The Impact of Cannabis on the Use of Alcohol and Tobacco: Findings from Observational Studies of Canadian Medical Cannabis Patients

by

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We acknowledge with respect the Lekwungen peoples on whose traditional territory the university stands and the Songhees, Esquimalt and W̱SÁNEĆ peoples whose historical relationships with the land continue to this day.

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Abstract

Background

A growing body of research suggests the therapeutic use of cannabis may affect the use of other substances, including reducing the use of alcohol, tobacco and prescription drugs such as opioid analgesics. However, most of the evidence stems from small, cross-sectional surveys or population-level studies, both of which have significant limitations, including the inability to conclusively determine causality for behavioural changes. Furthermore, very little detail has been gathered on the factors that potentially impact substitution, including patient characteristics and patterns of cannabis use (e.g., X, Y, Z).

Additionally, despite consistent calls by physicians, academics, patients and policy-makers around the globe citing the need for high quality studies to identify the risks and benefits of cannabis in both medical and non-medical applications, there are many pre-existing and ongoing challenges to conducting such research. These include shifting regulatory policies that may be impacting access to cannabis for both medical and non-medical use, and that could ultimately be affecting patient retention in prospective medical cannabis studies.

In the interest of learning more about how the use of cannabis effects the use of alcohol, tobacco and other substances, and to better understand factors that may be impacting retention in prospective cannabis research, I designed and conducted two studies:

1. The Canadian Cannabis Patient Survey 2019 (CCPS 2019) was a national cross-sectional survey of 2102 Canadian medical cannabis patients that examined demographics, patient patterns of cannabis use, and self-reported changes in the use of alcohol, tobacco, prescription drugs and illicit substances following medical cannabis initiation.

2. The Tilray Observational Patient Survey (TOPS) was a prospective, multi-site, observational study examining the impact of medical cannabis products on quality of life and the use of prescription drugs of 1145 patients over a 6 month period, which provided an opportunity to conduct a survival analysis and other analyses to assess variables potentially impacting retention in longitudinal cannabis studies.

Methods

This dissertation includes three analyses of the data resulting from these studies in the form of one published and two submitted manuscripts. The first paper provides an overview of research to date examining the impact of cannabis and cannabinoids on alcohol use, followed by an analysis of the 973 CCPS 2019 participants who either previously or currently use alcohol. The questionnaire gathered a detailed inventory of alcohol use prior and post medical cannabis initiation using two separate but related measures: drinking days per month, and standard drinks per week. The analyses used descriptive statistics as well as univariate and multivariate regression analyses to explore patient characteristics and other variables potentially associated with changes in alcohol use post medical cannabis, including assessing the impact of "intent" to use medical cannabis to reduce alcohol use, as well as participation in other substance use treatment modalities. Findings suggest that medical cannabis initiation is associated with significant reductions in alcohol use, and that younger age (<55 years of age), specific intent to use medical cannabis to reduce alcohol use, and greater patterns of alcohol use prior to medical cannabis initiation were associated with greater odds of reducing alcohol.

The second paper follows a similar methodology and format as the first paper, but with a focus on tobacco/nicotine (T/N) use. In this case, 650 survey participants reported past or current T/N use, and the analysis focused on assessing patient characteristics and other variables associated with changes in T/N uses per day, with the primary outcome of interest being no use in the 30 days prior to the survey, which

was considered to be complete cessation of T/N use. The findings suggest that odds of T/N cessation were greater amongst those who were age 55 or older or that reported >25 T/N uses per day prior to initiating medical cannabis use, and that specific intent to use medical cannabis in T/N reduction/cessation efforts resulted in significantly greater odds of reducing T/N use, while involvement with traditional T/N cessation treatments (pharmacological or psychobehavioral) was negatively associated with T/N cessation.

The third paper addresses the challenge of retaining patients in prospective observational medical cannabis studies at a time when there are major policy changes disrupting the legal supply while also increasing access options for adults who use cannabis. The Tilray Observational Patient Study (TOPS) was one of the largest national prospective medical cannabis studies ever conducted, taking place at 21 medical clinics in five provinces. The study was designed to assess the impact of medical cannabis on quality of life and prescription drug use over a six month period. However, initial data analysis on 1145 patients enrolled at/before Oct 15, 2018 that had completed at least one post baseline visit highlighted a significant rate of patients that were lost to follow up (LTFU). This high drop out rate, coupled with a compensation scheme that provided credits to help cover the cost of medical cannabis led to concerns of potential retention bias limited the conclusions that could be drawn from this data. However, the study and resulting data provided a unique opportunity to examine baseline patient characteristics that may have been protective of LTFU, so a survival analysis was conducted on this cohort. Additionally, since the study took place during the official launch of the legalization of adult non-medical use of cannabis in Canada on Oct. 17th, 2018, the potential impact of this significant increase in legal access options on the odds of study retention was the subject of additional analyses. The survival analysis found that baseline use of antidepressants or antiseizure medications, citing no preference for either THC or CBD, and inhalation as a primary method of use were associated with increased probability of survival/retention in the study at six months. Additionally, while the legalization of non-medical adult cannabis use in October 2018 resulted in more than three times the odds of participants being LTFU at six months, being under 55

years old, having a preference for THC, or citing inhalation as a primary method of use was partially protective of LTFU following legalization.

Discussion

The studies in this dissertation presented an opportunity to gather subjective and objective data on naturalistic patterns of medical cannabis use from large, heterogeneous cohorts of patients, and to explore associated impacts on the use of alcohol, tobacco and other substances. The results of these studies provide a more comprehensive understanding of the public health risks and benefits associated with the medical use of cannabis, and could subsequently inform policy decisions affecting access to cannabis vis-à-vis other drugs, private and public payer considerations related to cost-coverage for medical cannabis, and potentially lead to the development of novel alcohol and tobacco cessation strategies. Additionally, the survival analysis conducted on TOPS participants highlights some of the challenges of conducting medical cannabis research at a time when patients have a multitude of cannabis access options, including legal adult dispensaries and a still robust illicit market. Future longitudinal medical cannabis studies should consider the potential impact of policy changes effecting cannabis access on study retention/survival, and may want to focus on patient populations with characteristics associated with lower odds of LTFU.

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Dedication

"It is the responsibility of intellectuals to speak the truth and to expose lies."

- Noam Chomsky, 1967

Nothing in my first 25 years of life gave any indication of where I now find myself today, either academically or professionally, and the path that led me here was at times cratered with trauma, loss and personal challenges. However, this journey has never been dull, and for that I am extremely grateful! Additionally, with each setback came hard-earned lessons, growth, and ultimately progress, and the associated age and experience to learn that while time may not heal all wounds, it does ultimately help put them into perspective.

None of this would have been possible without the indefatigable determination I have learned and inherited from my mother Pierrette Lucas, along with an inherent optimism that with a bit of effort (mixed with a dash of delusion?), anything is possible, and all will ultimately work itself out. My wife Mary is both my motivation and my most unwavering supporter, and my courageous daughter Sophie all the inspiration I will ever need to continue to push myself and take chances in life; words cannot express the love and gratitude I feel for the three of you. Unfortunately, those in closest proximity to academics tend to suffer the most in the pursuit of knowledge and understanding (I know this from experience, as Mary has completed two MAs during our relationship), and I hope to make up for lost time once this dissertation is done.

I often say that the majority of what we know about medical cannabis didn't come about from clinical trials or other academic studies, but rather from what patients have willingly shared

with us. As academics our primary role is to find the best ways to translate patient experiences into data, and eventually into evidence-based treatments and policies. As such, I am forever in debt to the thousands of patients who have so openly shared their pain, suffering, and success stories with me over the last 25 years; this dissertation and all of my research is ultimately dedicated to them.

I owe a tremendous debt of gratitude to the personal and professional mentors I met along the way. Rick Doblin for demonstrating that deep human connection, integrity, and a bit of mischief can co-exist and be the basis of personal and professional success; Ethan Nadelmann for teaching me that combining passion and knowledge can move a crowd and many mountains; Ethan Russo for highlighting that the best use of significant knowledge is to share it openly; Susan Boyd for exemplifying an endless compassion and ongoing support for all people at every occasion, and without who's encouragement I would undoubtedly still be an undergrad; Zach Walsh for being as great a friend and collaborator as he is a mentor, and MJ Milloy for standing by my side to push large academic boulders up steep and challenging academic terrain. I'm extremely thankful to all of you for your unwavering dedication to uncovering new knowledge in order to make the world a better place.

Finally, my gratitude to following folks who pulled, pushed, or pointed me in the right direction when I strayed during this very long journey: Amanda Reiman, for the generosity of time, and ongoing support and friendship; Hilary Black, Debbie Goldsberry & Val Corral, who taught me to always put patients first; Pat Erickson, Eric Single, Lynne Belle-Isle and Donald McPherson, who showed me you could make a living advocating for evidence-based cannabis

and drug policy; Scott McDonald, Tim Stockwell, Emma Carter and CARBC, who provided academic and financial support and gave my research an academic home base; Pierre-Claude Nolin, Libby Davies and Sheila Malcolmson, who always made sure the voices of cannabis patients were heard and considered in federal policy decisions affecting them; and Kirk Tousaw, Mat Beren, Steve Roberts, Shad Cain, Matt Elrod, Bob Erb, and particularly Michelle Rainey, you are all my very dear cannabis reform colleagues, and inevitably lent a hand and/or helped me up when I stumbled somewhere along the way. Look around my friends; we f***en did it!

1 Integrative Chapter

1.1 Background

My extended journey researching the impact of cannabis on the use of other substances began with personal experience. In 1995, I was diagnosed with Hepatitis C; which I had contracted during a splenectomy when I was 12 years old. At the time, there was no cure or treatment available, so all my physician could do was suggest that I quit using alcohol and tobacco to lessen damage to my liver. As a 25-year-old French Canadian these were my (culturally-influenced) drugs of choice, but I went home from the University of Victoria medical clinic that afternoon and decided to give up these substances—both of which had certainly taken a toll on my health, and on the health of my near and distant relatives for a number of generations. While I was not a regular cannabis user at the time, it appeared to help address cravings for both alcohol and tobacco, so I began to use small amounts on a daily basis, and was successful in maintaining my abstinence from alcohol and tobacco. I was also pleasantly surprised to find that it relieved some of the symptoms of Hep-C, including nausea, lack of appetite, and inflammatory liver pain.

However, even for a university student in his late twenties, finding a safe, consistent supply was an ongoing challenge, leaving me to wonder how older, potentially cannabis-naïve patients would ever find a reliable source. A growing concern over safe access coupled with a far too sudden sense of my own mortality (reinforced by my father's sudden death) led me abandon plans to become a secondary school teacher, and to instead co-found the Vancouver Island Compassion Society (VICS), a non-profit society with the goal of providing a safe supply of cannabis-based medicines to patients who might benefit from its use within an environment that was conducive to healing. It was in my role as Executive Director of the VICS from 1999-2009 that I began my cannabis research career, and it was largely influenced by the personal stories I heard from the hundreds of patients who came through the VICS' doors.

The VICS launched the year before the *R v. Parker* ruling in the Ontario Court of Appeal that would recognize the rights of medical cannabis patients to access cannabis without having to fear arrest and prosecution (Court of Appeals for Ontario, 2000), and two years before the Canadian federal government responded to the Parker decision by launching Canada's federal medical cannabis program in 2001 (P. Lucas, 2008). It was a time when very few physicians supported the medical use of cannabis, and accessing it created significant legal risk to both patients and providers (P. Lucas, 2009). Every day the VICS opened and every patient served was a public act of civil disobedience with very real legal repercussions, as I can certainly attest after being arrested for trafficking medical cannabis at the VICS in 2000.

As a result of the stigma and legal risks associated with the medical use of cannabis, early VICS members were often patients with little to lose—such as the terminally ill or people who injected drugs and had contracted blood-borne pathogens like HIV and Hep-C—and who therefore faced much greater existential, legal and social threats than those related to the unauthorized possession and use of cannabis. The VICS worked hard to create a safe space for a patient population that often felt alienated from traditional health care settings, and in turn patients were incredibly generous in sharing their personal experiences with medical cannabis. Mingled amongst the many patient reports of pain relief, appetite stimulation, seizure reduction and other beneficial outcomes were accounts of cannabis being used to reduce the use of potentially more dangerous substances in keeping with the principles of harm reduction (Erickson, 1995; Lenton, Bennett, & Heale, 1999; Single, 1995).

Patients living with HIV/AIDS or Hep-C often shared that not only was cannabis helpful in alleviating some of the symptoms of these conditions or the side-effects of the limited and often toxic treatments that were available at the time, it also mitigated the withdrawal symptoms and cravings they occasionally felt for unregulated substances like heroin, crack/cocaine, and crystal methamphetamine. At the time, cannabis was still largely considered in mainstream society a so-called gateway or a stepping stone to higher-risk substance use and eventually addiction (Lessem et al., 2006). What I was hearing

from patient after patient was nothing short of revolutionary. If cannabis was not a gateway drug but actually an exit drug, the policy and public health implications were incredibly significant, particularly in light of the explosive outbreaks of HIV and hep-C coursing through Vancouver's Downtown Eastside—emergencies that would ultimately foreshadow the opioid overdose crisis now touching every part of the United States and Canada, and many jurisdictions beyond.

The challenge then became how to capture the phenomena that was starting to be known as the *cannabis substitution effect*. Despite well-meaning intentions, having a BA in English literature left me ill-prepared to conduct academic research, so academic partnerships presented the best option. When a graduate researcher from the UVic School of Nursing approached the VICS about conducting a retrospective survey of cannabis use as a treatment for severe nausea and vomiting related to pregnancy (i.e., hyperemesis gravidarum), we were all too happy to partner, and the resulting publication became the first peer-reviewed academic study ever conducted at a Canadian community-based dispensary (Westfall, Janssen, Lucas, & Capler, 2009, 2006).

While this study proved to be a valuable learning experience, my primary research interest was the use of cannabis as a substitute for other substances. Unfortunately, it proved difficult at the time to find academic researchers in Canada or elsewhere who were interested in this area of research, so I made plans to go back to school so I could pursue this area of research independently. This started with a few graduate classes at UVic that ultimately lead to an MA in Studies in Policy and Practice, during which I was exposed to the theoretical foundations of addiction and drug policy (Alexander, Coambs, & Hadaway, 1978; Boyd, 2004; Szasz, 1972), harm reduction (O'Hare, 2007; Tammi & Hurme, 2007), harm reduction (Erickson, 1995; Lenton & Single, 1998; Single, 1995), new social movement theory (Buechler, 1995; Young, 2011), community-based research (CBR) (Etmanski, Hall, & Dawson, 2014; Jurgens, 2005), and ultimately the substitution effect as well (Abrams et al., 2007; Hursh, Galuska, Winger, & Woods, 2005; Mikuriya, 2004; Model, 1993; Reiman, 2009), all of which continue to inform my work and research, including the papers that make up this PhD dissertation.

My earliest attempts at researching the substitution effect focused on determining the best methodological approach to quantify and aggregate the stories I was hearing from cannabis patients each and every day. Initially, I adapted measures from the few academics in the field studying the impact of medical cannabis on the use of other substances, and Amanda Reiman's seminal work in California-based dispensaries while at Berkeley was a major influence that led to a number of academic collaborations (P. Lucas et al., 2013; Reiman, 2009). These early publications opened up additional research opportunities with Canadian academics like Zach Walsh at UBC, who was quick to realize that the broad cohort of authorized cannabis patients provided a unique setting in which to examine patient patterns of use and associated outcomes in a naturalistic setting (P. Lucas & Walsh, 2017; P. Lucas et al., 2016a; Walsh et al., 2013a). While each subsequent study and publication attempted to improve on the last and added to the growing academic understanding of cannabis substitution effect, this body of research also highlighted ongoing gaps of knowledge and methodological limitations that merited attention.

The studies that form the basis of this dissertation represent my ongoing attempts to improve the methods and measures used to assess how cannabis affects the use of alcohol, tobacco, opioids, and other substances, and the associated impacts at the individual and community level. The novel measures and methodological approaches in these studies are reflective of over 10 years of asking patients about substitution, critiques from academics and policy-makers on the limitations of past surveys and study designs (including my own), and significant and ongoing communication and collaboration with like-minded academics interested in finding better ways to assess this fascinating phenomena.

The first study was the Canadian Cannabis Patient Survey 2019 (CCPS 2019), a 392 question national cross-sectional survey that launched in early 2019 and which gathered 2102 responses (Appendix A & B). In order to address the methodological limitations of past studies examining cannabis substitution, I coordinated online meetings with some of the top international academics currently researching this topic, including Kevin Boehnke (Boehnke, Litinas, & Clauw, 2016; Boehnke et al., 2019), Stephanie Lake (Lake et al., 2020; Socías et al., 2017), and Marcus Bachhuber (Bachhuber,

Salone, Cunningham, & Barry, 2014; Bachhuber, Arnsten, & Wurm, 2019), and these collaborative discussions informed many of the novel methodological approaches and measures in CCPS 2019.

While previous cross-sectional studies examining substitution effect (including my own) would typically ask participants whether or not they had ever specifically substituted cannabis for other substances (Boehnke et al., 2016; P. Lucas, Baron, & Jikomes, 2019; Reiman, Welty, & Solomon, 2017), this approach had rightly been critiqued as being somewhat leading, and therefore subject to response/social desirability bias. Instead, CCPS 2019 gathered a detailed inventory of alcohol, tobacco, prescription and illicit drug use prior to medical cannabis initiation, and then repeated the same substance use measures with a focus on the 30 days prior to the survey, allowing for a retrospective comparison of use pre-and-post medical cannabis initiation. While this methodological approach was not without limitations, including the potential for recall bias, it provided granular data that could actually quantify changes in substance use (e.g., in drinks per week/drinking days per month, tobacco/nicotine uses per day, etc.), increased equipoise by not presuming that substance use would only decrease rather than increase, and reduced the potential for response bias. Additionally, the study includes novel measures assessing the level of specific intent to use medical cannabis to reduce the use of other substances and eliciting information on participant experiences with other substance use treatments in order to broaden the understanding of contexts and potential factors that impact substitution effect.

The second study was the Tilray Observational Patient Study (TOPS), a national, multi-site, prospective assessment that recruited over 2100 participants in five provinces (Appendix C). The TOPS study had many methodological advantages over the cross-sectional studies I had previously conducted, largely due to its prospective design. Patient recruitment and data gathering took place in-clinic at baseline, one month, three months and six months, and included one validated measure: the World Health Organization Quality of Life Short Form (WHOQOL-BREF) (Appendix D); and two novel measures: the Cannabis Use Survey (CUS) (Appendix E), and the Prescription Drug Questionnaire (PDQ) (Appendix F), the latter of which gathered a very granular inventory of prescription drug use (including the

milligrams/day of each prescription drug used by patients) and was completed by physicians in cooperation with patients at each study visit in order to reduce the potential for recall bias. Coordinating this multi-site, national study proved incredibly complex, and required review by research ethics boards at UVic, the Health Research Ethics Board of Alberta, and Advarra, the latter of which conducted additional reviews for each of the 21 study sites. Despite these challenges, TOPS provided a unique opportunity to conduct a prospective examination of the impact of medical cannabis on prescription drug use and quality of life in a large, heterogeneous patient cohort, and it proved thrilling to be able to design and coordinate a study of this scope in my role as vice president of patient research at Tilray. Additionally, since TOPS took place over an extended period of time that included the legalization of the non-medical, adult use of cannabis in Canada, it ultimately presented a unique opportunity to assess how that external policy change and other internal variables affected retention in prospective medical cannabis studies, so a survival analysis and other analyses were conducted with the goal of identifying covariates that might be protective of participant being loss to follow up in future studies.

Data from these two studies ultimately informed three papers, one of which has been published, while two have been submitted for publication. The first paper (Lucas, Boyd, Milloy and Walsh, 2020) stems from the CCPS 2019 data on alcohol use, and found that medical cannabis initiation was associated with both alcohol reduction and reduction. Overall, 419 (44%) participants reported decreases in alcohol usage frequency over 30 days, 323 (34%) decreased the number of standard drinks they had per week, and 76 (8%) reported no alcohol use at all in the 30 days prior to the survey. Additionally, specific patient characteristics were associated with greater odds of reducing alcohol use, including being below 55 years of age, and reporting higher rates of alcohol use in the pre-medical cannabis period. Furthermore, it was found that intention to use medical cannabis to reduce alcohol consumption was associated with significantly greater odds of both reducing and ceasing alcohol use altogether.

The second paper (Lucas, Walsh, Hendricks, Boyd, Milloy, 2020) analyzed the tobacco/nicotine use data from CCPS 2019, finding that 320 (49%) of participants that used tobacco/nicotine (T/N) self-

reported reductions in use, with 160 (24.6%) reporting no T/N use in the 30 days prior to the survey. Odds of T/N cessation were greater amongst those who were age 55 or older, or that reported >25 T/N uses per day in the pre-period. Consistent with the results of the alcohol publication, the specific intent to use medical cannabis in order to quit resulted in significantly greater odds of reducing T/N use; however, involvement with traditional T/N cessation treatments (pharmacological or psychobehavioral) was negatively associated with T/N cessation.

In light of the high rates of morbidity and mortality stemming from alcohol and tobacco/nicotine use, and the associated public health and safety costs, the findings from these two papers could inform future substance use policies. Additionally, the finding that specific intent to use cannabis as a substance reduction strategy was associated with greater rates of reduction and/or cessation suggests that additional research should be conducted exploring cannabis as a potential treatment for alcohol or tobacco use disorder, particularly for those seeking alternatives to abstinence-based treatments.

The third paper consists of a survival analysis of TOPS participants exploring baseline patient characteristics potentially associated with study retention, and included an additional analysis of the impacts of cannabis legalization on the odds of participants being lost to follow up. The study found that baseline use of antidepressants or antiseizure medications, citing no preference for either THC or CBD, and inhalation as a primary method of use were all associated with increased probability of survival/retention in the study at six months. Additionally, the legalization of non-medical adult cannabis use in October 2018 resulted in more than three times greater odds of participants being LTFU at six months; however, being under 55 years old, having a preference for THC, or citing inhalation as a primary method of use were somewhat protective of LTFU following legalization.

Data suggests that participation in Canada's federal medical cannabis program has been in steady decline since September 2019 (Health Canada, 2020), therefore, it is becoming increasingly important to understand patient characteristics and policy factors that may be impacting the viability of prospective

studies involving this patient population. This final paper highlights potential challenges that increased legal access to cannabis might have on retention in prospective medical cannabis studies, and provides some insight into baseline patient characteristics that might be protective of LTFU and that could therefore inform future study design.

