Boston University

OpenBU **http://open.bu.edu**

Boston University Theses & Dissertations Boston University Theses & Dissertations

2020

Cognition and cannabis use disorder in recreational cannabis users and medical cannabis patients

https://hdl.handle.net/2144/41117

Downloaded from DSpace Repository, DSpace Institution's institutional repository

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Dissertation

COGNITION AND CANNABIS USE DISORDER IN RECREATIONAL CANNABIS USERS AND MEDICAL CANNABIS PATIENTS

by

KELLY A. SAGAR

B.A., Boston College, 2005
M.S., Northeastern University, 2013
C.A.G.S, Northeastern University, 2015

Submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

2020

© 2020
KELLY A. SAGAR
All rights reserved

Approved by

First Reader

Robert A. Stern, Ph.D.
Professor of Neurology, Neurosurgery, and Anatomy & Neurobiology

Second Reader

Staci A. Gruber, Ph.D.
Associate Professor of Psychiatry
Harvard Medical School

Third Reader

Maxine H. Krengel, Ph.D.
Assistant Professor of Neurology

DEDICATION

To Vovo. You used to always say *juízo* (use your head) and make your family proud – I think this would qualify. Love you always.

ACKNOWLEDGMENTS

"Alone we can do so little, together we can do so much" – I could not have completed this dissertation without the unwavering support from so many in my academic, professional and personal life. Many of you have not only supported me throughout the process of writing my dissertation, but have provided exceptional advice, unfailing guidance, and true care and compassion over many.

First and foremost, I want to thank Dr. Staci Gruber. Staci, I can without out a doubt say that I would not be where I am today without you. For the past 11 years (hard to believe!) you have given me the latitude to explore my interests both within and outside of the lab, and you often knew what was best for me far before I did. Your passion is contagious, your work ethic unprecedented, and your natural instinct to always lend a helping hand is something I hope I can emulate in my personal and professional life. I am beyond excited by what is on the horizon for the MIND program, and I am honored to work with such a great team. With that, I also want to thank my MIND family – especially Kate Dahlgren. You may think you're just numbers to me, but I can assure you it's "only the prime numbers!"

To my chair and all my committee members – Drs. Carole Palumbo, Robert Stern, Maxine Krengel, Richard Saitz, and Mieke Verfaellie – thank you for the time and energy that you put into helping me bring this dissertation to completion. Your feedback was instrumental in helping me learn, improve, and I know it will ultimately help me to become a better scientist. Throughout the past few years, my conversations with each of you have truly been thought-provoking, meaningful, and enjoyable. Most recently, I

appreciate the time you've taken for zoom meetings, prompt email responses, and flexibility with often-shifting schedules. Your encouragement and uplifting words were always so much appreciated.

I also want to acknowledge my family and friends who have all checked in on me regularly, offered kind words of support, and who have tolerated my sometimes quick hellos and fast goodbyes as I've worked against the clock – thank you. I am very much looking forward to spending more time together soon, even if it has to be virtually!

Matt, we have had some busy times to say the least. I know at points we have both been overwhelmed by the combination of graduate school and work, but we make an excellent team. I will also acknowledge that you have definitely earned the "and then some" distinction in the past few weeks. As we both wrap up grad school, I hope you're ready for the next challenge we face together – which brings me to the little one that keeps reminding me of his presence through tiny jabs, swift kicks, and what seems to be late night dance parties that make me laugh and keep me smiling. You unknowingly kept me company and brought me joy through some of the hardest times of my academic career, including both qualifying exams and the preparation of my dissertation. I am so excited to meet you!

COGNITION AND CANNABIS USE DISORDER IN RECREATIONAL CANNABIS USERS AND MEDICAL CANNABIS PATIENTS

KELLY A. SAGAR

Boston University School Medicine, 2020

Major Professor: Robert A. Stern, Ph.D. Professor of Neurology, Anatomy & Neurobiology, Neurosurgery

ABSTRACT

As legalization of cannabis continues to spread across the United States, many question the public health implications. The term "cannabis" is often used to refer to anything that comes from the plant and can be used recreationally (to get high or alter one's current state) or medically (to treat a medical condition). While previous research has primarily focused on the impact of recreational cannabis use, few studies have examined cognitive outcomes associated with medical cannabis (MC) use and the potential for development of problematic use in MC patients. Given important distinctions among recreational users and MC patients, it is likely that these distinct populations of cannabis consumers will experience differential cognitive effects and potential for problematic cannabis use.

This dissertation is comprised of three studies. The first is a cross-sectional study that explores executive function and verbal learning and memory in recreational cannabis users relative to healthy controls who do not use cannabis, while also assessing whether cannabis use patterns (e.g., age of onset, urinary THC levels) influence findings. The second study is an observational, longitudinal study which examines executive function

and memory, as well as changes in mood, anxiety, sleep, and quality of life in MC patients over 12 months of MC treatment relative to pre-MC treatment. In the third study, symptoms and behaviors associated with problematic cannabis use are examined in cohorts from study 1 and study 2. Specifically, scores on the Cannabis Use Disorder Identification Test – Revised (CUDIT-R) are assessed in MC patients over the course of treatment and also compared to a previously recruited cohort of recreational cannabis users; the validity of the CUDIT-R is also explored.

Despite previous research, in the current study recreational users did not exhibit cognitive decrements relative to healthy controls. In MC patents, cognitive performance was stable over the course of 12 months of MC treatment relative to pre-MC treatment performance, and overall they reported improved ratings of mood, anxiety, sleep, and some aspects of quality of life. Although the CUDIT-R suggests MC patients' average scores do not meet the threshold for possible cannabis use disorder, analyses revealed this measure is not valid and therefore not appropriate in MC patients.

Although changes in cognition were not detected in recreational users or MC patients in the current studies, a number of methodological limitations (e.g., sample size and limited ability to adjust for confounding variables) must be considered as these factors likely affected study results. Future studies evaluating the impact of cannabis use will benefit from carefully considering the definition of cannabis itself, goal of use, product choice, and age of onset of use. Researchers and clinicians will also benefit from the development of screening tools specifically designed to assess cannabis use disorder in those who use cannabis for medical purposes.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

2-AG ..... 2-arachidonoyl glycerol

AEA ..... anandamide

ANCOVA ..... analyses of covariance

ANOVA ..... analyses of variance

ASI ..... Addiction Severity Index

ASSIST ..... Alcohol, Smoking and Substance Involvement Screening Test

BAI ..... Beck Anxiety Inventory

BDI ..... Beck Depression Inventory

BIS-11 ..... Barratt Impulsiveness Scale - 11

CAN ..... cannabis

CAST ..... cannabis abuse screening test

CBC ..... cannabichromene

CBD ..... cannabidiol

CBG ..... cannabigerol

CBN ..... cannabinol

Cr ..... Creatinine

CSA ..... Controlled Substances Act

CUD ..... cannabis use disorder

CUDIT ..... Cannabis Use Disorder Identification Test

CUDIT-R ..... Cannabis Use Disorder Identification Test - Revised

CUPIT ..... Cannabis Use Problems Identification Test

CVLT .....California Verbal Learning Test

DEA..... Drug Enforcement Agency

DSM ..... Diagnostic and Statistical Manual of Mental Disorders

eCB.....endocannabinoid

ECS ..... endocannabinoid system

EMA .....ecological momentary assessment

FAAH ..... fatty acid amide hydrolase

FDA.....Food & Drug Administration

FTND ..... Fagerstrom Test for Nicotine Dependence

GC-MS ..... gas chromatography – mass spectrometry

GRP55 .....G protein-coupled receptor 55

HC .....healthy control

LNS ..... Letter Number Sequencing

LOCF..... Last Observation Carried Forward

MAG-L..... monoacylglycerol lipase

MAR.....missing at random

MC ..... medical cannabis

mg..... milligrams

MIND .....Marijuana Investigations for Neuroscientific Discovery

MTF.....Monitoring the Future

MWC.....Marijuana Withdrawal Checklist

NASEM.....National Academies of Science, Engineering, and Medicine

NDMA ..... N-methyl-D-aspartate

NIDA ..... National Institute on Drug Abuse

NSAID ..... Nonsteroidal Anti-Inflammatory Drug

NSDUH ..... National Survey on Drug Use and Health

OAE ..... O-Arachidonoyl-ethanolamine

PEA ..... palmitoylethanolamide

POMS ..... Profile of Mood States

PSQI ..... Pittsburgh Sleep Quality Index

RAVLT ..... Rey Auditory Verbal Learning Test

rmANCOVA ..... repeated measures analyses of covariance

SCID-P ..... Structured Clinical Interview for DSM-IV Patient Edition

SD ..... Standard Deviation

SDS ..... Severity of Dependence Scale

SF-36 ..... Short Form 36 Health Survey Questionnaire

STAI ..... State Trait Anxiety Index

THC delta-9-tetrahydrocannabinol

THCV ..... tetrahydrocannabivarin

TLFB ..... timeline followback

TRP ..... transient receptor potential

WAIS-R ..... Wechsler Adult Intelligence Scale - Revised

WASI ..... Wechsler Abbreviated Scale of Intelligence

WCST ..... Wisconsin Cart Sorting Test

GLOSSARY

For the purposes of this dissertation, recreational cannabis users and medical cannabis patients are defined as follows:

Recreational Cannabis Users – those who use cannabis products for the primary goal of feeling high or altering one's current state of being

Medical Cannabis (MC) Patients – those who 1) have a certification or physician's recommendation to use cannabis or cannabinoid-based products for the main goal of relieving symptoms related to one or more chronic medical conditions; or 2) plan to use non-intoxicating, federally legal hemp-based products for the main goal of relieving symptoms related to one or more chronic medical conditions

CHAPTER ONE

Brief History of Cannabis

Cannabis has been used for thousands of years; references to the use of cannabis for medicinal purposes appear in ancient texts and have been substantiated by evidence uncovered at archeological sites (Russo, 2007). However, public opinions of cannabis have changed drastically throughout the course of history, often due to political influences rather than scientific evidence. In the United States, cannabis-based therapies were widely used starting in the 19th century. In 1850, cannabis was added to the *United States Pharmacopoeia* (Bridgeman & Abazia, 2017), meaning that physicians could legally prescribe cannabis-based medications to their patients. During this time, numerous cannabis-based medications were patented and used to treat a variety of ailments.

Recreational use of cannabis, defined as using cannabis to feel high or alter one's current state of being, became part of the popular US culture in the early 1900s. Soon after, the US government began to restrict access to cannabis and an anti-cannabis revolution, often termed "Reefer Madness" after a 1936 film dramatizing the perils of cannabis use (Gasnier, 1936), ensued. This movement ultimately influenced popular views and attitudes towards cannabis, and in 1937, the Marihuana Tax Act made the sale of cannabis illegal. By 1942, cannabis was removed from the US Pharmacopeia, and in 1970 it was placed in Schedule I of the Drug Enforcement Agency's (DEA) Controlled Substances Act (CSA). Schedule I is the most restrictive category, which places cannabis alongside drugs like heroin and ecstasy. By definition, Schedule I substances have no

accepted medical value, high abuse liability, and no accepted safety profile (U.S. Department of Justice, 2019). Recently, this classification has been hotly contested, especially in light of a comprehensive review conducted by the National Academies of Science, Engineering and Medicine (NASEM). In this review, the authors stated they found "conclusive or substantial evidence" that cannabis/cannabinoids are effective for the treatment of three conditions: chronic pain, chemotherapy-induced nausea and vomiting, and muscle spasticity as a function of multiple sclerosis (NASEM, 2017). Specifically, the NASEM report concluded that treating chronic pain with cannabis is supported by well-controlled clinical trials based on 28 studies of cannabinoids for chronic pain, 22 of which utilized plant-derived (i.e., not synthetic) cannabinoids. For chemotherapy-induced nausea and vomiting, the authors reported that the evidence suggests synthetic, oral delta-9-tetrahydrocannabinol (THC) medications, were superior to placebo or equivalent to available antiemetic pharmaceutical treatments. Finally, randomized controlled trials examining both plant-derived and synthetic formulations of cannabinoids reported modest effect sizes for reductions of muscle spasticity in multiple sclerosis.

While these results seem compelling, many studies included in the report assessed products that are not representative of the products actually available to MC patients, calling into question whether these conclusions are generalizable to those enrolled in MC programs, who purchase products at dispensaries, online retailers, or other point-of-sale locations. In other words, MC patients generally do not use products such as synthetic THC or nabiximols. However, conducting clinical trials of any commercially available

products derived from the cannabis plant is extremely difficult in the US given its Schedule I classification. Currently, cannabinoid formulations that can be studied in clinical trials must be synthetically-derived formulations, sourced from cannabis grown by the National Institute on Drug Abuse (NIDA), or (as of 2018) hemp-based products that are *not* currently for sale to consumers. Further, in addition to numerous other state and federal requirements and restrictions, researchers must hold a DEA Schedule I license to access plant-derived cannabis products from NIDA, which can be difficult to obtain especially amidst conflicting state and federal guidelines.

In addition, not all studies included in the NASEM report meet rigorous standards typically utilized for evaluating pharmaceuticals and may have suffered from a high risk of bias and/or reflect only small effect sizes. Nonetheless, many see this review as an important cornerstone which, despite its limitations, suggests significant potential for cannabinoid-based treatments. Continued research assessing the therapeutic effects of cannabinoids is warranted not only for pain, chemotherapy-induced nausea/vomiting, and muscle spasticity related to multiple sclerosis, but also for the many other conditions that NASEM reviewed but found a lack of rigorous scientific studies from which to draw any definitive conclusions. Given current legal obstacles, as well as the complexities of the cannabis plant, although research on cannabis has been conducted for decades, many important questions about the impact of cannabis and cannabinoid use remain unanswered.

What is Cannabis?

Cannabis is a term used to describe the plant *Cannabis Sativa L* and, very often, any compounds derived from it. Although the botanical classification of cannabis has been debated over the years, cannabis is generally considered to have two main species, *sativa* and *indica*, although two less common species, *ruderalis* and *afghanica*, are also differentiated by some (Piomelli & Russo, 2016). Some anecdotal evidence suggests distinct effects for sativa and indica cultivars, where sativa is generally viewed as energy-inducing, and indica is thought to have more relaxing effects (Hazekamp & Fischedick, 2012); however, no empirical studies have directly assessed these claims. Given crossbreeding between sativa and indica plants, many believe that virtually all cultivars are a hybrid of the two strains, and as such cannabis may be better conceptualized as a single polymorphic species (Piomelli & Russo, 2016).

Cannabis is comprised of hundreds of chemicals, including over 100 phytocannabinoids, described as plant-derived compounds that interact directly with the body's endogenous cannabinoid receptors or exhibit similar structure to other cannabinoids (Gertsch, Pertwee, & Di Marzo, 2010). Delta-9-tetrahydrocannabinol (THC) is typically the most abundant phytocannabinoid found in cannabis plants and is responsible for the intoxicating effects of cannabis. Although a number of non-intoxicating phytocannabinoids exist, cannabidiol (CBD) is perhaps the most well-known and is often touted for its therapeutic properties (see *Cannabinoids* for more information).

It is also important to note that the term, "hemp" is used to classify cannabis varieties that contain less than 0.3% THC by weight (Hemp Farming Act, H.R.5485

C.F.R., 2018). Hemp has traditionally been grown for industrial use (e.g., hemp fiber) and is therefore cultivated to maximize size and yield, which has resulted in cannabis and hemp plants looking different from one another, despite belonging to the same plant species (Andre, Hausman, & Guerriero, 2016). More recently, hemp plants (as well as some cannabis plants) have also been cultivated to make products high in CBD.

The Endocannabinoid System

A number of cannabinoids interact with the body's endocannabinoid (eCB) system, a system responsible for maintaining homeostasis and for neuroplasticity, specifically neurogenesis, cell differentiation, and refinement of neuronal connections (Befort, 2015; Egerton, Allison, Brett, & Pratt, 2006; Katona & Freund, 2012; Maccarrone et al., 2015). Increased eCB signaling is related to reduced stress response, emotional regulation, and increased endogenous reward signaling (Befort, 2015; Hill & McEwen, 2010). Some preclinical studies also suggest a relationship between cognitive performance and activation of receptors within the endocannabinoid system (ECS) (Egerton et al., 2006).

The ECS is comprised of two main types of cannabinoid receptors, CB1 and CB2, although some acknowledge a third receptor type, G protein-coupled receptor 55 (GPR55) (Ryberg et al., 2007). Although CB1 and CB2 receptors are both found throughout the body, the majority of CB1 receptors are localized to the central nervous system, whereas CB2 receptors are mostly found in peripheral organs. The ECS also contains endogenous cannabinoids, including anandamide (AEA) and 2-arachidonoyl glycerol (2-AG), as well as a number of endocannabinoid-like compounds such as

palmitoylethanolamide (PEA) and O-Arachidonoyl-ethanolamine (OAE), among others. In addition, this system contains degradative enzymes: fatty acid amide hydrolase (FAAH) which degrades AEA, and monoacylglycerol lipase (MAG-L) which metabolizes 2-AG. The ECS is also affected by exogenous cannabinoids, including both phytocannabinoids and synthetic cannabinoids, which either bind directly to cannabinoid receptors, or moderate the ECS system via downstream effects.

Phytocannabinoids vs. Synthetic Cannabinoids

Phytocannabinoids are defined as any cannabinoids that are derived from the cannabis plant. However, synthetic analogues of cannabinoids can also be created in a laboratory. Throughout this dissertation, unless otherwise noted, the focus will be on phytocannabinoids and plant-derived cannabis products rather than synthetically-derived compounds, such as nabilone and dronabinol, which are FDA-approved synthetic versions of THC that fall under Schedule II of the CSA.

Cannabinoids & Additional Cannabis Constituents

Cannabinoids

THC, the cannabinoid responsible for the intoxicating effects of cannabis, is a partial agonist at both CB1 and CB2 receptors (Bolognini et al., 2013; Di Marzo & Piscitelli, 2015). As the ECS affects growth, differentiation, and connectivity of neurons, exposure to exogenous cannabinoids, particularly CB1 agonists like THC, may disrupt neural development, especially during adolescence. In fact, THC is typically considered responsible for the negative effects associated with cannabis use, including elevated risk

for cannabis use disorder (CUD) as well as symptoms of CUD (Freeman & Winstock, 2015a; van der Pol et al., 2014). Exposure to THC has also been linked to psychotic symptoms (Di Forti et al., 2015; Large & Nielssen, 2017), cognitive decrements (Kowal et al., 2015; Ramaekers et al., 2006), and structural brain changes (Rigucci et al., 2016). As the majority of research citing the impact of "cannabis" typically assesses recreational cannabis users, results generally reflect the effects associated with THC given that THC is the most abundant cannabinoid contained in recreational products. Importantly, levels of THC appear to be rising in recreational cannabis products. Analyses of government-seized cannabis flower revealed that between 1995 and 2017, average THC levels increased exponentially, rising from 3.96% in 1995 to 17.10% in 2017, an increase of 332% (Chandra et al., 2019; ElSohly et al., 2016).

In contrast to THC, CBD has low affinity for both CB1 and CB2 receptors and appears to exert its effects through indirect mechanisms and additional receptor types (Izzo, Borrelli, Capasso, Di Marzo, & Mechoulam, 2009; Zuardi, 2008). In fact, studies have identified more than 65 molecular targets of CBD; the most studied include $5HT_{1A}$ receptors, GPR55, transient receptor potential (TRP) channels, and cytochrome P450s (Elsaid & Le Foll, 2020). However, CBD may also exert antiepileptic effects through N-methyl-D-aspartate receptor (NDMA) receptors, anxiolytic effects through allosteric modulation of $GABA_A$ receptors, and antipsychotic effects via dopamine D2 receptors (Elsaid & Le Foll, 2020).

CBD has become well known for its efficacy in treating severe pediatric-onset seizure disorders (Devinsky et al., 2016). In fact, in 2018, the Food & Drug

Administration (FDA) approved Epidiolex, a highly purified CBD product, for the treatment of severe pediatric-onset seizure disorders. As a result of this approval, the DEA placed Epidiolex under Schedule V of the CSA, acknowledging the therapeutic benefit and low abuse liability of this specific cannabinoid-based formulation.

This multifaceted cannabinoid, which has demonstrated promise in treating a number of other medical conditions (Whiting et al., 2015), may also have to the potential to mitigate some of the negative effects associated with THC. For example, although THC is often said to be anxiogenic, particularly at high doses (Turna, Patterson, & Van Ameringen, 2017), evidence suggests that CBD has clear anxiolytic effects (Bergamaschi et al., 2011; Crippa et al., 2011; Zuardi, Shirakawa, Finkelfarb, & Karniol, 1982). Fusar-Poli et al. (2009) demonstrated that 10 mg of THC increased anxiety, whereas 600 mg of CBD decreased anxiety in healthy individuals viewing fearful faces. In addition, CBD may protect against cognitive decrements (Morgan et al., 2012), neural alterations (Yucel et al., 2016), and THC-related psychotic-like symptoms (Bhattacharyya et al., 2010; Morgan et al., 2012). Specifically, one study found that individuals with higher THC levels (measured in hair samples) exhibited poorer performance on tests of episodic and verbal memory, but those who had detectable amounts of CBD demonstrated better recognition memory (Morgan et al., 2012). Further, higher THC levels were correlated with increased symptoms of depression and anxiety, while the presence of CBD was associated with lower scores on scales assessing psychotic-like symptoms. Yucel and colleagues (2016) found that the presence of CBD, also measured in hair samples, protected against structural hippocampal alterations associated with THC exposure.

Despite the therapeutic properties of CBD and potential ability to mitigate risk and harms of THC, CBD levels have declined to nearly undetectable levels in recreational products, while THC levels have risen dramatically. In fact, it is now estimated that the average THC:CBD ratio has gone from 14:1 in 1995 to 104:1 in 2017 (Chandra et al., 2019).

