for the cannabinoids are commonly biphasic. That is, increasing dose produces increasing effect in the lower dose range, but after a peak effect is reached, further increase in dose causes a decrease and then a reversal of effect (Kalant, 2014). **However, just as with psychosis and depression, the link between cannabis and anxiety is complex. There is a need for both basic neurobiological and clinical studies to define the nature of the link, the direction of causality and the possible therapeutic use of CBD or other cannabinoid derivatives in the treatment of anxiety disorder**.

5.4.4 Addiction

The evidence reviewed by Le Foll (Chapter 3) leaves no doubt that heavy users of cannabis have a significant probability of becoming addicted to it, as defined in the DSM-IV (dependence) or the DSM-5 (cannabis use disorder, severe). Despite the change in terminology over the years, the term "addiction" continues in general use, and is usually equated with dependence or severe substance use disorder. There appears to be a greater vulnerability to addiction in young users than in adults. It has been estimated that among regular (daily or near-daily) users of cannabis, adults have an 8–10% risk of becoming addicted, while adolescents have a 16% risk (Anthony, 2006).

One of the continuing problems in assessing the significance of these figures, however, is that the concept of addiction differs markedly, depending on the disciplines of those who use the term. Passive exposure to drugs can produce tolerance and physical dependence without resulting in drug-seeking behaviour and addiction, whereas self-administration of the same drugs carries a real risk of addiction. The essential features of addiction are related to drug-seeking, self-administration, difficulty controlling the amount and frequency of use, and inability or difficulty in achieving and maintaining cessation of use when adverse effects of use make it desirable or necessary to do so.

Recent neurobiological research has emphasized the concept of addiction as a brain disorder caused by chronic exposure to a drug. It has focused on the neural mechanisms underlying tolerance, withdrawal reactions, the "reward system" in the brain and adaptive changes in the connections between nerve cells. It has identified specific tracts and nuclei in which functional alterations have been found in dependent subjects, both human and non-human. Research in the behavioural and social sciences has focused more on behavioural, environmental and economic factors that affect accessibility of the drug, encourage or discourage its use, and promote linkage of drug use to specific situational cues and internal sensory stimuli.

Most of the animal models used for studying the mechanisms of addiction have been criticized by behavioural scientists on the grounds that they study reinforcement and neuro-adaptation, but do not actually study addiction (Winger, Woods, Galuska, & Wade-Galuska, 2005).

Further research on addictions must bridge the gap between these two approaches and study how environmental and behavioural factors activate and modify the neural mechanisms that mediate the development of addiction (Kalant, 2010, 2015). Animal models continue to be used for preliminary testing of potential therapeutic agents for treatment of addictions. If they are to be useful for this purpose, they should be as close as possible to addiction in humans, not to individual features that are not essential to addiction, such as tolerance and physical dependence.

Knowledge of the extent of harm produced by cannabis use by Canadian youth and application of this knowledge to prevention efforts could be improved by immediate application of practical measures to the gathering of accurate data:

- Data should be routinely gathered on the diagnoses and outcomes of hospital admissions attributed to cannabis, as is now done for alcohol-related admissions. Since the number of cannabis-linked admissions each year is small, this should not be an onerous task. It would give physicians a better idea of the range and severity of health hazards attributable to cannabis.
- To help assess the harm produced specifically by cannabis, annual statistical data on drug offences in Canada should be divided into separate groups for cannabis, opioids, psychostimulants, sedative-anxiolytic agents and other major categories of drugs used by youth.

5.5 More effective prevention, early identification and treatment

As pointed out by McRae-Clark and Gray (Chapter 4), the treatment of established cannabis use problems in adolescents, just as in adults, relies mainly on psychotherapeutic methods rather than on pharmacotherapy. They note in their chapter that cognitive behavioural therapy, motivational enhancement therapy, multidimensional family therapy and contingency management have each been shown to have some efficacy in reducing cannabis use. Two further points arising from this summary provide additional suggestions for research: attitudinal change and longer-term follow-up.

5.5.1 Attitudinal change toward cannabis use

The importance of attitude in prevention of cannabis use was clearly demonstrated by Terry-McElrath et al. (2014). Attitude should be equally important in attempting to treat established cannabis abuse and dependence. One of the problems encountered in earlier years was that a high proportion of cases were referred for treatment by courts, police, school authorities or parents, rather than by the users' own recognition that they needed treatment (Reilly, Scantleton, & Didcott, 2002). In such cases, there is little opportunity to assess whether the referred adolescents believe they need treatment, or whether the experience has changed their attitude about cannabis use from favourable to unfavourable.