The common thread running through these three studies and much of my previous research is the opportunity to investigate and illuminate phenomena that might otherwise go unnoticed in order to make useful contributions to the field of cannabis and substance use research, inform substance use policy in Canada and around the globe, and improve the lives of critically and chronically ill patients. Despite certain limitations and unanticipated challenges, these studies introduced novel measures and methodological approaches to the study of cannabis substitution, and identified new lines of enquiry that future research efforts may be able to further elucidate.

In reflecting on a personal and professional relationship with medical cannabis which began 25 years ago (nearly to the day!), there is an undeniable link between the hep-C diagnosis I received in 1995 and the resulting use of cannabis to reduce cravings for alcohol and tobacco; the 25 years of patient advocacy and academic research that ensued; and the publications that now make up this dissertation. Despite the many ongoing challenges to safe access noted in these and other publications, we're extremely fortunate to live in a country that has evolved beyond criminalizing the possession and use of cannabis in adults. I can only hope that my work and research will continue to move Canada and other jurisdictions away from prohibitionist drug policies based on of fear, prejudice and misunderstanding, and towards evidence-based policies informed by science, reason and compassion.

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2 Paper 1: Reductions in alcohol use following medical cannabis initiation: results from a large cross-sectional survey of medical cannabis patients in Canada

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2.1 Abstract

Background

Evidence details how cannabis can influence the use of other psychoactive substances, including prescription medications, alcohol, tobacco and illicit drugs, but very little research has examined the factors associated with these changes in substance use patterns. This paper explores the self-reported use of cannabis as a substitute for alcohol among a Canadian medical cannabis patient population.

Methods

Data was derived from a survey of 2102 people enrolled in the Canadian medical cannabis program. We included 973 (44%) respondents who reported using alcohol on at least 10 occasions over a 12 month period prior to initiating medical cannabis, and then used retrospective data on the frequency and amount of alcohol use pre-and post medical cannabis initiation to determine which participant characteristics and other variables were associated with reductions and/or cessation of alcohol use.

Results

Overall, 419 (44%) participants reported decreases in alcohol usage frequency over 30 days, 323 (34%) decreased the number of standard drinks they had per week, and 76 (8%) reported no alcohol use at all in the 30 days prior to the survey. Being below 55 years of age and reporting higher rates of alcohol use in the pre-period were both associated with greater odds of reducing alcohol use, and an intention to use medical cannabis to reduce alcohol consumption was associated with significantly greater odds of both reducing and ceasing alcohol use altogether.

Conclusions

Our findings suggest that medical cannabis initiation may be associated with self-reported reductions and cessation of alcohol use among medical cannabis patients. Since alcohol is the most prevalent recreational substance in North America, and its use results in significant rates of criminality, morbidity and mortality, these findings may result in improved health outcomes for medical cannabis patients, as well as overall improvements in public health and safety.

2.2 Background

Globally, alcohol use causes substantial morbidity and mortality. According to the World Health Organization, alcohol-related harms result in three million deaths per year and is a causal factor in over 200 diseases and injury conditions. Approximately 5.1% of total global burden of accidental injury is attributable to alcohol, and there is a causal relationship between alcohol use and a range of communicable and non-communicable diseases, including mental health and behavioral disorders, resulting in significant impacts on public health and safety, and social and economic losses (Shield, Parry, & Rehm, 2013; World Health Organization, 2018; Zhou et al., 2016). In Canada, alcohol is the most commonly used psychoactive substance and in 2014 it directly contributed to 14,826 deaths, or 22% of all substance use-related fatalities, and was implicated in an additional 655 automobile-related mortalities (Brown, Vanlaar, & Robertson, 2017; CCSA, 2019). In 2017, 78.2% of Canadians aged 15 and over reported past year consumption, and alcohol caused hospitalizations at a rate of 249 per 100,000, which is higher than hospitalizations associated with heart attacks (243 per 100,000) (CCSA, 2019; G. Taylor, 2016). Unfortunately, studies suggest that patients affected by chronic health conditions like chronic pain and mental health challenges may be more susceptible to alcohol-related harms, dependence, and relapse (Alford et al., 2016; Apkarian et al., 2013; Berglund & Ojehagen, 1998; Boden & Fergusson, 2011; Bradizza, Stasiewicz, & Paas, 2006; Egli, Koob, & Edwards, 2012).

Cannabis and alcohol have been found to be both complements and substitutes under different contexts and circumstances (Cameron & Williams, 2001; Chaloupka & Laixuthai, 1994; Pape, Rossow, & Storvoll, 2009a; Reiman, 2009; Subbaraman, 2014). The co-use of alcohol and cannabis is common due a number of sociological, behavioural and biological factors (Yurasek, Aston, & Metrik, 2017). Physiologically, cannabis may slow absorption of ethanol, potentially reducing alcohol's psychoactive effects (Lukas et al., 1992). However, alcohol can increase levels of tetrahydrocannabinol (THC, the primary psychoactive component of most cannabis) in plasma if the two are used simultaneously or within a short duration of each other (Downey et al., 2013; Lukas & Orozco, 2001).

The co-use of cannabis and alcohol may be particularly prevalent in adolescents and young adults. A study of U.S. high school seniors found that 23% reported any simultaneous use, increasing to 62% in those that reported past year cannabis use (Terry-McElrath, O'Malley, & Johnston, 2013). A survey of 14 to 20 year old youth in Norway reported that about 80% of cannabis use events included alcohol use, leading the authors to suggest the two substances may be complements (Pape, Rossow, & Storvoll, 2009b).

There is evidence that the co-use of cannabis and alcohol can lead to greater potential harms than the individual use of either. A survey of university freshman in the United States found moderate drinkers who reported recent use of cannabis were more likely to drink more than intended and reported more associated problems such as blackouts, injuries and driving while impaired (Haas et al., 2015). A prospective population-level study of adults in the U.S. found that cannabis use was associated with higher rates of alcohol use disorder (AUD) onset and persistence over a three year period (Weinberger, Platt, & Goodwin, 2016). A study of 307 young adults diagnosed with a cannabis use disorder (CUD), AUD, or dual use disorder (DUD, combining both) found that those with DUD reported greater problems with alcohol and/or cannabis than both singly-diagnosed groups (Hayaki, Anderson, & Stein, 2016).

However, there is also evidence that cannabis may reduce the use of alcohol, mitigate alcohol-related harms, or even be a useful substitute or treatment for those with AUD. Reviews focused on pre-clinical *in vitro* and *in vivo* research suggests that the endocannabinoid system plays a significant role in alcohol intake and motivation to use, and could be a beneficial pharmacological target to treat alcohol dependence (Colombo, Serra, Vacca, Carai, & Gessa, 2005; Pava & Woodward, 2012).

Population-level research has also found a strong association between cannabis and alcohol access and use, and there is some evidence that under some circumstances, cannabis may act as a substitute for alcohol. A study examining the impact of increasing the alcohol drinking age on substance use in high school seniors in the U.S. found that while it did lead to reductions in alcohol use, there was an associated increase in cannabis use, suggesting the two may be substitutes (DiNardo & Lemieux, 2001). Other

studies have found that the implementation of medical cannabis regulations is often associated with reductions in alcohol sales, use and associated harms. An examination of the impact of medical cannabis legalization in 16 U.S. states found that passing such laws was associated with declines of alcohol sales and consumption, and a 9% reduction in traffic fatalities involving alcohol (D. M. Anderson, Hansen, & Rees, 2013). An examination of alcohol purchasing data in U.S. states from 2006-2015 before and after medical cannabis laws were introduced found a 15% decline in alcohol sales associated with medical cannabis laws, suggesting that cannabis and alcohol are substitutes (Baggio, Chong, & Kwon, 2017).

There also exists a good body of observational, individual-level data focused on the impacts of medical cannabis access and use on alcohol consumption rates. A case series by a California physician who had been using medical cannabis to treat alcohol use disorder suggests that 83 (90%) of his 92 patients found it was “effective” or “very effective” (Mikuriya, 2004). These findings are consistent with those of cross-sectional studies examining self-reported cannabis substitution for alcohol in patient populations in both Canada and the U.S. (Lucas et al., 2016; Lucas, Baron, & Jikomes, 2019; Lucas et al., 2013; Reiman, 2009).

There is also some evidence that alcohol is a common substitute for cannabis amongst individuals who use cannabis for non-medical reasons. Two U.S.-based studies involving non-treatment seeking individuals using cannabis daily found that alcohol use increased significantly during cannabis abstinence among those with a previous alcohol dependence diagnosis or those with low alcohol consumption at baseline (John R. Hughes, Peters, Callas, Budney, & Livingston, 2008; Peters & Hughes, 2010). A more recent Australian study found that alcohol and tobacco use increased in non-treatment seeking dependent individuals using cannabis who voluntarily abstained from cannabis use, and that both decreased once cannabis use resumed (Allsop et al., 2014). However, other research has found that some, but not all, levels of cannabis use can negatively impact alcohol treatment outcomes (Subbaraman, Metrik, Patterson, & Swift, 2016).

Although there is a lack of clinical research examining cannabis as a potential treatment for AUD, a randomized trial of various treatments for cigarette smoking cessation in heavy drinkers found that those participants reporting weekly cannabis use decreased drinking at a faster rate than non-users at the eight week follow-up, although this group also reduced their cannabis use by more than 24%, suggesting that lower cannabis use may lead to better alcohol outcomes, and that the two substances may be complementary (Metrik, Spillane, Leventhal, & Kahler, 2011). Finally, a literature review that assessed whether or not cannabis might be considered a substitute medicine for alcohol in the treatment of alcohol use disorder (AUD) found that all seven criteria examined were either satisfied or partially satisfied, though the authors note that since most of the studies relied on retrospective data from medical cannabis patients and a lack of accounting for factors such as severity of alcohol problems no firm conclusions can be reached, and therefore it would be premature to prescribe cannabis as a treatment for individuals with AUD (Subbaraman, 2014).

Whereas previous observational and clinical studies have identified a potential association between cannabis and alcohol use, this study aims to expand the current state of knowledge by comparing retrospective self-reported, individual-level rates of alcohol use in authorized cannabis patients before and after medical cannabis initiation, and including novel variables such as “intent”, as well as potential confounders such as involvement with other alcohol cessation treatments.

2.3 Methods

A 392-question cross-sectional survey was designed to gather comprehensive information from Canadian federally-authorized medical cannabis patients registered with Tilray, a Canadian Licensed Producer (LP) of medical cannabis. In Canada, once a patient and physician or nurse-practitioner agree that medical cannabis is a viable treatment option, the health care practitioner writes a recommendation for the patient, which is then sent to an LP such as Tilray from which the patient can subsequently obtain medical

cannabis products via mail (Health Canada, 2019). The survey included questions on participant demographics, patterns of cannabis use, and self-reported use of prescription drugs, alcohol, tobacco, and illicit substances before and after medical cannabis initiation. All respondents who provided informed consent and took the survey were entered into a draw to receive one of five $1000 credits applicable towards the purchase of medical cannabis. Data was gathered on REDCap (Vanderbilt University, Nashville, TN, USA), a secure online electronic data capture system. The inclusion criteria included being an authorized medical cannabis patient registered with Tilray, aged 18 years or over, capable of reading and understanding English and of legally consenting to participate in the study.

The survey received approval from the University of Victoria' Human Research Ethics Board on December 19, 2018. On January 11, 2019, an invitation to participate in the survey was sent to 16,664 federally-authorized medical cannabis patients who provided email addresses to Tilray. Individuals could participate in the survey from January 11 to 18, 2019.

2.3.1 Measures

The survey began by gathering self-reported demographic data, including: gender, age, current relationship status, highest education level completed, annual household income, and Canadian province/territory of residence. We also assessed the primary condition for which participants used medical cannabis by providing a list of common conditions associated with medical cannabis use (Lucas, Baron, & Jikomes, 2019a; Lucas & Walsh, 2017; Reiman, Welty, & Solomon, 2017; Walsh et al., 2013) that included an option of clicking "other", prompting a textual response (Table 1).

For this particular series of sub-analyses, the primary inclusion criteria was "regular" past/present alcohol use by participants, which we defined as using alcohol on 10 days or more over at least one 12 month period over a lifetime. A total of 973 participants responded positively to past/present lifetime use, and this sample formed the basis of the remaining analyses. We assessed both frequency and amounts of

alcohol used pre-and-post medical cannabis initiation, as both are relevant in assessments of problematic patterns of alcohol use/alcohol use disorder (Gmel & Rehm, 2004; Sobell & Sobell, 2004).

Frequency was assessed by inquiring about the number of days in a typical 30 day period when participants would have had at least one alcoholic beverage, with one drink defined in the survey as "1 drink = 1 beer/cider, 1 glass of wine, or 1 liquor drink", both prior to initiating medical cannabis use and in the 30 days prior to the survey. Amount was assessed by inquiring about the average number of drinks per 7 day week prior to medical cannabis initiation, as well as in an average 7 day week in the 30 days preceding the survey, with the following categorical ranges provided via multiple choice: 0; less than 5 drinks per week; 5-10 drinks per week; 11-20 drinks per week; 21-30 drinks per week; 31-40 drinks per week; 41-50 drinks per week; over 50 drinks per week. A reduction in frequency of use was therefore defined as lower self-reported use in the 30 days prior to the survey compared to the pre-medical cannabis period, and a response of "0" days of use in the 30 days prior to the survey was interpreted as complete cessation of alcohol use. Since alcohol and tobacco/nicotine use have been found to be complimentary substances (Allsop et al., 2014; Room, 2004; Tauchmann, Lenz, Requate, & Schmidt, 2013), tobacco/nicotine use was assessed in a similar manner, except the questions focused on "uses per day" and "days of use" over 30 days prior to initiating medical cannabis and in the 30 days prior to the survey, with no use in the last 30 days interpreted as complete cessation of use.

We gathered cannabis use information via multiple choice questions. Primary method of use was assessed by providing a list of common methods of use (i.e., vaporizer/flower, oral oil/drops, oral capsules, oral edibles, oral tincture, joint, pipe, waterpipe/bong, vape pen, concentrates, topical, juicing, and "other") limited to a single response. Those who identified flower use were asked about days per week of use, as well as typical rates of use per day, from "0.25 grams or less" to "4 grams or more". Participants were also asked to identify preferred flower types (i.e., indica, sativa, hybrid, 1:1 balanced CBD/THC; high CBD/low THC; or no favourite). Those that identified extract use (i.e., drops or capsules) answered questions specific to these products, including what type of extract they used most

(i.e., high THC/low CBD, high CBD/low THC, and 1:1 THC/CBD options). Frequency of use for extracts was assessed by inquiring about "days per past week" use and "times per day" use. We also assessed how long participants had been using medical cannabis by asking how old they were when they first began to use medical cannabis, and then subtracting that number from their age at the time of the survey.

Additionally, for all substances, including alcohol, the level of deliberate intent to use cannabis as a potential reduction/cessation strategy was assessed via single-answer multiple choice with the following options: I was surprised to find that my use of _____ changed after I began to use medical cannabis; I deliberately used medical cannabis with the goal of reducing my use of _____; My MD recommended medical cannabis in order to reduce my use of _____; My MD recommended medical cannabis and then worked with me to develop a specific tapering program to help reduce my use of _____; None of the above.

Participants were also asked about their potential use of other alcohol reduction strategies via multiple choice and the ability to click any or all of the following options: Alcoholics Anonymous; pharmacological treatment (i.e., Antabuse, residential addiction treatment; inpatient addiction treatment; outpatient addiction treatment; addiction counselling; other (prompting a textual response); none of the above.

2.3.2 Analysis

In these analyses, we sought to assess the relationship between changes in alcohol use and medical cannabis initiation and patterns of use, as well as associated variables. Our analyses included an examination of potential variables associated with either reduction or cessation in alcohol use due to their known or theoretical relationship with the primary outcome of interest.

First, using descriptive statistics, we assessed all participant sociodemographic characteristics possibly associated with alcohol use and/or reduction, including tobacco/nicotine (T/N) cessation,

involvement with traditional alcohol cessation strategies, frequency and type of cannabis use (e.g. CBD vs. THC; oral use vs. inhalation) and degree of self-reported intent to reduce or quit alcohol use, the latter of which was ultimately amalgamated into two binary groups to compare intent vs. no intent, with the former grouping consisting of participants who checked any of the following: *I deliberately used medical cannabis with the goal of reducing my use of alcohol; My MD recommended medical cannabis in order to reduce my use of alcohol; My MD recommended medical cannabis and then worked with me to develop a specific tapering program to help reduce my use of alcohol*; and the latter composed of those who checked either: *I was surprised to find that my use of alcohol changed after I began to use medical cannabis,* or *none of the above*. We then used Chi-square or Fisher's exact test as appropriate to assess the relationship between each independent variable and the primary binary outcomes of interest. Significance of the change in alcohol frequency/amounts in the entire cohort was assessed using the sign test, and comparison between subgroups was based on Kruskal-Wallis test.

Next, we proceeded with univariate and multivariate logistic regression analyses to estimate the association between potential covariates and the outcomes of interest: decreased alcohol frequency/amounts (yes vs. no), and cessation of alcohol use (yes vs. no). We included the following variables in our crude and adjusted logistic regression analyses: intent to use cannabis to reduce alcohol use (yes vs. no); gender (male vs. female), age (≥55 vs. <55), top 3 primary condition type (pain, mental health and insomnia, all yes vs. no), preferred type of cannabis (THC vs. CBD), daily cannabis use (yes vs. no), primary method of use (orally ingested vs. inhaled), use of other alcohol reduction strategies (yes vs. no), alcohol use frequency per month (per day increase), number of drinks per week in the pre-period (11-30 vs. 1-10, and >30 vs. 1-10), and cessation of T/N use in the post-cannabis period (yes vs. no). Effect measures were presented as odds ratio with 95% confidence interval, and only those findings with $p<0.05$ were considered significant. Missing data lead to variations in the sample sizes across comparisons in the univariate analysis (n=803-972), and the multivariate analysis only included patients with no missing data for all variables (n=696-710). In order to ensure that the exclusion of participants in

the multivariate analysis did not effect the primary outcomes of interest, we used Chi-square test to compare reductions in alcohol frequency/amounts and rates of cessation post medical cannabis initiation between those included in the multivariate analysis and those excluded.

Additionally, in order to assess for any potential bias or confounders that may have been associated with the increased period between the pre-and-post medical cannabis assessments, we conducted a sensitivity analysis restricted to those patients that initiated medical cannabis within the past 5 years to see if there were any obvious differences in outcomes between those with more recent medical cannabis use compared to those reporting a longer history of use.

Finally, when the regression analysis found that intent to use cannabis to reduce alcohol use and both frequency and amounts of alcohol used prior to medical cannabis were the variables with the strongest statistical association with reductions in alcohol use, we used the Wilcoxon rank sum test to examine the relationship between these variables to determine if they were indeed associated.

All analyses were conducted in SAS 9.4 (SAS Institute, Cary NC). All statistical tests were two-sided, with significance levels of 0.05 unless otherwise indicated.

2.4 Results

Between January 11 and 18 2019, 2102 individuals were recruited and completed the survey, 973 of which reported past/present alcohol use and were therefore included in this study. The primary sociodemographic and health-related characteristics of the sample are reported in Table 1. Individuals using alcohol were mostly male (59.6%; n=544), and the median age was 48 years old (IQR 37-58). A significant majority were married or equivalent (71.4%; n=691), white (91.7%, n=889), and 81.1% (n=787) reported having a college degree or higher. In terms of residence, Alberta and Ontario were over-

represented in the sample, which is consistent with Health Canada data on the geographic distribution of medical cannabis patients in Canada (Health Canada, 2019).

The five most common primary conditions cited by participants were chronic pain (30.1%; n=293), insomnia (14%; n=136), anxiety (12.1%; n=118), arthritis (11.3%; n=110), and depression (4.4%; n=43). In fact, when combined, pain, insomnia and mental health issues accounted for 84.4% (n=822) of all participants, which is consistent with past research on authorized medical cannabis patients in Canada and in other jurisdictions around the world (Boehnke et al., 2019; Campbell et al., 2018; de Hoop, Heerdink, & Hazekamp, 2018; Hazekamp, Ware, Muller-Vahl, Abrams, & Grotenhermen, 2013; Lucas et al., 2019a; Reiman et al., 2017; Walsh et al., 2013). (Table 1)

2.4.1 Table 1. Characteristics of 973 participants reporting alcohol use pre-medical cannabis initiation.

Characteristics	n (%)
Gender	
Unknown	60
Male	544 (59.6)
Female	366 (40.1)
Other	3 (0.3)
Age	
Unknown	148
Median (IQR)	48.0 (37.0, 58.0)
Range	(20.0, 83.0)
Current relationship status, n (%)	
Unknown	5
Widowed/Single/Divorced/Single, never married	277 (28.6)
Married/In a domestic partnership or civil union /Single, but cohabiting	691 (71.4)
Ethnicity, n (%)	
Unknown	4
Caucasian	889 (91.7)
Hispanic	4 (0.4)
Asian/South Asian	18(1.8)
Black	7 (0.7)
Aboriginal/First Nation/Metis	10 (1.0)
Other	41 (4.2)
Highest degree completed, n (%)	
Unknown	2
High school or lower	184 (18.9)
College or higher	787 (81.1)
Annual household income, n (%)	
Unknown	21
Less than $40,000	194 (20.4)
$40,000 - $69,999	253 (26.6)
$70,000 - $99,999	161 (16.9)
$100,000 - $129,999	161 (16.9)

$130,000 or more	183 (19.2)
Province/Territory, n (%)	
Unknown	4
AB	442 (45.6)
BC	155 (16.0)
MB	35 (3.6)
NB/NS/PEI/NL	61 (6.3)
NWT/YT/NU	4 (0.4)
ON	244 (25.2)
QC	8 (0.8)
SK	19 (2.0)
Primary condition, n (%)	
Unknown	0
ADD/ADHD	9 (0.9)
Addiction/dependence/withdrawal	1 (0.1)
AIDS/HIV	3 (0.3)
Anxiety	118 (12.1)
Arthritis	110 (11.3)
Autism	1 (0.1)
Brain Injury	1 (0.1)
Cancer/Leukemia	18 (1.8)
Chronic Pain	293 (30.1)
Crohn's Disease	12 (1.2)
Depression	43 (4.4)
Diabetes	5 (0.5)
Eating Disorder	2 (0.2)
Epilepsy	5 (0.5)
Fibromyalgia	41 (4.2)
Gastrointestinal Disorder	22 (2.3)
Glaucoma	0 (0.0)
Headache/migraine	27 (2.8)
Hepatitis	1 (0.1)
Insomnia	136 (14.0)
Mental Health Condition (other than anxiety, depression, OCD or PTSD)	14 (1.4)
Movement Disorder	7 (0.7)
Multiple Sclerosis	31 (3.2)
Obsessive Compulsive Disorder (OCD)	0 (0.0)
Osteoporosis	6 (0.6)
Post Traumatic Stress Disorder (PTSD)	40 (4.1)
Seizure Disorder	2 (0.2)
Skin Condition	5 (0.5)
Other	20 (2.1)

Table 2 highlights some of the primary patterns of cannabis use in this population. On average, the median age of medical initiation was 43 years (IQR 32-55), and participants report having used medical cannabis for a median of 3 years (IQR 1.0-5.0). In regards to patterns of cannabis use, 692 (72.8%) reported daily cannabis use, with a median of 14 (IQR 7.0-21.0) uses per week. The primary method of use reported by participants was via oral solution/drops (34.6%; n=336), followed by vaporization of

cannabis flower (24.1%; n=234) and joints (18.5%; n=180). In total, 654 (67.3%) participants reported non-smoked methods of ingestion as their primary method of use, while 312 (32.1%) reported smoking in one form or another.