Although vastly understudied, particularly in humans, additional cannabinoids, including cannabigerol (CBG), cannabichromene (CBC), cannabinol (CBN), tetrahydrocannabivarin (THCV), and many others also appear to have therapeutic potential, such as anti-inflammatory and neurogenic effects (Borrelli et al., 2013; Izzo et al., 2009; Shinjyo & Di Marzo, 2013; Valdeolivas et al., 2015), as well as a role in preventing oxidative stress and inhibiting growth of certain cancers (De Petrocellis et al., 2011; Pellati et al., 2018). For example, CBC has been shown to increase the viability of adult neural stem progenitor cells (Shinjyo & Di Marzo, 2013), and THCV appears to be neuroprotective, as study findings suggest it may also have the ability to inhibit some of the negative physiologic and cognitive effects of THC (Englund et al. 2016). More research is needed to elucidate the effects of these compounds, which are often termed "minor" cannabinoids, but studies are likely to become more prevalent as anecdotal evidence and preclinical studies reveal potential therapeutic applications.

Terpenoids, Flavonoids, and the Entourage Effect

Cannabis also contains other types of chemicals, including terpenoids and flavonoids. Terpenoids share a common precursor with phytocannabinoids and are the essential oils responsible for the various "flavors" and fragrances of different cannabis cultivars (i.e., strains of cannabis). Flavonoids are phenolic compounds, which typically

function as antioxidants and protect against oxidative stress in plants, including cannabis (Baron, 2018). Each of these constituents may also have biobehavioral effects alone and/or in combination with various cannabinoids.

In addition to the unique effects of each individual cannabinoid, when terpenoids, cannabinoids, and other naturally occurring compounds (e.g., flavonoids) are all present together, many posit an "entourage effect," which describes the synergistic actions that occur between these compounds and may result in stronger biobehavioral effects (Russo, 2011). The entourage effect may help explain why products from whole-plant extractions known as "full spectrum" preparations, appear to be more efficacious than single-compound extractions, sometimes referred to as "isolates" (Gallily, Yekhtin, & Hanuš, 2015). In fact, a recent meta-analysis found that when patients used "CBD-rich" (i.e., full-spectrum) products, lower doses were required to achieve a therapeutic effect, and fewer adverse events were reported compared to "purified" (i.e., single compound) products (Pamplona, da Silva, & Coan, 2018). Although this meta-analysis is limited by the fact that studies reporting efficacy of CBD-rich products were all retrospective study designs, whereas studies of purified CBD product utilized prospective study designs, this meta-analysis provides preliminary empirical data to support anecdotal evidence of potential entourage effects. Research directly comparing full- or broad-spectrum products to matched cannabinoid isolates is needed to further support or refute the existence of the entourage effect.

Cannabis Use Patterns in the United States

The most recent data from the National Survey on Drug Use and Health (NSDUH) suggest increasing rates of cannabis use; currently 43.8 million Americans aged 12 and older reported using cannabis within the past year, making it the second most widely used substance in the United States behind alcohol (Substance Abuse and Mental Health Services Administration, 2019). Rates of use also appear to be rising among certain age groups. According to the 2019 Monitoring the Future (MTF) survey, which tracks substance use patterns among the nation's youth, daily cannabis use increased significantly among 8th graders and 10th graders relative to 2018 (National Institute on Drug Abuse, 2019). In addition, trends showed that vaping cannabis increased significantly in the past year among all age groups assessed (8th, 10th, and 12th graders). Some of the most common reasons 12th graders reported vaping include experimentation, an enjoyable flavor, enjoying time with friends, and to relax and relieve tension. The number of high school seniors reporting that they vape because they are "hooked" also doubled in the past year, which warrants further investigation.

Statistics also suggest rising rates of cannabis use among other age groups in recent years, including young adults aged 18-25 (Substance Abuse and Mental Health Services Administration, 2019), and especially older adults aged 50 and over. In fact, older adults represent the largest growing population of cannabis consumers (Lloyd & Striley, 2018). From 2006/2007 to 2012/2013, the proportion of adults aged 55 and older who reported cannabis use in the past year increased by 71.4% from 2.8% to 4.8% (Han et al., 2017), and among those 65 and older, rates increased 250% from 0.4% to 1.4%. Further, more

recent data (Han & Palamar, 2020) also indicate that past year rates in those 65 and older rose significantly between 2015-2018 from 2.4% to 4.2%, representing another 75% increase in cannabis use among those in this age group. These fast-growing rates of use may be, at least in part, due to increased popularity of medical cannabis (MC) among older adults, who have higher rates of chronic medical disorders, including pain, mood disturbance, and insomnia.

In terms of MC use, although the NSDUH, MTF, and similar surveys do not differentiate between recreational and medical cannabis use when reporting use rates, an independent survey estimates that approximately 3.7 million MC patients are currently registered in the US (Hudock, 2019). The most common indications reported for MC use include chronic pain, anxiety, and insomnia (Walsh et al., 2013). Interestingly, Haug et al. (2017) found that while middle-aged adults were more likely to use MC for insomnia, older adults were more likely to use MC for chronic medical conditions, including cancer, glaucoma and HIV/AIDS.

Recreational vs. Medical Cannabis Use

Although recreational and MC products are derived from the same plant species, inherent differences often exist between those who use cannabis recreationally and those who use medically. In the following chapters, "recreational" users are defined as individuals who use cannabis for the main purpose of feeling high or altering one's state of consciousness, and the recreational users enrolled in the studies described in Chapter 2 and 4 do not have underlying medical or psychiatric conditions. In contrast, MC patients are defined as those who have been certified for MC use to treat one or more underlying

medical condition or who choose to use federally legal hemp-based products, which are considered to be non-intoxicating, in order to treat an underlying condition(s).

Although products sold to recreational users and MC patients can be the same, recreational users primarily seek products with considerable amounts of THC, as they desire the "high" or mood altering, often euphoric or mellowing, effects of cannabis (Wachtel, ElSohly, Ross, Ambre, & de Wit, 2002; Zeiger et al., 2010). In contrast, MC patients typically initiate use with the primary goal of symptom alleviation (Nunberg, Kilmer, Pacula, & Burgdorf, 2011), and often times look to actively avoid feelings of intoxication. As such, MC patients frequently seek products with rich and varied cannabinoid profiles (e.g., high-CBD products) that are more likely to confer a wide variety of medical benefits, relative to the traditional high-THC recreational products. However, this should not suggest that THC has no medical benefit or that MC patients do not use products containing THC. A number of studies have shown that THC appears to serve as an effective analgesic (De Vita, Moskal, Maisto, & Ansell, 2018), antiemetic, and appetite stimulant (Abrams, 2016; Walsh, Nelson, & Mahmoud, 2003).

Although recreational users and MC patients may use cannabis in similar ways with regard to route of administration, it is also possible that these groups of cannabis-using populations may choose distinct modes of use. Both recreational users and medical patients utilize traditional methods of cannabis consumption, including smoking, vaping and using edibles. However, some recreational users in particular have begun to utilize products with extremely high levels of THC, termed "concentrates," also referred to colloquially as "dabs," "wax," "shatter," "budder," and a variety of other names based on

the products' consistency. Recreational users who choose to use concentrates may utilize a method of administration known as "dabbing" in which a small amount of product (i.e., a "dab") is placed on the extremely hot metal surface of a "dab rig" to vaporize it; the user subsequently inhales an extremely high dose of THC all at once (Sagar, Lambros, Dahlgren, Smith, & Gruber, 2018). On the other hand, MC patients may be more likely to utilize other novel modes of use, such as sublingual solutions, topicals, transdermals, and even suppositories.

It is also important to recognize that while recreational users typically initiate use during adolescence and emerging adulthood, the majority of MC patients do not initiate MC treatment until they are adults/older adults, although there are exceptions, as in the case of those using Epidiolex or CBD products to treat severe epilepsy. Many studies assessing recreational cannabis users have demonstrated that earlier onset of cannabis use is related to poorer cognitive performance, which is likely due to exogenous cannabinoid exposure during the critical neurodevelopmental processes that take place during adolescence (Casey, Galvan, & Hare, 2005; Giedd et al., 1999; Gogtay et al., 2006). Accordingly, recreational users and MC patients may experience different effects given potential differences in their age of onset of cannabis use.

Many hold strong views regarding cannabis, and it is often considered either a problem or a panacea. However, it is critical to assess factors associated with both the possible harms as well as the potential benefits of recreational versus medical cannabis use. Further, it is imperative to assess those enrolled in MC programs and/or using commercially available cannabinoid-based products to determine the overarching effects

of “real world” MC treatment. These data will provide important foundational information, which can ultimately be used to guide the development of cannabinoid-based medicines that are optimized to treat specific conditions and to minimize potential for adverse effects and abuse liability. In the following chapters, the cognitive impact of recreational and medical cannabis use will be explored, as will symptoms and behaviors associated with problematic cannabis use in each of these discrete groups of consumers.

CHAPTER TWO

Recreational Cannabis Use & Cognition

Public opinion of cannabis has shifted drastically in recent years, and current reports suggest up to two-thirds of Americans believe cannabis use should be legalized (Daniller, 2019). Changing attitudes toward cannabis are also reflected in data from the National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration, 2017) which, according to data collected between 2012-2014, indicated that only 26.1% of people aged 12 or older believe monthly cannabis use is associated with "great harm." As additional states have voted for legalization of recreational cannabis use since the publication of that study, it is likely that perceived risk and harm associated with cannabis use will continue to drop. Although there may be great potential for cannabis and cannabinoids as therapeutic alternatives to conventional medications, it is imperative to keep in mind that certain populations may be vulnerable and experience negative effects of cannabis use.

In particular, children and adolescents are likely more vulnerable to the cognitive effects of cannabis use than older individuals given that they are in the midst of critical neuromaturation during this period. Between ages 10-12, children experience increased cerebral blood flow, an indicator of rapid neurodevelopment changes (Epstein, 1999). In fact, during this time myelination rates, cortical thickness (in frontal, temporal and parietal cortices), and amygdalar and hippocampal volume peak (Giedd et al., 1999; Tanaka, Matsui, Uematsu, Noguchi, & Miyawaki, 2012; Uematsu et al., 2012). At the start of puberty and continuing until at least the mid-20s, a period of synaptic pruning

occurs in these regions, leading to decreased volumes, and ultimately more efficient neural networks (Gogtay et al., 2006; Houston, Herting, & Sowell, 2014). During this period, white matter volume and integrity also increase, which are associated with improvements in neural conductivity (Giedd et al., 1999; Jernigan & Gamst, 2005).

As the brain undergoes these important processes to refine and strengthen neural networks, the endocannabinoid system (ECS) likely plays a critical role. The ECS, known for maintaining homeostasis, also helps refine structural connectivity between neurons and contributes to neural growth (Di Marzo & Piscitelli, 2015; Garcia-Arencibia, Molina-Holgado, & Molina-Holgado, 2018). As a CB1 agonist, THC has the potential to alter functioning of the ECS and potentially interfere with expected neurodevelopmental trajectories. Accordingly, adolescence, which is also often marked by increased risk-taking behaviors including experimentation with substance use, represents a period of vulnerability to exogenous influences, including cannabis.

For decades, researchers have examined the impact of cannabis use on cognitive function, with mounting evidence suggesting that cannabis users, particularly those who begin using regularly during adolescence, exhibit cognitive decrements relative to healthy controls (Mashhoon, Sagar, & Gruber, 2019) or their own pre-cannabis use levels of performance (Jacobus et al., 2015; Squeglia, Jacobus, Nguyen-Louie, & Tapert, 2014). The majority of studies have focused on the effects of cannabis on executive function and memory, both broad cognitive domains encompassing a variety of related, yet different skills.

Studies assessing executive function, including response inhibition, planning, and decision-making, demonstrate that recreational cannabis use appears to affect both current and recent users (Becker, Collins, & Luciana, 2014; Dougherty et al., 2013; Fontes et al., 2011; Hanson, Thayer, & Tapert, 2014; Harding et al., 2012; Infante et al., 2019; Jacobus, Bava, Cohen-Zion, Mahmood, & Tapert, 2009; Sagar et al., 2015; Winward, Hanson, Tapert, & Brown, 2014). Several investigations have also reported that executive function serves as a predictor of cannabis use (Dahlgren, Sagar, Racine, Dreman, & Gruber, 2016; Squeglia et al., 2014) and cannabis-related problems (Day, Metrik, Spillane, & Kahler, 2013). A number of studies have also examined working memory, often considered a core facet of executive function. Findings suggest poorer performance among recreational cannabis consumers on some paradigms but not others (Broyd, van Hell, Beale, Yucel, & Solowij, 2016).

Several reviews assessing memory function indicate that recreational cannabis use appears to affect a number of individual aspects of memory (Broyd et al., 2016; Ganzer, Broning, Kraft, Sack, & Thomasius, 2016; Solowij & Battisti, 2008). Findings within the memory domain are most robust for measures of verbal learning, where decrements have been observed in terms of encoding, recall, and recognition (Laspada et al., 2019; Solowij & Battisti, 2008); however, not all studies have observed an association between verbal learning decrements and cannabis use (Infante et al., 2019). It is also of note that findings assessing other aspects of memory function, including associative and visuospatial memory, are less clear. For example, only a handful of studies note decrements on

measures of visual short-term memory (Hermann et al., 2007; Sneider, Gruber, Rogowska, Silveri, & Yurgelun-Todd, 2013).

Although the majority of studies generally conclude that heavy, recreational cannabis use is related to adverse changes in executive function/working memory as well as verbal memory, some have argued that these decrements, which are often variable across studies, may be related to other factors and/or may not be clinically significant. In fact, a recent study, which examined twins discordant for cannabis use, reported that although cannabis use was related to poorer cognitive functioning, associations were either no longer observed after accounting for other substance use, or may be explained by lower cognitive functioning *before* initiation of cannabis use; overall, the authors concluded that the relationship between cannabis use and cognition is likely not causal (Ross et al., 2019).

Scott et al., (2018) conducted a meta-analysis of 69 studies of recreational cannabis users and concluded that although poorer cognitive function was associated with frequent or heavy cannabis use, the effect size was small overall. Further, among the 15 studies requiring more than 72 hours of cannabis abstinence, effect sizes were not only smaller than those studies with less rigorous abstinence criteria, but the effect sizes for these studies were not significantly greater than zero. Lovell, Akhurst, Padgett, Garry, and Matthews (2019) conducted a meta-analysis that suggested significant, albeit small, decrements in memory and executive functioning. The authors of this analysis concluded that recreational cannabis users who use regularly for prolonged periods of time might experience cognitive decrements, which ultimately result in poorer performance on

everyday tasks, including driving. Interestingly, these findings support a recent driving simulator study which suggest that in the absence of acute intoxication, cannabis users exhibit poorer driving performance than healthy controls, and that poorer performance appears to be localized to those who initiated regular use prior to age 16 (Dahlgren et al., 2020).

Taken together, it is imperative to continue to assess the cognitive impact of recreational cannabis use in light of recent trends, including increased potency of cannabis flower (Chandra et al., 2019), growing popularity of cannabis concentrates, and the advent of novel modes of use (e.g., dabbing), designed to deliver large doses of THC all at once (Sagar et al., 2018), as each of these factors has the potential to confer greater negative effects. The current study is designed to expand upon a previously published investigation (Gruber, Sagar, Dahlgren, Racine, & Lukas, 2012), which examined cognitive performance in chronic, heavy recreational cannabis users and found that poorer performance on tasks of executive function noted in cannabis users relative to healthy controls was primarily attributable to those with early onset of cannabis (regular use prior to age 16).

Hypotheses

Utilizing the previous sample (Gruber, Sagar, Dahlgren, Racine, et al., 2012) as well as newly recruited participants, it was hypothesized that cannabis users would display poorer performance on tasks of executive function and working memory relative to healthy controls and late onset cannabis users. In addition, given larger sample sizes, it was also hypothesized that decrements in verbal learning and memory, which were not

previously observed but have been noted widely throughout the literature, would be detected. Further, given the neurodevelopmental vulnerability of those who initiate use prior to age 16 as well as prior findings, it was also hypothesized that early onset cannabis users would perform significantly more poorly than healthy controls across cognitive measures, while findings would be less prominent in late onset users relative to healthy controls.

Methods

Participants

Participants included individuals recruited serially for three separate, but similar studies all designed to assess cognitive and clinical outcomes associated with recreational cannabis use. These three studies were conducted at McLean Hospital and funded by National Institute on Drug Abuse (NIDA) grants awarded to Dr. Staci Gruber (Frontal Neural Mechanisms and Risk for Substance Abuse, R03 DA016695; Marijuana and Mood: Frontal Predictors of Behavior, R21 DA021241; and Marijuana: Neurobiologic Correlates of Age of Onset, R01 DA03264601). Seventy-nine (66 male, 13 female) well-characterized, chronic, heavy, cannabis users (CAN) were included in this investigation, as well as 48 (28 male, 20 female) non-cannabis using healthy control (HC) participants. The CAN group was further divided into early (n=38) and late onset (n=40) groups based on age of onset of regular cannabis use. Although no uniformly accepted definition of early or late onset exists, a number of studies have used age 16 to differentiate early versus late cannabis use onset (Ehrenreich et al., 1999; Gruber, Dahlgren, Sagar, Gonenc, & Killgore, 2012; Gruber, Sagar, Dahlgren, Racine, et al., 2012; Gruber, Silveri,

Dahlgren, & Yurgelun-Todd, 2011; Kempel, Lampe, Parnefjord, Hennig, & Kunert, 2003). In order to ensure results are comparable to previous analyses, early onset was defined as regular cannabis use prior to age 16, while late onset was defined as regular use at age 16 or later.

Study participants were recruited from both urban and suburban locations within the Greater Boston area, including local colleges and universities, gyms, supermarkets, community centers, and other public locations. The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders [DSM-IV], Patient Edition (SCID-P) was administered to ensure all participants were free of Axis I pathology, including current or previous drug or alcohol abuse or dependence (but excluding cannabis abuse/dependence for the CAN group). In addition, participants were excluded if they reported binge drinking (5 or more drinks for males, and 4 or more drinks for females, within 2 hours), routinely had more than 15 drinks per week, or if they reported more than 15 lifetime uses of any category of illicit drugs. Upon arrival at the laboratory, participants also had to provide a urine sample and were excluded if they tested positive for other drugs (amphetamines, cocaine, THC, methamphetamine, opioids, phencyclidine, benzodiazepines, methadone, MDMA) according to an in-house drug assay (with the exception of THC for the CAN group). Current or previous use of psychotropic medications, history of neurological disorders or head injury with loss of conscious for more than five minutes were also considered exclusionary.

In order to qualify for study entry, cannabis users had to report a minimum of 1500 lifetime cannabis uses, use cannabis at least four of the last seven days, and test

positive for urinary cannabinoids (assessed using the in-house drug assay). Cannabis users were required to abstain from using cannabis for at least 12 hours prior to their study visit to ensure that they were not acutely intoxicated at the time of assessment. Any participants who reported use within the required abstinence period as assessed using a modified, detailed timeline followback (TLFB) procedure (Robinson, Sobell, Sobell, & Leo, 2014a; Sobell, Sobell, Leo, & Cancilla, 1988), or who appeared intoxicated based on staff's clinical judgment were rescheduled for a later date. All participants were required to be native English speakers, as necessitated by the cognitive test battery.

Study Design

Prior to participation, all study procedures were explained, and participants were required to read and sign an informed consent form, which described the procedures of the study and explained that participation was voluntary. This study was approved by the Partners Healthcare Institutional Review Board.

This study utilized a cross-sectional design to compare healthy, non-cannabis-using controls (HCs) to chronic heavy, recreational cannabis (CAN) users, and to compare HCs to early onset CAN users (regular cannabis use prior to age 16), and late onset CAN users (regular cannabis use at age 16 or later). Participants were asked to report the first time they tried cannabis and answer questions about their use patterns, including age of onset of regular use (once per month or more); general use patterns were then documented from that point to the present. Current use was assessed using a customized TLFB procedure, which supplements the traditional, validated TLFB methods (Sobell et al., 1998) with additional queries designed to facilitate recollection of

their initial use (e.g., *Who where you with? Where were you when this happened?*) and subsequent patterns of use. Participants are asked to report frequency of use, mode of use (smoking, vaping, edibles, concentrates, etc.), and amount of cannabis used (in grams). It is well known that quantifying the actual amount of cannabis used is often difficult to ascertain using self-report methods, but the optimized TLFB procedure required participants to report their use in a variety of ways and in great detail to help corroborate initial self-reports of use (e.g., *How much cannabis do you typically use each time you use it? How much cannabis do you buy? How long does the amount purchased last? Do you share cannabis with others, and if so how many others?*). In addition, visual aids were used which depict how much given weights (grams) of cannabis look like in real life across various product types. Further, a portion of the urine sample acquired for the in-house drug screen was also sent to an outside laboratory for quantification of urinary concentration of THC metabolites via gas chromatography–mass spectrometry (GC–MS). THC was normalized to creatinine (Cr) level in order to minimize the effects of metabolism. In addition, a subset of participants (those recruited for R01 DA03264601) completed a modified version of the Marijuana Withdrawal Checklist (MWC) (Budney, Novy, & Hughes, 1999), a 16-item self-report scale in which respondents rate current symptoms associated with cannabis withdrawal (e.g., irritability, craving, etc.) using a 0-3 point scale (none, mild, moderate, or severe); total scores on this version of the MWC range from 0-48.

Participants also completed scales to assess nicotine use, alcohol use, and impulsivity. The Fagerstrom Test for Nicotine Dependence (FTND) is a 6-item scale

scored from 0 to 10, where higher scores indicate more severe nicotine addiction. The Addiction Severity Index (ASI) was used to provide the number of days in the past 30 that the participant drank alcohol. The Barratt-Impulsiveness Scale (BIS-11) is self-report measure, which examines several aspects of impulsivity, including attention (e.g., "I don't pay attention"), motor impulsivity (e.g., "I act on impulse"), and non-planning (e.g., "I say things without thinking"). A total impulsiveness score was calculated to reflect overall levels of impulsivity; total scores can range from 30-120 where higher scores are indicative of higher levels of impulsivity.