Copeland and Maxwell (2007) examined the records of 27,198 adult Texans treated for a cannabis use problem in a publicly funded treatment program during six years ending in 2005. About 69% were referrals from the criminal justice system ("coerced"), while the remainder were referred by self, family, social service agencies or local medical and drug problem services ("non-coerced"). The coerced referrals were generally simpler cases, involved smaller amounts of drug use, were less distressed, had a shorter and simpler treatment period, and were more likely to have completed it than the non-coerced referrals. At the 90-day follow-up, the coerced subjects were less likely to have used cannabis during the preceding month, but this was by self-report only, without chemical verification. However, reviews of experience with police referral programs in Australia and the United States (Harvey, Shakeshaft, Hetherington, Sannibale, & Mattick, 2007; Tresidder & Homel, n.d.) have found that the great majority of such programs are poorly designed and evaluated, and there has been little attempt to assess outcome with respect to cannabis use at longer-term follow-ups.

Canadian youth are to a small but increasing extent referred for treatment or counselling when detained by police for simple possession of small amounts of cannabis. **A valuable line of research would be to compare those referred by the justice system with those referred by self or non-justice agencies with respect to their attitudes, expectations, cannabis-related problems, extent of use and long-term outcomes at repeated follow-ups**

for a total period of not less than two or three years. The findings could provide information on which to base future screening and referral systems, and develop more effective treatment methods.

5.5.2 Pharmacotherapy and long-term follow-up

Both Goodman and George (Chapter 2) and McRae-Clark and Gray (Chapter 4) refer to the need to develop effective pharmacotherapeutic agents to be used in combination with psychosocial therapies in the treatment of cannabis use problems in youth. This approach is widely used in the treatment of other drug use problems in adults, and has a logical, well-supported basis. Though their effect is usually modest, pharmacotherapies that relieve immediate symptoms of drug or withdrawal effects, and that in some cases also diminish the rewarding effects of the drugs in question, can result in better adherence to the treatment program, longer retention in treatment and more opportunity for the psychosocial measures to take effect. This pattern has been demonstrated, for example, with naltrexone and acamprosate in the treatment of alcoholism (Anton et al., 2006; Yahn, Watterson, & Olive, 2013). The well-designed, placebo-controlled trial of N-acetylcysteine combined with contingency management and counselling in the treatment of cannabis-dependent youth (mean age 18.9 years, range 15–21) represents a promising similar approach (Gray et al., 2012).

The problem with all such approaches to date is that the effect of the therapeutic agent gradually diminishes with time, so that the difference between the treated and the control groups in their abstinence from the problem drug gradually disappears. That is also evident in the study by Gray and colleagues (2012): at the follow-up visit four weeks after the end of treatment, the treated group and the placebo group no longer differed significantly in the percentage of urine testing negative for cannabinoids. This is not surprising because the nervous system has an ability to re-adapt to changing inputs of all kinds. The duration of effect of proposed pharmacotherapeutic agents must be measured to enable decisions about their utility in combined treatment programs. **There is a need for continued research on potential new therapeutic agents to enhance the overall efficacy of combined treatment programs, but long-term follow-up on their duration of effect is necessary to permit assessment of their utility in practice**.

5.6 Adverse effects of the legal prohibition of cannabis

The arguments for and against legalization of non-medical use of cannabis are not within the scope of the present report. Nevertheless, consideration of the adverse effects of cannabis use on youth would not be complete without recognition of the possibility of adverse effects of criminal records imposed on those convicted of possession. Numerous researchers have called for legalization of non-medical use of cannabis as a remedy for the adverse of effects of incarceration and criminal records on young people convicted of possession of small amounts of cannabis for personal use or for small-scale trafficking to friends and associates (e.g., Haden & Emerson, 2014; Rehm & Fischer, 2015). Others have presented evidence that this problem might not be as extensive as is believed (Pauls, Plecas, Cohen, & Haarhoff, 2012). At present, however, there is insufficient evidence about the outcomes of cannabis-related detentions by police in parts of Canada other than British Columbia. **It is important to analyze the outcomes of police detentions for cannabis possession in Canadian provinces and territories, so as to permit policy decisions based on knowledge of the effects of the current legal prohibition of non-medical use**.

There is still little research on the effects of cannabis legalization in a number of American states and other countries on the numbers of young cannabis users, their levels of use and the consequences of their use. There is no knowledge of the long-term effects of legalization. For purposes of policy planning, **it is important to gather information on the levels and consequences of cannabis use by young people after legalization in those jurisdictions where it has been adopted** (Canadian Centre on Substance Abuse, 2014).

5.7 Conclusions

While progress continues to be made in recognizing and understanding cannabis problems in youth, their causes and mechanisms, their long-term effects, and their prevention and treatment, there are still many questions. Prevention and treatment of cannabis problems in adolescents and young adults are not yet at the level of efficacy that our society would wish. This overview has identified research topics that would help to improve outcomes, and has suggested interim

steps based on existing knowledge that can be taken now to improve policy, prevent cannabis-linked harms, reduce the numbers of at-risk users, and improve the treatment of harmful consequences of their use.