2.4.2 Table 2. Patterns of cannabis use and level of intent to use medical cannabis to reduce alcohol use in 973 participants reporting alcohol use pre-medical cannabis.

Characteristics	n (%)
Number of days per week used cannabis	
Unknown	23
<7	258 (27.2)
7	692 (72.8)
Number of days per week used cannabis, n (%)	
# missing	23
Median (IQR)	7.0 (6.0, 7.0)
Range	(1.0, 7.0)
Frequency of cannabis use per week, n (%)~	
# missing	57
Median (IQR)	14.0 (7.0, 21.0)
Range	(1.0, 87.5)
Primary method of use, n (%)	
Unknown	1
Vaporizer - cannabis flower/bud	234 (24.1)
Oral Oil/Drops	336 (34.6)
Oral Capsules	27 (2.8)
Oral edibles	20 (2.1)
Oral tincture	8 (0.8)
Joint	180 (18.5)
Pipe	78 (8.0)
Waterpipe/bong	54 (5.6)
Vape pen	7 (0.7)
Concentrates	14 (1.4)
Topical	7 (0.7)
Juicing	1 (0.1)
Other	6 (0.6)
Used cannabis flower, n (%)	
Unknown	1
No	208 (21.4)
Yes	764 (78.6)
Cannabis flower per week (grams)	
# missing	11
Median (IQR)	5.0 (2.0, 10.0)
Range	(0.5, 35.0)
Cannabis flower per day for medical purposes (grams)	
# missing	19
Median (IQR)	0.75 (0.13, 2.00)
Range	(0.13, 5.00)
Currently using Tilray extract, n (%)	
Unknown	11
No	390 (40.5)
Yes	572 (59.5)
Favorite type of flower cannabis & extract currently using the most, n (%)	
Unknown	74

No preference	197 (21.9)
High THC	387 (55.1)
Balance CBD/THC	135 (19.2)
High CBD	180 (25.6)
Level of intention to use cannabis to reduce alcohol use, n (%)	
No intent	634 (65.2)
Surprised alcohol usage changed after medical cannabis	201 (20.7)
Deliberately used medical cannabis to reduce use of alcohol	131 (13.5)
MD recommended medical cannabis	3 (0.3)
MD recommended medical cannabis and developed tapering program	3 (0.3)

A majority (78.6%; n=764) reported using flower/bud, with a median of 5 grams per week (IQR 2.0-10.0). Most reported using extract products (59.5%; n=572), and overall 387 (55.1%) participants cited a preference for high THC flower or extract products, 180 (25.6%) preferred high CBD, 135 (19.2%) preferred products with similar amounts of THC and CBD, and 197 (21.9%) cited no specific preference.

In assessing the overall intention of participants to use cannabis to reduce their use of alcohol, 835 (85.9%) reported no such intent or being surprised their alcohol use changed after initiating medical cannabis use, while 131 (13.5%) deliberately used cannabis to reduce their alcohol use, and 6 (0.6%) reported some physician involvement in using cannabis as an alcohol reduction strategy (Table 2).

Table 3 highlights the changes in alcohol use frequency and number of drinks per week following medical cannabis initiation. In terms of frequency, 419 (43.5%) participants reported a decrease in alcohol use days, 347 (36%) stayed the same, 198 (20.5%) saw an increase in frequency. Median drinking days went from 10.5 (IQR 5.0-20.0) prior to medical cannabis, to 8.0 days (IQR 3.0-15.5). In regards to the number of drinks per week, 323 (34.1%) reported a decrease, 559 (59%) reported no change, and 66 (7%) increased the number of drinks per week. Overall, the median number of drinks per week went from 7.5 (IQR 3.0-15.5) to 3.0 (IQR 3.0-7.5). Additionally, 76 (7.8%) of the participants who saw a reduction in frequency reported using no alcohol at all in the 30 days prior to the survey, and were therefore classified as having ceased use altogether.

2.4.3 Table 3. Changes in alcohol use frequency and number of drinks pre-and-post medical cannabis use among 973 participants.

Variable	Pre-Medical Cannabis	Post-Medical Cannabis
Alcohol – number reporting change in days using alcohol per 30 days pre vs. post medical cannabis, n=964*		**n (%)**
Increased		198 (20.5)
Decreased		419 (43.5)
Stayed the same		347 (36.0)
Days used alcohol per month, n=964*	**Median (IQR)**	**Median (IQR)**
	10.5 (5.0, 20.0)	8.0 (3.0, 15.5)
Alcohol – number reporting change in number of drinks per week, pre vs. post medical cannabis, n=948*		**n (%)**
Increased		66 (7.0)
Decreased		323 (34.1)
Stayed the same		559 (59.0)
Median number of drinks per week^, n=948*	**Median (IQR)**	**Median (IQR)**
	7.5 (3.0, 15.5)	3.0 (3.0, 7.5)
Alcohol - complete cessation, post-medical cannabis, n=973		**n (%)**
Yes		76 (7.8)
No		897 (92.2)

* Sample size was reduced due to missing frequency or dosage data.
^ Mid-point of the reported range was used in the calculation. Those who reported using over 50 drinks were assumed to be using 1.25x50=62.5 drinks per week.

Table 4 examines the changes in alcohol use by participant characteristics. Both gender and age were strongly associated with reductions in alcohol use, but not with cessation. More men than women reported reductions in the number of drinks per week (40.5%; n=213 vs. 27.2%; n=98; $p<0.001$). In regards to age, a higher proportion of those below 55 years of age reported reducing the frequency of drinking days (49.5%; n=267 vs. 30.6%; n=85, $p<0.001$) and the number of drinks per week (38.3%, n=204 vs. 26.3%; n=71, $p<0.001$) than those 55 or over.

Of the three most common primary condition types reported by participants, those with mental health challenges were more likely than those with pain or insomnia to report reductions in the frequency of use over 30 days ($p=0.014$), number of drinks in a week ($p=0.007$), and cessation of use ($p<0.001$). Cannabis type was also associated with rates of reduction. Those reporting a preference for high THC (vs. high CBD) products saw a higher proportion reducing frequency of use (45.7%; n=174 vs. 34.1%, n=61,

p=0.01), drinks per week (39.0%; n=147 vs. 22.6%; n=40, p<0.001) and ceasing alcohol use altogether (8.8%; n=34 vs. 2.2%; n=4, p=.004). Similarly, those reporting inhalation as a primary method of use saw a higher proportion reducing frequency of use (47.4%; n=265 vs. 37.3%; n=146, p=0.002), drinks per week (37.9%; n=209 vs. 28.9%; n=111, p=0.004), as well as greater rates of cessation (9.9%; n=56 vs. 4.8%; n=19, p=0.004) (Table 4).

We also found a linear association between greater frequency and amounts of alcohol use pre-medical cannabis initiation and reductions post-medical cannabis initiation. In regards to frequency, those reporting drinking from 21 to 30 days per month in the pre-period saw a higher percentage reporting reductions in frequency (59.1%; n=130) compared to those that drank between 11 to 20 days (51.1%; n=134) or 1 to 10 days (32.2%; n=155) (p<0.001). Rates of cessation followed a similar pattern, with 12.1% (n=27) of those reporting from 21 to 30 days of drinking ceasing use altogether, compared to 6% (n=16) of those who drank from 11 to 20 days, and 6.8% (n=33) of those who drank from 1 to 10 days prior to medical cannabis association (p=0.023). We also found a strong linear correlation between greater number of drinks per week and rates of reduction and cessation, with 70.4% (n=50) of those who reported over >30 per week prior to medical cannabis citing reductions in use, 83.6% (n=61) reporting reductions in weekly drinks, and 27.4% (n=20) ceasing use altogether when compared to 1-10 drinks and 11-30 drinks per week (p<0.001) (Table 4).

2.4.4 Table 4. Changes in alcohol use stratified by primary socio-demographic, behavioural, health- and cannabis use-related characteristics among 973 participants.

	Reduction in usage frequency		Reduction in number of drinks		Complete cessation	
Characteristics	**Percentage**	**P***	**Percentage**	**P***	**Percentage**	**P***
All £	419/964 (43.5)	-	323/948 (34.1)	-	76/973 (7.8)	-
Gender		0.080		<0.001		0.136
Male	253/537 (47.1)		213/526 (40.5)		49/544 (9.0)	
Female	150/364 (41.2)		98/360 (27.2)		23/366 (6.3)	
Age		<0.001		<0.001		0.142
<55	267/539 (49.5)		204/533 (38.3)		47/546 (8.6)	
≥55	85/278 (30.6)		71/270 (26.3)		16/279 (5.7)	
Primary condition		0.014		0.007		<0.001
Pain	183/467 (39.2)		140/456 (30.7)		26/471 (5.5)	
Mental health issues	115/214 (53.7)		93/214 (43.5)		31/217 (14.3)	
Insomnia	59/136 (43.4)		40/132 (30.3)		6/136 (4.4)	
Preferred type of cannabis		0.010		<0.001		0.004

High THC	174/381 (45.7)		147/377 (39.0)		34/387 (8.8)	
High CBD	61/179 (34.1)		40/177 (22.6)		4/180 (2.2)	
Primary method of use		0.002		0.004		0.004
Inhaled	265/559 (47.4)		209/551 (37.9)		56/567 (9.9)	
Orally ingested	146/391 (37.3)		111/384 (28.9)		19/392 (4.8)	
Usage frequency in the pre period		<0.001		<0.001		0.023
1-10 days per month	155/482 (32.2)		97/466 (20.8)		33/483 (6.8)	
11-20 days per month	134/262 (51.1)		101/262 (38.5)		16/265 (6.0)	
21-30 days per month	130/220 (59.1)		125/218 (57.3)		27/223 (12.1)	
Number of drinks per week in the pre period		<0.001		<0.001		<0.001
1-10 drinks	248/670 (37.0)		132/664 (19.9)		37/673 (5.5)	
11-30 drinks	119/218 (54.6)		130/211 (61.6)		19/221 (8.6)	
>30 drinks	50/71 (70.4)		61/73 (83.6)		20/73 (27.4)	
Intent to use cannabis to reduce alcohol use		<0.001		<0.001		<0.001
None/Surprised	325/829 (39.2)		233/815 (28.6)		45/835 (5.4)	
Deliberately/MD recommended/MD developed	93/134 (69.4)		89/132 (67.4)		30/137 (21.9)	
Any alcohol reduction strategies		<0.001		<0.001		<0.001
No	394/929 (42.4)		299/915 (32.7)		66/937 (7.0)	
Yes	16/20 (80.0)		16/18 (88.9)		7/21 (33.3)	
Tobacco - complete cessation (among pre-users only)		0.326		0.027		0.030
Yes	50/89 (56.2)		45/90 (50.0)		18/90 (20.0)	
No	109/218 (50.0)		79/217 (36.4)		24/223 (10.8)	

*For comparison between subgroups, p value was based on Chi-square test, Fisher's exact test or Kruskal-Wallis test as appropriate.

£ For assessing the change in the entire cohort, sign test with one-sided alternative hypothesis of median less than zero was used.

Both the level of intent to use cannabis to reduce alcohol use, as well as experience with other alcohol reduction strategies were strongly associated with greater rates of reduction and cessation. Those reporting actual intent to use cannabis to reduce alcohol consumption saw a greater percentage reducing frequency of use (69.4%, n=93 vs. 39.2%, n=325, p<0.001), drinks per week (67.4%, n=89 vs. 28.6%, n=233, p<0.001), and ceasing use altogether (21.9%, n=30 vs. 5.4%, n=45, p<0.001). Those with experience with traditional alcohol reduction strategies also saw a higher percentage reporting reductions in alcohol use frequency (80%, n=16, vs. 42.4%, n=394, p<0.001), drinks per week (88.9%, n=16 vs. 32.7%, n=299, p<0.001), and alcohol cessation (33.3%, n=7 vs. 7%, n=66, p<0.001) (Table 4).

Finally, in light of the high rate of alcohol and tobacco/nicotine co-use reported by participants (32.2% of individuals using alcohol also reported T/N use in the pre-period, n=314) and evidence suggesting that these two substances are complementary (Allsop et al., 2014; Room, 2004; Tauchmann et al., 2013), we examined the association between tobacco/nicotine (T/N) cessation and alcohol reduction/cessation, finding that while T/N cessation was not associated with reductions in alcohol use frequency (p=0.326), it was associated with a greater number reporting reductions in alcohol drinks per week (p=0.027), and with nearly double the rates of alcohol cessation (20%, n=18 vs. 10.8%, n=24, p=0.03) (Table 4).

Table 5 presents the results of the univariate and multivariate logistic regression analyses of the primary variables associated with alcohol reduction: intent, gender, age, primary condition, preferred type of cannabis, daily cannabis use, primary method of use, use of alcohol reduction strategies, alcohol use frequency and amounts, and tobacco/nicotine cessation. This analysis found that greater intent to use cannabis to reduce alcohol consumption, and greater frequency and amounts of alcohol use in the pre-period were the primary variables associated with alcohol reduction following medical cannabis initiation. Identifying any level of intent to use cannabis to reduce alcohol resulted in Adjusted Odds Ratio (AOR) of 2.02 (95% CI 1.25-3.27) of reducing the number of drinking days, and an AOR of 2.54 (95% CI 1.49-4,33) of reducing the number of drinks per week. Additionally, intent was associated with greater adjusted odds of complete cessation of alcohol use (AOR 2.57, 95% CI 1.28-5.14). Regression analysis of the association between the frequency and amount of alcohol use in the pre-period showed a consistent positive association with reductions in use post-medical cannabis, but not with actual cessation. Every per day increase in alcohol use frequency over 30 days in the pre-period was associated with AOR 1.05 (95% CI 1.04-1.07) of reducing use frequency in the 30 days prior to the survey. Similarly, the greater the number of drinks per week reported in the pre-period, the greater the odds of reducing use: >30 compared to 1-10 resulted in AOR 10.47 (95% CI 5.10-21.47), and of ceasing alcohol use altogether (AOR 3.04, 95%CI 1.32-7.03) (Table 5).

2.4.5 Table 5. Sociodemographic, behavioural, health and cannabis use-related factors associated with changes in alcohol usage among 973 participants.

	Reduction in use frequency per 30 days				Reduction in number of drinks per week				Complete cessation			
	Univariate (n=817-949)*		Multivariate (n=706)*		Univariate (n=803-948)*		Multivariate (n=696)*		Univariate (n=825-972)*		Multivariate (n=710)*	
Variable and comparison	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**
Level of intention to use cannabis to reduce alcohol use												
Deliberately/MD Recommended/MD Developed vs. None/Surprised	3.52 (2.37, 5.21)	<0.001	2.02 (1.25, 3.27)	0.004	5.17 (3.48, 7.67)	<0.001	2.54 (1.49, 4.33)	<0.001	4.93 (2.98, 8.15)	<0.001	2.57 (1.28, 5.14)	0.008
Gender												
Male vs. Female	1.27 (0.97, 1.66)	0.080	1.09 (0.78, 1.53)	0.598	1.82 (1.36, 2.43)	<0.001	1.36 (0.92, 2.00)	0.122	1.46 (0.88, 2.43)	0.146	1.35 (0.70, 2.62)	0.371
Age												
<55 vs. ≥55	2.23 (1.64, 3.03)	<0.001	2.12 (1.46, 3.09)	<0.001	1.74 (1.26, 2.40)	<0.001	1.35 (0.89, 2.06)	0.163	1.52 (0.85, 2.71)	0.159	0.86 (0.42, 1.75)	0.677
Primary condition												
Pain – Y vs. N	0.80 (0.60, 1.08)	0.146	1.04 (0.72, 1.50)	0.829	0.81 (0.59, 1.10)	0.182	1.00 (0.67, 1.52)	0.982	0.58 (0.33, 1.00)	0.049	0.67 (0.33, 1.35)	0.266
Mental health issues – Y vs. N	1.63 (1.15, 2.31)	0.006	1.44 (0.94, 2.22)	0.097	1.56 (1.09, 2.24)	0.015	1.46 (0.90, 2.36)	0.126	2.02 (1.18, 3.46)	0.011	1.99 (0.99, 4.01)	0.053
Insomnia – Y vs. N	0.99 (0.66, 1.49)	0.966	0.84 (0.51, 1.39)	0.494	0.80 (0.51, 1.23)	0.305	0.70 (0.39, 1.26)	0.229	0.47 (0.20, 1.11)	0.085	0.38 (0.13, 1.11)	0.078
Preferred type of cannabis												
THC vs. CBD	1.63 (1.12, 2.35)	0.010	1.01 (0.62, 1.64)	0.979	2.19 (1.45, 3.29)	<0.001	1.44 (0.81, 2.55)	0.216	3.83 (1.41, 10.42)	0.009	2.32 (0.72, 7.46)	0.160
Used cannabis daily												
Yes vs. No	1.10 (0.82, 1.47)	0.525	1.07 (0.74, 1.53)	0.732	1.41 (1.03, 1.93)	0.031	1.11 (0.74, 1.68)	0.613	1.83 (1.00, 3.36)	0.050	1.24 (0.60, 2.55)	0.568
Primary method of use												
Inhaled vs. Orally ingested	1.51 (1.16, 1.97)	0.002	0.98 (0.67, 1.45)	0.934	1.50 (1.14, 1.99)	0.004	0.85 (0.55, 1.33)	0.487	2.12 (1.24, 3.60)	0.006	1.13 (0.55, 2.33)	0.741
Use of other alcohol reduction strategies												
Yes vs. No	4.98 (1.70, 14.60)	0.003	2.35 (0.68, 8.14)	0.177	13.58 (3.44, 53.65)	<0.001	4.72 (0.93, 23.96)	0.061	6.78 (2.66, 17.29)	<0.001	4.20 (1.21, 14.66)	0.024
Alcohol use frequency per month in the pre period												
Per day increase	1.05 (1.04, 1.07)	<0.001	1.05 (1.03, 1.07)	<0.001								
Number of drinks per week in the pre period												
11-30 vs. 1-10					6.47 (4.62, 9.06)	<0.001	5.34 (3.52, 8.11)	<0.001	1.63 (0.92, 2.89)	0.091	0.99 (0.48, 2.05)	0.984
>30 vs. 1-10					20.49 (10.72, 39.15)	<0.001	10.47 (5.10, 21.47)	<0.001	6.50 (3.54, 11.96)	<0.001	3.04 (1.32, 7.03)	0.009
Cessation of tobacco/nicotine												
Yes vs. No	1.28 (0.78, 2.10)	0.326	1.21 (0.65, 2.23)	0.546	1.75 (1.06, 2.87)	0.028	1.60 (0.81, 3.16)	0.177	2.08 (1.07, 4.03)	0.031	2.04 (0.83, 5.03)	0.119

* Sample size in the univariate analysis varied across comparisons due to missing data. Multivariate analysis only included patients with no missing data for all variables.
Odds ratio was based on logistic regression

Additionally, being below age 55 was also associated with greater adjusted odds of seeing a reduction in the frequency of use over 30 days (AOR = 2.12, 95% CI: 1.46-3.09) compared to those 55 or over. In examining the impact of the top three primary condition types on alcohol reduction and cessation, mental health was indeed associated with reduction and cessation of use in univariate analysis, however multivariate analysis suggested no significant association with reductions, but did identify a borderline statistical association with cessation (AOR 1.99, 95% CI 0.99-4.01, p=0.053). As noted earlier, we also used Chi-square test to compare reductions in alcohol frequency/amounts and rates of cessation post medical cannabis initiation between those included in the multivariate analysis and those excluded, finding no statistically significant difference in these primary outcomes (Appendix A).

Table 6 highlights the relationship between the primary variables associated with alcohol reduction: intent to use medical cannabis to reduce alcohol use, and amount and frequency used pre-and-post medical cannabis. This exploratory analysis found a strong association between these characteristics, with those intending to use medical cannabis to reduce alcohol use reporting far greater median frequency of days using alcohol over 30 days in the pre-period compared to those reporting no intent (median 20.0 (IQR 10.0-30.0 vs. median 10.0 (IQR 5.0-20.0), p<0.001), and greater median drinks per week in the pre-period as well (median 15.5 (IQR 7.5-25.5) vs. median 7.5 (IQR 3.0-7.5), p<0.001). Additionally, intent was also associated with fewer median days per month of alcohol use post-medical cannabis initiation compared to no intent (median 7.0 (IQR1.0-15.0) vs. 8.0 (IQR 3.0-18.0), p=0.017), although no such association was found in the number of drinks per week (p=0.203).

2.4.6 Table 6. The relationship between frequency and amounts of alcohol used and intent to use medical cannabis to reduce alcohol use pre-and-post medical cannabis initiation.

	Unintentional	Intentional	P*
Alcohol usage days per month in the pre-period			<0.001
Median (IQR)	10.0 (5.0, 20.0)	20.0 (10.0, 30.0)	
Mean (SD)	13.0 (9.4)	18.4 (9.8)	
Range	(1.0, 30.0)	(1.0, 30.0)	

Number of drinks per week in the pre-period			<0.001
Median (IQR)	7.5 (3.0, 7.5)	15.5 (7.5, 25.5)	
Mean (SD)	9.6 (10.2)	20.2 (16.1)	
Range	(3.0, 62.5)	(3.0, 62.5)	
Alcohol usage days per month in the post-period			0.017
Median (IQR)	8.0 (3.0, 18.0)	7.0 (1.0, 15.0)	
Mean (SD)	10.8 (8.9)	9.2 (8.9)	
Range	(0.0, 30.0)	(0.0, 30.0)	
Number of drinks per week in the post-period			0.203
Median (IQR)	3.0 (3.0, 7.5)	3.0 (3.0, 7.5)	
Mean (SD)	7.0 (7.7)	7.4 (10.0)	
Range	(0.0, 62.5)	(0.0, 62.5)	

*For comparison between subgroups, p value was based on Chi-square test, Fisher's exact test or Kruskal-Wallis test as appropriate.