All subjects completed a battery of neuropsychological tests over one to two visits. An estimated IQ was first ascertained using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). For the WASI, total raw scores on each subtest are converted to *T* scores, and *T* scores are summed in order to calculate a full-scale IQ estimate; these IQ scores are based on a nationally representative normative sample. A number of additional tests were utilized to assess various aspects of executive function as well as verbal learning and memory given that previous research suggests that these domains are the most sensitive to cannabis use. In order to minimize multiple comparisons, the most relevant variables were chosen from a larger battery of tests, and include Stroop Interference Time, Trails B Time, Wisconsin Card Sorting Test (WCST) Categories, WCST Perseverative Errors, Letter Number Sequencing (LNS), Phonemic Fluency, California Verbal Learning Test (CVLT) Trials 1-5 Correct, CVLT Short Delay, and CVLT Long Delay. Each of these task variables are described below.

The Stroop Color Word Test (MacLeod, 1991) is a widely used measure of executive function. The task is comprised of three conditions: color naming (participants name blocks of colors), word reading (participants read words printed in black ink), and interference, the latter of which examines the ability to establish competing response tendencies, inhibit inappropriate responses, and resist interference. During this condition, participants are presented with color words printed in an incongruous ink color (e.g., "RED" printed in green ink); they must inhibit the natural tendency to read the words and instead must name the color of the ink. Performance was assessed by interference completion times; lower numbers (i.e., faster times) are indicative of better performance.

The Trail Making Test (Lezak, Howieson, Bigler, & Tranel, 2012) is divided into two parts. Trails A measures psychomotor speed and attention (participants connect a series of numbered circles), whereas Trails B is considered a measure of executive function, as it utilizes an alternative set-shifting demand to measure cognitive flexibility (participants alternate between connecting numbers and letters). Performance on this task was measured by the time to complete Trails B. Maximum time allowed is 180 seconds, and faster times (i.e., lower numbers) indicate better performance.

The WCST, often considered the 'gold standard' measure of executive function, assesses the ability to shift and maintain set and ability to adjust one's behavior by utilizing feedback (Berg, 1948). Participants are given a deck of 64 cards and must sort them according to specific criteria, which unbeknownst to the participant, changes throughout the task. Participants must adjust to the new sorting principle based on examiner feedback (whether each sort is correct or incorrect). Primary variables for

analyses included categories completed (higher numbers are better and can range from 0-6) and number of perseverative errors (lower numbers are better).

The LNS task (Wechsler, 1987) was also utilized to assess executive function and working memory abilities. During this task, the examiner reads increasingly longer strings of numbers and letters, and participants are asked to re-sequence the string of characters by repeating the numbers in order, followed by the letters in alphabetical order. There are 21 potential sequences, and the total number of correct sequences serves as the primary outcome variable.

The Phonemic Fluency task is considered a measure of executive function. During this task, participants must generate words beginning with three specific letters within a 60 second time frame for each letter (Lezak et al., 2012). The number of unique words generated across all three letters given is calculated, and higher scores reflect better performance.

The CVLT is a measure of verbal learning and memory (Delis, Karmer, E., & Ober, 1987). During this task, participants are presented with a list of 16 words over the course of five trials and must remember as many words as they can. Overall verbal learning is measured by the number of correct responses over all five trials (Trials 1-5 Correct). After the presentation of a distractor list, verbal memory is assessed immediately (Short Delay) and again after a 20-minute delay (Long Delay). For total correct responses over Trials 1-5, the maximum score is 80, and for both delay variables, maximum scores are 16; higher scores equate to better task performance.

Statistical Analyses

Descriptive statistics (e.g. mean and standard deviation) were calculated for demographic (age, education, IQ, days of alcohol intoxication, FTND and BIS-11 scores) and cannabis use variables. Analyses were conducted to assess the HCs vs CAN users, while additional comparisons (HC vs early onset CAN and HC vs late onset CAN) were used to examine the impact of age of onset of cannabis use relative to HCs. Specifically, in order to assess any potential demographic differences between groups, chi-squared analyses were used to compare sex and race (white vs non-white) frequencies between the HC and CAN groups, and for continuous variables (age, IQ, education, frequency of cannabis use, magnitude of cannabis use, and duration of cannabis use), one-way analyses of variance (ANOVAs) were conducted.

Cognitive performance data were screened for outliers, and any individual that had an estimated IQ of 85 or lower was removed from all analyses; 4 participants (1 HC, 2 early onset CAN users, 1 late onset CAN user) were removed, resulting in final samples sizes of 47 HCs and 76 CAN users, of which 36 were early onset and 40 were late onset users. For cognitive data, although raw scores were utilized, one-way analyses of covariance (ANCOVAs) were conducted, controlling for age, sex, and education when comparing HCs vs all recreational CAN users, HCs vs Early Onset CAN users, and HCs vs Late Onset CAN users. Results from each of these analyses are reported with effect sizes (partial eta squared) and 95% confidence intervals which are based on estimated marginal means. All analyses of cognitive performance were Bonferroni-corrected for multiple comparisons: $\alpha \leq .05/6 = .008$ for tasks in the executive function domain, and

α<.05/3=.017 for tasks in the verbal learning and memory domain. The few cases where Levene's test of equality of error variance was violated are noted in within the results tables; however, for all comparisons where the assumption of homogeneity was violated, ANCOVA results were not significant. Therefore, it would be unlikely that non-parametric statistics with reduced statistical power would produce significant findings.

As significant differences were not noted between-groups, exploratory analyses were also conducted to determine whether, within the CAN users, cognitive performance may be related urinary THC levels; these analyses were conducted in light of the fact that potency of cannabis products is rising and may be an important factor to consider in subgroups of CAN users who utilize products with higher levels of THC. Partial correlations controlling for age, sex, and education (2-tailed) were utilized for these preliminary analyses.

Statistical Models	**Covariates**	**Independent Variables**	**Dependent Variables**
Analysis 1: ANCOVA	All Analyses: Age Education Sex	Analysis 1: HCs vs. CAN Users	All Analyses: *Executive function:* Stroop Interference Time Trails B Time WCST Categories WCST Perseverative Errors LNS Phonemic Fluency *Verbal learning & Memory* CVLT Trials 1-5 Correct CVLT Short Delay CVLT Long Delay
Analysis 2: ANCOVA		Analysis 2: HCs vs. Early Onset CAN HCs vs. Late Onset CAN	
Analysis 3 (exploratory): Partial correlations		Analysis 3: Urinary THC levels	

Table 2.1 Chapter 2: Statistical Analyses Overview

Results

Demographics & Cannabis Use

Forty-seven HCs and 76 recreational CAN users were included in the current analyses, after excluding 1 HC and 3 CAN users as IQ outliers. Among CAN users, 36 were characterized as early onset (onset of regular use prior to age 16) and 40 were characterized as late onset (onset of regular use at age 16 or later). Demographics are presented for HC vs CAN users in **Table 2.2**; HC vs early onset and HC vs late onset CAN users are presented in **Table 2.3.**

Overall, HCs and CAN users were well matched for age, IQ, race, and levels of nicotine dependence (FTND scores). Participants were generally young adults in their early twenties with well above average IQ scores. Approximately three-quarters of individuals enrolled in the HC and CAN groups were white, and participants reported zero to minimal levels of nicotine dependence on the FTND. However, a number of significant differences emerged between the two groups for other demographic variables. Sex distribution, education, days of alcohol use (in the past 30 days), and BIS-11 impulsivity scores were significantly different between groups; the CAN group was comprised of a smaller proportion of females, had about one year less of education, drank alcohol more frequently, and had higher self-reported impulsivity relative to HCs.

When comparing HCs to early and late onset CAN users, the groups had similar age, IQ, and race frequencies. However, the proportion of female participants was significantly higher in the HC group relative to both the early and late onset groups. In addition, HCs had completed more years of education than early onset CAN users, but no

differences were observed for education between HCs and late onset users. Comparisons of impulsivity, alcohol and nicotine use also revealed significant between-group differences. BIS-11 impulsivity scores were significantly elevated in the early and late onset CAN groups relative to HCs. Both early and late onset CAN users reported higher alcohol use than HCs. In addition, early onset CAN users reported significantly higher levels of nicotine dependence than HCs. However, this difference is attributed to the fact that HCs all reported an FTND of 0, and although early onset users had higher scores, on average ratings were not indicative of nicotine dependence and reflect only light nicotine use in a handful of early onset CAN users.

In terms of cannabis use (see **Table. 2.4**), early and late onset users were well-matched on the majority of cannabis use variables with the exception of age of onset of use, which was expected given that this variable was used to stratify the two groups, and grams of cannabis used per week; the early onset group reported using almost twice as much cannabis as the last onset group. Both early and late onset users reported similar duration of cannabis use and episodes of cannabis use per week. Urinary THC levels also did not differ significantly between groups. On the MWC, both groups had similar low scores, suggesting low levels of withdrawal symptoms at the time of assessment.

Demographics	Healthy Controls *n*=47		Recreational Cannabis Users *n*=76		Chi-Square	
					X^2	*p*
Sex[a]	27 (57.4%) Male 20 (42.6%) Female		63 (82.9%) Male 13 (17.1%) Female		**9.58**	**<.01**
Race[a]	35 (74.5%) White 12 (25.5%) Non-White*		59 (78.7%) White 16 (21.3%) Non-White*		0.29	.59
	Mean (SD)	**Median [range]**	**Mean (SD)**	**Median [range]**	**ANOVA**	
					F	***p* (η^2)**
Age[b]	24.19 (6.70)	22 [18-47]	23.33 (6.25)	21.5 17-46	0.52	.47 (<.01)
Education[b]	15.26 (2.22)	16 [12-21]	14.07 (1.93)	14 [10-20]	**9.72**	**<.01 (.07)**
WASI IQ[c]	122.41 (11.17)	124.5 [88-142]	119.38 (11.20)	120.5 [89-144]	2.10	.15 (.02)
FTND[d†]	0.00 (0.00)	0 [0-0]	0.19 (0.69)	0 [0-4]	2.47	.12 (.03)
Days of alcohol use in past 30[e]	4.59 (4.93)	3 [0-20]	7.06 (5.35)	5.5 [0-20]	**6.43**	**.01 (.05)**
BIS-11 Total Impulsiveness [f]	55.82 (11.09)	52.5 [38-84]	64.76 (10.07)	64.5 [38-82]	**19.96**	**<.01 (.15)**

Significant values ($p \leq .05$) are bolded

WASI= Wechsler Abbreviated Scale of Intelligence, FTND = Fagerstrom Test for Nicotine Dependence, BIS-11=Barratt Impulsiveness Scale

*Healthy Controls: Non-white=2 Black, 9 Asian, 1 Other; Recreational Cannabis Users: Non-white= 9 Black, 4 Asian, 2 Multiracial

†Levene's test of equality of error variances was violated; however, non-parametric Kruskal-Wallis tests also indicated no significant difference between groups (X^2=2.94, p=.09)

[a]Degrees of freedom (df)=1; [b]df=1,121; [c]df=1,120; [d]df=1,87; [e]df=1,115; [f]df=1,114

Table 2.2 HC vs CAN users: Demographics

	Healthy Controls		Early Onset Cannabis Users		Late Onset Cannabis Users		HC vs Early Chi-Square		HC vs Late Chi-Square	
Demographics	*n*=47		*n*=36		*n*=40		X^2	*p*	X^2	*p*
Sex[a]	27 (57.4%) Male 20 (42.6%) Female		31 (86.1%) Male 5 (13.9% Female)		32 (80.0%) Male 8 (20.0%) Female		**7.96**	**<.01**	**5.03**	**.03**
Race[a]	35 (74.5%) White 12 (25.5%) Non-White*		30 (83.3%) White 6 (16.7%) Non-White*		29 (74.4%) White 10 (25.6%) Non-White*		0.94	.33	0.00	.99
	Mean (SD)	**Median [range]**	**Mean (SD)**	**Median [range]**	**Mean (SD)**	**Median [range]**	**HC vs Early ANOVA**		**HC vs Late ANOVA**	
							F	***p* (η^2)**	***F***	***p* (η^2)**
Age[b]	24.19 (6.70)	22 [18-47]	22.83 (7.05)	20 [17-46]	23.78 (5.47)	22 [18-39]	0.80	.37 (.01)	0.10	.75 (<.01)
Education[b]	15.26 (2.22)	16 [12-21]	13.54 (1.67)	13 [10-17]	14.55 (2.04)	14.5 [12-20]	**14.49**	**<.01 (.16)**	2.35	.13 (.27)
WASI IQ[c]	122.41 (11.17)	124.5 [88-142]	119.19 (12.92)	122.5 [89-144]	119.55 (9.56)	119 [91-136]	1.46	.23 (.02)	1.64	.23 (.02)
FTND[d†]	0.00 (0.00)	0 [0-0]	0.36 (0.95)	0 [0-4]	0.06 (0.35)	0 [0-2]	**4.60**	**.04 (.08)**	1.00	.32 (.02)
Days of alcohol use in past 30[e]	4.59 (4.93)	3 [0-20]	7.25 (5.16)	5.5 [0-20]	6.89 (5.58)	5.5 [0-20]	**5.54**	**.02 (.07)**	**3.97**	**.05 (.05)**
BIS-11 Total Impulsiveness[f]	55.82 (11.09)	52.5 [38-84]	65.19 (9.76)	65 [46-80]	64.43 (10.42)	64.5 [38-82]	**14.60**	**<.01 (.17)**	**13.37**	**<.01 (.14)**

Significant values (p≤.05) are bolded

WASI= Wechsler Abbreviated Scale of Intelligence, FTND = Fagerstrom Test for Nicotine Dependence, BIS-11=Barratt Impulsiveness Scale

*Healthy Controls: Non-white=2 Black, 9 Asian, 1 Other; Early Onset: Non-white= 3 Black, 1 Asian, 1 Multiracial; Late Onset: Non-white= 6 Black, 3 Asian, 1 Multiracial

[a]Degrees of freedom (df)=1; [b]df=2,120; [c]df=2,119; [d]df=2,86; [e]df=2,114; [f]df=2,113

[†]Levene's test of equality of error variances was violated; however, non-parametric Kruskal-Wallis tests did not impact results

Table 2.3 HC vs Early Onset CAN vs Late Onset CAN Users: Demographics

	Recreational Cannabis Users *n*=76		Early Onset Cannabis Users *n*=36		Late Onset Cannabis Users *n*=40		Early vs Late ANOVA	
Cannabis Use	**Mean (SD)**	**Median [Range]**	**Mean (SD)**	**Median [Range]**	**Mean (SD)**	**Median [Range]**	***F***	***p* (η^2)**
Age of onset[a†]	16.00 (2.20)	16 [11-23]	14.22 (1.10)	15 [11-15]	17.60 (1.65)	17 [16-23]	**104.82**	**<.01 (.59)**
Episodes of use/week[b]	17.25 (15.28)	14.00 [2.05-105.00]	19.72 (18.18)	14.5 [4.5-105.0]	14.90 (11.67)	13.35 [2.05-63.00]	3.33	.07 (.05)
Grams/week[b†]	8.17 (11.40)	4.50 [0.27-74.39]	10.81 (14.72)	6.65 [0.78-74.39]	5.67 (6.17)	4.34 [0.27-32.65]	3.34	**.05 (.05)**
Duration of Use (yrs)[a]	7.32 (6.33)	5.00 [1.00-35.00]	8.61 (7.48)	6 [3-35]	6.15 (4.89)	4 [1-23]	3.28	.09 (.04)
Urinary THC/Cr Ratio (ng/ml)[c†]	417.17 (513.23)	248.17 [27.67-2595.00]	312.31 (108.77)	264.75 [46.00-789.00]	494.07 (650.78)	212.50 [27.67-2595.00]	1.49	.21 (.03)
MWC[d]	6.62 (3.64)	6 [1-15]	7.33 (4.08)	6 [2-15]	6.14 (3.31)	5.5 [1-12]	0.96	.33 (.03)

Significant values ($p \leq .05$) are bolded

THC/Cr=delta-9-tetrahydrocannabinol/Creatinine, MWC=Marijuana Withdrawal Checklist

[a] n=76 All users, n=36 Early onset, n=40 Late onset
[b] n=74 All users, n=36 Early onset, n=38 Late onset
[c] n=51 All users, n=22 Early onset, n=30 Late onset
[d] n=37 All users, n=15 Early onset, n=22 Late onset

[†]Levene's test of equality of error variances was violated; however, non-parametric Kruskal-Wallis tests did affect significance of result

Table 2.4 All Recreational Users and Early Onset vs Late Onset: Cannabis Use Information

Cognitive Performance

See **Table 2.5** (HC vs CAN) and **Table 2.6** (HC vs Early Onset and HC vs Late Onset) for cognitive performance data. On measures of executive function (Stroop Interference, Trails B Time, WCST Categories and Perseverative Errors, LNS, and Phonemic Fluency) no significant between-group differences were noted between healthy controls and recreational cannabis users. Similarly, when comparing HCs to early onset and late onset users, no significant differences were observed.

Similarly, on the CVLT, a measure of verbal learning and memory, ANCOVAs comparing healthy controls to recreational users did not detect any significant between-group differences that surpassed the Bonferroni-corrected significance threshold. In addition, analyses of HCs vs early onset and HCs vs late onset CAN users did not reveal significant between-group differences on the CVLT after implementing Bonferroni corrections.

	Healthy Controls	Recreational Cannabis Users	ANCOVA	
Domain Task Variable	**Mean (SD)**	**Mean (SD)**	***F* [95% CI]**	***p* (η^2)**
Executive Function				
Stroop Interference Time[a]	88.13 (14.86)	90.32 (21.68)	0.01 [-6.99, 7.83]	.91 (<.01)
Trails B Time (sec)[b]	44.11 (13.56)	51.76 (17.34)	2.49 [-11.13, 1.26]	.12 (.02)
WCST Categories[c]	4.24 (1.26)	3.87 (1.21)	0.26 [-0.36, 0.62)	.61 (<.01)
WCST Perseverative Errors[c†]	4.07 (3.82)	6.64 (6.35)	2.08 [-4.04, 0.64]	.15 (.02)
LNS[d]	12.81 (2.51)	12.73 (2.98)	0.19 [-1.44, 2.24]	.66 (<.01)
Phonemic Fluency[e]	48.29 (9.04)	48.13 (11.61)	0.37 [-6.18, 3.28]	.55 (<.01)
Verbal Learning & Memory				
CVLT Trials 1-5 Correct[f]	58.44 (7.84)	53.51 (9.20)	*4.36* *[0.18, 6.96]*	*.04 (.04)*
CVLT Short Delay[f]	12.73 (2.66)	11.50 (2.70)	2.95 [-0.14, 2.01]	.09 (.03)
CVLT Long Delay[h]	13.11 (2.41)	11.93 (2.78)	3.09 [-0.12, 2.00]	.08 (.03)

Analyses of covariance (ANCOVA) were not significant after Bonferroni corrections: p≤.05/6=.008 for Executive Function tasks, and p<.05/3=.017 for Verbal Learning and Memory tasks. Results that were significant before Bonferroni corrections are *italicized*.

[†]Levene's test of equality of error variances was violated; however, non-parametric Kruskal-Wallis tests yielded the same results as the ANOVAs

[a]Degrees of freedom (df)=1,113; [b]df=1,117; [c]df=1,106; [d]df=1,48; [f]df=1,89; [g]df=1,110; [h]df=1,109

Table 2.5 HC vs CAN users: Cognitive Performance

	Healthy Controls	Early Onset CAN	Late Onset CAN	HC vs Early ANCOVA		HC vs Late ANCOVA	
Task Variable	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	***F* [95% CI]**	***p* (η^2)**	***F* [95% CI]**	***p* (η^2)**
Executive Function							
Stroop Interference Time[a]	88.13 (14.86)	88.51 (21.44)	92.08 (22.08)	0.57 [-5.31, 11.85]	.45 (<.01)	0.40 [-10.97, 5.67]	.53 (.01)
Trails B Time (sec)[b]	44.11 (13.56)	50.14 (13.03)	53.18 (20.45)	1.34 [-10.89, 2.88]	.25 (.02)	3.22 [-13.27, 0.68]	.08 (.04)[†]
WCST Categories[c]	4.24 (1.26)	3.79 (1.32)	3.94 (1.12)	0.58 [-0.58, 0.74]	.81 (<.01)	0.37 [-0.37, 0.69]	.55 (.01)
WCST Perseverative Errors[c†]	4.07 (3.82)	7.62 (7.75)	5.72 (4.61)	2.07 [-5.61, 0.91]	.15 (.03)	2.28 [-3.57, 0.50]	.13 (.03)
LNS[d]	12.81 (2.51)	13.53 (3.38)	12.18 (2.61)	0.14 [-3.14, 2.17]	.71 (.01)	1.30 [-0.80, 2.79]	.26 (.04)
Phonemic Fluency[e]	48.29 (9.04)	48.39 (11.81)	47.93 (11.65)	0.37 [-7.11, 5.87]	.85 (<.01)	0.20 [-6.19, 3.91]	.65 (<.01)
Verbal Learning & Memory							
CVLT Trials 1-5 Correct[f]	58.44 (7.84)	53.53 (8.78)	53.50 (9.69)	2.57 [-0.78, 7.1]	.11 (.03)	*4.13 [0.08, 8.10]*	*.05 (.05)*
CVLT Short Delay[f]	12.73 (2.66)	11.74 (2.50)	11.28 (2.89)	0.35 [-0.92, 1.69]	.56 (.01)	3.75 [-0.04, 2.53]	.06 (.11)
CVLT Long Delay[g]	13.11 (2.40)	12.15 (2.59)	11.72 (2.96)	0.94 [-0.65, 1.85]	.35 (.01)	3.60 [-0.06, 2.43]	.06 (.05)

Analyses of covariance (ANCOVA) were not significant after Bonferroni corrections: $p \leq .05/6 = .008$ for Executive Function tasks, and $p < .05/3 = .017$ for Verbal Learning and Memory tasks. Results that were significant before Bonferroni corrections are *italicized*.