This chapter makes the following recommendations for research:

- Identify the attitudes and values of Canadian adults about cannabis that have contributed to the high level of use by Canadian youth;
- Analyze the motives specific to youth for cannabis use, including the evolution of the individual's motives in the course of transition from exploratory to regular use;
- Study the predictive value of different motives as indicators of the outcome of use;
- Identify the individual differences of personality, motivation and temperament between responders and non-responders to different types of preventive education programs;
- Undertake comparative study of methods for changing beliefs and expectations in school-based programs of preventive education, and therapeutic programs for heavy users;
- Explore reasons for lesser efficacy of teachers than of outside experts in school programs;
- Study changing patterns of adverse effects with increasing potency of "street" cannabis;
- Conduct a longitudinal cohort study to replicate the Dunedin study under Canadian conditions;
- To guide the development of new therapeutic approaches, conduct a clinical and neurobiological study of the links between cannabis use and psychosis, depression and anxiety;
- Conduct functional imaging studies of the interaction between environmental factors and neurobiological mechanisms in the development of cannabis addiction in youth;
- Develop pharmacological agents, analogous to those used in alcohol and opioid addictions, to prolong retention of cannabis-dependent youth in treatment; and
- Compare long-term outcomes of self-referred and health- or police-referred youth in treatment programs.

In addition to these longer-term research projects, the chapter proposes a number of practical measures to improve the gathering of data, and early detection and prevention programs:

- In cooperation with healthcare professional societies, encourage physicians to use brief screening procedures for cannabis and other drug use by young patients;
- Recruit a pool of experts to take part in school-based preventive education programs;
- Separate data recording for different drug types in police incident reports;
- Record diagnoses for cannabis-linked hospital admissions and emergency service visits, and begin national collection of the data, as is done for alcohol;
- Begin systematically collecting data on sources of cannabis used by youth and tracking the diversion of medical marijuana to young non-medical users;
- Begin monitoring effects on cannabis use, addiction, vehicular accidents and other adverse consequences in youth of legalization in selected American states; and
- Convene meetings of federal and provincial agencies to discuss and implement programs for routine roadside collection of oral fluid from suspected impaired drivers for laboratory analysis of cannabinoid levels, and publicize this program in schools, colleges and universities.

It is urgent that the evidence reviewed in this report and the need for further research, as well as for the immediate measures that are already possible, be taken seriously into account by governments and research agencies now, when important policy issues are being contemplated.

CURRENTLY ACCEPTED FACTS

- Canadian youth, 15–25 years of age, have a higher proportion of users of cannabis than their counterparts in any other advanced country. They also constitute a majority of Canadian users of all ages.
- Young users' motives for use of cannabis differ from those of older users, but are not sufficiently well explored and understood.
- Young users have many incorrect ideas and beliefs concerning the actions, effects and long-term consequences of cannabis use, especially of regular use.
- Youth cannabis use is inversely related to the extent of their favourable attitudes and expectations about the effects of cannabis, which are more strongly influenced by the views of their peers than by those of their parents or teachers.
- Though most occasional users do not suffer serious problems, even occasional use can cause acute problems such as motor vehicle accidents, injuries and fatalities. Youth are at greater risk from these problems than adult users.
- Combined use of cannabis and alcohol carries greater risk of these consequences than use of either one alone.
- Adolescents who begin use before the age of 15 years are at considerably increased risk of adverse effects on physical and mental health, psychosocial adjustment, school and work performance, other drug use, and career opportunities.
- The earlier that adolescents begin use and the longer their use continues, the more serious are structural and functional brain changes that impair maturation of executive functions such as working memory, learning, problem solving, judgment, planning and control of impulsivity.
- Early commencement and persistence of use by adolescents predict increased risk of addiction, psychosis, depression and anxiety disorders.
- Preventive education programs delivered in schools or healthcare facilities are highly variable in content and execution, but the best ones can delay the commencement of use by 20–40% compared to the outcome in groups not exposed to such programs.
- Treatment of established hazardous use or addiction is primarily based on psychosocial interventions and there are not yet pharmacotherapeutic aids of proven efficacy.

AREAS OF UNCERTAINTY

- It is unclear what are the determinants of the long-term changes in attitudes and beliefs of youth concerning the safety and desirability of using cannabis.
- Most preventive education and treatment programs have insufficiently long follow-up to permit adequate assessment of their long-term efficacy.
- The adverse effects of early, continued use by adolescents on the maturation of brain structures and mental functions have not yet been studied in well-designed longitudinal studies to permit conclusions as to whether the changes are reversible.
- Changes in control policies in different parts of the world have not yet been observed for long enough to assess how the effects on youth are affected by different patterns of cannabis availability or by different social norms.

ON THE HORIZON

- New pharmacotherapeutic tools, aimed at facilitating the retention of patients in combined treatment programs, are now beginning to be tested clinically.
- Recent data from Canadian and American sources indicate that youth are again beginning to recognize the potential dangers of cannabis, and are starting to decrease use. This data offers an opportunity to learn more about effective methods of prevention.

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