Finally, in noting the significant period of time between medical cannabis initiation and the 30 days prior to the survey reported by some participants (median 3 yrs, IQR 1.0-5.0), we conducted a sensitivity analysis comparing the results of the multivariate analysis in those that initiated medical cannabis within the past 5 years with those of the full study population, and the outcomes remained similar (Appendix B).

2.5 Discussion

In this study using data from a large survey involving 973 medical cannabis patients wo reported past or current alcohol use, we observed significant self-reported reductions in alcohol use following medical cannabis initiation. In examining variables associated with alcohol reduction, we found a linear association between frequency and amount of use in the pre-period, and rates of decline in both post-medical cannabis initiation. In fact, rates of use and a specific intent to use medical cannabis to reduce alcohol use were the most consistent variables resulting in alcohol reduction and/or cessation, potentially suggesting that those who used more alcohol were also likely impacted by greater rates of alcohol-related problems, and therefore identified a greater intent to explore cannabis as an alcohol-reduction strategy.

We tested this theory by examining the relationship between greater rates of use in the pre-period and a stated intent to use cannabis to reduce/cease use, and found that there was indeed a strong statistical relationship ($p<0.001$) between these variables (Table 6). Previous longitudinal research has found that the deliberate intent to use cannabis as a substitute for crack cocaine was effective in reducing use (Socías et al., 2017), and studies assessing treatment outcomes for substance use disorders have consistently reported a relationship between motivation/intent to change and treatment success (Breda & Heflinger, 2007; McKay & Weiss, 2001; Shields et al., 2014). The significant association between the intention to use cannabis to reduce alcohol and greater subsequent rates of reduction/cessation in this study adds to these previous findings, and suggests a need to conduct more comprehensive assessments of intent/motivation for cannabis use in polysubstance use research. Such investigations could be particularly relevant for those that have either had poor success with, or are looking for alternatives, to abstinence-based treatment options.

The higher rates of reduction/cessation in those reporting mental health conditions has potentially significant implications, since mood disorders and substance use disorders (including AUD) are common psychiatric comorbidities (Boden & Fergusson, 2011; Petrakis, Gonzales, Rosenheck, & Krystal, 2002; Quello, Brady, & Sonne, 2005; Shield et al., 2013; Shivani, Goldsmith, & Anthenelli, 2002; Zhou et al., 2016). Additionally, those with a dual diagnosis of alcohol use disorder comorbid with additional mental health conditions are a higher risk for suicide (Berglund & Ojehagen, 1998), and are at greater risk of relapse when attempting to stop using alcohol (Bradizza et al., 2006). Since research has found an association between the implementation of state-level medical cannabis laws and reductions in the rate of suicides in some populations theoretically due to reduced alcohol consumption (D. Anderson, Rees, & Sabia, 2012), the high rate of medical cannabis use for mental health disorders (Turna, Simpson, Patterson, Lucas, & Van Ameringen, 2019; Walsh et al., 2017) and the association between starting medical cannabis and reducing and/or eliminating alcohol use documented in our study and other observational research (Lucas et al., 2019a, 2013; Reiman, 2009) is notable and suggests further research

is warranted to better elucidate the relationship between mental health conditions, alcohol and cannabis use.

Finally, while the present results do not speak to the desirability of substituting cannabis for alcohol, there exists significant evidence that the personal and public health burden of cannabis use is far less than that of alcohol. A Swiss study found that while alcohol use was associated with a relative risk of injury of 3.00 (CI 1.78 - 5.04) compared with no alcohol use, cannabis use was associated with a reduced risk of injury (RR: 0.33; CI 0.12 - 0.92). An assessment of drug harms in the United Kingdom conducted by the Independent Scientific Committee on Drugs (ISCD) applied multicriteria decision analysis (MCDA) modeling to assess the harms of 20 commonly-used licit and illicit substances (Nutt, King, & Phillips, 2010). They employed 16 weighed criteria—nine focused on harms to the individual, and seven assessing harms to others—scoring substances out of 100 points, with higher scores indicating greater harms. Overall, researchers scored alcohol the highest at 72, followed by heroin at 55. Cannabis scored 20, recognizing the relatively modest harms associated with its use compared to other substances. A more recent comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs used a Margin of Exposure (MOE) approach (Lachenmeier & Rehm, 2015). The MOE is the ratio between the point on the dose response curve that characterizes adverse effects in human or animal studies and the estimated human intake of the substance. Therefore, the lower the MOE, the larger the risk to people who use the substance. Using this criteria, cannabis was found to have the highest MOE and considered relatively safer than prescription drugs like diazepam and methadone, while alcohol and heroin had the lowest and were therefore considered to present the greatest biological risk to end users.

Furthermore, there's growing evidence that cannabis/cannabinoids may mitigate alcohol related harms. While a study of vaporization of cannabis with and without alcohol found that combining alcohol and cannabis leads to higher THC bioavailability and is associated with greater impairment (Hartman et al., 2016), those findings also suggest that those individuals who co-use may be able to reduce their use of alcohol and/or cannabis while achieving the same level of impairment, potentially reducing short-and-

long-term harms associated with both substances. Additionally, preclinical studies suggest that CBD can reduce alcohol consumption and potentially protect against certain harmful effects of alcohol, such as liver and brain damage (Nona, Hendershot, & Le Foll, 2019), and other research has found that cannabis can reduce inflammation associated with alcohol use (Karoly, Bidwell, Mueller, & Hutchison, 2018). Ultimately, whether cannabis represents a viable harm reduction strategy for alcohol use or treatment for AUD is beyond the scope of the current study, but certainly remains a pertinent question for future research. In light of the considerable public safety and health impacts associated with alcohol use, particularly in populations affected by chronic health conditions, these findings add a new dimension to the growing literature examining the impact of cannabis on the use of other substances, and perhaps suggest a previously unexplored avenue by which increased access to medical cannabis might benefit public health by subsequently reducing alcohol use amongst patients with chronic health conditions.

Limitations of this study include restricting the population to patients registered with Tilray as their provider of medical cannabis. While this was a national sample, it may have yielded data not representative of the broader population of medical cannabis patients in Canada, and since this sample was drawn from patients registered with a medical cannabis company, participants may be more likely to report positive effects related to the medical use of cannabis.. Additionally, as all information regarding the use of cannabis or alcohol was self-reported and did not benefit from biological drug detection to verify substance use or non-use, this data is vulnerable to recall bias, socially desirable responding, and other biases associated with self-report retrospective surveys. In particular, since the average duration of medical cannabis use in this population at the time of the survey was 5 years (median of 3 years), self-reported estimates of substance use frequency and amounts pre-medical cannabis may be particularly vulnerable to recall bias as well as other unobserved variables and confounders that may have impacted alcohol use in the interim. However, the sensitivity analysis we conducted to compare outcomes of those who had initiated medical cannabis use within the past five years with the total study population found

similar outcomes in both groups, suggesting that the time span between pre-and-post data points do not appears to have impacted the outcomes of the study.

Further, it is unknown if results from a medical cannabis patient study are generalizable to a non-patient population, as there may be characteristics inherent to a patient population – including an active intent to improve personal health outcomes – that may not be mirrored in a non-patient cannabis use population. Prospective studies examining changes in alcohol use in non-medical populations following cannabis initiation could better assess what role cannabis contributes to alcohol cravings, withdrawals and rates of reduction/cessation. Finally, social policy changes may have also impacted patient patterns of use as well as some of the outcomes of this study. Since the non-medical adult use of cannabis was legalized in Canada prior to this survey, and as there are many regulated and unregulated sources of cannabis available to Canadian patients, it is highly probable that some participants used sources of cannabis other than those accounted for in this study.

However, the large sample size, detailed measurement of alcohol use frequency and amounts pre-and-post medical cannabis use, inclusion of a measurement of intent to use medical cannabis to reduce alcohol use as well as potential confounders such as participation in other substance use treatment programs in the analysis addresses some of these limitations and previous cross-sectional surveys examining the impact of cannabis use on the use of alcohol and other substances, and could inform future studies of this kind. In light of these limitations, it would be premature to promote cannabis-based therapies for alcohol reduction/cessation, and these results should be interpreted with caution pending replication by research that employs more systematic recruitment, longitudinal designs and biological drug testing.

2.6 Authors' Contributions

PL designed the study and survey, coordinated its administration and analysis, and is the primary author of this manuscript. SB, MJM and ZW reviewed and edited the manuscript.

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3 Paper 2: Self-reported reductions in tobacco and nicotine use following medical cannabis initiation; results from a cross-sectional survey of authorized medical cannabis patients in Canada

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3.1 Abstract

Background

Despite decades of campaigns aimed at reducing Tobacco/Nicotine (T/N) use and the development of many different T/N reduction and cessation strategies, the impacts on international public health remain significant. This paper explores the self-reported use of cannabis and associated changes in T/N use among a Canadian medical cannabis patient population.

Methods

An online cross-sectional survey examining demographics, patterns of medical cannabis use, and the impact of medical cannabis on the use of various substances including tobacco/nicotine was completed by participants. This study examines the impact of medical cannabis on T/N use by comparing patterns of use before and after the initiation of medical cannabis, and then analyzing novel variables potentially associated with T/N reduction and cessation, including assessing the impact of specific "intent" to use medical cannabis to reduce T/N use, as well as potential confounders such as experience with other pharmacological or psychobehavioral T/N cessation strategies.

Results

In total, 2102 individuals were recruited, of whom 650 were current or former T/N users. Following initiation of medical cannabis use 320 (49%) of T/N users self-reported reductions in use, with 160 (24.6%) reporting no T/N use in the 30 days prior to the survey. Odds of T/N cessation were greater amongst those who were age 55 or older (Adjusted Odds Ratio [AOR] = 2.56, 95% Confidence Interval [CI] 1.53-4.26), or that reported >25 T/N uses per day in the pre-period (AOR = 2.11, 95% CI 1.14–3.92). Specific intent to use medical cannabis in order to quit resulted in significantly greater odds of reducing T/N use (AOR = 2.79, 95% CI 1.49-5.22); however, involvement with traditional T/N cessation

treatments (pharmacological or psychobehavioral) was negatively associated with T/N cessation (AOR 0.39, 95% CI 0.18-0.86).

Conclusions

Results from this retrospective survey of medical cannabis users suggest that that initiation of medical cannabis use was associated with self-reported reductions and/or cessation of T/N use in nearly half of study participants. In light of the significant morbidity, mortality and healthcare costs related to T/N dependence, future research should further evaluate the potential of cannabis-based treatments to support efforts to reduce or cease tobacco/nicotine use.

Keywords

Cannabis; marijuana; tobacco; nicotine, substitution; harm reduction

3.2 Background

The past decade has witnessed a dramatic increase in popular and scientific interest in therapeutic applications of cannabis and cannabinoids for the treatment of a variety of conditions, including chronic pain, anxiety/depression, and treatment-resistance epilepsy (Lucas, Baron, & Jikomes, 2019; MacCallum & Russo, 2018). The potential benefits of therapeutic cannabis use identified in observational studies include impacts on the use of more harmful substances (Boehnke et al., 2019; Lucas et al., 2019; Lucas & Walsh, 2017; Nutt, King, Phillips, et al., 2010). For example, a growing literature highlights the potential for cannabis to substitute for alcohol (Anderson, Rees, & Sabia, 2012; Sewell, Poling, & Sofuoglu, 2009; Subbaraman, 2014), opioids (Lucas et al., 2019; Shi et al., 2019; Wen & Hockenberry, 2018) and cocaine (Labigalini et al., 1999; Socías et al., 2017). The public health benefits of cannabis substitution are suggested in publications noting reduced opioid overdose fatalities (Liang, Bao, Wallace, Grant, & Shi, 2018; Livingston, Barnett, Delcher, & Wagenaar, 2017) traffic accidents (Anderson et al., 2013; Santaella-Tenorio et al., 2017), and dispensation of pharmaceuticals (Bradford & Bradford, 2017; Shi et al., 2019; Wen & Hockenberry, 2018) in jurisdictions that have created licit access to medical or non-medical cannabis. As this research is largely limited to observational cross-sectional surveys and population-level studies, it is not possible to conclude the presence of a causal mechanism between cannabis use and reduced frequency of other substances. However, preliminary evidence suggests some people who use substances are intentionally employing cannabis to reduce the harms of other substances. Cross-sectional surveys of cannabis patients in the US and Canada have found a high rate of self-reported deliberate substitution of cannabis for opioids and other pharmaceuticals, alcohol, tobacco and illicit substances (Boehnke et al., 2019; Lake et al., 2020; Lucas et al., 2019b). Additionally, a prospective study of intentional cannabis use to reduce crack use among 122 people who use illicit drugs (PWUD) in Vancouver, Canada, found that intentional cannabis use to reduce crack use was associated with decreased frequency of crack use (Socías et al., 2017).

Canada was one of the first nations in the world to initiate a federal programme to facilitate the legal use of medical cannabis through a physician's authorization (Belle-Isle et al., 2014; Lucas, 2009; Lucas, 2008). The most recent iteration of the program – the Access to Cannabis for Medical Purposes Regulations (ACMPR) – resulted in the licensing of large-scale cultivators (known as licensed producers, or LPs) who provide medical cannabis products to authorized patients via mail. These products include dried flower cannabis, as well as extracts for oral consumption in the forms of oils and capsules (Capler et al., 2017; Lucas, 2017; Lucas & Walsh, 2017). As of June 2019, there were more than 360,000 Canadians authorized to use medical cannabis under the ACMPR (Health Canada, 2019).

The World Health Organization estimates suggest there are approximately 1.1 billion adult smokers, and at least 367 million people using smokeless tobacco globally (*WHO global report on trends in prevalence of tobacco smoking 2000-2025, second edition*, 2018). Tobacco/nicotine (T/N) use is not only implicated in 12% of all deaths around the globe in adults aged 30 or older but also a source of substantial healthcare-related costs (WHO, 2012). However, the topic of tobacco harm reduction has long posed challenges to tobacco scientists and policy experts, and remains a source of significant debate, especially with regard to the use of electronic cigarettes (Cobb, Hendricks, & Eissenberg, 2015; *WHO Report on the Global Tobacco Epidemic, 2019*, 2019; Zeller & Hatsukami, 2009), with some arguing that since research on the overall efficacy of e-cigarettes in tobacco cessation is inconclusive (Khoudigian et al., 2016; Lindson-Hawley et al., 2016; Malas et al., 2016), and that if the long-term harms of many smokeless tobacco products is unknown, only prevention and/or abstinence-based strategies should be considered. Data on the high rate of adoption of e-cigarettes/vaping by youth (Miech, Johnston, O'Malley, Bachman, & Patrick, 2019; *WHO Report on the Global Tobacco Epidemic, 2019*, 2019), and the 2019 health crisis that led to serious lung damage in thousands of people who use T/N and THC oil vapes in the United States have only heightened the debate around T/N harm reduction (Layden et al., 2020).

In light of the heavy burden of morbidity and mortality associated with T/N dependence, a number of pharmacological, psychological/behavioral, and nicotine replacement therapies (NRT) have

been developed and evaluated for their potential impact on tobacco cessation. Overall, evidence suggests that combined pharmacotherapy (including NRTs) and behavioural treatment may assist with tobacco reduction/cessation (Cahill, Stevens, Perera, & Lancaster, 2013; Leyro, Hendricks, & Hall, 2015; Lindson, Klemperer, Hong, Ordóñez-Mena, & Aveyard, 2019; Stead, Koilpillai, Fanshawe, & Lancaster, 2016; L. Taylor, Gidal, Blakey, Tayo, & Morrison, 2018; *WHO Report on the Global Tobacco Epidemic, 2019*, 2019). Unfortunately, the success rates of these treatments are low, highlighting the need for additional tools and strategies to address T/N use and associated harms.

There is a consistent association between tobacco use and cannabis use. Current cigarette smokers report higher rates of cannabis use than non-smokers, with over 90% of Canadian students in grade 7-12 who are current cigarette smokers reporting they have also tried cannabis on at least one occasion, while only 21.8% of grade 7-12 students overall report every trying cannabis (Leos-Toro et al., 2017). Similarly, research has found that approximately 90% of people who use cannabis also report smoking tobacco (Agrawal, Budney, & Lynskey, 2012). The concurrent and co-use use of cannabis and tobacco is common due to a number of proposed behavioral, biological, socio-cultural and genetic mechanisms, including that some people who use cannabis combine it with tobacco when rolling joints/blunts (Agrawal et al., 2012; Schauer, Rosenberry, & Peters, 2017; Weinberger et al., 2019, 2020), which may increase both harms and dependence (Meier & Hatsukami, 2016; Tucker et al., 2019). Despite the well-established relationship between cannabis and T/N use, few studies have evaluated the potential impacts of cannabis use on tobacco cessation.

Population-level, cross-sectional, and prospective observational studies examining the relationship between cannabis and tobacco use and cessation have not resulted in consistent conclusions. A series of longitudinal, population-level studies focused on large US-based data sets such as the National Epidemiologic Survey on Alcohol and Related Conditions, the Population Assessment of Tobacco and Health Study, and the annual National Survey on Drug Use and Health, suggests that cannabis use may be associated with increased risk of cigarette smoking initiation, persistence and relapse, as well as reduced odds of quitting amongst some people who use cannabis, suggesting the two may be complements

(Weinberger et al., 2019, 2020; Weinberger, Platt, Copeland, & Goodwin, 2018). While a cross-sectional study found that individuals that use cannabis had a higher prevalence of current tobacco use and a lower prevalence of sustained tobacco abstinence than those who never used cannabis (Schauer, King, & McAfee, 2017), a more recent cross-sectional survey of adult individuals that use cannabis and tobacco in the US found a high rate (62%) of self-reported increases in tobacco use during cannabis quit attempts, as well as a self-reported 50% increase in rates of cannabis use during tobacco cessation (McClure et al., 2019), suggesting the two may be substitutes. An Australian prospective study of voluntary cannabis abstinence in a non-treatment seeking cannabis using population found an increase in both tobacco and alcohol use during cannabis abstinence, followed by a decrease in both once cannabis use resumed (Allsop et al., 2014), suggesting substitution, and leading us to consider the potential impact of alcohol cessation on T/N use in this analysis as well.

Qualitative, quantitative and behavioral studies examining the relationship between tobacco and cannabis use have also yielded mixed results. A qualitative study of 48 young adult individuals 18-34 that use cannabis and tobacco in the US found these substances may both substitute for and complement one another under different circumstances and within different substance use populations, with the highest rates of tobacco use associated with the strongest co-relationship between both substances. (Schauer et al., 2016). A later quantitative study of 432 US adults examining the interrelatedness of tobacco and cannabis in those who co-use both substances came to similar conclusions (Akbar, Tomko, Salazar, Squeglia, & McClure, 2019). However, a behavioural economic evaluation found that cannabis and tobacco are neither complements nor substitutes, but rather that they were independent of each other (Peters, Rosenberry, Schauer, O'Grady, & Johnson, 2017).

Prospective studies specific to tobacco cessation have also come to contradictory conclusion. Whereas one study found that any pre-treatment cannabis use led to decreased odds of tobacco smoking cessation (Gourlay et al, 1994), another study found that any illicit substance use in the pre-treatment phase reduced the likelihood of tobacco cessation. However, in the latter study, the tobacco abstinence rate among individuals that only use cannabis (40%) exceeded that of individuals that use other illicit

substances (11%), though lagged behind that of nondrug users (55%) (Stapleton, Keaney, & Sutherland, 2009). Four other studies reported no statistical relationship between cannabis use and tobacco abstinence (Hendricks et al., 2012; Humfleet et al., 1999; Metrik et al., 2011; Rabin et al., 2016). In 2020 a large Canadian study of 35,246 patients enrolled in the Smoking Treatment for Ontario Patients (STOP) study found that cannabis use was associated with 15% lower odds of quitting. However, when cannabis use was broken down by intent (i.e., medical or recreational use) and the results were adjusted for confounders, recreational cannabis use was associated with lower odds of quitting (OR 0.84, 95% CI 0.75-0.94 p=0.002), but medical cannabis use was not (Voci, Zawertailo, Baliunas, Masood, & Selby, 2020) suggesting that reasons for cannabis use, be they medical or recreational, may play a role in the overall success of tobacco cessation attempts for those who use both substances.

Very little clinical research has been conducted in this area to date, but a 2013 examination of the use of cannabidiol (CBD), a non-intoxicating cannabinoid, as adjunct to smoking cessation efforts reported that cigarette smokers randomized to a CBD inhaler evinced reductions in tobacco consumption without increased craving (Morgan et al., 2013). However, the small pilot study was limited by a relatively brief follow-up period. Further, the extent to which the effects of vaporized CBD might generalize to herbal cannabis use with various levels of different cannabinoids is not clear. A more recent study found that a single 800-mg oral dose of CBD reduced the salience and pleasantness of cigarette cues compared with placebo, but did not influence cravings or withdrawal (Hindocha et al., 2018)

In sum, despite contradictory findings, some evidence suggests a potential role for cannabis/cannabinoids in tobacco reduction/cessation, particularly amongst those using cannabis for medical purposes. However, to the best of our knowledge, to date no studies have evaluated the prevalence of changes in tobacco use following medical cannabis initiation, or assessed how potential correlates—such as intent to use medical cannabis to reduce/cease T/N use, involvement in other T/N treatment, and changes in alcohol use—may be associated with such changes. This analysis will examine self-reported changes in T/N use among individuals participating in a large national cross-sectional

survey of Canadian medical cannabis patients, with a focus on variables potentially associated with T/N reduction and/or cessation.

3.3 Methods

A 392-question cross-sectional survey was designed to gather information from Canadian federally authorized medical cannabis patients registered with Tilray, a Canadian licensed producer of medical cannabis. The survey included questions on participant demographics, patterns of cannabis use, and self-reported changes in the use of prescription drugs, alcohol, tobacco, and illicit substances following medical cannabis initiation. All respondents who provided digital informed consent and completed the survey were entered into a draw to receive one of five $1000 credits applicable towards the purchase of medical cannabis. Data was gathered on REDCap (Vanderbilt University, Nashville, TN, USA.) The inclusion criteria included being an authorized medical cannabis patient registered with Tilray, aged 18 years or older, capable of reading and understanding English and of legally consenting to participate in the study. For this particular analysis examining the impact of medical cannabis on tobacco use, only those who identified previous/current tobacco/nicotine use were included.

The survey received approval from the University of Victoria' Human Research Ethics Board December 19 2018. On January 11 2019 an invitation to participate in the survey was sent to 16,664 federally authorized medical cannabis patients who provided email addresses to Tilray. Individuals could participate in the survey from January 11 to 18, 2019.