[a]HC vs Early: df=1,77; HC vs Late: df=1,79 [b]HC vs Early: df=1,77; HC vs Late: df=1,82
[c]HC vs Early: df=1,70; HC vs Late: df=1,73 [d]HC vs Early: df=1,26; HC vs Late: df=1,33
[e]HC vs Early: df=1,57; HC vs Late: df=1,67 [f]HC vs Early: df=1,74; HC vs Late: df=1,77
[g]HC vs Early: df=1,73; HC vs Late: df=1,77

[†]Levene's test of equality of error variances was violated; non-parametric Kruskal-Wallis tests yielded the same results as the ANOVAs

Table 2.6 HC vs Early Onset CAN vs Late Onset CAN: Cognitive Performance

Correlations: Cannabis Use vs Cognitive Performance

Although significant findings were not observed between groups after correcting for multiple comparisons, exploratory partial correlations (controlling for age, education, and sex) were utilized in order assess whether overall exposure to THC may influence cognitive performance. Results revealed that higher urinary THC levels were associated with slower completion times on Trails B ($r(49)=.37$, $p=.01$). Significant findings were not observed between any other cognitive performance variable and urinary THC levels.

Discussion

It was hypothesized that heavy recreational cannabis users would exhibit decrements on tasks of executive function as well as verbal learning and memory; however, significant between-group differences were not observed. It was also hypothesized that once cannabis users were divided into those with early onset (before 16) versus late onset (age 16 or alter) of regular cannabis use, early onset users would demonstrate decrements relative to healthy controls. However, significant differences were also not observed for these comparisons. These findings are in contrast to a large number of studies that have reported poorer executive function and memory decrements in recreational cannabis users, particularly those with early onset of use (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013; Crean, Crane, & Mason, 2011; Lisdahl, Wright, Kirchner-Medina, Maple, & Shollenbarger, 2014; Sagar & Gruber, 2018b; Solowij & Battisti, 2008). Although it is possible that results suggest recreational cannabis use itself does not cause decrements in cognitive function, which has been reported previously (e.g., Ross et

al., 2019), it is likely that null findings in the current study may be related to a number of important factors.

First, it is possible that results were influenced by ceiling effects, as participants in both groups generally performed quite well across many study measures. In fact, participants in the current study had very high estimated IQ (average across all participants: 121.06), which has been observed in similar previous studies conducted at McLean Hospital. High IQ of study participants may be related to the fact that this institution is located near several of the country's top universities. As recruitment of cannabis users is often successful at these educational institutions, it is not surprising that individuals enrolled in the current studies would exhibit high IQs. Similarly, McLean Hospital is located in affluent suburb of Boston which often attracts individuals of higher occupational attainment and socioeconomic status. Importantly, intelligence, education and occupation attainment are considered proxies of cognitive reserve, a term which refers to an individual's ability to adapt cognitive processes and underlying neural networks in the context of brain insult (Stern et al., 2018). As such, individuals with higher cognitive reserve would be able to employ compensatory strategies if neural processes are negatively impacted by cannabis use. Interestingly, some functional neuroimaging studies in cannabis users have demonstrated that even when cognitive performance remains intact, altered patterns of brain activation are observed relative to healthy controls (Sagar & Gruber, 2018a).

Results may have also been vulnerable to Type II error given the statistical approach used with this moderate sample size. In order to address the fact that raw scores

were used for analyses, all cognitive test variables were covaried for age, education, and sex. Although it is necessary to control for these variables when raw scores are utilized in lieu of normed scores, entering three covariates into a statistical model with moderate sample sizes may have led to a failure to detect subtle differences between groups due to low statistical power. The potential for Type II error is also compounded by the fact that a conservative approach was taken to correct for multiple comparisons. Even though numerous research studies have observed poorer cognitive performance on tasks of executive function and verbal learning and memory in heavy recreational cannabis users, two recent meta-analyses reported only small effect sizes for cannabis-related cognitive decrements (Lovell et al., 2019; Scott et al., 2018), suggesting that potential decrements may not be detectable in a small sample using a conservative statistical approach.

It is of note that previous studies of cognition in recreational cannabis users have utilized a variety of approaches when examining neuropsychological performance, many of which are less stringent than the current approach, while others provide alternative options that could be considered for future analyses. For example, Becker et al (2014) utilized raw scores adjusted for sex, IQ, and alcohol use, but did not appear to adjust for multiple comparisons. Fontes et al. (2011) also utilized raw scores but did not adjust for covariates. Further, like the current study, the authors only examined select neuropsychological variables based on previous literature and *a priori* hypotheses. As a result of this more targeted approach, however, Fontes and colleagues stated that they chose not to correct for multiple comparisons. Some studies, such as Medina et al. (2007) have utilized pre-existing neuropsychological test batteries which generate standardized

scores; this ensures that all scores are adjusted in the same way (e.g., age- and sex-corrected, or age- and education-corrected). The current study employed a customized selection of cognitive tasks, several of which have different methods of generating normed scores; these differences limited the ability to utilize available standardized scores from each test. An alternative approach that is often used when examining a variety of tests is the use of composite scores. Although this method could be considered for future studies and analyses, it is important to recognize that composite scores can be calculated using a number of different theoretical approaches (e.g., data-driven or based on existing theories of neuropsychological constructs). Importantly, for whichever approach is chosen, it is vital to ensure that the composites created actually reflect the construct of interest (Jonaitis et al., 2019); otherwise, the composite score is not considered valid.

No significant between-group results were detected following the conservative Bonferroni correction approach. However, the results which were significant *prior* to correction bear some discussion. First, cannabis users overall had fewer correct responses on CVLT Trials 1-5, which is consistent with the *a priori* hypothesis of poorer cognitive performance in cannabis users relative to healthy controls. Interestingly, although it was predicted that early onset users would demonstrate decrements relative to healthy controls and late onset users, the significant results observed prior to Bonferroni corrections indicated poorer performance on CVLT Trials 1-5 in the *late* onset users. Despite the fact that these findings were ultimately not statistically significant between

the two groups, this potential pattern raises important considerations for future investigations if similar findings are observed.

Previous research has demonstrated that cognitive decrements are largely attributed to those with earlier onset of cannabis use, likely related to neurodevelopmental vulnerabilities (Battisti et al., 2010; Dahlgren et al., 2016; Fontes et al., 2011; Gruber, Sagar, Dahlgren, Racine, et al., 2012; Jacobus et al., 2009; Sagar et al., 2015; Schneider, 2008). In the current study, it is important to acknowledge that cananbis users were divided into two discrete groups using age 16 as a cut-off score. This threshold is often employed when examining the impact of early versus late onset cananbis use (Ehrenreich et al., 1999; Kempel et al., 2003) and is also consistent with previously published data using subsets of the current sample (Dahlgren et al., 2016; Gruber, Dahlgren, et al., 2012; Gruber, Dahlgren, Sagar, Gonenc, & Lukas, 2014; Gruber, Sagar, Dahlgren, Racine, et al., 2012; Gruber et al., 2011; Sagar et al., 2015). However, given that neuromaturation occurs throughout the second and into the third decade of life (Giedd et al., 1999; Gogtay et al., 2006; Lebel & Deoni, 2018; Sowell, Thompson, Tessner, & Toga, 2001), evidence suggests that regular exposure to cannabis during adolescence and throughout emerging adulthood is likely to confer cognitive decrements (Lisdahl, Gilbart, Wright, & Shollenbarger, 2013). The average age of cannabis onset within the late onset group was approximately 17 years old, with only three participants having initiated regular cannabis user after age 21, and all having initiated by age 23. It is therefore possible, and even likely, that even those defined as "late onset" users in this study are still vulnerable to the effects of cannabis. It is also

likely that a relationship between earlier age of onset and poorer cognition may be observed if participants with a wider age range of cannabis onset are included in future studies (e.g., examining differences between those who initiated use in adolescence as well as those who initiated use in later adulthood).

In addition, potential decrements noted specifically in the late onset cannabis users would also be unexpected in the current study given that few statistically significant differences in patterns of cannabis use were observed between early and late onset users for the majority of variables measured (episodes of use/week, duration of cannabis use, urinary THC levels). Moreover, the early onset users tended to use cannabis more frequently (although not statistically significant) and used significantly higher amounts. Specifically, early onset users reported using 1.3 times more frequently (19.72 vs. 14.90 episodes of use/week) and almost twice as much cannabis (10.81 vs. 5.67 grams/week) compared to late onset users. Therefore, it could be posited that factors other than frequency and amount of cannabis used may mediate the impact of cannabis on cognition.

Exploratory, hypothesis-generating analyses assessing the relationship between urinary THC levels and cognitive performance revealed a significant correlation between higher urinary THC levels and slower Trails B completion times ($r(46)=.37$, $p=.01$). In the context of previous studies which have shown that THC has a dose-dependent relationship on cognitive performance (Kowal et al., 2015; Morgan et al., 2012; Ramaekers et al., 2006), this relationship provides additional, yet very preliminary, evidence that exposure to individual cannabinoids, namely THC, is critical to consider.

Accordingly, exposure to individual cannabinoids should be quantified in future studies of cannabis and cognition.

For the current study, cannabinoid exposure, specifically the amount of THC contained in actual products used was not directly assessed via laboratory analyses for the vast majority of participants. Interestingly, however, a small dataset gathered as a pilot arm of this study has revealed that some participants, particularly those recruited most recently, reported use of high potency cannabis and/or cannabis concentrates. Concentrates (e.g., dabs, wax, shatter, budder, kief) are extremely potent cannabis products that have gained popularity in more recent years (Sagar et al., 2018). Some studies analyzing THC levels in concentrate products indicate average THC levels of 60-70% (Raber, Elzinga, & Kaplan, 2015; Smart, Caulkins, Kilmer, Davenport, & Midgette, 2017), while other studies have shown that levels can reach up to 75-80% (Stogner & Miller, 2015). Anecdotally, dispensaries frequently sell products with even higher potencies listed on packaging (>90% THC). In addition, the average potency of cannabis flower has also increased dramatically in recent years, raising the possibility that some cannabis users are exposed to much higher amounts of THC than others. Data from 11 samples of participants' cannabis flower products submitted in 2016-2017 to an outside laboratory for cannabinoid quantification demonstrated that THC potency ranged from 11.37-24.35%, with an average of 17.93%. This average is consistent with national estimates of cannabis flower potency (17.10% in 2017), which Chandra and colleagues (2019) notes represents a significant increase in THC levels relative to prior years, including only three years earlier when estimated average potency for cannabis flower

was 11.85%. Further, 3 of 17 early onset users (17.65%) and 5 of the 21 late onset users (23.81%) in this study specifically endorsed the used of concentrate products. Two patients also supplied concentrate products (wax and shatter) for cannabinoid quantification; average potency of these products was 68.03% THC (range: 58.45-77.60%). In addition, preliminary analyses examining cognition in a small pilot group of healthy controls, cannabis flower users, and cannabis concentrate users also revealed interesting patterns. Specifically, on tests of executive function (Stroop Color Word Test and the Trail Making Test) and verbal fluency (Controlled Oral Word Association Test), cannabis flower users performed more poorly than healthy controls and, moreover, concentrate users performed more poorly than both healthy controls and those who use only cannabis flower products. These patterns support previous data suggesting that cognitive decrements in cannabis use are related to the negative impact of THC on cognition – particularly at higher doses (Kowal et al., 2015; Morgan et al., 2012; Ramaekers et al., 2006).

Cannabis users in the current study did not display significant cognitive performance deficits relative to non-cannabis users; however, it is important to note that study participants included in the current analyses were recruited for three studies between 2003-2019. Thereore, it is likely that across participants, THC potency varied significantly and a subgroup of participants with use of more potent THC products may have exhibited poorer performance if they were specifically identified and compared to healthy controls and/or cannabis users with use of more traditional, lower potency

products. Given current trends regarding the use of higher potency cannabis, future studies of cannabis users may be more likely to detect cognitive performance deficits.

Limitations and Future Directions

Results must be considered in the context of several limitations. As previously noted, the statistical approach utilized in the current study was conservative in terms of adjustment for multiple comparisons. Future analyses should explore the use of more advanced, General Linear Modeling, approaches, especially given the inherent complexities of assessing cannabis use (frequency, amount used, potency, individual cannabinoid exposure) as well as the potential interplay between cannabis and a number of important demographic variables. These statistical models, particularly when coupled with larger sample sizes, could also help address whether additional potential confounds, several of which were assessed but not controlled for in the current study (e.g., alcohol use or impulsivity), impact cognition. On the other hand, given that higher alcohol use and impulsivity are typically associated with poorer cognitive performance, it is unlikely that these variables impacted overall study findings. However, it is possible that additional factors not assessed in the current study could have influenced results. For example, socioeconomic status, occupational attainment, history of contact sports involvement and subconcussive injuries, or genetic factors, could have impacted study findings.

It is also of note that results may not be generalizable to all populations of cannabis consumers. In addition to those who may have lower IQ or education (and thus potentially lower cognitive reserve), results may also not be generalizable to those with

light or casual cannabis use. In the current study, recreational users were required to use cannabis at least 4 times per week and reported about 17 uses/week on average. Although it would seem intuitive that less frequent users would experience less significant cognitive deficits due to lower exposure to cannabinoids, it may also be possible that light users are not as habituated to cannabinoid exposure as heavy users. Accordingly, recent cannabis use in light users may lead to a change in their typical homeostasis that could lead to more marked cognitive consequences. For example, a number of studies have found that those who are cannabis naïve exhibit more significant cognitive and behavioral changes after THC administration relative to those with previous cannabis exposure (Colizzi et al., 2018; Cortes-Briones et al., 2015; Ramaekers, Kauert, Theunissen, Toennes, & Moeller, 2009), and those who have used cannabis more recently display more significant changes than those who have been abstinent for longer periods of time (Cortes-Briones et al., 2015). Future studies are needed, however, to specifically assess the residual (i.e., non-acute) impact of less frequent cannabis use on cognitive outcomes.

Results of the current study may also not be applicable to those with certain medical or psychiatric conditions or disorders. The current sample excluded those with a history of psychiatric illness (e.g., mood, anxiety, psychotic, or other substance use disorders) as well as those with serious or chronic illnesses. Interestingly, some research has shown that cannabis users diagnosed with certain psychiatric disorders, such as schizophrenia (Power et al., 2015; Yucel et al., 2012) or bipolar disorder (Braga, Burdick, Derosse, & Malhotra, 2012), demonstrate *improved* cognition relative to non-cannabis

users although not all studies have observed such findings (Rabin et al., 2017). In addition, those who treat medical conditions with cannabis may choose products with vastly different cannabinoid profiles, which is likely to moderate cognitive effects. Those who use medically may also derive a clinical benefit from their cannabis use which, in turn, may influence cognitive processes as well (see Chapter 3).

As previously noted, the current study did not quantify individual cannabinoid concentration from actual products used. However, this is a limitation with the majority, if not all, observational studies of recreational cannabis users to date, and many studies do not assess THC levels at all. In the current study, detailed information was gathered about frequency and magnitude of use. Additionally, urinary THC levels, which were normalized to creatinine to help control for metabolic differences, were analyzed in order to obtain quantifiable information about cannabis use. Further, pilot results described above are promising, and future studies will benefit from conducting laboratory analyses of all participants' cannabis products to obtain quantifiable data regarding specific cannabinoid concentrations. For example, higher overall exposure to THC could be associated with poorer cognitive performance, while exposure to other non-intoxicating cannabinoids, including but not limited to CBD, could confer protective effects.

Conclusions

No significant differences were observed between healthy controls and heavy recreational cannabis users on tasks of executive function and verbal learning and memory, despite hypothesizing that cognitive decrements would be observed in the cannabis users. Further, no significant differences were observed when the recreational

users were stratified into those with early and late onset of regular cannabis use. Null findings, which are in contrast to a large body of evidence suggesting decrements in cannabis users, particularly those with early onset, may be related to methodological approaches, substantial cognitive reserve, or additional factors not assessed in the current study.

CHAPTER THREE

Medical Cannabis Use & Cognition

As of March 2020, 48 of 50 states in the US have voted for full or partial medical cannabis (MC) programs, leaving only two states without legal access to MC products. Although decades of research have examined the association between recreational cannabis use and cognitive outcomes, a paucity of studies have specifically examined the relationship between MC use and cognitive function. Given the inherent differences between medical and recreational cannabis use, it is possible that MC patients may not exhibit the same pattern of decrements on neuropsychological measures that have traditionally been observed in adolescent/emerging adult heavy recreational users (Crean et al., 2011; Jacobus & Tapert, 2014; Lisdahl et al., 2014).

Interestingly, in the very first study to directly assess the impact of MC treatment pre- vs. post-MC treatment in patients using "real world" MC products, Gruber and colleagues (2016) conducted a pilot study which examined 11 patients at baseline, prior to initiating MC use, and reassessed patients after three months of regular MC treatment (all patients chose their own products and selected their treatment regimen). As part of a larger longitudinal study, patients were administered a neuropsychological test battery which included several measures assessing executive function in order to determine whether MC patients would exhibit the similar cognitive decrements to those often observed in recreational cannabis users. Interestingly, in contrast to the executive function decrements typically observed in recreational cannabis users, after three months of MC treatment, MC patients exhibited improved performance on the Stroop Color

Word Test and Trail Making Test, reflected by increased speed without loss of accuracy. In addition, patients completed self-report measures of mood, anxiety, quality of life, impulsivity, and sleep. Results suggested that MC patients experienced cognitive improvements in the context of moderate improvements symptoms of depression, attenuated impulsivity, improved sleep, and better quality of life.

Recent work conducted by Olla et al (2019) examined the short-term effects of delta-9-tetrahydrocannabinol (THC) in 22 MC patients (mean age of 36) at three timepoints: at baseline while not intoxicated, immediately after using high THC (20%) cannabis products, and several hours later. Although the authors hypothesized poorer cognitive performance while intoxicated, study findings revealed stable or improved neuropsychological performance across several cognitive domains. This study is limited by a lack of a control group and may have been significantly impacted by practice effects given that alternate versions of tests did not appear to be utilized and only a short amount of time occurred between assessments. It is also of note that this study only examined the impact of THC and did not consider the impact of cannabidiol (CBD) or other non-intoxicating "minor" cannabinoids, which are often present in products used by MC patients. Although no additional information beyond THC content was provided, the authors reported administration of joints, vapes, and dabs; thus, it appears likely that the products administered were full-spectrum, meaning that they contained additional cannabinoids which could have influenced results. Nonetheless, given that a number of studies have shown decreased cognitive performance after acute cannabis administration (Desrosiers, Ramaekers, Chauchard, Gorelick, & Huestis, 2015; Hart et al., 2010; Hart,

van Gorp, Haney, Foltin, & Fischman, 2001), results provide further evidence that MC patients who use cannabis to relieve medical and/or psychiatric symptoms may not experience the same cognitive decrements as in some of those who use cannabis recreationally.

As studies of MC and cognition are in their infancy, additional research is needed, especially given that findings in recreational cannabis consumers are likely not directly applicable to MC patients as a function of a number of important factors. For example, recreational cannabis use is most likely to begin during adolescence and emerging adulthood (Substance Abuse and Mental Health Services Administration, 2019), during which critical neurodevelopmental changes occur (Casey et al., 2005; Giedd et al., 1999; Gogtay et al., 2006; Houston et al., 2014; Lebel & Deoni, 2018; Sowell et al., 2001). In contrast, the majority of MC patients initiate use as adults; MC patients may therefore be less vulnerable to exogenous influences, including cannabis.

Further, if MC treatment is effective at reducing physical or psychological symptoms, it is also possible that cognitive function may not be negatively impacted, or may even improve, in the context of patients feeling better. For example, chronic pain, the most common indication for MC use (Park & Wu, 2017), has been shown to adversely impact cognitive performance, specifically on tasks requiring attention and executive function (Moriarty, McGuire, & Finn, 2011). Accordingly, cognition may improve if patients experience a reduction in pain-related symptoms secondary to MC treatment. Research has also demonstrated that sleep quality is associated with cognitive functioning; good sleep quality promotes better cognitive functioning and protects against

age-related cognitive decline and dementia (Minakawa, Wada, & Nagai, 2019; Scullin & Bliwise, 2015; Shi et al., 2018; Spira, Chen-Edinboro, Wu, & Yaffe, 2014). In addition to physical symptoms, it is also possible that alleviation of psychiatric symptoms as a function of MC use may be an important moderating factor. In a previous study utilizing ecological momentary assessment (EMA) to examine mood and cognition in patients with bipolar disorder, results revealed that those who used cannabis regularly report improvement in clinical symptoms within four hours of smoking cannabis (Gruber, Sagar, Dahlgren, Olson, et al., 2012; Sagar et al., 2016). Moreover, the cannabis-using patients performed similarly to patients with bipolar disorder who did not use cannabis on measures of cognitive performance. Further, studies have demonstrated that anxiety, one of the most common indications for MC treatment (Grella, Rodriguez, & Kim, 2014), often interferes with both attention and executive function (Vytal, Cornwell, Letkiewicz, Arkin, & Grillon, 2013). Certain cannabinoids, particularly CBD, appear to have anxiolytic properties as demonstrated by acute administration studies in both healthy volunteers (Zuardi, Cosme, Graeff, & Guimaraes, 1993) and individuals with anxiety disorders (Bergamaschi et al., 2011). A large case series also reported a 79% improvement in retrospective anxiety ratings after one month of CBD treatment (Shannon, Lewis, Lee, & Hughes, 2019). MC treatment could therefore result in better concentration and enhanced cognitive performance if symptoms of anxiety are reduced.

In order to more thoroughly examine the impact of MC treatment on cognition, the current study built upon up the previous pilot investigation (Gruber et al., 2016), which utilized a pre- vs. post-treatment, longitudinal design where MC patients

completed baseline assessments prior to initiation of MC use and were reassessed at multiple time points after initiation of MC treatment. In the current study, additional participants enrolled for longer periods of time (up to 12 months) were included in the current analyses. All patients were administered a comprehensive neuropsychological test battery, which contained the executive function measures previously reported as well as additional measures assessing verbal learning and memory. However, select variables were chosen for these preliminary analyses based on *a priori* hypotheses: Stroop Interference Time, Trails B Time, Wisconsin Card Sorting Test (WCST) Categories, WCST Perseverative Errors, Letter Number Sequencing, Phonemic Fluency, Rey Auditory Verbal Learning Test (RAVLT) Trials 1-5 Correct, RAVLT Short Delay, and RAVLT Long Delay. Each of these task variables are described in the Methods section below. Participants also completed self-report ratings related to physical and mental health (e.g., overall mood, symptoms of depression and anxiety, sleep quality, quality of life). Information regarding MC treatment regimens including frequency of use and exposure to THC and CBD were also quantified in order to determine if certain MC use variables contribute to cognitive and clinical changes.