3.3.1 Measures

The primary outcome of interest was changes in T/N use prior-and-post medical cannabis initiation. This was assessed by inquiring about typical T/N uses per day prior to using medical cannabis, and then comparing this with typical T/N uses per day in the 30 days prior to the survey, followed by varied

analyses of demographic and other variables that may have affected rates of T/N use. Demographic data was gathered via multiple choice questions, and included gender, age, current relationship status, ethnicity, education levels, annual household income, and Canadian province/territory of residence.

To gather data on the medical reason for which participants used cannabis, participants could select one primary condition from a list of common conditions associated with medical cannabis use (Lucas, Baron, & Jikomes, 2019a; Lucas & Walsh, 2017; Reiman, Welty, & Solomon, 2017; Walsh et al., 2013) (Table 1). This question also included an option of clicking "other", which prompted a textual response to capture primary conditions that may not have appeared on the provided list.

T/N use was initially assessed by inquiring if participants had ever used tobacco/nicotine five or more times per day. A positive answer led to questions assessing the number of years of regular use, and typical rates of T/N per day use in the 30 days prior to initiating medical cannabis use, as well as in the 30 days prior to the survey. Reduction of use was defined as lowering in the usage category in the "post" period, and a response of "none" in the 30 days prior to the survey was interpreted as complete cessation of use. Alcohol use was assessed in a similar manner, but with the addition of inquiring about the typical number of drinking days over a 30-day period prior to medical cannabis initiation, as well as in the 30 days prior to the survey. Once again, no use of alcohol in the 30 days prior to the survey was interpreted as complete cessation of use.

Cannabis use data was gathered via multiple choice questions and VAS. Primary method of use was assessed by providing a list of common methods of use and limiting responses to a single answer. Those who identified flower use were asked about typical rates of use per day, ranging from "0.25 grams or less" to "4 grams or more". Participants were also asked to identify favorite flower types (indica; sativa; hybrid, 1:1 balanced CBD/THC; high CBD/low THC; or "I don't have a favorite). Those that identified extract use (drops or capsules) answered questions specific to these products, including what type of Tilray extract formulations they used most via multiple choice options. Frequency of use for extracts was assessed by inquiring about "days per past week" use and "times per day" use (1 to 10 or more per day).

Additionally, for all substances the level of deliberate intent to use cannabis as a reduction/cessation strategy was assessed via single-answer multiple choice with the following options: I was surprised to find that my use of _____ changed after I began to use medical cannabis; I deliberately used medical cannabis with the goal of reducing my use of _____; My MD recommended medical cannabis in order to reduce my use of _____; My MD recommended medical cannabis and then worked with me to develop a specific tapering program to help reduce my use of _____; None of the above. Participants were also asked about their potential use of other T/N reduction strategies via multiple choice listing common treatment options for nicotine dependence.

The following variables were considered in subsequent analyses: gender (male vs. female), age (≥55 vs. <55), top three primary condition types (pain, mental health, and insomnia), preferred type of cannabis (THC vs. CBD), daily cannabis use (yes vs. no), primary method of use (orally ingested vs. inhaled), use of other tobacco reduction strategies (yes vs. no), number of T/N uses per day in the pre-period (>25 vs. ≤ 25), years of T/N use (≤ 10 vs. >10), and cessation of alcohol use in the post-cannabis period (yes vs. no). While the single participant that reported a non-binary gender identity by clicking "other" rather than male or female was included in the initial analysis, they had to be excluded from the multivariate analysis as it would be numerically unstable to include them.

Additionally, varied degrees of intent to quit reported by participants were separated into two groups: those that reported deliberately using medical cannabis to reduce their use of T/N and participants reporting their MD recommended the use of medical cannabis to reduce T/N or developed a tapering strategy to reduce the use of T/N were grouped into an "active intent" group, and compared with a "no intent" group composed of those who reported either "no intent" or expressed surprise to find that they had changed their use of T/N following medical cannabis initiation.

3.3.2 Analysis

Initial analysis summarized patient characteristics such as age and gender, alcohol use, involvement with traditional tobacco cessation strategies, frequency and type of cannabis use (CBD vs. THC; oral use vs. inhalation) and degree of self-reported intent to quit using median, inter-quartile range, and percentages (Table 1). Only the top three primary condition types cited by patients – pain, mental health and insomnia - were included in subsequent analysis, as these accounted for over 83.2% of participants (n=541), with the rest grouped as "other".

Change in T/N usage was examined as a categorical variable based on the T/N uses per day categories presented in the methods section, except that using <1 per day and 1-5 were grouped as a single category (<6), and the mid-point of each category was used to determine medians. Change was defined as moving from one category to another between the pre-and-post period, and was ultimately analyzed as a binary variable as well (decreased - yes/no; quit - yes/no). Significance of the change in number of T/N uses per day in the entire cohort was assessed using the sign test, and the Krustal-Wallis test was used to assess the significance of variables of interest in patterns of T/N use in the pre-period, as well as median changes in use post-medical cannabis between subgroups. Chi-square or Fisher's exact test were used as appropriate to assess the statistical significance of potential variables impacting rates of T/N reduction and/or cessation.

This was followed by univariate and multivariate logistic regression analyses to estimate the relationship between each variable and the two primary outcomes of interest: decreased T/N use (yes/no), and ceased T/N use (yes/no). Effects measures were presented as Odds Ratios (OR) with 95% Confidence Intervals. Additionally, in order to ensure that the exclusion of participants in the multivariate analysis due to missing data did not effect the primary outcomes of interest, Chi-square test was used to compare reductions in T/N use and rates of cessation post medical cannabis initiation between those included in the multivariate analysis and those excluded.

Finally, in order to assess for any potential bias or confounders associated with the increased period between the pre-and-post medical cannabis assessments, a multivariate analysis restricted to those patients that initiated medical cannabis within the past five years (n=233) was conducted a to see if there

were any obvious differences in outcomes between those with more recent medical cannabis use when compared to those reporting a longer history of use.

All analyses were conducted in SAS 9.4 (SAS Institute, Cary NC). All statistical tests were two-sided, with significance levels of 0.05. No special statistical treatment was used to handle missing data, other than reporting it where relevant in the appropriate tables.

3.4 Results

The survey received 3768 responses, 2102 (55.8%) of which provided a verifiable Tilray patient number, thereby identifying participants as authorized medical cannabis patients. Of these 2102 respondents, 650 (30.9%) identified as individuals with previous or current T/N use and were therefore included in this analysis. The demographic, geographic and health-related characteristics of the sample are reported in Table 1. This cohort was mostly male (339, 54.9%), with a median age of 45 (IQR = 36-56) years. A substantial percentage were married or equivalent (401; 61.8%), and the sample was largely white (567; 87.8%), and well educated, with 69.5% (451) reporting a college degree or higher. In terms of geography, Alberta and Ontario were over-represented in the sample, which is consistent with Health Canada data on medical cannabis patients in Canada (Health Canada, 2019). The top five primary conditions cited by patients were chronic pain (31.4%), anxiety (11.6%), insomnia (9.7%), arthritis (9.6%), and depression (6.2%), therefore the majority of this population used medical cannabis to treat chronic pain, mental health conditions and insomnia.

3.4.1 Table 1. Characteristics of 650 participants reporting tobacco/nicotine use pre-medical cannabis initiation.

Characteristics	n (%)
Gender, n (%)	
Unknown	32
Male	339 (54.9)
Female	278 (45.0)
Other	1 (0.1)
Age	
Unknown	94
Median (IQR)	45.0 (36.0, 56.0)

Range	(21.0, 77.0)
Current relationship status, n (%)	
Unknown	1
Widowed/Single/Divorced/Single, never married	248 (38.2)
Married/In a domestic partnership or civil union/Single, but cohabitating	401 (61.8)
Ethnicity, n (%)	
Unknown	4
White	567 (87.8)
Hispanic	2 (0.3)
Asian/South Asian	10 (1.6)
Black	4 (0.6)
Aboriginal/First Nation/Metis	20 (3.1)
Other	43 (6.7)
Highest degree completed, n (%)	
Unknown	1
High school graduate or lower	198 (30.5)
College degree or higher	451 (69.5)
Annual household income, n (%)	
Unknown	10
Less than $40,000	228 (35,7)
$40,000 - $69,999	171 (26.7)
$70,000 - $99,999	93 (14.5)
$100,000 - $129,999	73 (11.4)
$130,000 or more	75 (11.7)
Province/Territory, n (%)	
Unknown	0
AB	298 (45.8)
BC	63 (9.7)
MB	33 (5.1)
NB/NS/PEI/NL	39 (6.1)
NWT/YT/NU	4 (0.7)
ON	191 (29.4)
QC	5 (0.8)
SK	17 (2.6)
Primary condition, n (%)	
Unknown	1
ADD/ADHD	14 (2.2)
Addiction/dependence/withdrawal	2 (0.3)
AIDS/HIV	0 (0.0)
Anxiety	75 (11.6)
Arthritis	62 (9.6)
Autism	1 (0.2)
Brain Injury	3 (0.5)
Cancer/Leukemia	7 (1.1)
Chronic Pain	204 (31.4)
Crohn's Disease	9 (1.4)
Depression	40 (6.2)
Diabetes	3 (0.5)
Eating Disorder	3 (0.5)
Epilepsy	4 (0.6)
Fibromyalgia	31 (4.8)
Gastrointestinal Disorder	15 (2.3)
Glaucoma	1 (0.2)
Headache/migraine	19 (2.9)
Hepatitis	0 (0.0)

Insomnia	63 (9.7)
Mental Health Condition (other than anxiety, depression, OCD or PTSD	12 (1.8)
Movement Disorder	4 (0.6)
Multiple Sclerosis	14 (2.2)
Obsessive Compulsive Disorder (OCD)	0 (0.0)
Osteoporosis	7 (1.1)
Post Traumatic Stress Disorder (PTSD)	35 (5.4)
Seizure Disorder	2 (0.3)
Skin Condition	3 (0.5)
Other	16 (2.5)

Table 2 reports the change in T/N use and proportion who reduced or ceased use by primary patient characteristics. Most respondents had used T/N for over 10 years (75.7%; n=491), with 15.4% citing 6-10 years of use (n=110), and 8.9% having used for five years or less (n=58). Gender was associated with greater median amounts of T/N use per day, with men reporting 20.5 (IQR 10.5-20.5) and women reporting a median of 10.5 (IQR 10.5-20.5) (p=0.009). Years of T/N use were also associated with greater median amounts of T/N per day (20.5 for those who used tobacco >10 years vs. 10.5 for those who used tobacco <10 years, p<0.001), as was alcohol use in the pre-period (20.5, IQR 10.5-20.5 vs. 10.5, IQR 10.5-20.5, p=0.018).

When comparing self-reported T/N uses per day before medical cannabis initiation, and then again in the 30 days prior to completing the survey, 49.2% (n=320) reported decreased use, 45.7% (n=297) reported no change, and 5.1% (n=33) reported increased use. Of those who reported decreased use, 50% (n=160) reported complete cessation. The mean number of T/N uses per day prior to medical cannabis initiation was 17 (SD 10.3) while the mean number of T/N uses per day in the 30 days prior to the survey was 10.8 (SD 10.7), resulting in an average decline of 6.2 T/N uses per day (SD 10.8), or approximately 37.5%. Additionally, while a significant percentage of patients reported decline or cessation of T/N use following medical cannabis initiation, only six respondents (0.3%) reported initiating T/N after beginning to use medical cannabis.

A number of characteristics were associated with tobacco reduction and/or cessation. Reporting higher rates of daily T/N use prior to medical cannabis initiation resulted in greater overall reductions in use: 64.1% (n=59) of those using T/N >25 per day reported reducing use, with a median decline of 11.6

(IQR -30.5-0.0, p<0.001). Intent to use cannabis specifically to quit T/N use was also associated greater reductions in use, with those citing this intent seeing both a higher percentage successfully reducing use (68.6%, n=59) compared to those with no intent (46.4%, n=261, p<0.001), as well as a greater median reduction of T/N use (-10, IQR -17-0.0 vs. 0.0, IQR -10.0-0.0, p<0.001).

More years of T/N use were also associated with greater median reductions. Those that reported over 10 years of use saw reductions of 20.5 (IQR 10-5-20.5) compared to those reporting 6-10 years of use (10.5, IQR 10.5-20.5) or 5 or fewer years of use (10.5, IQR 3.5-10.5) (p<0.001). However, the percentage who reported ceasing use was greatest in the middle tier (36%, n=36 for those having used 6-10 years vs. 32.8%, n=19 for those using 5 or fewer years and 21.4%, n=105 for those using over 10 years). Reporting a complete cessation of alcohol use in the post-period was also strongly associated with greater T/N reductions per day, and higher rates of cessation. Stopping alcohol use resulted in an associated median -10 T/N uses per day (IQR -20.5 - -3.5), compared to -2.5 (IQR -10.5-0.0) for those using alcohol that didn't quit, and was also associated with a far greater percentage reporting reductions in T/N use (78.6%, n=33 vs. 51.3%, n=139, p=0.001) as well as complete cessation (42.9%, n=18 vs. 26.6%, n=72, p=0.03).

Greater age was also associated with a higher quit ratio (37%, n=57 for those 55 or over, compared to 20.1%, n=81 for those below 55, p<0.001), but not with greater pre-medical cannabis T/N use, reductions in daily T/N use, or greater percent of those reporting reductions. Finally, reporting participation in past or present T/N reduction treatments was negatively associated with T/N cessation, with only 10.9% (n=12) of those who used other treatments reporting cessation post-medical cannabis compared to 27.6% (n=147) who didn't (p<0.001).

3.4.2 Table 2. Changes in tobacco/nicotine (T/N) use by primary patient characteristics in 650 participants reporting T/N use pre-medical cannabis.

	Number of T/N per day in the pre-period, N (%)					Number of T/N per day - pre*		Change in number of T/N per day*		Reduction in number of T/N per day		Complete cessation	
Subgroup	**<6**	**6-15**	**16-25**	**>25**	**P**	**Median (IQR)**	**P**	**Median (IQR)**	**P**	**N (%)**	**P**	**N (%)**	**P**
Entire cohort £	84 (12.9)	229 (35.2)	245 (37.7)	92 (14.2)	-	20.5 (10.5, 20.5)	-	0.0 (-10.5, 0.0)	0.638	320/650 (49.2)	-	160/650 (24.6)	-
Gender					0.035		0.009		0.107		0.223		0.214
Male	42 (12.4)	104 (30.7)	136 (40.1)	57 (16.8)		20.5 (10.5, 20.5)		-3.0 (-10.5, 0.0)		174/339 (51.3)		89/339 (26.3)	
Female	39 (14.0)	111 (39.9)	97 (34.9)	31 (11.2)		10.5 (10.5, 20.5)		0.0 (-10.0, 0.0)		129/278 (46.4)		61/278 (21.9)	
Age					0.883		0.589		0.090		0.834		<0.001
<55	53 (13.2)	147 (36.6)	148 (36.8)	54 (13.4)		20.5 (10.5, 20.5)		0.0 (-10.0, 0.0)		197/402 (49.0)		81/402 (20.1)	
≥55	19 (12.3)	52 (33.8)	62 (40.3)	21 (13.6)		20.5 (10.5, 20.5)		-0.5 (-10.5, 0.0)		77/154 (50.0)		57/154 (37.0)	
Primary condition					0.448		0.524		0.602		0.863		0.207
Pain	33 (10.4)	122 (38.6)	123 (38.9)	38 (12.0)		20.5 (10.5, 20.5)		0.0 (-10.5, 0.0)		154/316 (48.7)		78/316 (24.7)	
Mental health issues	31 (18.8)	53 (32.1)	58 (35.2)	23 (13.9)		10.5 (10.5, 20.5)		0.0 (-10.0, 0.0)		76/165 (46.1)		36/165 (21.8)	
Insomnia	9 (14.3)	19 (30.2)	26 (41.3)	9 (14.3)		20.5 (10.5, 20.5)		0.0 (-10.5, 0.0)		31/63 (49.2)		23/63 (36.5)	
GI	3 (12.5)	6 (25.0)	9 (37.5)	6 (25.0)		20.5 (10.5, 25.5)		-3.3 (-20.3, 0.0)		13/24 (54.2)		6/24 (25.0)	
Movement Disorder	2 (11.1)	6 (33.3)	7 (38.9)	3 (16.7)		20.5 (10.5, 20.5)		-7.0 (-10.5, 0.0)		11/18 (61.1)		5/18 (27.8)	
Preferred type of cannabis					0.332		0.807		0.463		0.409		0.887
High THC	52 (15.0)	111 (32.1)	134 (38.7)	49 (14.2)		20.5 (10.5, 20.5)		0.0 (-10.5, 0.0)		162/346 (46.8)		83/346 (24.0)	
High CBD	9 (10.5)	36 (41.9)	29 (33.7)	12 (14.0)		10.5 (10.5, 20.5)		0.0 (-10.0, 0.0)		36/86 (41.9)		20/86 (23.3)	
Number of days per week used cannabis					0.091		0.396		0.263		0.530		0.590
<7	21 (18.3)	39 (33.9)	35 (30.4)	20 (17.4)		10.5 (10.5, 20.5)		0.0 (-10.0, 0.0)		54/115 (47.0)		26/115 (22.6)	
7	60 (11.7)	180 (35.2)	204 (39.8)	68 (13.3)		20.5 (10.5, 20.5)		-1.8 (-10.5, 0.0)		257/512 (50.2)		128/512 (25.0)	
Primary method of use					0.952		0.806		0.478		0.733		0.389
Inhaled	64 (13.3)	168 (34.8)	182 (37.7)	69 (14.3)		20.5 (10.5, 20.5)		0.0 (-10.5, 0.0)		237/483 (49.1)		115/483 (23.8)	
Orally ingested	20 (12.7)	57 (36.1)	61 (38.6)	20 (12.7)		20.5 (10.5, 20.5)		-0.8 (-10.5, 0.0)		80/158 (50.6)		43/158 (27.2)	
Number of T/N uses per day in the pre-period					-		-		<0.001		0.003		0.088
≤ 5	84 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)		3.5 (3.5, 3.5)		0.0 (-3.5, 0.0)		33/84 (39.3)		25/84 (29.8)	
6 to 25	0 (0.0)	229 (48.3)	245 (51.7)	0 (0.0)		20.5 (10.5, 20.5)		0.0 (-10.5, 0.0)		228/474 (48.1)		106/474 (22.4)	
>25	0 (0.0)	0 (0.0)	0 (0.0)	92 (100.0)		30.5 (30.5, 43.8)		-11.6 (-30.5, 0.0)		59/92 (64.1)		29/92 (31.5)	
Intent re. cannabis and T/N reduction					0.471		0.295		<0.001		<0.001		0.069
None/Surprised	76 (13.5)	197 (35.1)	212 (37.7)	77 (13.7)		20.5 (10.5, 20.5)		0.0 (-10.0, 0.0)		261/562 (46.4)		132/562 (23.5)	
Deliberately/MD recommended/MD developed	7 (8.1)	32 (37.2)	32 (37.2)	15 (17.4)		20.5 (10.5, 20.5)		-10.0 (-17.0, 0.0)		59/86 (68.6)		28/86 (32.6)	
Any T/N reduction treatments					0.270		0.375		0.173		0.510		<0.001
No	74 (13.9)	182 (34.2)	202 (38.0)	74 (13.9)		20.5 (10.5, 20.5)		0.0 (-10.5, 0.0)		265/532 (49.8)		147/532 (27.6)	
Yes	8 (7.3)	43 (39.1)	42 (38.2)	17 (15.5)		20.5 (10.5, 20.5)		0.0 (-10.0, 0.0)		51/110 (46.4)		12/110 (10.9)	
Years of T/N use					<0.001		<0.001		0.260		0.056		0.003
≤ 5	26 (44.8)	21 (36.2)	7 (12.1)	4 (6.9)		10.5 (3.5, 10.5)		-3.5 (-9.5, 0.0)		33/58 (56.9)		19/58 (32.8)	
6-10	23 (23.0)	42 (42.0)	25 (25.0)	10 (10.0)		10.5 (10.5, 20.5)		-7.0 (-10.5, 0.0)		58/100 (58.0)		36/100 (36.0)	
>10	35 (7.1)	165 (33.6)	213 (43.4)	78 (15.9)		20.5 (10.5, 20.5)		0.0 (-10.5, 0.0)		229/491 (46.6)		105/491 (21.4)	
Alcohol - complete cessation (among pre-users only)					0.003		0.018		<0.001		0.001		0.030
Yes	3 (7.1)	10 (23.8)	25 (59.5)	4 (9.5)		20.5 (10.5, 20.5)		-10.0 (-20.5, -3.5)		33/42 (78.6)		18/42 (42.9)	
No	48 (17.7)	104 (38.4)	83 (30.6)	36 (13.3)		10.5 (10.5, 20.5)		-2.5 (-10.5, 0.0)		139/271 (51.3)		72/271 (26.6)	

*For comparison of median and percentages between subgroups, p value was based on Chi-square test, Fisher's exact test or Kruskal-Wallis test as appropriate.

Table 3 presents the results of the univariate and multivariate regression analyses of the primary covariates identified in earlier analyses. In examining baseline characteristics associated with changes in T/N use, univariate analysis reported that being over 55 was not associated with greater odds of reducing or ceasing use, but when adjusted for other variables such as gender, intent to quit, preferred type of cannabis, years of tobacco use, and other covariates, a strong association was found between being age 55 or older and ceasing T/N use altogether (AOR = 2.56, 95% CI 1.53-4.26). Greater number of T/N uses per day (>25) was positively associated with reduction in use in both univariate (OR 2.03, 95% CI 1.29-3.21) and multivariate analyses (AOR 2.83, 95% CI 1.53-5.24), but only with cessation in the adjusted analysis (AOR 2.11, 95% CI 1.14-3.92). Additionally, reporting 10 years of more of T/N use was associated with greater odds of cessation (AOR 2.00, 95% 1.20-3.33).

3.4.3 Table 3: Sociodemographic, behavioural, health and cannabis use-related factors associated with changes in T/N usage among 650 participants.

	Reduction in number of T/N uses per day				Complete cessation of T/N use			
	Univariate (n=533-650)*		Multivariate (n=460)*		Univariate (n=533-650)*		Multivariate (n=460)*	
Variable and comparison	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**
Level of intention to use cannabis to reduce T/N use								
Deliberately/MD recommended/MD developed vs. None/Surprised	2.52 (1.55, 4.09)	<0.001	2.79 (1.49, 5.22)	0.001	1.57 (0.96, 2.57)	0.071	1.54 (0.82, 2.89)	0.184
Gender								
Female vs. Male	0.82 (0.60, 1.13)	0.224	0.99 (0.66, 1.48)	0.945	0.79 (0.54, 1.15)	0.215	0.80 (0.50, 1.27)	0.340
Age								
≥55 vs. <55	1.04 (0.72, 1.51)	0.834	1.05 (0.66, 1.67)	0.844	2.33 (1.55, 3.50)	<0.001	2.56 (1.53, 4.26)	<0.001
Primary condition type								
Pain – Y vs N	0.85 (0.59, 1.23)	0.386	0.84 (0.51, 1.37)	0.483	0.94 (0.62, 1.43)	0.789	0.87 (0.51, 1.48)	0.607
Mental health issues – Y vs N	0.75 (0.49, 1.14)	0.177	0.66 (0.38, 1.14)	0.139	0.78 (0.48, 1.28)	0.332	0.69 (0.37, 1.26)	0.224
Insomnia – Y vs N	0.87 (0.49, 1.53)	0.631	0.79 (0.37, 1.68)	0.540	1.87 (1.02, 3.40)	0.042	1.30 (0.59, 2.86)	0.515
Preferred type of cannabis								
THC vs. CBD	1.22 (0.76, 1.97)	0.409	1.35 (0.68, 2.69)	0.387	1.04 (0.60, 1.82)	0.887	1.38 (0.59, 3.21)	0.454
Used cannabis daily								
Yes vs. No	1.14 (0.76, 1.71)	0.531	1.32 (0.79, 2.21)	0.284	1.14 (0.71, 1.84)	0.591	1.61 (0.87, 2.98)	0.129
Primary method of use								
Orally ingested vs. Inhaled	1.06 (0.74, 1.52)	0.733	1.43 (0.82, 2.49)	0.205	1.20 (0.80, 1.80)	0.389	1.35 (0.72, 2.52)	0.350
Use of other T/N reduction strategies								
Yes vs. No	0.87 (0.58, 1.31)	0.511	0.72 (0.41, 1.26)	0.252	0.32 (0.17, 0.60)	<0.001	0.39 (0.18, 0.86)	0.019
Number of T/N per day in the pre-cannabis period								
>25 vs. ≤25	2.03 (1.29, 3.21)	0.002	2.83 (1.53, 5.24)	<0.001	1.50 (0.93, 2.43)	0.098	2.11 (1.14, 3.92)	0.018
Years of T/N use								
≤10 vs. >10	1.55 (1.08, 2.23)	0.017	1.53 (0.96, 2.42)	0.073	1.96 (1.33, 2.91)	<0.001	2.00 (1.20, 3.33)	0.008
Complete cessation of alcohol								
Yes vs. No	3.48 (1.60, 7.55)	0.002	2.04 (0.82, 5.08)	0.127	2.07 (1.06, 4.04)	0.032	2.36 (0.97, 5.74)	0.058

* Sample size in the univariate analysis varied across comparisons due to missing data. Multivariate analysis only included patients with no missing data for all variables.

Other explanatory variables associated with tobacco reduction and/or cessation were intent to quit T/N, involvement with other T/N treatments, and alcohol cessation. Active intent to use medical cannabis in order to quit resulted in significantly greater odds of reducing T/N use (OR = 2.52, 95% CI 1.55-4.09), even after adjustment for confounders (AOR = 2.79, 95% CI 1.49-5.22), but was not associated with increased odds of cessation. Involvement with traditional T/N cessation treatments (pharmacological or nicotine replacement) was negatively associated with T/N cessation (AOR 0.39, 95% CI 0.18-0.86), While this may appear counter-intuitive, it could suggest that previous/current (potentially unsuccessful) attempts to quit via other treatment modalities may be associated with a greater overall dependence to T/N, and therefore lower odds of cessation/reduction following medical cannabis initiation. To test this theory, the relationship between years of T/N use and participation in T/N cessation strategies was further examined, finding a strong association between the two, with 19% (n=92) of those who reported over 10 years of T/N use also reporting experience with T/N cessation strategies, compared to 11.1% (n=11) and 10.5% (n=6) for those who reported 6-10 or 5 or fewer years of T/N use respectively (see Appendix A). While complete cessation of alcohol use was found to be associated with increased odds of reducing T/N uses per day (OR 3.48, 95% CI 1.60-7.55) and cessation of use (OR 2.07, 95% CI 1.06-4.04), the adjusted analysis did not reach a level of statistical significance.

Additionally, the following variables were examined but were not found to be associated with either T/N reduction or cessation: gender, primary condition type, THC vs. CBD preference, daily vs. non-daily cannabis use, and oral ingestion vs. inhalation. Finally, in noting the significant period of time between medical cannabis initiation and the 30 days prior to the survey reported by some participants (median 3 yrs, IQR 2.0-10.0), a supplementary multivariate analysis was conducted in order to compare the primary outcomes in those that initiated medical cannabis within the past five years with the full study population, and the results remained largely the same (Appendix B).

3.5 Discussion

Overall, 49.2% (n=320) of participants that reported T/N use prior to initiating medical cannabis saw a reduction in use, and 24.6% (n=160) reported complete cessation of use in the 30 days prior to the survey. Moreover, expressing a specific intent to use cannabis to reduce T/N use increased the rate of cessation to 32.6% (n=28). Although this was a much smaller cohort and the observation period extended over a number of years following medical cannabis initiation, participants reporting an intent to use medical cannabis to reduce/cease T/N use actually reported a higher 30 day cessation rate than the 28.4% (n=4081) 30 day cessation rate reported in Smoking Treatment for Ontario Patients (STOP), a large-scale primary care-based smoking cessation program in Ontario which focused on a combination of counseling and pharmacotherapies such as the nicotine-replacement patch (Voci et al., 2020). Furthermore, unlike STOP, most participants in this survey did not report using NRT or other T/N cessation strategies, and those that did actually reported lower quit ratios compared to those that did not. Since studies assessing treatment outcomes for substance use disorders have consistently reported a relationship between motivation/intent to change and treatment success (Breda & Heflinger, 2007; McKay & Weiss, 2001; Shields et al., 2014), the significant association between the intention to use cannabis to reduce T/N use and greater subsequent rates of reduction in this study adds to these previous findings, and suggests a need to conduct more comprehensive assessments of intent/motivation for cannabis use in polysubstance use research. Such investigations may be particularly relevant for those that have either had poor success with, or are looking for alternatives, to traditional pharmacologic or psychobehavioral treatments for T/N dependence. However, since only 13.2% (n=86) of participants reported intentionally using cannabis as a T/N cessation strategy, no firm conclusions can be drawn, and further research will be needed to assess the association between intentional use of cannabis as a T/N reduction strategy and it's impact on reduction and cessation.

Additionally, the association between alcohol and T/N use reinforces previous findings of complementarity between these substances (Room, 2004; Tauchmann et al., 2013), and could further

inform cannabis-based harm reduction strategies aimed at reducing the use of both alcohol and T/N, while also providing a strong rationale for quitting alcohol use in those wishing to increase the odds of success in T/N cessation efforts. This may be of particular relevance to those affected by chronic physical and mental health conditions, since both are associated with an increased risk of problematic substance use, including dependence on alcohol and/or T/N (Hunt, Large, Cleary, Lai, & Saunders, 2018; Hunt, Malhi, Cleary, Lai, & Sitharthan, 2016; John & Wu, 2020; Walsh et al., 2017; Wu, Zhu, & Ghitza, 2018)

Our findings are roughly consistent with research examining the use of CBD as aids to tobacco cessation (Hindocha et al., 2018; Morgan et al., 2013); however, those studies examined the use of isolated CBD, while our analyses indicate that T/N reduction/cessation was not associated with a specific preference for THC or CBD. This suggests that the mechanism proposed to underlie the effects observed in Morgan et al (2013), such as reductions in T/N cravings associated with THC-related CB1 receptor activation and alterations of attentional processes that highlight tobacco-related cues, may contribute to these observed effects. However, more focused research will be required to better specify the specific mechanisms that might underlie cannabis substitution for tobacco/nicotine, and how THC or CBD might play a part in these, both in isolation or when combined.

Limitations of this study include restricting the population to patients registered with Tilray as their provider of medical cannabis. Although this was a national sample, it may have yielded data not representative of the broader population of medical cannabis patients in Canada. Furthermore, since this sample was drawn from patients registered with a medical cannabis company, participants may be more likely to report positive effects related to the medical use of cannabis. Additionally, the study focused on the most prevalent forms of T/N use - cigarettes, e-cigs and pipes - but did not inquire about the use of cigars/cigarillos, blunts (joints that include tobacco), or non-smoked forms of T/N use such as snus or snuff, and it is possible that not accounting for these may have confounded our results.

It is unknown if results from a medical cannabis patient cohort are generalizable to a non-patient population, as there may be characteristics inherent to a patient population—including an active intent to improve personal health outcomes—that may not be mirrored in a non-patient cannabis use population. It

is also notable that despite the legalization of both medical and recreational adult cannabis use in Canada, many continue to find challenges in accessing the legal medical cannabis program (L. Belle-Isle et al., 2014; Capler et al., 2017; Valleriani et al., 2020), and a report from 2020 suggests that only 29.4% of Canadians who use cannabis obtain all of their cannabis products from legal sources (Rotermann, 2020), and it is unknown how this might further confound these outcomes, or the generalizability of those findings. Prospective studies examining changes in T/N use in non-medical populations following cannabis initiation could better assess what role cannabis contributes to T/N cravings, withdrawals and reduction/cessation. Since all information regarding the use of cannabis or tobacco was self-reported and did not benefit from biological drug detection to verify substance use or non-use, this data is vulnerable to recall bias, socially desirable responding and other biases associated with self-report retrospective surveys. In particular, since the average duration of medical cannabis use in this population at the time of the survey was a mean/median of 7.2 years and 3 years respectively, self-reported estimates of substance use frequency and amounts pre-medical cannabis may be particularly vulnerable to recall bias as well as other unobserved variables and confounders that may have impacted T/N use other than medical cannabis in the interim. However, a supplemental analysis comparing those who initiated medical cannabis use within the past five years with the entire cohort found largely similar results, suggesting that the time span between pre-and-post data points does not appear to have significantly impacted the primary outcomes of the study (Appendix B).

Furthermore, since the questions regarding patient characteristics were optional, missing data resulted in a smaller sample size (n=460) in the multivariate analysis. In order to assess if this may have impacted the primary outcomes of the study, a sensitivity analysis was conducted comparing T/N reduction and cessation between those included and excluded in the multivariate analysis, and no statistically significiant difference in outcomes was found (Appendix C). Additionally, this data may have been influenced by unobserved variables and confounders, and the lack of a control group suggests that causation cannot be assumed. However, the large sample size, detailed measurement of tobacco use prior and post-medical cannabis initiation, and inclusion of potential variables such as “intent” and

participation in other substance use treatment programs in regards to T/N reduction may address some of the limitations of previous cross-sectional surveys examining the impact of cannabis on the use of tobacco and other substances, and could inform future studies of this kind. In light of these limitations, it would be premature to promote cannabis-based therapies for T/N reduction/cessation, and these results should be interpreted with caution pending replication by research that employs more systematic recruitment, longitudinal designs, control groups, and biological drug testing.

Finally, the present results do not speak to the desirability of substituting cannabis for tobacco. Reviews of the relative health impacts of widely used psychoactive substances rate the harms associated with tobacco as substantially higher than those associated with cannabis (Nutt et al., 2010). Although cannabis use results in a comparatively low risk of dependence and harms to individuals and society compared to tobacco use, it is not benign. Chronic use has been associated with potential cognitive deficits, and the psychoactive effects of use and associated impairment can lead to increased personal health and public safety risks (Fischer et al., 2011). Evidence also suggests that regular cannabis smoking may be associated with bronchial issues (Tashkin, 2013). However, the evidence of associations between cannabis smoking and cancer is inconclusive, with some research reporting a moderate increased risks of lung cancer among heavy users (Aldington et al., 2008; Callaghan et al., 2013), and others concluding no causal association (Hashibe et al., 2006; Huang et al., 2015; Ribeiro & Ind, 2016; Tashkin, 2013). Additionally, these risks can be further mitigated by using non-inhaled forms of ingestion, which our study suggests result in similar rates of T/N reduction and cessation. In contrast, the association between tobacco use and cancer is supported by a large body of evidence (WHO, 2012). Tobacco use is particularly prevalent among individuals with chronic pain (Ditre et al., 2011) and mental health conditions (Aubin et al., 2012; Williams & Ziedonis, 2004), which are the most common conditions for which patients report using medical cannabis (Boehnke et al., 2019; Lucas et al., 2019b; Reiman et al., 2017; Walsh et al., 2013), so this intersection may present an opportunity for further investigations.

Ultimately, whether cannabis represents a viable T/N harm reduction strategy is beyond the scope of the current study, but certainly remains a pertinent question for future research. In light of the

considerable health costs associated with tobacco and nicotine use, particularly in populations affected by chronic health conditions, these findings add a new dimension to the growing literature examining the impact of cannabis on the use of other substances, and perhaps suggest a previously unexplored avenue by which increased access to cannabis might benefit public health by subsequently reducing tobacco and nicotine use amongst medical cannabis patients.

3.6 Authors' Contributions

Philippe Lucas: Conceptualization, Methodology, Funding acquisition, Investigation, Writing - Original draft preparation. **Zach Walsh**: Writing - Original draft preparation, Writing – Reviewing and Editing. **Peter Hendricks**: Writing – Original draft preparation, Writing – Reviewing and Editing. **Susan Boyd:** Writing – Reviewing and Editing. **M-J Milloy** Writing – Reviewing and Editing.

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4 Paper 3: The impact of non-medical cannabis legalization and other exposures on retention in longitudinal cannabis research: a survival analysis of a prospective study of Canadian medical cannabis patients

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4.1 Abstract

Background

Although there is consensus on the urgent need for high-quality evidence on the harms and benefits of cannabis, there are ongoing methodological challenges to conducting observational and clinical studies on cannabis, including a high rate of patients that are lost to follow up (LTFU). This study explores factors potentially associated with retention in a national study of Canadian medical cannabis patients.

Methods

The Tilray Observational Patient Study (TOPS) was a multi-site, prospective examination of authorized Canadian cannabis patients. We conducted a series of exploratory analyses assessing the potential association between variables including patient characteristics, cannabis and prescription drug use, quality of life, and the legalization of non-medical cannabis, and retention in TOPS.

Results

Overall, 1011 participants were included in this analysis, contributing 287 patient-years of data. Our analyses found that legalization and the use of prescription opioids were both associated with increased odds that patients would be LTFU, while a higher baseline WHOQOL-Bref psychological score and the use of anti-seizure medications were both associated with increased odds of retention.

Conclusion

Our findings highlight some of the challenges of conducting medical cannabis research at a time when patients have a multitude of cannabis access options. Evidence-based strategies to reduce study burden on participants, such as minimizing in-person visits and ensuring adequate participant compensation, could improve retention. Additionally, policy-related changes aimed at improving access to medical cannabis, including increased cost-coverage and community-based distribution, could encourage patients to remain in the federal medical cannabis program and thereby reduce LTFU in associated studies.

4.2 Background

In 2001, Canada became one of the first nations to regulate medical cannabis at a federal level, and in 2018 it was the second country to legalize the non-medical use of cannabis by adults (Fischer, Lee, O'Keefe-Markman, & Hall, 2020; Lucas, Baron, & Jikomes, 2019). Despite consistent calls by the Canadian Medical Association and American Medical Association citing the need for high quality studies to identify the risks and benefits of cannabis in both medical and non-medical applications ("Cannabis | CMA Health Topics," n.d.; Harris, 2019) , there are many historical and ongoing challenges to conducting such research. As a result, many systematic reviews examining the available evidence in a number of primary therapeutic applications for cannabis have cited both a lack of and need for well-designed longitudinal observational and controlled studies (Bonaccorso et al., 2019; Hoch et al., 2019; Kosiba, Maisto, & Ditre, 2019; Okusanya et al., 2020).

There are a number of challenges to conducting high-quality cannabis research in Canada and in other jurisdictions. These include social stigma resulting from the long-standing international prohibition on cannabis possession and use (Belle-Isle et al., 2014; Bottorff et al., 2013; Lucas, 2009), a lack of funding and regulatory obstacles and associated delays (Geary, 2019; National Academies of Sciences, Division, Practice, & Agenda, 2017), and methodological difficulties, such as blinding THC-based products in controlled studies due to its potential for impairment (National Academies of Sciences et al., 2017; Russo, 2016). Additionally, legalizing the adult, non-medical use of cannabis in Canada in October 2018 has significantly changed how medical and non-medical adult users access cannabis, and this may have subsequent impacts on recruitment, adherence and retention in prospective medical cannabis studies in Canada.

The legalization of the adult non-medical use of cannabis in Canada is in its nascency, and the federal, provincial and municipal policies governing access continue to evolve. However, some data

suggests that one of the impacts of legalization has been a decline in participation in the federal medical cannabis program. Recent statistics from Health Canada show that the number of authorized patients peaked in September 2019 at 369,614, declining to 303,221 in June 2020, the latest month for which data was available (Health Canada, 2020). This steady migration away from the medical cannabis program may be due to a number of factors. Over the years many barriers have been identified in accessing medical cannabis in Canada, including stigma, lack of support from the medical community, limited product selection, and high costs (Belle-Isle & Hathaway, 2007; Bottorff et al., 2013; Capler et al., 2017; Lucas, 2009). By contrast, both the illicit market as well as the legal, non-medical cannabis dispensaries offer many advantages not currently available in the mail-order only federal medical cannabis program, including the opportunity for in-person, community-based interactions, a large selection of products from hundreds of different producers, and highly competitive pricing. Furthermore, a few studies examining the impact of legalization on patient access to medical cannabis report that product shortages in the medical system immediately following legalization led patients to purchase cannabis from non-medical sources, including the illicit market (Hawley, 2020; McTaggart-Cowan et al., 2020). This research and data suggest a need to examine if the increase in access options following legalization could also be affecting retention in prospective medical cannabis studies.

Therefore, we conducted an exploratory study and survival analysis to examine the potential relationship between variables such as baseline patient characteristics, patterns of medical cannabis use, prescription drug use, quality of life scores, and retention in a large, multi-site prospective observational study of medical cannabis patients. Additionally, we analyzed variables related to the legalization of non-medical adult cannabis to assess the impact of policy changes affecting access to medical and non-medical cannabis on the rates of patients lost to follow up (LTFU). Our objectives were to identify factors associated with retention, and to recommend clinical strategies and policy options that might reduce LTFU in future longitudinal medical cannabis studies.

4.3 Methods

The Tilray Observational Patient Study (TOPS) was a national, multi-site, prospective medical cannabis study that took place at 21 medical clinics in five Canadian provinces, with the goal of gathering detailed information on patient characteristics and examining the impact of medical cannabis use on quality of life and prescription drug use over six months. TOPS used a pre-test/post-test repeated measures design, with data gathering at baseline, one month, three months, and six months. The study was reviewed and approved by Advarra (formerly Institutional Review Board Services) on January 22, 2016, the University of Victoria on April 7, 2016, and the Alberta Health Research Ethics Board of Alberta October 3, 2016, and sponsored by Tilray, a licensed medical cannabis production and research company based in British Columbia, Canada.

Physicians identified, recruited and screened patients in-clinic during regularly scheduled appointment, guided by ethics-approved Health Care Provider Talking Points provided by the study sponsor (Appendix A). Participants were federally authorized, English speaking medical cannabis patients 18 years old and over with the capacity to consent for themselves who received a new cannabis recommendation from a participating physician, and subsequently registered with Tilray to obtain their medical cannabis products via mail. As compensation for their time, participants received a $25 credit towards their medical cannabis costs after completing each set of surveys. Clinics and participating physicians were identified and trained in the administration of the study by the principal investigator and colleagues, and data was gathered digitally via REDCap, a secure electronic data capture system (Harris et al., 2019, 2009). Study analyses included 1011 participants who enrolled in TOPS before July 16, 2018 to ensure all those included had the opportunity to be in the study at least six months and therefore could have completed all study visits.

4.3.1 Measures

TOPS was composed of a combination of validated and novel instruments made up of multiple-choice questions, rating and rankings, Visual Assessment Scales (VAS) and Likert scales, as well as matrix and dropdown questions. Many questions also included an "other" option that then provided a text box for short textual responses. The primary outcome of interest for this analysis was retention in the study at six months, and the explanatory variables we hypothesized may be related to retention included primary patient demographics, baseline quality of life scores, and patterns of medical cannabis and prescription drug use, as well as whether patients participated in the study prior to or after the legalization of adults non-medical use of cannabis in Canada on October 17, 2018.

Demographic data (such as age, gender, marital status, education level, employment status, and province of residence) and primary condition were self-reported and gathered via multiple choice questions informed by past longitudinal and cross-sectional surveys (Lucas et al., 2019; Lucas & Walsh, 2017; Walsh et al., 2013). The study included three additional instruments: the World Health Organization Quality of Life Short Form, the Cannabis Use Survey, and the Prescription Drug Questionnaire.

The World Health Organization Quality of Life Short Form (WHOQOL-Bref) (WHOQOL Group, 1998) is a validated 26-item questionnaire derived from data collected using the WHOQOL-100. It produces scores for four domains related to quality of life: physical health, psychological, social relationships and environment. (Saxena, Carlson, & Billington, 2001). The Cannabis Use Survey (CUS) is a 17-question self-administered patient questionnaire designed to gather cross-sectional and/or prospective information on medical cannabis patient primary conditions, symptoms, and patterns of medical cannabis use such as amounts used, preferred methods of use, and cannabis type preferences. The Prescription Drug Questionnaire (PDQ) was designed to produce an accurate inventory of current prescription drug use by a patient, and is completed by physicians and/or medical clinic staff in cooperation with the patient in order to limit the potential for recall bias. It gathers detailed information

on daily and non-daily prescription drug use in mg per dose, and doses per day or week (where applicable), and has an auto-fill function connected to the National Drug Data File (NDDF), a US-based national prescription drug database, to ensure that consistent generic prescription drug names are used across participants and medical clinics in order to facilitate analysis.

This battery was administered at four different time points: at baseline after a patient has received a medical cannabis recommendation from the participating physician, and then at one month (M1), three months (M3) and six months (M6).

4.3.2 Data analysis

Summary statistics were calculated for the following patient characteristics: age, gender, education level and marital status, as well as for primary condition, and past/present cannabis usage (naïve vs. non-naïve; method of use; frequency of use). Cannabis-naïve patients were defined as those who had used cannabis four times or fewer in the previous 12 months.

In order to assess quality of life, the four domains of the WHOQOL-Bref were tabulated at each study visit, and mixed-effects linear regression was used to model the time trend of the four domains over the six month period for all patients, as well as by different levels of demographic variables and other baseline patient characteristics.