Hypotheses

Based on pilot work as well as the fact that MC patients are often older and more often choose non-intoxicating products or those with more varied cannabinoid profiles, it was hypothesized that MC patients would experience improvements in cognitive function and ratings of physical and mental health after initiation of MC treatment. Exploratory analyses to aid in hypothesis-generation were also planned to provide preliminary data

about whether any observed changes in cognitive function or self-report ratings may be related to cannabinoid use (e.g., frequency of MC use, THC exposure, or CBD exposure.

Methods

Participants

Data from this study were derived from an ongoing observational, longitudinal study led by Dr. Staci Gruber at McLean Hospital in Belmont, MA and funded by private donors, foundations, and unrestricted gifts to the Marijuana Investigations for Neuroscientific Discovery (MIND) program at McLean Hospital.

To be considered for study entry for the longitudinal study, participants had to be 21 or older and either have a valid certification for MC or report a desire to use hemp-based products, which are currently federally legal and do not require MC certification. These criteria were employed in an attempt to enroll only participants who are interested in using cannabis exclusively for medical purposes, and to limit recreational use of cannabis in the current sample. MC patients could plan to use MC for a variety of indications, such as chronic pain, anxiety, mood, sleep, or other medical/psychiatric conditions. In addition, MC patients must not have begun regular MC treatment prior to baseline assessments. Specifically, participants were either required to be cannabis naïve or, if they reported a history of recreational cannabis use, had to report abstinence for one year or more to limit the effects of recent cannabis exposure. To help confirm this entry criterion, all patients were required to test negative for urinary THC metabolites at baseline. Participants also completed the two-factor version of the Wechsler Abbreviated

Scale of Intelligence (WASI) (Wechsler, 1999), which provides an estimate of overall cognitive functioning, to ensure an estimated IQ of 75 or higher.

To date, 54 MC patients have been successfully enrolled and have completed at least one follow-up assessment over the course of 12 months of MC treatment (follow-up visits at 3 months, 6 months, 12 months). A schematic summarizing the study status of participants is provided in **Figure 3.1.** Of the 54 MC patients included in the current analyses, 51 patients completed a 3-month follow-up, 43 completed a 6-month follow-up, and 30 returned after 12 months. Additional examination of the data releveled that, of the 54 patients, 28 completed all four visits. Six patients missed an interim visit (1 of these 6 patients missed 2 interim visits), but all completed baseline and 12-month follow-ups. Ten participants are currently "in progress" as they remain enrolled but are awaiting their next follow-up timepoint. Ten patients were discontinued or withdrew from the study because they either stopped MC use (n=3) or were lost to follow-up (n=7). Of those who were lost to follow-up, three indicated that they discontinued for reasons unrelated to MC treatment; however, four individuals stopped responding to study staff and no information about the reason for discontinuation could be gathered. See *Statistical Analyses* for information about how missing data were handled.

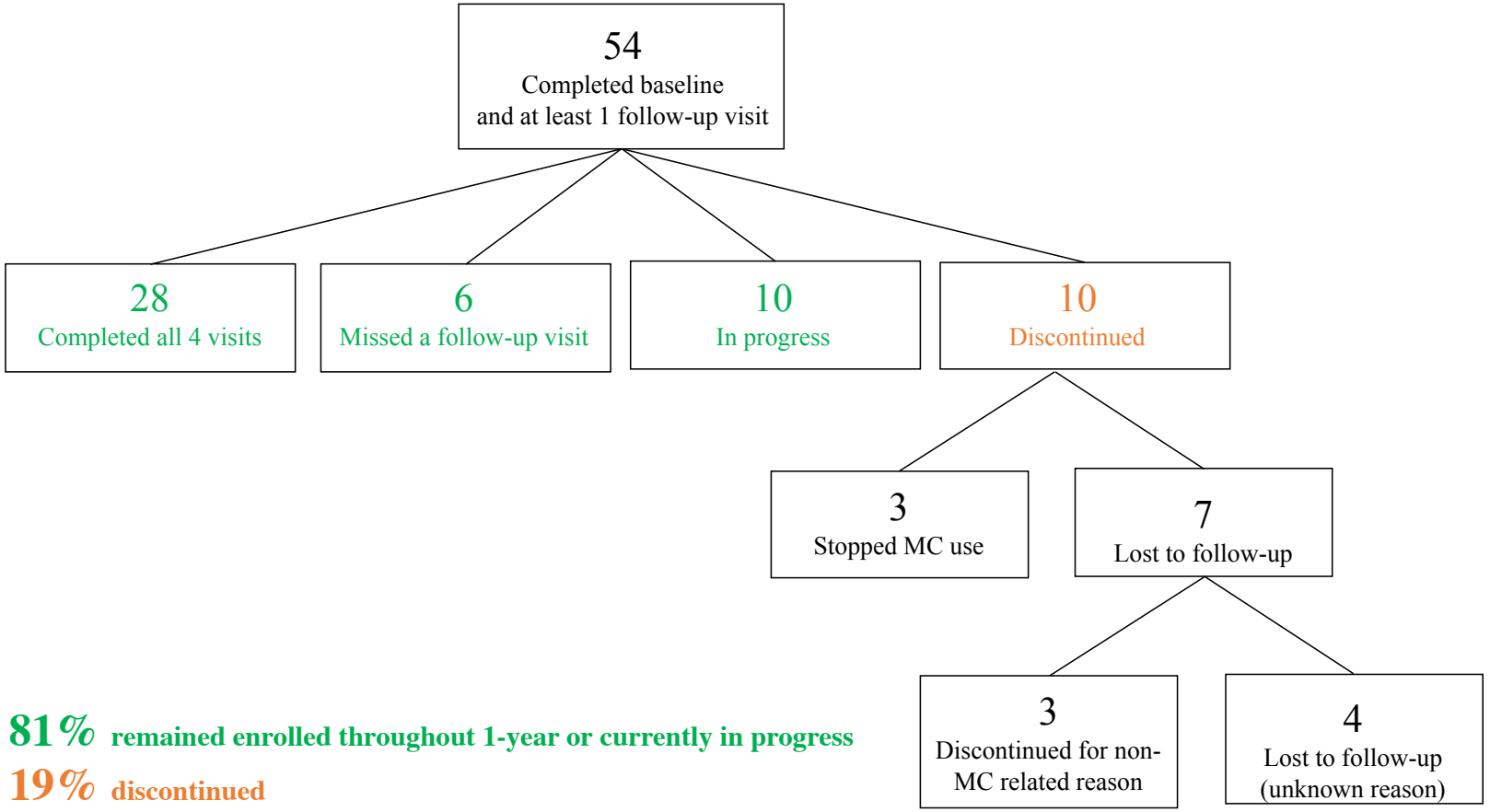

Figure 3.1. Enrollment Status and Attrition of MC Patients

Study Design

Upon arrival, study procedures were thoroughly explained, and all participants were required to read and sign an informed consent form approved by the Partners Institutional Review Board. Prior to initiating MC treatment, all enrolled participants completed a neuropsychological test battery as well as measures of overall mood state, symptoms of depression, symptoms of anxiety, sleep, and quality of life. Following three, six, and twelve months of regular MC treatment, participants returned for follow-up visits and repeated all study measures (with the exception of the WASI, which was only administered at baseline to generate an estimated IQ). For this study, participants completed the two-factor version of the WASI in which the Vocabulary and Matrix Reasoning subtests are administered. Raw scores for each of these measures are transformed into T-scores based on each participant's age; T-scores are then summed, which generates a standardized IQ estimate.

The neuropsychological test battery was specifically designed to assess executive function and memory, as these domains appear to be most vulnerable to cannabis use, based on studies of recreational users (Sagar & Gruber, 2018b). In order to examine various aspects of executive function, all participants completed the Stroop Color Word Test, Trail Making Test, Wisconsin Card Sorting Test (WCST), Letter-Number Sequencing (LNS) subtest of the Wechsler Adult Intelligence Scale - Revised (WAIS-R), and a phonemic fluency task. In addition, verbal learning and memory was assessed using the Rey Auditory Verbal Learning Test (RAVLT).

The Stroop Color Word Test (MacLeod, 1991) is a widely used measure of executive function, which contains three conditions in order to assess the ability to inhibit an automatic, overlearned response. The first two conditions prime the individual for the Interference condition, which is considered the executive function component of the task. During the Interference condition, color words are printed in an incongruous ink color (i.e., *red* printed in green, or *blue* printed in red), and participants must inhibit the natural tendency to read the words and instead name the color of the ink. Performance was assessed by interference completion times; lower numbers (i.e., faster times) are indicative of better performance (MacLeod, 1991).

The Trail Making Test is comprised of two timed conditions (Lezak et al., 2012). While Trails A measures psychomotor speed and attention (participants connect a series of numbered circles), Trails B utilizes an alternative set-shifting demand to measure cognitive flexibility (participants alternate between connecting numbers and letters). Performance on this task was measured by the time to complete Trails B. Three versions of the Trail Making Test were rotated across visits to minimize practice effects (Wagner, Helmreich, Dahmen, Lieb, & Tadic, 2011). Maximum time allowed is for Trails B is 180 seconds; lower numbers (i.e., faster times) indicate better performance.

The WCST is considered a gold standard measure of executive functioning, which focuses on cognitive flexibility and set-shifting (Berg, 1948; Lezak et al., 2012). For this study, all participants completed the WCST:CV4, a computerized version of the task (Heaton & PAR Staff). For this task, participants are to match 64 cards based on sorting rules that change throughout the task; participants must utilize feedback (e.g., "correct"

or “incorrect”) to adjust to the changing set demands. Primary variables for analyses included categories completed (higher numbers are better and can range from 0-6) and number of perseverative errors (lower numbers are better).

The Letter-Number Sequencing (LNS) test (Wechsler, 1987) is also considered a measure of executive function, specifically working memory abilities. For this task, the examiner reads increasingly longer strings of numbers and letters, and participants are asked to re-sequence the string of characters by repeating the numbers in order, followed by the letters in alphabetical order. At every other visit, an alternate version was presented in which the strings of numbers and letters from the original task were presented in reverse order. The total number of correct trials serves as the primary outcome variable.

The Phonemic Fluency task was also utilized to assess executive function. During this task, participants must generate as must words as they can that begin with a given letter; they are given three letters and for each letter must generate as many words as possible within a 60 second timeframe. Alternate versions were utilized at each visit (FAS, BHR, PRW, CFL) (Strauss, Sherman, & Spreen, 2006). The number of unique words generated for all three letters is calculated, and higher scores reflect better performance.

Verbal learning and memory was assessed with the Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 2016). For this task, the examiner reads a 15-item word list, and participants must recall as many words as they can. The word list is presented over the course of five trials; overall learning is reflected by the total number of

words remembered across all five trials. Memory for the list is then assessed immediately after presentation of a distractor last (Short Delay) and re-assessed after a 20-minute delay (Long Delay). Alternate word lists were utilized at each visit to minimize practice effects (Crawford, Stewart, & Moore, 1989; Geffen, Butterworth, & Geffen, 1994; Majdan, Sziklas, & Jones-Gotman, 1996). For total correct responses over Trials 1-5, the maximum score is 75, and for both short and long delay variables the maximum score is 15; higher scores equate to better task performance.

To determine if patients experienced any clinical changes (e.g., mood, anxiety sleep, quality of life) related to MC use, which could also potentially impact cognitive performance, all MC patients completed a battery of clinical rating scales at each visit. Specifically, participants completed scales assessing various aspects of mood, including the Profile of Mood State (POMS) (Pollock, Cho, Reker, & Volavka, 1979) and the Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). MC patients also completed the Beck Anxiety Inventory (BAI) (Beck & Steer, 1990), State Trait Anxiety Index (STAI) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983); Pittsburgh Sleep Quality Index (PSQI) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), and a questionnaire reflecting quality of life (Short Form 36 Health Survey Questionnaire [SF-36]) (Ware & Sherbourne, 1992).

The POMS is comprised of 65 adjectives commonly used to describe mood states. Individuals are asked to indicate how they feel at that moment in relation to each of the adjectives using a five-point scale ranging from “not at all” (0) to “extremely” (4). The POMS consists of 6 subscales, which measure vigor, anger, depression, confusion,

tension, fatigue, and depression. These scores are used to calculate an overall composite score of Total Mood Disturbance (TMD). TMD = (anger + confusion + tension + fatigue + depression) – vigor. TMD scores can range from -32 to 200; lower scores are considered better as they reflect lower levels of mood disturbance.

The BDI is a 21 item-self-report measure that can be used to assess the severity of depression and is one of the most widely-used measures to assess symptoms related to depression. Each item on the BDI relates to a symptom of depression and is rated by the subject using a 0-3 scale; total scores can range from 0-63 where higher scores reflect higher levels of depressive symptomatology (i.e., lower scores are better). Generally, scores of 0-9 represent no or minimal depression, 10-18 represent mild depression, 19-29 represent moderate depression, and 30 or higher represents severe depression (Beck, Steer, & Garbin, 1988).

The BAI is a 21 item-self-report measure of anxiety that assesses subjective, somatic, and panic-related symptoms of anxiety. Each item on the BAI is rated on a scale of 0 to 3, and is descriptive of subjective, somatic, or panic-related symptoms of anxiety. Total scores range from 0-63. BAI scores of 0 to 7 are classified as minimal anxiety, 8 to 15 reflects mild anxiety, 16-25 denotes moderate anxiety, and 30 or more is considered severe anxiety (Beck & Steer, 1990).

The STAI form is comprised of two 20-item scales that measure the more temporary condition of "state" anxiety and the more general and long-standing quality of "trait anxiety." For each scale, each item is scored on a scale that ranges from 0 to 4, and

total scores for each range from 0-80 (higher scores indicate higher levels of either state or trait anxiety).

The PSQI assesses current sleep quality and disturbance. This scale queries aspects of subject sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction, which are then summed to generate a global score. Scores range from 0-21 where a score of 0 indicates no disturbance and score of 21 would reflect severe sleep difficulties in all areas. As such, lower scores indicate better sleep.

The SF-36 is a multi-purpose, short-form health survey that gives an 8-scale profile of functional health and well-being scores: 1) Physical Functioning (limitations in normal role/work activities due to physical health); 2) Role Limitations: Physical Health (limitations in usual physical activities); 3) Role Limitations: Emotional Problems (limitations in activities because of emotional problems); 4) Energy/Fatigue (vitality); 5) Emotional Well-Being (psychological distress and mental health); 6) Social Functioning (limitations in social activities); 7) Pain (severity and the degree to which pain affects quality of life by interfering with normal work); and 8) General Health (perceptions about one's health). On the SF-36, each scale is scored from 0-100 where 0 is considered "completely dysfunctional" and 100 is "no dysfunction." Accordingly, higher scores indicate better quality of life.

After the completion of their baseline visit, MC patients were asked to use either paper-and-pencil or electronic drug diaries (based on patient preference) to track their MC use once they began using MC regularly. Between visits, they were also contacted by

phone for monthly check-in visits to corroborate drug diary entries, which included information about product type (e.g., flower, cartridge/pod, solution/tincture, edibles, capsules, topicals), number of MC episodes, amount of MC used, mode of use (e.g., smoke, vape, ingest, sublingual, cutaneous) via a timeline follow-back procedure (TLFB; Sobell et al., 1998) and additional follow-up queries tailored to MC treatment. To gather information about cannabinoid constituent levels in each product, information was collected from product labels and certificates of analyses posted on product websites. Each participant was also asked to provide a sample of his/her most frequently used MC product(s) to be analyzed by an outside laboratory (ProVerde Laboratories, Inc.) for cannabinoid constituent profiling. Although information was gathered about a wide range of cannabinoids, specific focus was placed on THC and CBD, the primary intoxicating and non-intoxicating constituents, respectively. A standard metric of cannabinoid use, measured in milligrams (mg) of THC and CBD used per week, was then calculated for all patients using available data from laboratory-based data, drug diary entries, and information gathered via the modified TLFB (see Appendix A).

MC patients also provided information for conventional medications used at least weekly, including the name of the medications, indication for use, frequency, and dose. Medications were then sorted into categories (opioids, benzodiazepines, antidepressants, anti-inflammatories, over-the-counter analgesics, etc.), and mg/week of medications used was closely tracked and recorded according to drug type. Given the various medications reported and small sample sizes for each drug class, only baseline medication is reported for the current analyses.

Statistical Analyses

Descriptive statistics (e.g. mean, standard deviation, median, and range) were calculated for demographic and MC use variables. As not all patients included in the current analyses completed all four study timepoints, those with missing data were divided into two discrete groups: 1) data missing at random (MAR; *n*=47) and 2) unknown whether data were MAR (*n*=7). Data were considered MAR for MC patients who completed the study but had missed a visit(s), enrolled individuals who are still considered "in progress," and those who reported withdrawing from the study due reasons *unrelated* to MC use. For those who stopped MC treatment or were lost to follow-up for unknown reasons, analyses were conducted to determine whether missing data could be considered MAR. Specifically, changes in self-report ratings of MC treatment outcomes (e.g., mood, anxiety, sleep, and quality of life) between baseline and 3 months were compared between 1) those who remained enrolled throughout the 12-month timepoint, are "in progress," or withdrew from the study for reasons unrelated to MC use and 2) those who stopped using MC or were lost to follow-up for unknown reasons. As no significant between-group differences emerged for any of these variables, it was determined that data were MAR. Accordingly, imputation for missing data was conducted using last observation carried forward (LOCF) for those who were in progress, stopped using MC, or lost to follow-up. For the six participants with missed interim visits, missing data for these visits were imputed by taking an average of scores from the visits preceding and following the missed timepoint(s) for each variable.

Repeated measures analyses of covariance (rmANCOVAs) were used to assess within-subject changes from baseline to follow-up visits for cognitive and self-reporting rating scales. For all analyses, raw scores were utilized for cognitive performance data and self-report ratings. However, rmANCOVAs controlling for age, sex, and education were conducted for the cognitive data, and rmANCOVAs controlling for age and sex were performed for the self-report rating scales. In cases where the rmANCOVA yielded significance, additional rmANCOVAs were utilized to compare baseline data to each follow-up (e.g., baseline vs. 3 months, baseline vs. 6 months, and baseline vs. 12 months); results from each of these analyses are reported with effect sizes (partial eta squared) and 95% confidence intervals based on estimated marginal means. All analyses of cognitive performance were Bonferroni-corrected: $\alpha \leq .05/6 = .008$ for variables in the executive function domain (Stroop Interference Time, Trails B Time, WCST Categories and Perseverations, LNS, and Phonemic Fluency), and $\alpha < .05/3 = .017$ for variables in the verbal learning and memory domain (RAVLT Trials 1-5, Short Delay, and Long Delay). Similarly, clinical ratings scales were also Bonferroni-corrected: $\alpha \leq .05/2 = .025$ for measures of mood (POMS TMD, BDI), $\alpha \leq .05/3 = .017$ for measures of anxiety (BAI, State Anxiety, Trait Anxiety), and $\alpha \leq .05/8 = .006$ for the 8 SF-36 subscales. As only one scale (PSQI) was used to assess sleep, no correction was utilized for this domain.

As previously noted, in order to assess whether MC use variables impacted outcomes measures, standard metrics of THC and CBD exposure were calculated for each participant at all follow-up visits using information from laboratory analyses, certificates of analyses, and product labels. Partial correlation analyses (2-tailed)

covarying for age, sex, and education were used to assess the relationship between cannabinoid exposure (THC and CBD mg/week) and changes in cognitive performance and self-report ratings. For these correlations, data from comparisons of baseline to 3 months were utilized; as 51 of 54 patients completed this visit, this timepoint contained the fewest imputed data points.

Statistical Models	Covariates	Independent Variables	Dependent Variables
rmANCOVA	Age Education Sex	Study Visit Baseline 3 months 6 months 12 months	Cognition Stroop Interference Time Trails B Time WCST Categories WCST Perseverative Errors LNS Phonemic Fluency RAVLT Trials 1-5 Correct RAVLT Short Delay RAVLT Long Delay
rmANCOVA	Age Sex	Study Visit Baseline 3 months 6 months 12 months	Rating Scales POMS BDI BAI STAI PSQI SF-36
Partial correlations	Age Education Sex	MC Use Episodes/week THC mg/week CBD mg/week	Rating Scales POMS BDI BAI STAI PSQI SF-36

Table 3.1 Chapter 3: Statistical Analyses Overview

Results

Demographics

At the time of analysis, 54 MC patients (20M, 34F) had completed a baseline visit and returned for at least one follow-up visit. MC patients were between the ages of 22-78

and reported an average of 23.57 years (range 3-47) of abstinence from regular recreational cannabis use; see **Table 3.2**[1]. MC patients used MC to treat a variety of symptoms and conditions, including pain (*n*=33), anxiety (*n*=31), sleep (*n*=22), mood (*n*=14) attention (*n*=4), and other medical conditions (e.g., gastrointestinal disorders; *n*=4); 36 patients reported using MC to treat more than one condition. In terms of MC use, over the course of the one-year study, patients reported using approximately MC 9-11 times/week on average (see **Table 3.3** for specific MC use information at each visit). Interestingly, standardized metrics of cannabinoid use revealed that, overall, THC exposure (mg/week) was notably lower than CBD exposure (mg/week) at each visit.