The analysis of prescription drug use data included descriptive summaries of the number and percentage of patients who used each medication stratified by baseline usage of the particular medication, as well as by patient characteristics. To assess the dosage and usage frequency data among those who used the medication at baseline, milligrams (mg) per dose was first converted to mg per day by multiplying mg per dose with the frequency per day. The reported dosage for each drug was then divided by its Defined Daily Dose (DDD) to facilitate a summary of dosage data across patients (WHO Collaboration Center for Drug Statistics Methodology, 2019), and then the most prevalent drugs were

grouped into five primary drug classes for further analysis: opioid and non-opioid pain medications, benzodiazepines, antidepressants and anti-seizure drugs.

As the survival analysis focused on two time points (M3 and M6), we used the Kaplan-Meier method and log-rank test were used, with the primary outcome of interest being retention at M6. If a patient did not complete both M3 and M6, the patient was considered to be dropped out at M3. If a patient completed M3 visit but not M6, the patient was considered to be dropped out at M6. The completion rate of M6 was initially summarized by patient characteristics, change in QOL and change in drug usage. The Kaplan–Meier estimator then reported the probability (P) of remaining in the study at M3 and M6, and we used the log-rank test for between group comparisons, defining continuous variables at baseline by the median outcome of the 1011 patients included in this analysis. Groups with less than five patients were not assessed.

We then proceeded with a univariate logistic regression analysis in order to better understand the association between the variables assessed in the Kaplan-Meier estimator and retention at M6, with the addition of a binary variable to assess potential impact of legalization by comparing retention between patients enrolled prior to April 17, 2018 (so that M6 would be before legalization) and those enrolled between April 17 to July 15, 2018 (so M6 would be post-legalization). This was followed by a multivariate analysis that included all significant variables from the univariate analysis, using a Chi-Square test for homogeneity.

All analyses were conducted in SAS 9.4 (SAS Institute, Cary NC) and/or R 3.6.3 (R Core Team). All statistical tests were two-sided, with significance levels of 0.05 unless otherwise indicated.

4.4 Results

Overall, 1011 were included in this analysis and contributed 287 patient-years of observation. Retention was 728 (72%) at three months, and 419 (41.4%) at six months. Table 1 and 2 provide an overview of the primary baseline characteristics of the 1011 patients included in this analysis, along with the associated percentage that remained in the study at M6, and the results of the Kaplan-Meier estimator probability of remaining in the study at M3 and M6. Most participants were female (578, 57%) and 560 (55%) had at least a college degree. The median age was 51.0 (IQR 38–61) at baseline, and most were married or equivalent (561, 56%). The top five primary conditions reported by participants were chronic pain (703, 70%), anxiety disorders (98, 10%), arthritis (63, 6%), insomnia (48; 5%), and headache (23, 2%). Therefore, pain, mental health issues and insomnia accounted for approximately 94% of all participant primary conditions. No statistically significant associations were found between patient characteristics such as gender, education, marital status, age, previous cannabis experience, and primary condition and the probability of remaining in the study.

4.4.1 Table 1. Percent completing M6 and probability of retention at M3 and M6 by patient baseline characteristics and primary condition in 1011 participants.

Patient Baseline Characteristics		Kaplan–Meier Estimator		
		Probability of Remaining in Study		
	Completed M6 (%)	M3	M6	P
Gender				0.382
Male	175/432 (40.5)	0.70	0.41	
Female	244/578 (42.2)	0.74	0.42	
Education				0.299
High school or lower	178/451 (39.5)	0.71	0.39	
College or higher	241/560 (43.0)	0.73	0.43	
Marital status				0.272
Single/Divorced/Widowed/Separated	175/450 (38.9)	0.72	0.39	
Married/Living as Married	244/561 (43.5)	0.72	0.43	
Age				0.279
<25	5/18 (27.8)	0.78	0.28	
25-39	102/264 (38.6)	0.69	0.39	
40-55	141/345 (40.9)	0.70	0.41	
>55	171/384 (44.5)	0.75	0.45	
Age				0.107

<55	238/602 (39.5)	0.70	0.40	
≥55	181/409 (44.3)	0.74	0.44	
Used cannabis 5 or more times in the last 12 months				0.459
No	245/580 (42.2)	0.73	0.42	
Yes	168/415 (40.5)	0.70	0.40	
Primary medical condition you currently treat with medical cannabis				0.913
Anxiety Disorder	37/98 (37.8)	0.73	0.38	
Arthritis	27/63 (42.9)	0.75	0.43	
Cancer/Leukemia	8/15 (53.3)	0.73	0.53	
Chronic Pain	298/703 (42.4)	0.72	0.42	
Crohn's Disease	1/6 (16.7)	0.67	0.17	
Epilepsy	3/5 (60.0)	0.80	0.60	
Gastrointestinal Disorder	3/6 (50.0)	0.83	0.50	
Headache	8/23 (34.8)	0.78	0.35	
Insomnia	20/48 (41.7)	0.65	0.42	
Movement Disorder	2/8 (25.0)	0.63	0.25	
PTSD	2/8 (25.0)	0.63	0.25	
Other	8/18 (44.4)	0.78	0.44	
Primary medical condition you currently treat with medical cannabis				0.862
Pain	333/789 (42.2)	0.72	0.42	
Mental health issues	40/109 (36.7)	0.73	0.37	
Insomnia	20/48 (41.7)	0.65	0.42	
Other	26/64 (40.6)	0.77	0.41	

Table 2 highlights the rate of study completion and probability of retention at M3 and M6 by baseline prescription drug use and quality of life. Overall, 283 participants were LTFU at M3, and a further 309 were LTFU at M6. The five most commonly used prescription drug classes were opioids, with 290 (29.4%) reporting baseline opioid use, followed by non-opioid pain medications (215, 21.8%), antidepressants (166, 16.9%), anti-seizure drugs (159, 16.1%), and benzodiazepines (67, 6.8%).

Baseline opioid use was associated with lower rates of completion, with 44% of non-opioid users completing M6 (n=306) compared to 35% of opioid users (n=102). This was also reflected in the lower probability of people reporting opioid use remaining in the study at M3 and M6 (Probability (P) = 0.66 at M3 and 0.35 at M6 for opioid users compared to P=0.74 and 0.44 for non-opioid users; p=0.004). However, the use of antidepressants and of anti-seizure drugs were both associated with greater percentage of M6 completion, and associated increases in probability of retention at M3 and M6. Probability of retention at M3 and M6 for those using antidepressants was P=0.78 and P=0.50 respectively, compared to P=0.71 at M3 and P=0.40 at M6 for those not using antidepressants (p=0.011).

Those using anti-seizure medications saw similar outcomes: P=0.79 (M3) and 0.52 (M6) compared to P=0.71 and P=0.39 for non-users (p=0.003).

For quality of life, median baseline scores were used to create a binary comparison, and only a higher baseline score for the psychological measure of WHOQOL-Bref was associated with increased probability of remaining in the study. Those scoring 54 or better had a P=0.73 probability of remaining in the study at M3, and P=0.44 at M6, compared to P=0.71 at M3 and P=0.38 at M6 for those who scored below 54 (p=0.042).

4.4.2 Table 2. Percent completing M6 and probability of retention at M3 and M6 by baseline prescription drug use and quality of life (QOL) in 1011 participants.

Baseline Prescription Drug Use and QOL		Kaplan–Meier Estimator		
		Probability of Remaining in Study		
	Completed M6 (%)	M3	M6	P
Use of opioid				0.004
No	306/697 (43.9)	0.74	0.44	
Yes	102/290 (35.2)	0.66	0.35	
Opioid – defined daily dose (DDD)				0.321
<0.57	44/108 (40.7)	0.64	0.41	
≥0.57	34/108 (31.5)	0.66	0.31	
Use of non-opioid pain medications				0.721
No	314/770 (40.8)	0.73	0.41	
Yes	94/215 (43.7)	0.70	0.44	
Non-opioid pain medications - defined daily dose (DDD)				0.245
<0.43	37/76 (48.7)	0.72	0.49	
≥0.43	36/89 (40.4)	0.64	0.40	
Use of benzodiazepine				0.151
No	375/918 (40.8)	0.71	0.41	
Yes	32/67 (47.8)	0.82	0.48	
Benzodiazepine - defined daily dose (DDD)				0.151
<0.38	13/29 (44.8)	0.71	0.41	
≥0.38	15/27 (55.6)	0.82	0.48	
Use of antidepressant				0.011
No	324/818 (39.6)	0.71	0.40	
Yes	83/166 (50.0)	0.78	0.50	
Antidepressant - defined daily dose (DDD)				0.342
<1	14/35 (40.0)	0.74	0.40	
≥1	45/90 (50.0)	0.78	0.50	
Use of anti-seizure				0.003
No	326/827 (39.4)	0.71	0.39	
Yes	83/159 (52.2)	0.79	0.52	
Anti-seizure - defined daily dose (DDD)				0.542
<0.5	24/46 (52.2)	0.80	0.52	
≥0.5	34/72 (47.2)	0.75	0.47	
WHOQOL - Physical Health (baseline)				0.671
<36	218/526 (41.4)	0.74	0.41	
≥36	199/481 (41.4)	0.70	0.41	

WHOQOL - Psychological (baseline)				0.042
<54	166/442 (37.6)	0.71	0.38	
≥54	251/565 (44.4)	0.73	0.44	
WHOQOL - Social relationships (baseline)				0.168
<58	147/384 (38.3)	0.71	0.38	
≥58	270/623 (43.3)	0.72	0.43	
WHOQOL - Environment (baseline)				0.166
<66	222/556 (39.9)	0.70	0.40	
≥66	195/451 (43.2)	0.75	0.43	

Table 3 highlights the rate of study completion and probability of retention at M3 and M6 by baseline medical cannabis use. Median cannabis use was 5.0 grams (IQR 2.0 - 7.5). In regards to preferred types of cannabis products, the most cited was high CBD (461, 46.8%), and more patients cited "no preference" (286, 29%) than those who identified a preference for THC (239, 24.2%). For primary method of use, oral ingestion was cited by 546 (54.7%) while inhaled methods (e.g., vaporizers, joints, pipes and bongs) accounted for 44.6%. Additionally, most participants reported using at least some extract (orally ingested) products (619, 61.9%).

Citing no preference for either THC or CBD significantly increased the probability of retention at M6 (P=0.49 vs. P=0.44 for THC, and 0.38 for CBD, p=0.044), as did inhalation vs. oral ingestion (P=0.46 vs. 0.38 for oral ingestion, p=0.027). However, this analysis found no association between the amount of cannabis used per week, frequency of use per week, and reporting use of extract products, and the probability of retention at M3 or M6.

4.4.3 Table 3. Percent completing M6 and probability of retention at M3 and M6 by baseline medical cannabis use in 1011 participants.

Baseline Cannabis Use		**Kaplan–Meier Estimator**		
		Probability of Remaining in Study		
	Completed M6 (%)	**M3**	M6	**P**
Cannabis use per week (g)				0.567
<5	211/495 (42.6)	0.74	0.43	
≥5	208/505 (41.2)	0.72	0.41	
Frequency of cannabis use per week				0.587
<14	186/428 (43.5)	0.72	0.43	
≥14	233/571 (40.8)	0.73	0.41	
Currently using Tilray extract products				0.751
No	165/381 (43.3)	0.71	0.43	
Yes	254/619 (41.0)	0.74	0.41	
Preferred type of cannabis				0.044
THC	105/239 (43.9)	0.72	0.44	
High CBD	174/461 (37.7)	0.73	0.38	

No preference	139/286 (48.6)	0.74	0.49	
Primary method of use				<0.001
Vaporizer - cannabis flower	99/167 (59.3)	0.80	0.59	
Vaporizer/nail - cannabis extracts	2/10 (20.0)	0.50	0.20	
Joint	73/194 (37.6)	0.71	0.38	
Oral	209/546 (38.3)	0.72	0.38	
Pipe	11/33 (33.3)	0.58	0.33	
Waterpipe/bong	18/35 (51.4)	0.80	0.51	
Topical	5/11 (45.5)	0.82	0.45	
Primary method of use				0.027
Inhaled	203/439 (46.2)	0.74	0.46	
Orally ingested	209/546 (38.3)	0.72	0.38	

Table 4 presents the results of the univariate logistic regression as the unadjusted odds of completing M6 by baseline patient characteristics and other variables of interest, including the legalization of non-medical adult use of cannabis in Canada. Overall, primary patient characteristics such as gender, education, marital status, age, previous experience with cannabis, and primary condition were not found to be associated with retention. However, baseline prescription drug use, quality of life, aspects of cannabis use, and cannabis legalization were associated with significant impacts on the odds of completing M6 (Table 4).

Using opioids was associated with lower unadjusted odds of completing the study (p=0.011), and this outcome appeared to be independent of the daily dose used by participants. Conversely, patients using antidepressants had greater odds of retention (p=0.014), as did those using anti-seizure medication (p=0.003); however, as with opioids, these outcomes were not associated with specific Defined Daily Doses. In regards to baseline quality of life as measured by WHOQOL-Bref, a score of 54 or more in the psychological domain was associated with greater odds of retention compared to those scoring below 54 (p=0.028). None of the other three domains assessed – physical health, social relationships, or environment – appeared to be associated with retention.

Specific to cannabis use, citing no preference for either THC or CBD was associated with greater odds of retention compared to citing a preference for CBD, while a preference for THC was not associated with retention (p=0.11). Moreover, using cannabis via oral ingestion was found to result in

lower odds of completing M6 compared to those who inhale cannabis as their primary method of use (p=0.012).

Finally, cannabis legalization was found to have a significant impact on retention at M6. Participants who enrolled in the study in the period that would have resulted in M6 being after legalization had significantly lower odds of completing the study than those who enrolled prior to that period (p<0.001).

4.4.4 Table 4: Unadjusted odds of completing M6 in 1011 participants by baseline patient characteristics and other variables.

Patient Characteristics	Univariate Analysis		
	OR*	95% CI^	P
Gender			
Female	—	—	
Male	0.93	0.72, 1.20	0.590
Education			
College or lower	—	—	
High school or lower	0.86	0.67, 1.11	0.250
Marital status			
Married/Living as Married	—	—	
Single/Divorced/Widowed/Separated	0.83	0.64, 1.06	0.140
Age			
<55	—	—	
≥55	1.21	0.94, 1.57	0.140
Used cannabis for any reason 5 or more times in the last 12 months			
No	—	—	
Yes	0.93	0.72, 1.20	0.579
Primary illness or medical condition you currently treat with medical cannabis			
Pain	—	—	
Mental health issues	0.79	0.52, 1.20	0.270
Insomnia	0.98	0.54, 1.76	0.940
Other	0.94	0.55, 1.57	0.810
Use of opioid			
N	—	—	
Y	0.69	0.52, 0.92	0.011
Use of non-opioid pain medications			
N	—	—	
Y	1.13	0.83, 1.53	0.440
Use of benzodiazepine			
N	—	—	
Y	1.32	0.80, 2.18	0.270
Use of antidepressant			
N	—	—	
Y	1.52	1.09, 2.13	0.014
Use of anti-seizure			
N	—	—	
Y	1.68	1.19, 2.36	0.003
Opioid - dose per day (DDD)			
>0, <0.57	—	—	

≥0.57	0.67	0.38, 1.17	0.16
Non-opioid pain medications - dose per day (DDD)			
>0, <0.43	—	—	
≥0.43	0.72	0.38, 1.33	0.29
Benzodiazepine - dose per day (DDD)			
>0, <0.38	—	—	
≥0.38	1.54	0.54, 4.49	0.42
Antidepressant - dose per day (DDD)			
>0, <1	—	—	
≥1	1.50	0.68, 3.37	0.32
Anti-seizure - dose per day (DDD)			
>0, <0.5	—	—	
≥0.5	0.82	0.39, 1.72	0.60
WHOQOL - Physical Health (baseline)			
<36	—	—	
≥36	1	0.78, 1.28	0.980
WHOQOL - Psychological (baseline)			
<54	—	—	
≥54	1.33	1.03, 1.71	0.028
WHOQOL - Social relationships (baseline)			
<58	—	—	
≥58	1.23	0.95, 1.60	0.110
WHOQOL - Environment (baseline)			
<66	—	—	
≥66	0.87	0.68, 1.12	0.290
Cannabis use per week (g)			
<5	—	—	
≥5	1.06	0.83, 1.36	0.640
Frequency of cannabis use per week			
<14	—	—	
≥14	1.11	0.86, 1.44	0.400
Currently using Tilray extract products			
N	—	—	
Y	0.91	0.70, 1.18	0.480
Preferred type of cannabis			
CBD	—	—	
THC	1.29	0.94, 1.77	0.110
No Preference	1.56	1.16, 2.10	0.004
Primary method of use			
Inhaled	—	—	
Orally ingested	0.72	0.56, 0.93	0.012
Enrollment period re. completion pre/post legalization			
Enrolled prior to Apr 17, 2018 (M6 would be pre-legalization)	—	—	
Enrolled between Apr 17 and Jul 15, 2018 (M6 would be post legalization)	0.32	0.22, 0.46	<0.001

*OR = Odds Ratio

^CI = Confidence Interval

Table 5 presents the results of a multivariate model that included all variables found to be significant in the univariate analyses. The primary factor impacting retention was legalization (AOR = 0.28, 95% CI: 0.18-0.41). Additionally, the use of opioids continued to be significantly associated with reductions in the adjusted odds of retention at M6 (AOR = 0.62, 95% CI: 0.46-0.85). Moreover, the use of anti-seizure

medications continued to be associated with significantly greater adjusted odds of retention at M6 (AOR 1.91, 95% CI: 1.08-1.90), as was WHOQOL-Bref psychological scores of ≥54 (AOR 1.43, 95% CI: 1.08-1.90), with both associations actually increasing in the multivariate model. However, this analysis also found that the use of antidepressants was no longer associated with retention (p=0.061), nor was using a specific primary method of use, citing a preference for THC or CBD, or citing no preference for either.

4.4.5 Table 5: Adjusted odds of remaining in the study at M6 by variables found to be significant in univariate regression analysis.

Significant Variables	Multivariate Regression Analysis		
	AOR*	95% CI^	P
Use of opioid			
N	—	—	
Y	0.62	0.46, 0.85	0.003
Use of antidepressant			
N	—	—	
Y	1.42	0.98, 2.07	0.061
Use of anti-seizure			
N	—	—	
Y	1.91	1.30, 2.81	<0.001
WHOQOL - Psychological (baseline)			
<54	—	—	
≥54	1.43	1.08, 1.90	0.013
Preferred type of cannabis			
CBD	—	—	
THC	0.87	0.59, 1.27	0.5
No Preference	1.16	0.82, 1.63	0.4
Primary method of use			
Inhaled	—	—	
Orally ingested	0.87	0.64, 1.19	0.4
Enrollment period			
Enrolled prior to Apr 17, 2018 (M6 would be pre-legalization)	—	—	
Enrolled between Apr 17 and Jul 15, 2018 (M6 would be post-legalization)	0.28	0.18, 0.41	<0.001

*AOR = Adjusted Odds Ratio
^CI = Confidence Interval

4.5 Discussion

In this study, we found that non-medical cannabis legalization was independently associated with retention in the Tilray Observational Patient Survey. Additionally, the survival analysis and subsequent logistic regressions identified specific participant characteristics that were associated with the percentage, probability and adjusted odds of retention at M6. Specifically, the use of opioids was strongly associated with greater probability and adjusted odds that participants would be LTFU before completing the study,

while a higher baseline psychological score and the use of anti-seizure medications and were both associated with increased retention at M6.

The finding that the adjusted odds of participants being LTFU were three-fold higher compared to the pre-legalization period is consistent with other data examining the impacts of legalization on medical cannabis access in Canada. National polling data from January 2019 that included over 800 adult Canadian medical cannabis patients found that 26% of patients reported that medical cannabis had become more difficult to access since legalization, and that 48% of patients polled accessed cannabis via the illegal market, while 44% accessed cannabis via the legal non-medical market (Abacus, 2019). Furthermore, a study of Canadian cancer patients that compared medical cannabis access and use both before (n=821) and after legalization (n=852) cited significant challenges obtaining cannabis products post-legalization (Hawley, 2020). News reports from that time and subsequent academic studies suggest that industry-wide shortages of both legal medical and non-medical cannabis products likely resulted from the emergence of novel licensed retail outlets and online sales channels and the associated increase in demand, which diluted the available legal supply to both medical and non-medical markets channels (M. Armstrong, 2019; M. J. Armstrong, 2021; P. Armstrong, 2019). The lack of authorized cannabis products in the months immediately following legalization led Ontario, Canada's most populous province, to temporarily halt the licensing of legal storefront dispensaries (P. Armstrong, 2019; Mazur, 2019). News reports suggest this shortage lasted for many months, and likely led to a diversion of medical and non-medical cannabis consumers to access via illicit channels (M. Armstrong, 2019). While there were no measures in this study assessing whether patients LTFU in TOPS left the care of the participating clinics, stopped using medical cannabis, or simply accessed it from alternative sources, it is reasonable to presume that policy changes having a national impact on legal access to medical cannabis in Canada would also affect authorized patients involved in prospective medical cannabis studies over the same period, and that the reported product shortages provide a rationale for the significant decrease in retention seen in TOPS post-legalization.

While the supply situation appears to have been rectified, data from Health Canada highlights an 18% decline in patients registered in the federal medical cannabis program between September 2019 and June 2020 (the latest available data at the time of writing), suggesting the patient migration away from the federal medical cannabis program may be a longer-term trend (Health Canada, 2020). That same period saw a steady expansion of regulated community-based non-medical retail outlets offering a large selection of different products at prices that are often lower than those in the legal medical market, which stands in sharp contrast to the online-only medical cannabis market that many patients have long complained is too expensive and difficult to access (Belle-Isle et al., 2014; Capler et al., 2017; Valleriani et al., 2020). However, there are some policy options the federal government could consider that might address some of the perceived shortcomings of the federal medical cannabis program, including allowing pharmacy-based access, which would have the important ancillary benefit of increased engagement with health care providers, since pharmacists could provide in-person information about safe use, adverse events and potential contraindications. Additionally, reducing the cost of medical cannabis by extending the tax-exempt status of other prescription medicines in Canada to all medical cannabis products, and/or by expanding opportunities for cost coverage via private or public payers could also incentivize patients to access cannabis products via the medical system, as has been the case in Germany (Pascual, 2020), thereby reducing the odds that patients enrolled in prospective medical cannabis studies would opt out of the federal medical cannabis program and subsequently be LTFU.