DEMOGRAPHICS (*n*=54)	**Mean (SD)**	**Median [Range]**
Sex	20 Male (37.04%) 34 Female (62.96%)	--
Race	48 White (88.89%) 5 Non-White (9.26%) 1 Prefer Not to Answer (1.85%)	--
Age	49.17 (16.45)	52.5 [22-78]
Education	16.58 (2.08)	16 [12-21]
WASI IQ	121.02 (7.54)	120.5 [99-134]
BASELINE CONVENTIONAL MEDICATION USE (mg/week)		
Opioids[a]	200.81 (339.78)	87.50 [1.72-1225.00]
NSAIDs[b]	2247.44 (4704.60)	567 [33.60-19600.00]
Over-the-Counter Analgesics[c]	4014.18 (3693.84)	2100 [26.00-9100.00]
Benzodiazepines[d]	12.57 (32.32)	4.50 [0.03-140.00]
Antidepressants[e]	835.17 (713.42)	630.00 [70.00-12100.00]
Mood Stabilizer[f]	4618.50 (5020.19)	2450.00 [84.00-18900.00]
Sedative[g]	58.08 (53.83)	70.00 [3.45-150.00]

WASI=Wechsler Abbreviated Scale of Intelligence
NSAIDs = Nonsteroidal anti-inflammatory drugs
[a] *n*=12, [b] *n*=20, [c] *n*=7, [d] *n*=18, [e] *n*=29, [f] *n*=14, [g] *n*=11

Table 3.2. MC Patient Demographics.

[1] Although marital and occupation status were collected as part of the study, these data were not accessible due to restrictions during the COVID-19 pandemic.

CANNABIS USE	Mean (SD)	Median [Range]
Duration of cannabis abstinence (years)[b]	23.57 (14.20)	25 [3-47]
MC Uses/Week		
Baseline to 3 Months[a]	9.25 (7.91)	7.91 [1.14-30.02]
3 Months to 6 Months[b]	10.18 (8.35)	7.0 [0.66-38.50]
6 Months to 12 Months[c]	11.60 (8.26)	9.0 [0.75-30.63]
THC mg/week		
Baseline to 3 Months[d]	64.48 (186.69)	9.93 [0-1000.50]
3 Months to 6 Months[e]	43.13 (79.79)	12.07 [0-321.55]
6 Months to 12 Months[f]	40.23 (52.43)	19.98 [0-210.92]
CBD mg/week		
Baseline to 3 Months[d]	158.04 (290.61)	29.00 [0-1303.99]
3 Months to 6 Months[e]	204.97 (58.58)	62.73 [0-1434.26]
6 Months to 12 Months[f]	99.27 (269.99)	47.25 [0.24-1228.12]

MC = medical cannabis; THC=delta-9-tetrahydrocannabinol; CBD=cannabidiol
[a] *n*=52, [b] *n*=46, [c] *n*=28, [d] *n*=38, [e] *n*=32, [f] *n*=21

Table 3.3. Medical Cannabis/Cannabinoid Use.

Cognitive Performance

Over the course of one year of MC treatment, patients did not exhibit any significant changes across measures executive functioning or verbal learning and memory after correcting for multiple comparisons (see **Table 3.4**). Importantly, although significant improvements were not noted on any measure, no significant declines in cognitive performance were observed.

(*N*=54)	**Baseline**	**3 Months**	**6 Months**	**12 Months**	**rmANCOVA**	
Task Variable	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	***F***	***p* (η^2)**
Executive Function						
Stroop Interference Time (sec)	105.30 (25.32)	98.06 (24.89)	94.91 (23.55)	93.37 (22.94)	*2.89*	*.05 (.05)*
Trails B (sec)	60.15 (17.58)	55.94 (15.41)	65.56 (26.62)	63.85 (28.46)	0.33	.80 (.01)
WCST Categories	3.06 (1.43)	3.31 (1.41)	3.58 (1.40)	3.52 (1.54)	1.20	.31 (.02)
WCST Perseverative Errors	9.17 (6.17)	8.83 (7.22)	8.21 (6.71)	7.83 (6.49)	0.77	.51 (.02)
LNS	11.93 (2.57)	12.91 (2.89)	12.88 (3.35)	12.93 (3.57)	0.28	.84 (.01)
Phonemic Fluency	49.57 (13.89)	48.73 (13.70)	51.27 (14.34)	50.13 (13.48)	0.76	.52 (.02)
Verbal Learning and Memory						
RAVLT Trials 1-5 Correct	51.15 (8.69)	49.97 (8.24)	52.43 (8.39)	51.76 (8.74)	0.21	.89 (<.01)
RAVLT Short Delay	10.78 (3.01)	10.44 (2.70)	10.95 (2.79)	10.96 (2.79)	0.65	.58 (.01)
RAVLT Long Delay	10.80 (3.16)	10.34 (2.96)	10.67 (2.91)	10.50 (3.05)	0.82	.49 (.02)

rmANCOVAs were not significant after Bonferroni corrections: p≤.05/6=.008 for Executive Function tasks, and p<.05/3=.017 for Verbal Learning & Memory tasks. Results that were significant before Bonferroni corrections are *italicized*.
Degrees of freedom (df)=1,50

Table 3.4 Changes in Performance on Tasks of Cognitive Function Over the Course of 3, 6, and 12 Months of MC Treatment

Self-Report Ratings of Mood, Anxiety, Sleep, and Quality of Life

Ratings of current mood state as well as symptoms of syndromal depression and anxiety are reported in **Table 3.5**. On the POMS, patients exhibited significantly decreased scores. Follow-up analyses indicated that TMD was significantly decreased at after 3 and 12 (but not 6) months of MC treatment relative to baseline. Overall, significant improvements were not observed on the BDI.

On measures of anxiety, BAI scores were significantly reduced, and additional comparisons revealed that these reductions were observed at every follow-up visit relative to baseline. In addition, significant changes were noted on the on the STAI; both state and trait anxiety were significantly lower following 3 and 12 months of MC use, but findings did not reach statistically significant levels after 6 months of MC treatment.

Self-report ratings of sleep and quality of life are reported in **Table 3.6**. On the PSQI, patients reported improved sleep quality. Specifically, lower sleep disturbance was observed at all follow-up visits relative to baseline. Quality of life ratings indicated no significant improvements overall after Bonferroni corrections.

Notably, significant worsening of mood, anxiety, sleep, or quality of life was not reported after initiation of MC treatment.

(*N*=54)	**Baseline**	**3 Months**	**6 Months**	**12 Months**	**rmANCOVA**		**rmANCOVA Baseline vs 3 Months**		**rmANCOVA Baseline vs 6 Months**		**rmANCOVA Baseline vs 12 Months**	
Task Variable	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	***F***	***p*** ***(η^2)***	***F*** **[95% CI]**	***p*** ***(η^2)***	***F*** **[95% CI]**	***p*** ***(η^2)***	***F*** **[95% CI]**	***p*** ***(η^2)***
Profile of Mood States (POMS)												
Total Mood Disturbance	33.30 (41.50)	26.06 (39.81)	20.53 (34.93)	19.54 (29.35)	**3.90**	**.02 (.07)**	**8.70 [0.24, 14.24]**	**.01 (.15)**	3.33 [4.00, 21.54]	.07 (.06)	**5.69 [4.93, 22.59]**	**.02 (.10)**
Beck Depression Inventory (BDI)												
BDI Total	12.28 (10.07)	8.30 (9.74)	6.48 (7.50)	6.50 (6.69)	1.79	.15 (.03)	--	--	--	--	--	--
Beck Anxiety Inventory (BAI Total)												
BAI Total	10.61 (9.45)	8.54 (8.98)	8.01 (8.54)	6.83 (6.94)	**7.57**	**<.01 (.13)**	**11.12 [-0.18, 4.33]**	**<.01 (.18)**	**8.15 [0.45, 4.76]**	**.01 (.14)**	**12.21 [1.59, 5.97]**	**<.01 (.19)**
State-Trait Anxiety Inventory (STAI)												
State Anxiety	34.83 (10.51)	33.18 (9.63)	31.63 (9.31)	31.37 (9.00)	**4.20**	**.01 (.08)**	**7.45 [-0.61, 3.91]**	**.01 (.13)**	3.23 [0.75, 5.65]	.08 (.06)	**6.81 [0.86, 6.06]**	**.01 (.12)**
Trait Anxiety	42.26 (14.17)	39.00 (13.00)	37.50 (11.05)	37.04 (11.19)	**4.69**	**.01 (.08)**	**9.50 [1.29, 5.23]**	**<.01 (.16)**	*5.72 [2.44, 7.07]*	*.02 (.10)*	**7.48 [2.89, 7.56]**	**.01 (.13)**

Significant based on the following Bonferroni corrections are **bolded**: p≤.05/2=.025 for mood scales (POMS TMD and BDI); p<.05/3=.017 for anxiety scales. Results that were significant before Bonferroni corrections are *italicized*.
Degrees of freedom (df)=1,51

Table 3.5 Changes in Self-Reported Ratings of Overall Mood, Depression and Anxiety Symptoms Over the Course of 3, 6, and 12 Months of MC Treatment

(*N*=54)	**Baseline**	**3 Months**	**6 Months**	**12 Months**	**rmANCOVA**		**rmANCOVA Baseline vs 3 Months**		**rmANCOVA Baseline vs 6 Months**		**rmANCOVA Baseline vs 12 Months**	
Task Variable	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	***F***	***p*** ***(η^2)***	***F*** **[95% CI]**	***p*** ***(η^2)***	***F*** **[95% CI]**	***p*** ***(η^2)***	***F*** **[95% CI]**	***p*** ***(η^2)***
Pittsburgh Sleep Quality Index (PSQI)												
PSQI Total	8.93 (4.30)	7.23 (3.71)	6.87 (3.87)	6.65 (3.55)	**3.67**	**.02 (.07)**	**4.35 [0.71, 2.68]**	**.04 (.08)**	**4.72 [1.07, 3.04]**	**.03 (.09)**	**9.76 [1.46, 3.10]**	**<.01 (.16)**
Short Form 36 Health Survey Questionnaire (SF-36)*												
Physical Functioning	72.04 (21.02)	77.22 (21.45)	78.24 (21.19)	78.89 (21.21)	1.54	.21 (.03)	--	--	--	--	--	--
Role Limitations: Physical Health	55.09 (43.27)	62.81 (43.34)	61.50 (41.44)	70.37 (40.07)	1.03	.38 (.02)	--	--	--	--	--	--
Role Limitations: Emotional Problems	61.73 (41.16)	64.81 (42.67)	67.90 (39.77)	70.37 (40.26)	1.42	.24 (.03)	--	--	--	--	--	--
Energy/Fatigue	43.98 (23.54)	48.69 (20.89)	53.16 (22.52)	54.54 (21.94)	2.50	.08 (.05)	--	--	--	--	--	--
Emotional Well-Being	66.52 (22.98)	67.40 (24.94)	71.05 (18.78)	72.22 (18.75)	1.63	.19 (.03)	--	--	--	--	--	--
Social Functioning	66.67 (25.12)	71.10 (25.65)	76.23 (23.16)	78.24 (24.18)	*3.03*	*.03 (.06)*	--	--	--	--	--	--
Pain	55.83 (27.18)	64.04 (25.26)	64.55 (22.98)	66.39 (24.69)	3.15	*.04 (.06)*	--	--	--	--	--	--
General Health	59.81 (20.28)	63.36 (17.69)	65.99 (18.71)	63.70 (19.89)	1.94	.13 (.04)	--	--	--	--	--	--

Significant results based on the following Bonferroni corrections are **bolded**: p<.05/8=.006 for quality of life ratings (no correction was used for sleep as only a single measure was used). Ratings that were significant before Bonferroni corrections are *italicized.*

*Higher score indicates improvement on the SF-36

Degrees of freedom (df)=1,51

Table 3.6. Changes in Self-Reported Sleep Quality and Quality of Life Over the Course of 3, 6, and 12 Months of MC Treatment

Correlations: MC Use vs Self-Report Ratings

Although correlations were planned between MC use and cognition, no significant differences were observed across any measures; therefore, these analyses were ultimately not conducted. However, correlation analyses were utilized to examine the potential relationship between MC use and changes in self-report ratings between baseline and 3 months, as a number of significant improvements were noted on these measures. Analyses indicated that improvement on self-reporting ratings were not related to frequency of MC use in general, but interesting relationships were revealed when specific cannabinoid exposure was assessed. Higher CBD exposure was related to improvements in mood as measured by POMS TMD ($r(33)=.51$, $p=<.01$) and BDI scores ($r(33)=.40$, $p=.02$). On scales of anxiety, improvements on STAI state ($r(33)=.50$, $p=<.01$) and trait anxiety ($r(33)=.51$, $p=<.01$) measures were each related to higher levels of CBD exposure. No significant relationship was noted between cannabinoid use and BAI ratings. On the SF-36, while improvement on certain subscales was related to higher CBD use, for other subscales, higher THC exposure was related to improvements. Specifically, Physical Functioning ($r(33)=-.36$, $p=.03$), Role Limitations due to Emotional Problems ($r(33)=-.34$, $p=.05$), and Emotional Wellbeing ($r(33)=-.38$, $p=.02$) subscales were related to increased CBD exposure, whereas Role Limitations due to Physical Health($r(33)=-.38$, $p=.02$), Social Functioning ($r(33)=-.42$, $p=.01$), and Pain ($r(33)=-.52$, $p=<.01$) subscales were related to higher THC exposure. See **Table 3.7**.

	MC Episodes/week *r*	THC mg/week *r*	CBD mg/week *r*
POMS TMD	0.20	0.04	**0.51****
BDI	0.25	0.20	**0.40****
BAI	0.17	0.07	0.21
BAI	0.17	0.07	0.21
STAI			
State Anxiety	0.13	-0.09	**0.50****
Trait Anxiety	0.21	-0.03	**0.51****
PSQI	-0.14	0.25	0.05
SF-36†			
Physical Functioning	-0.06	-0.09	**-0.36****
Role Limitations: Physical Health	-0.02	**-0.38****	-0.28
Role Limitations: Emotional Problems	-0.18	-0.22	**-0.34***
Energy/Fatigue	-0.10	0.02	-0.28
Emotional Well-Being	-0.16	0.11	**-0.38****
Social Functioning	-0.10	**-0.42****	-0.26
Pain	-0.06	**-0.52****	-0.26
General Health	0.07	-0.08	-0.24

***p<.05 **p<.01**
Df= 45 for MC use; df=33 for THC and CBD mg/week.
†Reverse scored (improvements are denoted by negative numbers on the SF-36)

Table 3.7. MC Use and Cannabinoid Exposure vs. Self-Report Ratings

Discussion

The current study was designed to extend findings from a previous pilot study which reported some improvement on measures of executive function in a small sample of 11 patients following three months of MC treatment (Gruber et al., 2016). Updated analyses, which examined a larger sample of MC patients over a longer period, utilized additional cognitive performance data, and controlled for covariates, did not detect significant improvements across measures of cognition over the course of one-year of MC treatment. However, a number of significant improvements were noted for self-report ratings related to mood, anxiety, and sleep.

These findings, which demonstrate stable cognition in patients after initiation of MC use may be considered to be in contrast to previous literature in recreational cannabis users that has consistently documented evidence of *decrements* on measures of executive function (Crean et al., 2011; Lisdahl et al., 2014; Sagar & Gruber, 2018b) as well as verbal learning and memory (Lisdahl et al., 2014; Sagar & Gruber, 2018b; Schwartz, Gruenewald, Klitzner, & Fedio, 1989; Solowij et al., 2011). However, not all studies have demonstrated such decrements, including the results presented in Chapter 2. Although few other studies have examined cognitive performance in those who use cannabis medically, a recent 12-month longitudinal study examined 69 individuals who report using cannabis to self-medicate chronic medical conditions (Bouso et al., 2020). This study, which utilized a self-report measure of cognition, the Cognitive Failures Questionnaire, also found that although no improvements were reported over time, no evidence of cognitive deterioration was reported over the course of 12 months. However,

as participants were not cannabis-naïve at baseline, this investigation is limited by the lack of a cannabis-naïve assessment in addition to the fact that a self-report measure of cognition was utilized.

In the current study, MC patients exhibited significant improvements after initiation of treatment across measures of mood, anxiety, sleep. Although quality of life improvements were not statistically significant, when examining results prior to Bonferroni corrections, findings suggest that some subscales did improve, including pain and social functioning. Although Buoso and colleagues (2020) reported only modest improvements in medical symptoms in their study and did not detect significant changes in quality of life, it is possible that improvements in that study may not have been detected due to several additional methodological differences between studies. Importantly, Buoso and colleagues recruited "therapeutic members" of "social cannabis clubs" located in in Spain, where formalized medical cannabis programs are not yet established. Accordingly, it is quite plausible that participants in that study may not have used cannabis solely for medical purposes and may have also used cannabis recreationally. Without medical cannabis programs, it is also likely that individuals wishing to use cannabis medically had limited access to cannabis products, including those containing significant amounts of cannabinoids other than THC, including CBD and others posited to have therapeutic benefit.

Current study findings are also supported by a number of other studies which suggest clinical improvements secondary to medical cannabis/cannabinoid use among various patient populations. For example, a survey study of California residents found

that of the 5% of Californians who reported having tried MC, 92% reported that MC helped treat a serious medical condition (Ryan-Ibarra, Induni, & Ewing, 2015). Another study of MC patients in Arizona found that, among those who endorsed anxiety symptoms, 83% reported "a lot or almost complete relief" from anxiety when using MC (Troutt & DiDonato, 2015). In addition to these survey studies, acute administration studies, observational studies, a handful of clinical trials, and several reviews have reported improvements in medical and psychiatric symptoms secondary to MCs or cannabinoid use across a range of conditions and symptoms, including chronic pain (National Academies of Sciences, 2017; Pawasarat et al., 2020; Poli, Crestani, Salvadori, Valenti, & Sannino, 2018), anxiety (Bergamaschi et al., 2011; Masataka, 2019; Shannon et al., 2019; Zuardi et al., 1993; Zuardi et al., 1982), and sleep (Kuhathasan et al., 2019).

Several factors likely contributed to the current findings. First, the current study represents the first to directly assess the specific impact of THC and CBD on cognition and health-related variables (mood, sleep, anxiety, and quality of life) in "real world" MC patients, using a quantifiable, standardized metric. On average, MC patients in the current study reported higher CBD exposure relative to THC at all follow-up visits, after initiation of MC use. As higher amounts of THC are often linked to cognitive decrements in recreational cannabis users (Kowal et al., 2015; Morgan et al., 2012; Ramaekers et al., 2006), and CBD has demonstrated efficacy in mitigating or preventing THC-related negative effects on cognition (Englund et al., 2013; Morgan et al., 2012), this overall pattern of cannabinoid exposure may have been protective against potential cognitive decrements. In addition, correlation analyses, although preliminary, demonstrated that

higher CBD exposure was associated with improved mood (POMS TMD, BDI) and anxiety symptoms on the STAI. On the SF-36, CBD exposure also appeared to be related to measures of mental health, as increased CBD was correlated with improvements on scales assessing role limitations due to emotional problems and emotional wellbeing. Higher CBD was also related to improvements on the SF-36 physical functioning subscale. In terms of THC, correlations revealed higher THC exposure was associated with improvements on the SF-36 subscales reflecting role limitations due to physical health, pain, and social functioning. Overall, this pattern appears to suggest that CBD may confer benefits to aspects related to emotional health (i.e., mood, anxiety, and emotional wellbeing), while THC may exert beneficial effects on physical health, including pain, and potentially social functioning. However, as these results are preliminary, these hypotheses will need to be tested more thoroughly in future studies.

Limitations

Results from the current study provide an important foundation for future MC research, and while results are promising, findings must be considered in light of several limitations. First, the contribution of practice effects cannot be ruled out. Although alternate forms of tests were utilized, alternate versions were not available for the Stroop and WCST, the latter of which is particularly vulnerable to practice effects. However, it is possible that the minimum of 3 to 6-months between administration of cognitive measures may have reduced the influence of practice effects. For example, some studies have reported no practice effects on the Letter Number Sequencing and Trail Making tasks with even weekly administration (Beglinger et al., 2005). In addition, studies noting

practice effects on the Stroop test have typically utilized a daily to weekly administration schedule (Gul & Humphreys, 2015), which is significantly more frequent than the current testing schedule. Even though improvements were not observed, it is possible that practice effects could have masked potential decrements that patients could be experiencing in their day-to-day cognitive functioning. In order to address this potential issue, a study arm has recently been added to allow recruitment of a group of treatment-as-usual (TAU) patients who have similar conditions but who do not use MC. Once a large enough group is recruited, changes in each of these groups can be examined over time and in comparison to one another in order to rule out practice effects and directly compare MC treatment to conventional treatments.

An additional limitation of the current study is the possibility that treatment expectancy or the "placebo effect" may have impacted current results. Future MC studies should include measures which control for this potential confounding variable by assessing the degree to which patients believe MC treatment can positively and/or negatively impact symptoms of their medical condition(s), cognition, physical and mental health, and quality of life prior to initiation of treatment. Measures to assess MC treatment expectancy are currently in development.

Further, a number of factors beyond treatment expectancy, including the underlying reasons why an individual chooses to use or not use MC, could have also impacted study findings. For example, the number of conventional treatments or medications an individual has tried in the past, efficacy of conventional treatments, societal factors or social stigma, and/or affordability and access to MC are all important

considerations. Future studies are needed to examine each of these variables. Data collected from individuals who transition from the TAU to MC group, as well as individuals who cease MC use, could provide critical preliminary information that would inform researchers of potential confounds that should be measured and controlled for in future investigations.

Although the current sample size is considered moderate for some analyses, it is still too small to control for additional potential covariates. The sample size also limits the statistical approaches available; more advanced analyses are planned once larger statistical power is attained. In addition, a number of data points are missing; while this is primarily due to the fact that many participants are still "in progress," other patients missed visits or were lost to follow-up. Analyses determined that data were missing at random, and commonly used imputation methods were there implemented; however, drawbacks of mean imputation and LOCF approaches must be acknowledged. Although each are relatively straightforward and easily implemented, they greatly reduce the variance of the dataset. Further, LOCF assumes that the data will not change over time and has the potential to generate data that may not be an inaccurate reflection of the true data (Shoop, 2015). Future analyses will benefit from more advanced imputation strategies, including multiple or Bayesian imputation, which can help address some of the limitations of imputed data.

Finally, as this is a longitudinal, observational study of MC patients, it is also of note that indications for MC use varied widely, and thus conclusions cannot be drawn about the efficacy of MC for specific medical conditions. However, results provide an

overarching view of the cognitive effects related to MC treatment. Similarly, modes of MC use were also somewhat heterogenous across patients, as patients chose different and sometimes multiple product types and administration routes. While this information was collected, larger sample sizes are needed to clarify how discrete modes of use may affect symptom alleviation, alter the onset and duration of therapeutic effects, and ultimately impact safety.

Future Directions

In the future, once larger sample sizes are attained, path analyses are warranted to further clarify the relationships between variables assessed in this study, including cognitive performance, self-report ratings, and overall cannabinoid exposure. In addition, studies examining the contribution of potential changes in conventional medication use are also important, particularly given the recent attention and focus on the relationship between MC use and opioid exposure (Parsons & Hurd, 2015; Piper et al., 2017; Shover, Davis, Gordon, & Humphreys, 2019; Takakuwa, Hergenrather, Shofer, & Schears, 2020). As epidemiological studies have revealed mixed results, prospective data gathered via face-to-face visits, as was done in the current study, will be valuable to assess.

As previously noted, preliminary data raise the possibility that THC and CBD could differentially impact MC treatment outcomes. However, it is also important to note that other cannabinoids present in patients' products may have also impacted study findings. Given that laboratory analyses of products quantified 12 cannabinoids, future analyses with larger sample sizes will more closely explore the unique contributions of individual cannabinoids and combinations of cannabinoids. Clinical trials, which control

the dose of individual cannabinoids, will help provide definitive information on each of these cannabinoids but are currently difficult given federal restrictions limiting clinical trials of cannabis-based products.

In addition, it is important to assess whether age of the consumer is a moderating variable. Unlike most studies of recreational users which assess young adults, often with onset of cannabis use in their adolescent years, those enrolled in the current study were significantly older (average age of 49). Not only is this important because of the critical neurodevelopment that takes place during adolescence, but older adults experience marked changes in the endocannabinoid system (ECS) relative to younger individuals. For example, preclinical studies have revealed decreased levels of the endocannabinoid 2-arachidonoylglycerol (2-AG) in the aging mouse brain (Piyanova et al., 2015). Rodent studies have also reported that CB1 binding peaks in puberty, remains stable early to mid-adulthood, and ultimately declines in older adulthood; human studies have similarly revealed higher CB1 receptor binding in younger individuals relative to older adults (Di Marzo, Stella, & Zimmer, 2015). In addition, although there is a paucity of studies examining cognition secondary to MC use in older adults, several animal studies highlight the potential for cannabis to improve cognition in this population (Weinstein & Sznitman, 2020), including one study which demonstrated that administration of low-dose THC reversed age-related decline in older adult mice (Bilkei-Gorzo et al., 2017). Although cognitive improvement was not observed in the current study, it is also important to acknowledge that cognitive decrements were not observed over time in MC

patients. It is possible that specific formulations designed to address age-related ECS changes could yield beneficial effects; however, more research is needed.

Conclusions

In a 12-month longitudinal, observational study, patients using MC for various medical conditions exhibited stable performance on measures of executive function and verbal learning and memory; however, the potential influence of practice effects cannot be completely disregarded and must be more fully addressed in future studies and analyses. Significant improvements on self-report measures of mood state, depressive symptomatology, symptoms related to anxiety, sleep disturbance, and some aspects of quality of life were noted after initiation of MC treatment relative to pre-MC use levels. Although results could have been influenced by MC treatment expectancies, findings extend previous research studies which have observed clinical improvements secondary to MC use. However, investigations examining the effects of individual cannabinoids, the impact of MC treatment on the use of conventional medications, and age of the consumer are warranted in order to elucidate the public health implications associated with MC treatment. Ultimately, it will be critical to examine the relationship between these variables in order to maximize the therapeutic potential of cannabis while minimizing potential risks and harms.

CHAPTER FOUR

Cannabis Use Disorder

Cannabis use disorder (CUD) is defined in the Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (DSM-5) as "a problematic pattern of cannabis use leading to clinically significant impairment or distress," which is manifested by two or more of the following symptoms occurring in a 12-month period: 1) using cannabis in larger amounts or over a longer period than intended; 2) persistent desire or unsuccessful effort to cut down; 3) spending significant time obtaining, using, or recovering from cannabis; 4) failure to meet obligations; 5) using in spite of social/interpersonal problems caused or exacerbated by cannabis use; 6) giving up or limiting important activities because of cannabis use; 7) using in hazardous situations; 8) use despite persistent/recurrent physical or psychological problems that are caused or exacerbated by cannabis; 9) tolerance; 10) cravings or desire to use cannabis; and 11) symptoms of withdrawal (American Psychiatric Association, 2013). Although there is general consensus that the majority of recreational users do not develop CUD, estimated rates of CUD are highly variable across studies. For example, data from two large epidemiological survey studies indicate that rates of CUD in recreational cannabis users range from 11-15% (Compton, Han, Jones, Blanco, & Hughes, 2016) to approximately 30% (Hasin et al., 2015). Interestingly, a more recent study found that increased access to medical cannabis (MC) programs (at the time of the study 28 states and Washington DC had legalized MC) was associated with higher rates of adult cannabis use, but was *not* associated with higher rates of CUD (Williams, Santaella-Tenorio, Mauro, Levin, &

Martins, 2017), raising the question of whether MC use could be associated with a lower risk for CUD than recreational cannabis use.

As a full diagnostic assessment is quite time-consuming and therefore often not feasible in many clinical settings, several tools have been developed to screen for CUD in both clinical and research settings, including the Severity of Dependence Scale (SDS) (Gossop et al., 1995); Cannabis Abuse Screening Test (CAST) (Legleye, Kraus, Piontek, Phan, & Jouanne, 2012); Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) (WHO Assist Working Group, 2002); Cannabis Use Problems Identification Test (CUPIT) (Bashford, Flett, & Copeland, 2010); Cannabis Use Disorders Identification Test (CUDIT) (Adamson & Sellman, 2003) and its revised version (CUDIT-R) (Adamson et al., 2010). While each has strengths, the CUDIT-R was selected for inclusion in the current study as it is commonly used for clinical and research applications, is based on DSM criteria, and offers sound psychometric properties when used to assess recreational cannabis users (Adamson et al., 2010).

To date, no studies thus far have directly addressed whether MC patients develop symptoms/behaviors associated with problematic cannabis use. Given the growing number of MC patients, it is important to accurately assess potential problematic cannabis use in this population. Accordingly, data was collected from patients interested in using MC *prior* to their initiation of use, and all patients were re-queried following 3, 6 and 12 months of MC treatment.

Hypotheses

Using the CUDIT-R, symptoms and behaviors related to problematic cannabis use were examined over the course of treatment with the hypothesis that MC patients would exhibit increased frequency of use, but endorse few problems associated with MC use given their primary motivation for use is symptom alleviation. Further, it was predicted that increased exposure to non-intoxicating constituents like cannabidiol (CBD) would not be associated with higher CUDIT-R scores in MC patients, whereas increased exposure to delta-9-tetrahydrocannabinol (THC), the primary intoxicating constituent of cannabis, may be related to higher CUDIT-R scores. It was also hypothesized that MC patients would exhibit lower CUDIT-R scores relative to a cohort of recreational (i.e., non-medical) cannabis users, whose primary motivation for cannabis use is to feel intoxicated or "high." Importantly, a recent study assessing the internal consistency and structural validity of the CUDIT-R in veteran MC patients reported that although the CUDIT-R demonstrated acceptable, yet modest, internal consistency in this cohort, the traditional single-factor structure of the scale "showed poor fit" (Loflin, Babson, Browne, & Bonn-Miller, 2018). As results raise the possibility that CUDIT-R scores may not accurately reflect problematic use in certain populations of MC patients, analyses were also conducted to determine whether the CUDIT-R has acceptable internal consistency and reliability in the current sample of MC patients.

Methods

Prior to participation, all participants completed an informed consent process in which study procedures were thoroughly explained. Participants interested and willing to

participate read and signed an informed consent form, which describes the procedures, risks, benefits, and voluntary nature of the study. This study was approved by the Partners Healthcare Institutional Review Board.

Participants & Study Design

As part of an ongoing, longitudinal study of MC patients conducted at McLean Hospital (PI: Dr. Staci Gruber; funded private donors, foundations, and unrestricted gifts to the Marijuana Investigations for Neuroscientific Discovery [MIND] program at McLean Hospital), individuals interested in using MC, but who had not yet begun treatment were recruited. All study participants were enrolled between September 2014–November 2019 and completed assessments at McLean Hospital. Individuals were considered eligible for the current study if they were aged 21 or older, had an estimated IQ of at least 75 assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), and planned to use cannabinoid-based products to treat medical/psychiatric conditions. All patients were required to have a certification for MC or plan to use products not requiring certification (i.e., hemp-derived products). At baseline, participants were required to be cannabis naïve or, if they reported a history of previous recreational cannabis use, were required to be abstinent from regular use for one year or more in order to minimize the effects of previous cannabis exposure. All patients were required to test negative for urinary THC and could not have begun MC treatment.

Patients completed baseline assessments, including medical history questionnaires, cognitive testing, and self-report rating scales (reported in Chapter 3), as well as multimodal neuroimaging prior to initiation of regular MC treatment; however,

only data from the CUDIT-R self-report scale are reported in this chapter. MC patients returned for follow-up visits after three, six, and twelve months of MC use. At follow-up visits, patients' MC regimen information was captured using detailed MC diary information and a timeline followback procedure (TLFB) (Robinson, Sobell, Sobell, & Leo, 2014b; Sobell et al., 1988), which was modified and optimized to collect recent cannabis use data through the additional of targeted queries regarding specifics of MC treatment (product used, mode of use, amount purchased, amount used, etc.). At the time of analyses, 54 patients completed a baseline visit and had returned for at least one follow-up visit. Of the 54 MC patients included in the current analyses, 28 completed all four visits. Six patients missed an interim visit (1 of the 6 patients missed 2 interim visits), but all completed baseline and 12-month follow-ups. Ten MC patients are "in progress" as they are currently enrolled but are awaiting their next follow-up timepoint. Ten individuals were discontinued from the study as they either stopped MC use (n=3) or were lost to follow-up (n=7). Of those who were lost to follow-up, three reported that they discontinued for reasons unrelated to MC treatment; however, four individuals stopped responding to contact by study staff and information about the reason for discontinuation could not be gathered. A schematic summarizing this info is presented in Chapter 3 (**Figure 3.1**). See *Statistical Analyses* for information about how missing MC patient data were handled.

In addition, as a comparison, previously acquired CUDIT-R data from 38 heavy recreational cannabis users was included from participants enrolled in a previous study (Marijuana: Neurobiologic Correlates of Age of Onset, R01 DA03264601); all

participants in this cohort reported more than 1500 lifetime cannabis uses and reported current cannabis use four or more days per week, as assessed using the modified TLFB. Recreational cannabis users were also required to be free of Axis I pathology including current or previous drug/alcohol use disorders (other than cannabis) as assessed by the Structured Clinical Interview for DSM-IV – Patient Edition (SCID-P) (First, Spitzer, Gibbon, & Williams, 1994).

CUDIT-R

The CUDIT-R is an 8-item self-report screening tool designed to detect problematic cannabis use. Symptoms assessed include frequency of use; hours stoned during days of cannabis use; inability to stop using once started; failure to meet expectations; time spent getting cannabis, using cannabis, or recovering from cannabis; memory or concentration problems after cannabis use; using in hazardous situations (e.g., driving, operating machinery, caring for children); and desire to stop/reduce cannabis use. Seven of the eight items are scored on a scale ranging from 0-4 (higher frequency/severity of symptoms are reflected by higher ratings), while the final question regarding thoughts about cutting down use is scored as 0 (no), 2 (yes, but not in the past 6 months), and 4 (yes, during the past 6 months). Scores are summed to generate a total score, ranging from 0 to 32. A total score of 8 or more reflects "hazardous cannabis use," while scores of 13 or more indicate "possible CUD"; diagnostic measures, such as the SCID, are needed for definitive CUD diagnosis.

Cannabinoid Exposure in MC Patients

As an observational study, all patients chose their own MC treatment regimens, which were closely tracked using a number of metrics. All MC patients were asked to record MC treatment regimen information in paper-and-pencil or electronic drug diaries (based on patient preference) once a regular MC use regimen was established. Further, study participants were contacted by phone to complete monthly check-in visits to corroborate drug diary information using the modified TLFB. Through these methods, patients were asked to provide qualitative information regarding product type and mode of use (i.e., joint, vaporizer, solution/tincture, edibles, capsules, topicals, etc.) and quantitative information regarding frequency (episodes of MC use/week) and amount of product used. These data were then reviewed and clarified at in-person visits and allowed for the calculation of average number of MC uses per week. MC patients were also asked to provide constituent information based on product labels and/or certificates of analyses from dispensaries or product websites. Additionally, patients sent samples of their most frequently used MC products to an outside laboratory for analyses (ProVerde Laboratories, Inc.), including cannabinoid constituent profiling. These analyses provide information about THC and CBD levels as well as a number of other cannabinoids. For all patients with available product data, standard metrics of cannabinoid exposure (mg of THC and CBD used per week) were calculated for each interval between study visits using drug diary, product label, certificate of analyses, and laboratory-based data.

Statistical Analyses

Over the course of MC treatment, MC patients' CUDIT-R scores (total scores and individual item scores) were examined using repeated measures analyses of covariance (rmANCOVAs), controlling for age, sex, and education. In cases where significance was noted, follow-up rmANCOVAs were conducted to compare baseline data to each follow-up visit (e.g., baseline vs. 3 months, baseline vs. 6 months, baseline vs. 12 months).

As not all patients included in the current analyses completed all four study visits, those with missing data were divided into two discrete groups: 1) data missing at random (MAR; n=47) and 2) unknown whether data were MAR (n=7). Data were considered MAR for MC patients who completed the study but had missed a visit(s), enrolled individuals who are still considered "in progress," and those who reported withdrawing from the study due reasons *unrelated* to MC use. For those who stopped MC treatment or were lost to follow-up for unknown reasons, analyses were conducted to determine whether missing data could be considered MAR. Specifically, changes in self-report ratings related to MC treatment outcomes between baseline and 3 months were compared between 1) those who remained enrolled throughout the 12-month timepoint, are "in progress," or withdrew from the study for reasons unrelated to MC use and 2) those who stopped using MC or were lost to follow-up for unknown reasons. As no significant between-group differences emerged for any of these variables, it was determined that data were MAR. Accordingly, imputation for missing data was conducted using last observation carried forward (LOCF) for those who were in progress, stopped using MC, or lost to follow-up. For those who missed only interim visits, missing CUDIT-R data

were imputed by taking an average of scores from the visits preceding and following the missed timepoint(s) for each variable.

To examine the impact of MC use variables on abuse liability, partial correlations (2-tailed) controlling for age, sex, and education were utilized to explore the relationship between total CUDIT-R scores and frequency of MC use (episodes of use/week), THC exposure (mg/week), and CBD exposure (mg/week). Given that the 3-month study visit contained the fewest imputed data points, CUDIT-R scores from this visit were utilized for these analyses.

Two-group comparisons were conducted in order to compare MC patients to recreational cannabis users. Chi-squared analyses were used to compare sex and race frequencies between groups, and for continuous variables (age, education, IQ, cannabis use episodes, and CUDIT-R scores), one-way ANOVAs were conducted. One-way ANCOVAs controlling for age, education, and sex were also conducted to compare CUDIT scores between groups, and results are reported with effect sizes (partial eta squared) and 95% confidence intervals based on estimated marginal means. Again, given that the 3-month timepoint had the greatest sample size (n=51) and therefore contained the least amount of imputed data, CUDIT-R scores from MC patients' 3-month follow-up visits were compared to scores in the recreational cannabis users. Although Levene's test of homogeneity was violated when comparing the two groups, non-parametric tests did not change the significance level of results; therefore, results from the ANCOVAs are reported.

Finally, to assess the internal consistency and reliability of the CUDIT-R in MC patients and recreational cannabis users, corrected item-scale correlations were performed for the MC patient group as well as the recreational cannabis-using group. Total Cronbach's alpha was calculated for the entire scale and item-deletion analyses were completed to assess the internal consistency of each CUDIT-R item. Data from MC patients' follow-up visit after 3 months of use were also utilized for Cronbach's analyses.

Statistical Models	Covariates	Independent Variables	Dependent Variables
rmANCOVA	Age Education Sex	Study Visit Baseline 3 months 6 months 12 months	CUDIT-R Total Scores Item Scores
Partial correlations	Age Education Sex	MC Use Episodes/week THC mg/week CBD mg/week	Total CUDIT-R Scores
ANCOVA	Age Education Sex	Group MC Patients Recreational Users	CUDIT-R Total Scores Item Scores
Note: Cronbach's Alpha analyses were also conducted to assess the validity of the CUDIT-R in the MC patients as well as the recreational cannabis users.			

Table 4.1. Chapter 4: Statistical Analyses Overview

Results

MC Patients: Demographics

MC patients (20M, 34F) were between the ages of 22-78, primarily White (88.89%), reported approximately 16 years of education, and exhibited above average IQ. See **Table 4.2** for demographics. Patients reported using MC to treat symptoms of pain

(*n*=33), anxiety (*n*=31), sleep (*n*=22), mood (*n*=14) attention (*n*=4), and other general medical conditions (e.g., gastrointestinal disorders; *n*=4); 36 patients reported using MC for more than one indication. As noted in **Table 4.3**, MC patients reported abstinence from regular recreational cannabis use from 3-47 years upon enrolling in the current study, and none had initiated a MC treatment regimen, as this was a requirement for the study. Over the course of the study, patients reported using MC 9-11 times/week on average, and THC exposure was notably lower than CBD exposure at each visit.

DEMOGRAPHICS (*n*=54)	**Mean *(SD)***	**Median [Range]**
Sex	20 Male (37.04%) 34 Female (62.96%)	--
Race	48 White (88.89%) 5 Non-White (9.26%) 1 Prefer Not to Answer (1.85%)	--
Age	49.17 *(16.45)*	52.5 [22-78]
Education	16.58 *(2.08)*	16 [12-21]
WASI IQ	121.02 *(7.54)*	120.5 [99-134]
WASI=Wechsler Abbreviated Scale of Intelligence; NSAIDs = Nonsteroidal anti-inflammatory drugs [a] *n*=12, [b] *n*=20, [c] *n*=7, [d] *n*=18, [e] *n*=29, [f] *n*=14, [g] *n*=11		

Table 4.2. MC Patient Demographics.

CANNABIS USE	Mean *(SD)*	Median [Range]
Duration of cannabis abstinence (years)[b†]	23.57 (*14.20)*	25 [3-47]
MC Uses/Week		
Baseline to 3 Months[a]	9.49 *(6.26)*	9 [1.14-30.02]
3 Months to 6 Months[b]	10.17 *(8.10)*	7.2 [0.66-38.50]
6 Months to 12 Months[c]	11.48 *(8.14)*	8.8 [0.75-30.63]
THC mg/week		
Baseline to 3 Months[d]	63.64 *(184.22)*	10.22 [0-1000.50]
3 Months to 6 Months[e]	41.78 *(78.83)*	11.62 [0-321.55]
6 Months to 12 Months[f]	38.43 *(51.76)*	18.56 [0-210.92]
CBD mg/week		
Baseline to 3 Months[d]	154.97 *(287.28)*	29.43 [0-1303.99]
3 Months to 6 Months[e]	205.39 *(320.84)*	83.33 [0-1434.26]
6 Months to 12 Months[f]	101.91 *(262.46)*	47.61 [0.24-1228.12]

MC = medical cannabis; THC=delta-9-tetrahydrocannabinol; CBD=cannabidiol
[a] *n*=52, [b] *n*=46, [c] *n*=28, [d] *n*=38, [e] *n*=32, [f] *n*=21
[†]Average abstinence is reported for *n*=28 with a previous history of regular cannabis use; *n*=26 reported no previous regular cannabis use or were cannabis naïve

Table 4.3. MC Patient Medical Cannabis/Cannabinoid Use.

MC Patients: CUDIT-R

rmANCOVAs demonstrated that total CUDIT-R scores increased in MC patients over the course of the study. Analyses comparing each follow-up visit to baseline revealed that increases were significant after 3 and 6 months of use, but not at 12 months (see **Table 4.4; Figure 4.1**). Although ratings increased, average total CUDIT-R scores for MC patients fell below the threshold for 'hazardous use' (score of 8 or more) at each visit and well below the cutoff for possible CUD (score of 13 or more); average total CUDIT-R scores were ≤6.10 across all follow-up visits. Of the 54 patients included in the study, the number of MC patients who surpassed the threshold for *possible* CUD at each visit is as follows: Visit 1 = 0, Visit 2 = 2, Visit 3 = 2, Visit 4 = 3.

In order to determine which specific symptoms/behaviors contributed to total CUDIT-R score increases, changes in individual item scores were also examined (**Table 4.4; Figure 4.2**). "Frequency of use" and "failure to meet expectations" were the only two variables for which significant changes were observed over time. Follow-up analyses revealed that frequency of use was significantly higher at each visit relative to baseline, whereas failure to meet expectations was only significant at 3 months relative to baseline. However, an examination effect sizes and power indicated that while observed power for changes in frequency of use ranged from 80-95%, statistical power was low for failure to meet expectations (54%). Moreover, significant increases in scores for "failure to meet expectations" were not detected at the other follow-up visits relative to baseline.