The outcomes of this study also suggest that patient capacity and study burden may have impacted retention. While only a few variables were shown to be associated with adjusted odds of retention at M6, most seem to be consistent with characteristics that may be indicative of overall patient capacity. Primarily, the finding that baseline opioid use reduced survival/retention in the TOPS study could be reflective of a patient population with less stable physical and psychological health conditions sometimes associated with or resulting from chronic opioid therapy (Baldini, von Korff, & Lin, 2012; Dobscha, Morasco, Duckart, MacEy, & Deyo, 2013; Sullivan, 2018), and which research has shown may

impact retention in prospective studies (O'Connor, Cousins, Durand, Barry, & Boland, 2020; Zweben, Fucito, & O'malley, 2009). Similarly, the finding that having a higher baseline score for the psychological measure of WHOQOL-Bref was associated with increased odds of retention further suggests that patient capacity may have been a significant internal factor affecting the odds of patients being LTFU in TOPS. The only relevant finding that appeared unrelated to patient capacity was that the use of anti-seizure medications was associated with greater odds of retention. This outcome may be reflective of the well-established relationship between treatment adherence, reduced seizure frequency and severity, and improved quality of life in patients affected by seizure disorder (Hamedi-Shahraki et al., 2019; Lin, Chen, & Pakpour, 2016; Sancho et al., 2010), which may have increased the motivation of this particular patient cohort to continue using cannabis within the scope of the federal medical cannabis program, and to subsequently remain in the study as well.

While recruiting participants with greater capacity could improve retention in future medical cannabis studies, it might also lead to recruitment bias and ultimately confound findings. Additionally, since such a significant portion of medical cannabis patients also use opioids (Campbell et al., 2018; Chen et al., 2019; Lucas et al., 2019; Safakish et al., 2020), it would be hard to justify excluding these patients from future research. Therefore, a better option to improve retention would be find ways to reduce study burden on this vulnerable patient population. Studies and systematic reviews specifically examining retention in prospective studies have found that study burden is one of the most significant factors affecting the odds of patients being LTFU, and have identified a number of barrier-reduction strategies that can significantly increase retention (Kearney et al., 2017; Naidoo et al., 2020; Sommer et al., 2018; Teague et al., 2018). These include reducing the number of study visits and associated assessments, improving patient compensation, and providing flexibility in data collection methods such as conducting follow ups via web-based surveys, phone or telemedicine (Abshire et al., 2017; Svendsen et al., 2017; Teague et al., 2018; Zweben et al., 2009).

This study has a number of strengths and limitations. This was a convenience sample recruited at 21 medical clinics across five Canadian provinces, and there is no guarantee this sample is representative of the general Canadian medical cannabis patient population. Since many of the clinics specialize in the treatment of chronic pain, there may be an over-representation of patients affected by chronic pain. Data regarding the use of cannabis was self-reported by patients and did not benefit from biological drug detection to confirm use or non-use of cannabis, so is subject to potential recall bias.

These limitations are counterbalanced by several methodological strengths, including the large number of participants (to the best of our knowledge this is the largest national prospective survey of Canadian medical cannabis patients to date), gathering of highly detailed data on patterns of cannabis and prescription drug use, and data entry of prescription drug use by physicians, rather than relying on patient self-report.

4.6 Conclusion

Cannabis legalization in Canada has successfully shifted the regulation of cannabis from a predominantly criminal justice approach to one focused on public health and harm reduction. However, an ancillary and perhaps unexpected outcome has been its subsequent impact on patient access to medical cannabis, and associated efforts to study this population. While this analysis cannot determine if the association between legalization and reduced odds of retention in TOPS is unique to this study and/or the period immediately following legalization or indicative of a broader trend, researchers conducting prospective studies on cannabis in Canada and around the globe should anticipate and attempt to mitigate the potential impacts of increased access options on study retention. Evidence-based barrier reduction strategies that could reduce the odds of patients being lost to follow up include minimizing the number of study visits and assessments, ensuring adequate patient compensation, and conducting follow ups via online surveys, phone-based interviews, and telemedicine. Should increased access options continue to

erode patient participation in Canada's federal medical cannabis program and subsequently in studies assessing the harms and benefits of medical cannabis, pragmatic policy solutions designed to better meet the needs of patients—such as pharmacy-based access and increased cost-coverage—could form part of a more comprehensive strategy to improve patient access to medical cannabis and improve retention in prospective studies of this population.

4.7 Authors' Contributions

PL designed the study, coordinated its administration and analysis, and is the primary author of this manuscript. SB, MJM and ZW reviewed and edited the manuscript.

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4.9 References

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5 Closing Chapter

The earliest known medical evidence for the use of cannabis in the treatment of substance use disorder dates to *The use of Indian hemp in the treatment of chronic chloral and chronic opium poisoning* in *The Lancet* in 1889. In his report, Dr. Edward A. Birch noted that cannabis extract appeared to relieve the symptoms of withdrawal resulting from a dependence on laudanum, a tincture of opium, thereby improving sleep, appetite, constipation, and delusions (Birch, 1889). At the time, I suspect that Dr. Birch could not have anticipated this early report would prove so prescient 130 years later, and serve as the cornerstone for an entire field of cannabis research and associated harm reduction initiatives related to the harms associated with opioids, alcohol, tobacco and other substances.

In a similar fashion, the relevance of the findings of the three papers that make up my dissertation go beyond their individual outcomes and immediate policy implications. These publications contribute to a larger body of work that, along with other similar studies dating back to Dr. Birch's publication, effectively re-contextualize our understanding of the impact of cannabis on the use of other substances and, in turn, provide insights to improve public health and influence future research.

In reviewing the first two chapters of this dissertation, a few primary outcomes appear consistent across both papers, namely that patients self-reported reductions in both alcohol and tobacco/nicotine (T/N) following medical cannabis initiation, and that the intent to use medical cannabis to reduce the use of these substances is associated with greater odds of reduction. However, it's also notable that only 6 (<1%) of study participants cited any direct involvement in their substance reduction efforts by their health care provider (HCP), which certainly highlights

an opportunity to better inform HCPs about the impact of cannabis on other substance use so they can proactively work with their patients to safely and successfully reduce their use of alcohol, T/N and other substances via formal tapering programs and other harm reduction strategies. In light of these findings and similar research on the deliberate use of cannabis in the reduction of opioid and/or stimulant use, outreach and education efforts aimed at health care providers should be developed as part of a broader national harm reduction strategy for substance use disorder.

Notably, the first two studies also identified participants that either did not reduce their use of alcohol or T/N, or that self-reported increases in use following medical cannabis initiation. While the focus of these publications was on identifying characteristics associated with reduction/cessation, there may also something to be learned from the remainder of this patient population as well. Specifically, since citing "no intent" significantly reduced the odds of reduction, the broad outreach and education campaign suggested above should target all medical cannabis patients and health care providers in Canada to ensure that opportunities to discuss and reduce the use of alcohol or T/N are not missed when patients begin their use of medical cannabis. Additionally, while those that reported greater patterns of use alcohol or T/N in the pre-period had higher associated odds of reducing use, there may be an opportunity for future research to examine whether or not medical cannabis initiation can be prophylactic of increased, potentially problematic use, either independently or as an adjunct to traditional alcohol or T/N treatments. Since our data suggests that participation in T/N treatment was actually associated with lower odds of decreasing T/N use, the interaction between cannabis use and T/N treatment merits further exploration to better understand whether either sequentiality or adjunct/parallel use of cannabis in T/N treatment-related quit attempts impact outcomes.

As with many academic publications, the first two papers end with a call for further research, with a focus on prospective observational and experimental studies examining cannabis as an adjunct or alternative treatment for alcohol or tobacco use disorder. However, since the survival analysis we conducted found that the odds of patients being lost to follow up (LTFU) more than tripled following legalization, there may be unanticipated obstacles and impediments to cannabis research in a post-prohibition era. While I am strongly supportive of the Canadian government's policies to end cannabis prohibition, this regulatory shift has had an undeniable impact on participation in the federal medical cannabis program, leading to a steady decline in patient participation since September 2019 (Health Canada, 2020). Our study suggests this migration away from medically-supervised cannabis access may also be impacting retention in prospective research efforts involving this patient population. There may be a number of factors spurring on this patient exodus. What research is making increasingly apparent is that both the unregulated market as well as legal, non-medical cannabis dispensaries now provide Canadian adults with many advantages not currently available via the mail-order only medical cannabis program, including the opportunity for in-person, community-based interaction, a strong selection of products from hundreds of different producers, and competitive pricing. Whether this disruption to medically-supervised cannabis-based treatments and related research is in the best interest of cannabis patients or public health as a whole is beyond the scope of this dissertation. However, it certainly bears some consideration, as do policy options that might stem the patient migration to the non-medical cannabis market, including allowing community-based access via pharmacies and specialized medical cannabis dispensaries, and improving cost-coverage for patients.

However, since to the best of our knowledge this is the first study to analyze the impact of increased legal access options on retention in longitudinal, individual-level cannabis research, no firm conclusions should be drawn until these findings are corroborated by other studies.

5.1 Lessons Learned and Future Research

I would be remiss if I did not spend a few moments reviewing some of the lessons learned of the last seven years of this doctoral process. While it would be impossible to run through all the new knowledge that was gained with every challenge and success in this dissertation, a few major insights stand out and have subsequently impacted the design and direction of my subsequent studies.

1. Ensure that key variables and patient characteristics that might be associated with the primary outcome of interest are mandatory in surveys. Unfortunately, this was not the case in the TOPS study, in which the response to the measure for gender was left optional out of respect for those who prefer not to self-identify in a gender normative fashion. As a result, the multivariate analysis included far fewer participants than the univariate analysis, leading us to conduct a sensitivity analysis comparing outcomes of those that were included in the multivariate analysis with those that were not.
2. Let the primary outcomes of interest guide and determine the instruments, measures and analysis strategy subsequently included in the study. While this may seem obvious in retrospect, in exploratory studies such as CCPS and TOPS, it often seemed more practical to design a questionnaire and then figure out what to do with the data once we saw how

participants responded. However, this ultimately led to significantly more analytical work than was initially anticipated or necessary.

3. Remain keenly vigilant of the potential for bias and/or confounders throughout the study design process, and ensure every methodological strategy is taken to reduce both. Ultimately, the primary outcomes of a study are only as significant as the protocols potential methodological limitations.
4. Language matters! It is important not to overstate academic findings, particularly in areas of research that have a significant potential to attract public attention beyond academia and that may ultimately have policy implications. It has been suggested that interpreting 30 day abstinence in the first two studies as total cessation of alcohol or T/N use may be an overreach, and I agree that more accurate terminology would help ensure these results are not subject to misinterpretation. Despite some evidence that 30 day abstinence of alcohol is associated with potential personal health improvements (De Visser, Robinson, & Bond, 2016) and that it can be an important short-term marker of success in T/N quit attempts (J. R. Hughes et al., 2003; Messer et al., 2015; Russell, Haseen, & McKeganey, 2019), more prudent language could have been used to better reflect the nature of this primary outcome of interest. In future studies, I will replace “cessation” with the acronym 30DA as a more accurate and descriptive term for “30 day abstinence”.
5. As noted previously, further research should also focus on patient populations that reported either no change or increases in alcohol or T/N use in order to broaden understanding of the range of potential impacts associated with medical cannabis initiation on the use of other substances.

These insights have already informed my research, and a new multi-site prospective study focused on chronic pain I recently designed called Cannabis and Pain Study Canada (CAPS-Can) improves significantly on my past efforts by including validated instruments for pain, sleep and anxiety, tracking adverse events, and reducing the number of data points and allowing the option of data gathering via phone or telemedicine in order to minimize study burden. While this protocol will not completely eliminate the potential for bias/confounders, or fully mitigate the potential impact of legalization on study adherence and retention, it does build and improve upon past research efforts, and will hopefully provide methodological approaches that can inform future observational and clinical studies examining the therapeutic effects of cannabis.

Finally, in light of the millions of lives impacted or lost around the globe due to the problematic use of alcohol, tobacco and opioids, and the growing international movement to depenalize and regulate cannabis use, I sincerely hope the ever-expanding body of research supporting cannabis as a safer substitute for potentially more dangerous substances encourages academics and policy-makers the world over to further efforts to better understand the cannabis substitution effect and its impacts on public health that Dr. Edward Birch first noted over 130 years ago.

5.2 References

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6 Appendices

6.1 Study Instruments and Consent Forms

6.1.1 Appendix A: Canadian Cannabis Patient Survey 2019 Informed Consent Form

Adobe Acrobat Document

6.1.2 Appendix B: Canadian Cannabis Patient Survey 2019

Adobe Acrobat Document

6.1.3 Appendix C: TOPS Informed Consent Form

Adobe Acrobat Document

6.1.4 Appendix D: World Health Organization Quality of Life Short Form

Adobe Acrobat Document

6.1.5 Appendix E: TOPS Cannabis Use Survey

Adobe Acrobat Document

6.1.6 Appendix F: TOPS Prescription Drug Questionnaire

Adobe Acrobat Document

6.2 Study Proof of Publication or Submission

6.2.1 Paper 1 Proof of Publication in the International Journal of Drug Policy

Adobe Acrobat Document

6.2.2 Paper 2 Proof of Submission Email From the Journal of Substance Abuse Treatment

Wednesday September 23. 2020

Journal of Substance Abuse Treatment

To Philippe Lucas

Self-reported reductions in tobacco and nicotine use following medical cannabis initiation; results from a cross-sectional survey of authorized medical cannabis patients in Canada

Dear Mr. Lucas,

We have received the above referenced manuscript you submitted to Journal of Substance Abuse Treatment.

To track the status of your manuscript, please log in as an author at https://www.editorialmanager.com/josat/, and navigate to the "Submissions Being Processed" folder.

Thank you for submitting your work to this journal.

Kind regards,
Journal of Substance Abuse Treatment

6.2.3 Paper 3 Proof of Submission Email From the Journal of Cannabis Research

December 4, 2020

Journal of Cannabis Research Editorial Office

to Philippe Lucas

JCAN-D-20-00128

The impact of non-medical cannabis legalization and other exposures on retention in longitudinal cannabis research: a survival analysis of a prospective study of Canadian medical cannabis patients
Philippe Lucas; Susan Boyd; M-J Milloy; Zach Walsh
Journal of Cannabis Research

Dear Mr. Lucas,

Thank you for submitting your manuscript 'The impact of non-medical cannabis legalization and other exposures on retention in longitudinal cannabis research: a survival analysis of a prospective study of Canadian medical cannabis patients' to Journal of Cannabis Research.

The submission id is: JCAN-D-20-00128
Please refer to this number in any future correspondence.

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6.3 Paper 1 Appendices

6.3.1 Appendix A. Comparison of primary outcomes between those included and those excluded due to missing data in the multivariate analysis in Table 5

	Included	Excluded	P*
Alcohol analysis			
Reduction in use frequency per 30 days	311/706 (44.1)	108/258 (41.9)	0.544
Reduction in number of drinks per week	245/696 (35.2)	78/252 (31.0)	0.222
Complete cessation	54/710 (7.6)	22/263 (8.4)	0.695

*p based on Chi-square test.

6.3.2 Appendix B. Multivariate analysis of change in alcohol use among participants that initiated medical cannabis use within the past 5 years.

	Reduction in use frequency per 30 days		Reduction in number of drinks per week		Complete cessation	
	Multivariate (n=533)		Multivariate (n=527)		Multivariate (n=536)	
Variable and comparison	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**
Level of intention to use cannabis to reduce alcohol use						
Deliberately/MD recommended/MD developed vs. None/Surprised	2.22 (1.23, 3.99)	0.008	2.10 (1.13, 3.93)	0.020	2.98 (1.24, 7.19)	0.015
Gender						
Male vs. female	1.08 (0.74, 1.59)	0.687	1.37 (0.87, 2.15)	0.169	1.40 (0.61, 3.26)	0.429
Age						
<55 vs. ≥55	2.09 (1.35, 3.22)	<0.001	1.21 (0.74, 1.96)	0.448	0.73 (0.31, 1.75)	0.479
Primary condition						
Pain – Y vs. N	1.06 (0.69, 1.62)	0.784	1.04 (0.64, 1.68)	0.871	0.57 (0.24, 1.34)	0.197
Mental health issues – Y vs. N	1.36 (0.82, 2.24)	0.231	1.42 (0.81, 2.47)	0.222	2.03 (0.87, 4.77)	0.103
Insomnia – Y vs. N	0.60 (0.33, 1.10)	0.097	0.57 (0.28, 1.15)	0.115	0.20 (0.04, 1.02)	0.053
GI – Y vs. N	1.44 (0.50, 4.13)	0.494	1.80 (0.59, 5.53)	0.305	3.32 (0.71, 15.39)	0.126
Movement Disorder – Y vs. N	0.61 (0.23, 1.61)	0.321	0.44 (0.14, 1.37)	0.157	2.77 (0.69, 11.13)	0.150
Preferred type of cannabis						
THC vs. CBD	1.01 (0.58, 1.77)	0.963	1.16 (0.61, 2.22)	0.645	1.95 (0.55, 6.92)	0.300
Used cannabis daily						
Yes vs. No	1.18 (0.78, 1.79)	0.427	1.04 (0.65, 1.66)	0.868	0.88 (0.39, 2.01)	0.764
Primary method of use						
Inhaled vs. Orally ingested	1.13 (0.71, 1.79)	0.601	0.97 (0.57, 1.64)	0.909	0.96 (0.39, 2.37)	0.922
Use of other alcohol reduction strategies						
Yes vs. No	2.06 (0.48, 8.91)	0.331	4.39 (0.79, 24.50)	0.092	4.71 (0.94, 23.59)	0.059
Alcohol use frequency per month in the pre period						
Per day increase	1.05 (1.03, 1.07)	<0.001				
Number of drinks per week in the pre period						
11-30 vs. 1-10			5.77 (3.54, 9.41)	<0.001	1.31 (0.54, 3.19)	0.555
>30 vs. 1-10			9.21 (4.06, 20.87)	<0.001	3.53 (1.23, 10.12)	0.019
Cessation of tobacco/nicotine						
Yes vs. No	1.30 (0.59, 2.88)	0.520	1.84 (0.77, 4.43)	0.171	1.94 (0.55, 6.87)	0.303

6.4 Paper 2 Appendices

6.4.1 Appendix A. Association between years of T/N use and participation in T/N cessation strategies.

	Years of tobacco use			
	≤ 5	6-10	>10	P*
Any substance use reduction strategies, n (%)				0.028
No	51 (89.5)	88 (88.9)	393 (81.0)	
Yes	6 (10.5)	11 (11.1)	92 (19.0)	
Pharmacological treatment, n (%)				0.160
No	55 (96.5)	97 (98.0)	456 (94.0)	
Yes	2 (3.5)	2 (2.0)	29 (6.0)	
Nicotine replacement therapy, n (%)				0.010
No	55 (96.5)	91 (91.9)	419 (86.4)	
Yes	2 (3.5)	8 (8.1)	66 (13.6)	

* p value based on Cochran-Armitage Trend Test.

6.4.2 Appendix B. Multivariate analysis for change in T/N usage among those initiated medical cannabis within the past five years.

	Reduction in number of T/N uses per day		Complete cessation of T/N use	
	Multivariate (n=233)*		Multivariate (n=233)*	
Variable and comparison	**Odds ratio (95% CI)**	**P**	**Odds ratio (95% CI)**	**P**
Level of intention to use cannabis to reduce T/N use				
Deliberately/MD recommended/MD developed vs. None/Surprised	1.79 (0.77, 4.17)	0.178	1.74 (0.70, 4.31)	0.233
Gender				
Female vs. Male	0.90 (0.54, 1.50)	0.690	0.78 (0.43, 1.44)	0.430
Age				
≥55 vs. <55	0.84 (0.46, 1.53)	0.570	1.88 (0.97, 3.67)	0.062
Primary condition				
Pain -- Y vs N	0.49 (0.22, 1.11)	0.086	0.68 (0.34, 1.35)	0.265
Mental health issues – Y vs N	0.48 (0.20, 1.14)	0.094	0.44 (0.20, 0.99)	0.046
Insomnia -- Y vs N	0.27 (0.09, 0.86)	0.026	0.99 (0.34, 2.86)	0.978
Preferred type of cannabis				
THC vs. CBD	1.41 (0.59, 3.34)	0.435	1.58 (0.54, 4.58)	0.404
Used cannabis daily				
Yes vs. No	1.47 (0.81, 2.68)	0.203	1.51 (0.74, 3.08)	0.257
Primary method of use				
Orally ingested vs. Inhaled	1.55 (0.76, 3.18)	0.231	1.93 (0.85, 4.40)	0.119
Use of other T/N reduction strategies:				
Yes vs. No	0.80 (0.39, 1.63)	0.539	0.39 (0.14, 1.07)	0.068
Number of T/N per day in the pre-cannabis period				
>25 vs. ≤ 25	2.65 (1.17, 6.03)	0.020	1.91 (0.82, 4.48)	0.136

Years of T/N use				
≤ 10 vs. >10	1.60 (0.91, 2.82)	0.099	2.16 (1.13, 4.13)	0.019
Complete cessation of alcohol				
Yes vs. No	1.69 (0.51, 5.60)	0.394	2.53 (0.73, 8.75)	0.142

* Sample size in the univariate analysis varied across comparisons due to missing data. Multivariate analysis only included patients with no missing data for all variables.

6.4.3 Appendix C. Comparison of primary outcomes between those included and those excluded due to missing data in the multivariate analysis.

Outcome	Included	Excluded	P*
Tobacco analysis			
Reduction in number of T/N uses per day	229/460 (49.8)	91/190 (47.9)	0.661
Complete cessation of T/N use	116/460 (25.2)	44/190 (23.2)	0.579

* p value based on Chi-square test

6.5 Paper 3 Appendices

6.5.1 Appendix A. TOPS Health Care Provider Talking Points

Tilray Observational Patient Survey (TOPS)

Health Care Provider Talking Points

Once a patient and physician agree that medical cannabis is an appropriate treatment option for the patient, the physician can present the TOPS project to the patient by using the following talking points:

- TOPS is a study being conducted by Tilray, a federally authorized Licensed Producer of medical cannabis.
- The study is an online survey protocol to examine the impact of medical cannabis on quality of life and prescription drug use.
- While we are assisting with the recruitment and administration of the TOPS study, this project is sponsored and conducted by Tilray.
- Your services and relationship with either me/this clinic or Tilray will not be affected in any way should you chose not to participate in this study, and/or to withdraw at a later point in time.

For in-person visits:

- If you're interested in learning more about the TOPS study, I'd like to provide you with an informed consent form on an iPad that will provide more information about the study, and provide you with an opportunity to participate if you chose.

For telemedicine:

- If you're interested in learning more about the TOPS study, I'd like to read you an informed consent form that will provide more details about the study, and provide you with an opportunity to participate if you chose.