	Baseline	3 Months	6 Months	12 Months	rmANCOVA		rmANCOVA Baseline vs 3 Months		rmANCOVA Baseline vs 6 Months		rmANCOVA Baseline vs 12 Months	
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	***F***	***p* (η^2)**	***F* [95% CI]**	***p* (η^2)**	***F* [95% CI]**	***p* (η^2)**	***F* [95% CI]**	***p* (η^2)**
Total CUDIT-R Score	1.41 (2.03)	5.99 (2.71)	6.19 (2.98)	6.13 (3.30)	**3.47**	**.03**	**6.62 [-5.31, -3.87]**	**.01 (.12)**	**8.07 [-5.66, -3.91]**	**.01 (.14)**	2.06 [-5.68, -3.77]	.16 (.04)
Frequency	0.57 (0.66)	3.45 (0.81)	3.54 (0.82)	3.54 (0.86)	**7.79**	**<.01 (.14)**	**8.32 [-3.17, -2.59]**	**.01 (.14)**	**13.48 [-3.25, -2.68]**	**<.01 (.21)**	**11.98 [-3.26, -2.67]**	**<.01 (.19)**
Hours Stoned	0.43 (0.74)	0.69 (0.97)	0.43 (0.74)	0.72 (0.96)	1.17	.32 (.02)	--	--	--	--	--	--
Can't Stop	0.00 (.00)	0.12 (0.48)	0.10 (.47)	0.11 (0.57)	0.36	.78 (.01)	--	--	--	--	--	--
Failure to Meet Expectations	0.02 (0.14)	0.21 (0.60)	0.13 (0.39)	0.13 (0.39)	**3.67**	**.03 (.07)**	**4.41 [-0.35, -0.04]**	**0.04 (.08)**	0.14 [-0.23, 0.01]	.72 (<.01)	0.09 [-0.23, 0.01]	.76 (<.01)
Time Spent	0.04 (.027)	0.15 (0.36)	0.26 (0.71)	0.22 (0.63)	0.22	.89 (<.01)	--	--	--	--	--	--
Memory/ Attention	0.07 (0.26)	0.45 (0.90)	0.31 (0.70)	0.24 (0.61)	0.35	.79 (.01)	--	--	--	--	--	--
Hazardous Situations	0.06 (0.23)	0.20 (0.63)	0.37 (0.93)	0.24 (0.75)	2.44	.08 (.05)	--	--	--	--	--	--
Cutting Down Use	0.22 (0.84)	0.71 (1.45)	0.75 (1.48)	0.93 (1.59)	1.15	0.33 (.02)	--	--	--	--	--	--
Significant values ($p \leq .05$) are **bolded**. Degrees of freedom (df)=1,50												

Table 4.4. MC Patients: Changes in CUDIT Score Over Time.

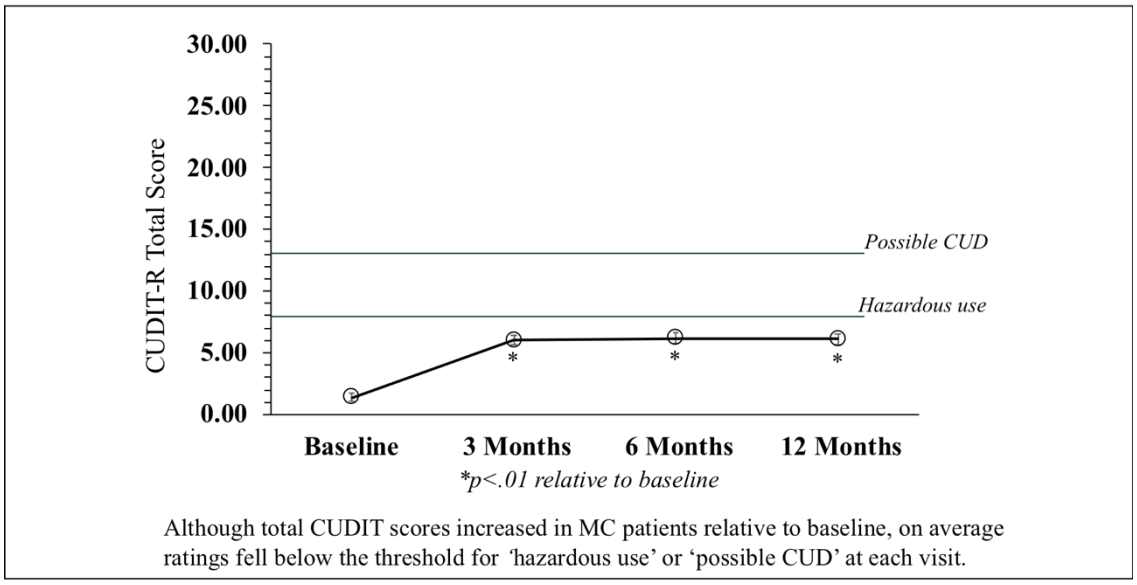

Figure 4.1. Total CUDIT Scores over 12 months of MC Treatment.

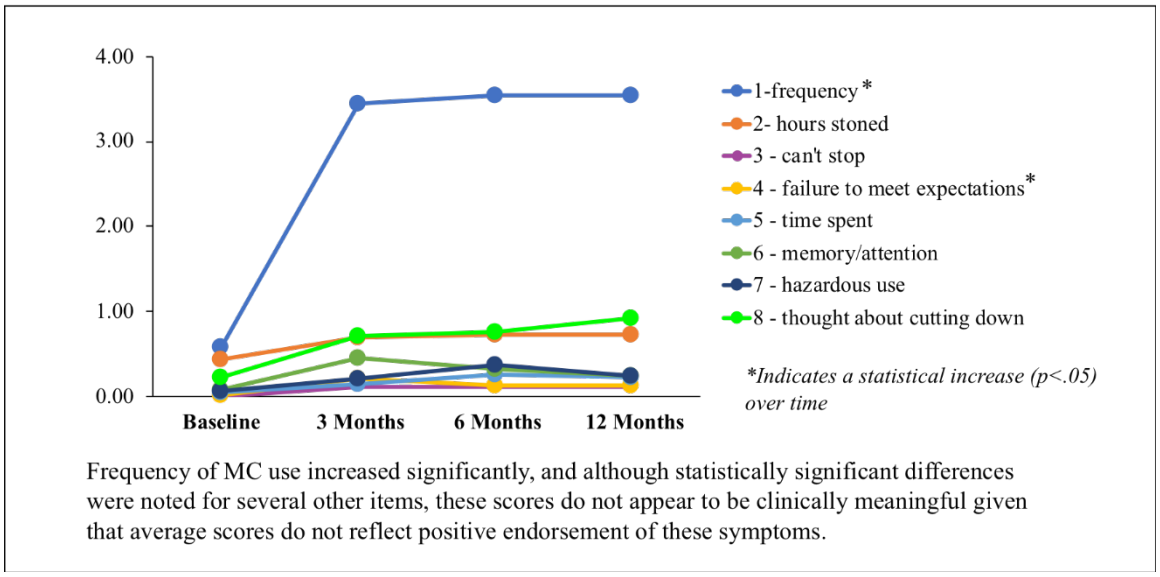

Figure 4.2. Individual CUDIT Item Scores over 12 months of MC Treatment.

Correlation Analyses: CUDIT-R and MC Use Variables

Partial correlations assessing the relationship between total CUDIT-R scores and MC use variables revealed no significant relationships between number of MC episodes per week ($r(44)=.11$, $p=.46$), THC mg/week ($r(32)=.27$, $p=.12$) or CBD mg/week ($r(32)=.07$, $p=.72$).

MC Patients vs Recreational Cannabis Users

MC patients and recreational users were also directly compared in order to examine potential differences in CUD symptoms among these groups. Demographic and cannabis use information for MC patients and recreational users is reported in **Table 4.5.** In terms of cannabis use, TLFB data indicated that recreational users significantly reported more episodes of cannabis use per week relative to MC patients, although on average both cohorts reported more than daily use. Analyses examining differences in CUDIT-R scores between MC patients and recreational cannabis users revealed significant differences for total CUDIT-R scores, as well as all individual items (see **Table 4.6**).

Variable	Mean (*SD*)		Chi-Square	
	MC Patients *n*=54	**Recreational Cannabis Users *n*=39**	X^2	*p*
Sex[a]	(20M, 34F)	(30M, 9 F)	**14.49**	**<.01**
Race[a]	48 White (88.8%) 5 Non-White (9.26%) 1 Prefer Not to Answer (1.85%)	26 White (66.67%) 12 Non-White (30.77%) 1 Prefer Not to Answer (2.56%)	**10.14**	**.04**
			ANOVA	
			F	***p* (η^2)**
Age[b]	49.17 *(16.45)*	23.18 *(5.84)*	**88.95**	**<.01 (.49)**
Education[b]	16.56 *(1.99)*	14.18 (1.99)	**32.40**	**<.01 (.26)**
WASI IQ[c]	121.02 *(7.54)*	118.92 *(9.49)*	**6.77**	**.01 (.07)**
Cannabis uses/week[d]	9.26 *(6.33)*	15.89 *(11.51)*	**11.81**	**.01 (12)**

Significant values (p≤.05) are **bolded**.
WASI= Wechsler Abbreviated Scale of Intelligence
[a]*Degrees of freedom (df)=1;* [b]*df=1,91;* [c]*df=1,90;* [d]*df=1,86*

Table 4.5. Demographics: MC Patients vs. Recreational Cannabis Users.

	MC Patients *n*=51	**Recreational Cannabis Users** *n*=39	**ANCOVA[a]**	
	Mean *(SD)*	**Mean *(SD)***	***F***	***p* (η^2)**
Total Score	5.99 (2.71)	15.36 (5.31)	**50.05**	**<.01 (.36)**
Frequency	3.45 (0.81)	3.92 (0.27)	**7.71**	**<.01 (.08)**
Hours Stoned	0.69 (0.97)	2.13 (0.95)	**12.34**	**<.01 (.12)**
Can't Stop	0.12 (0.48)	1.15 (1.51)	**22.22**	**<.01 (.11)**
Failure to Meet Expectations[b]	0.21 (0.60)	0.67 (1.06)	**6.45**	**.01 (.07)**
Time Spent Getting Cannabis/Recovering	0.15 (0.36)	1.59 (1.48)	**13.35**	**<.01 (.13)**
Memory/Attention Problems	0.45 (0.90)	1.54 (1.31)	**9.68**	**<.01 (.10)**
Use in Hazardous Situations	0.20 (0.63)	1.54 (1.60)	**12.58**	**<.01 (.13)**
Thought about Cutting Down Use	0.71(1.45)	2.82 (1.35)	**26.60**	**<.01 (.23)**

Significant values (p≤.05) are **bolded**.
[a] Degrees of freedom (df)=1,88

Table 4.6. CUDIT Scores: MC Patients vs. All Recreational Consumers.

CUDIT-R Internal Consistency and Reliability

Although the CUDIT-R has been validated in recreational cannabis users, it remains questionable whether this tool is appropriate for use in MC patients. Given that MC patients demonstrated increases in total overall scores on the CUDIT-R in the absence of significant increases in problematic symptoms, analyses were conducted to examine internal consistency and reliability of the CUDIT-R in MC patients as well as in recreational cannabis users. In the current sample of MC patients, the CUDIT-R had an *unacceptable* level of internal consistency (alpha=.27). As noted in **Table 4.7**, unacceptable levels are indicative of $\alpha < 0.5$, whereas acceptable levels begin at $\alpha \leq 0.7$.

Cronbach's alpha	Internal consistency
$0.9 \leq \alpha$	Excellent
$0.8 \leq \alpha < 0.9$	Good
$0.7 \leq \alpha < 0.8$	Acceptable
$0.6 \leq \alpha < 0.7$	Questionable
$0.5 \leq \alpha < 0.6$	Poor
$\alpha < 0.5$	Unacceptable

Table 4.7 Cronbach's Alpha Descriptors

Moreover, removing frequency of use from the analyses increased internal consistency and reliability (alpha=.39), as did removal of thoughts about cutting down use (alpha=.45). Given that alpha increased after removing these items, it appears that frequency of use and thoughts of cutting down cannabis use are *not* assessing the same construct as the remainder of CUDIT-R items in a cohort of MC patients. In addition, following removal of these items, alpha remained below the level of acceptable internal consistency, suggesting that the CUDIT-R is likely not an appropriate measure for assessing CUD among MC patients. Conversely, when Cronbach's alpha was calculated for recreational users' CUDIT-R scores, internal consistency was much improved, but by

some conventional standards is considered questionable (alpha=.63). As alpha did *not* improve with the removal of any individual CUDIT-R items, results suggest that all items assess a similar construct (CUD) in recreational users.

Discussion

Findings from the CUDIT-R suggest that, on average, MC patients in this study do not meet the threshold for 'hazardous' cannabis use over the course of 12 months of MC treatment. When examining total CUDIT-R scores in each individual MC patient, a small number of individuals did surpass the threshold for *possible* CUD following initiation of MC treatment (2 patients after 3 months and 6 months, and 3 patients after 12 months). However, findings revealed that CUDIT-R ratings, including total scores and all individual item scores were significantly lower in MC patients relative to heavy recreational cannabis users. Moreover, Cronbach's alpha analyses revealed that the CUDIT-R does not have acceptable levels of internal consistency within MC patients.

Overall, despite significantly increased frequency of use, individual item analysis also revealed other signs of problematic use were generally not endorsed. It is of note that while failure to meet expectations demonstrated a statistically significant increase after 3 months of treatment, this was the only visit for which an increase was considered significant and observed statistical power for this finding was low (1-β=.54).

Despite the fact that the frequency of use CUDIT-R item score significantly increased at follow-up visits relative to baseline in MC patients, correlation analyses more closely examining the relationship between MC use variables and CUDIT-R scores found that frequency of use, in terms of specific number of MC episodes per week, is not

significantly correlated with increased total CUDIT-R scores in MC patients. Therefore, frequency of MC use does not appear to be a useful indicator of problematic use in MC patients, especially as patients taking a medicine generally do so on a daily basis; the same is to be expected with MC. Although it was expected that individual cannabinoid exposure would be related to MC use, correlation analyses did not reveal significant relationships between THC or CBD exposure and total CUDIT-R scores.

As noted above, comparisons between MC patients and recreational cannabis consumers suggest that those with heavy recreational use demonstrate significantly higher levels of problematic cannabis use, while most MC patients do not appear to exhibit symptoms consistent with a diagnosis of CUD. Notably, recreational consumers did report using cannabis about 1.7 times as often as MC patients. It is therefore possible that higher frequency of use beyond a certain threshold could be a factor that may predict the manifestation of some of the symptoms of CUD. However, as previously mentioned, no relationship was observed between MC episodes of use per week and CUD symptoms in this sample of MC patients who use cannabis quite frequently (more than daily on average) and exhibit few signs of problematic use. It is therefore likely that factors other than frequency of use contribute to the development of CUD symptoms and behaviors. To date, additional contributing factors have yet to be empirically examined, but motivation for use, product choice, and age of onset of cannabis use are important variables to consider.

Although the CUDIT-R is considered a well-validated screening tool for CUD, it was developed for use with recreational cannabis users, and not for MC patients. The

current analyses suggest that the CUDIT-R does not appear to be valid as a screening tool among those who use cannabis for medical purposes given both the extremely low Cronbach's alpha, as well as qualitative analysis of the CUDIT-R items and review of their applicability to MC patients. Accordingly, although some patients did surpass the threshold for potential CUD at follow-up visits, these numbers are likely not a valid representation of the number of MC patients who actually develop a use disorder.

To date, one other study has assessed the validity of the CUDIT-R in a subpopulation of veteran MC populations (Loflin et al., 2018). Although the authors reported that the CUDIT-R's internal consistency fell within the acceptable range, Cronbach's alpha calculated in that study is considered modest (alpha=.73), and confirmatory factor analysis revealed that the single-factor model used by the CUDIT-R to indicate potential CUD only accounted for 38.34% of variance in their sample. Similarly, in the current study, within the MC group removal of "frequency of use" and "thoughts about cutting down use" increased the overall alpha of the CUDIT-R, which suggests that these items may be assessing a different construct than the other items of this scale. For example, taking a medication regularly can be a sign of treatment adherence rather than a sign of problematic use. Instead, it may be more helpful to differentiate regular use from using more than needed to achieve a therapeutic benefit, as the former could potentially be more indicative of problematic use. In addition, thoughts about cutting down use could indicate that patients may feel as though they do not need as much MC to get the same effect, or endorsement of this item may be a function of individuals feeling the financial burden related to the cost of MC treatment, especially as

it is not covered by insurance. In addition, other questions on the CUDIT-R may not be directly reflective of problematic use in MC patients either. Specifically, "time spent getting cannabis" may not be problematic, but simply reflect the geographic distance some patients travel, or the time patients wait to purchase MC products for symptom relief that, in some cases, is not achieved with conventional medications.

Taken together, current views of CUD may need to be amended in order to capture signs of problematic use among MC patients (Sznitman & Room, 2018). As in the case of opioid use disorder, for example, tolerance and withdrawal criteria are not considered to be met for individuals who are using opioids under appropriate medical supervision. With regard to cannabis, similar exclusions from these DSM-5 criteria may need to be applied. It also is likely that signs of problematic use manifest differently in MC patients who have a markedly different motivation for cannabis use – symptom alleviation – relative to recreational users who use cannabis specifically to alter their state of being or to feel "high." As a result, MC patients and recreational users tend to seek different cannabis products and therefore often have different levels of exposure to specific cannabinoids. Typically, recreational users seek products with high levels of THC, which is generally associated with negative neurobiologic outcomes, to achieve mood-altering effects. Further, chronic exposure to THC is thought to alter excitatory and inhibitory signaling in certain brain regions that could ultimately affect reward processing (Parsons & Hurd, 2015). Altered reward processing is closely linked to addictive disorders given that intoxication produces pleasurable feelings, which leads to repeated use as an individual seeks achieve these rewarding effects (Everitt & Robbins, 2016). In

addition, it is important to note that using products with higher levels of THC has also been associated with increased addiction severity (Freeman & Winstock, 2015b).

MC patients may use products containing THC, but many seek products with varied cannabinoid constituent profiles that are often less intoxicating or even non-intoxicating. Specifically, many MC patients choose products with high levels of CBD, known for its therapeutic benefits and potential neuroprotective properties (Blessing, Steenkamp, Manzanares, & Marmar, 2015; de Mello Schier et al., 2014; Fernandez-Ruiz et al., 2013; Iseger & Bossong, 2015; Zuardi, 2008). Calculations of overall THC and CBD exposure suggest that this preference is reflected in the current study sample, as MC patients as a group had substantially higher CBD exposure at each study visit relative to THC exposure. CBD has also been shown to limit or mitigate negative effects associated with THC (Englund et al., 2013; Morgan & Curran, 2008; Morgan et al., 2012; Morgan, Schafer, Freeman, & Curran, 2010; Yucel et al., 2016; Zuardi et al., 1982), and preliminary data from both animal and human studies suggest that CBD may have efficacy in the treatment of substance use disorders, including nicotine (Morgan, Das, Joye, Curran, & Kamboj, 2013), cocaine (Lujan, Castro-Zavala, Alegre-Zurano, & Valverde, 2018), and opioids (Hurd et al., 2019; Hurd et al., 2015). Further, one case study suggests positive effects of CBD in treating CUD (Shannon & Opila-Lehman, 2015). Although relationships between individual cannabinoid exposure and CUDIT-R levels were not detected in the current study, future studies are encouraged to continue to examine this as a possibility, particularly once valid screening measures of CUD are developed for MC patients.

It is also of note that our analyses of a previously recruited cohort of recreational CAN users revealed "questionable" levels internal consistency. However, a number of factors impacting the interpretation of Cronbach's alpha must be considered and may account for this only modest alpha level (Field, 2013). First, Cronbach's alpha is often more robust when scales contain a large number of items; as the CUDIT only has eight items, this may have diminished internal consistency. Further, for this study, a well-characterized group of heavy, cannabis users with specific cannabis use criteria, limited other drug use, and no other psychopathology was recruited, which inherently restricts the range and variability among the sample. In validation studies, a wider range of individuals is typically recruited to represent a more varied population. Accordingly, the modest level of alpha is recreational users may be a function of these factors, rather than an indication that this scale is not appropriate for CUD screening in recreational cannabis users.

Limitations & Future Directions

Data from the current study indicate that most MC patients do not reach the threshold of symptom severity using a common screening tool for CUD. These findings must be considered in light of several limitations. First, a definitive diagnosis of CUD can only be made using a diagnostic interview like the SCID. In the current study, MC patients receive the SCID at baseline (prior to initiation of MC use) in order to rule out exclusionary psychopathologies. The CUDIT-R was selected for use in this study as it is widely used screening tool in both research and clinical settings and sometimes serves as a proxy for diagnostic instruments generating data regarding CUD. Further, items on the

CUDIT-R have high overlap with DSM-5 criteria for CUD. However, it is important to note that this instrument was developed before the release of the DSM-5, and therefore based on DSM-IV criteria. Although most criteria are similar between these two versions of the DSM, "craving or desire to use cannabis" is a new addition to the DSM-5 criteria and is not reflected in the CUDIT-R. Interestingly, however, when the original CUDIT was revised, an item assessing legal problems related to cannabis use was removed; this criterion was also eliminated in the transition from DSM-IV to DSM-5. All other CUDIT-R items reflect current DSM-5 CUD criteria which is, at least in part, why it remains a popular screening tool for CUD assessment.

Currently, sample sizes are moderate for follow-up visits following 3- and 6-months visits, but fewer participants have completed a 12-month follow-up. In addition, due to the fact that a number of participants are still "in progress," and a small group was also lost to follow-up, missing data was imputed after it was determined these data appear to be missing at random. Commonly used mean imputation and LOCF methods were implemented; however, drawbacks must be acknowledged when using these approaches. Although mean imputation and LOCF are both straightforward and easily implemented, they greatly reduce the variance of the dataset. Further, LOCF assumes that the data will not change over time and has the potential to produce values that may not actually be reflective of the true data (Shoop, 2015). Future analyses will benefit from more advanced imputation strategies, including multiple or Bayesian imputation which can help address some of the limitations of the current approach.

Plans for the ongoing, longitudinal study involve monitoring CUDIT-R scores in larger samples and over longer durations of time (up to two years). However, longitudinal studies assessing patients over the course of several years may be necessary to detect potential development of problematic cannabis use. In addition, MC patients who were cannabis naïve or who had limited recent cannabis exposure were specifically recruited, and all patients reported a primary goal of symptom alleviation. Given that many MC patients in the current sample appear to be "pure" medical users, they may represent a unique group of patients. As such, results may not be generalizable to other populations of cannabis consumers such as "mixed" users who use cannabis both medically and recreationally.

Similarly, findings may not apply to MC patient populations who tend to choose products with higher amounts of THC than CBD, as patients in the current sample overall reported notably higher exposure to CBD. Despite potential limited generalizability, this study represents the first face-to-face, direct assessment of CUD in MC patients pre- vs post-MC treatment. Although findings may appear to be in contrast with the limited existing literature suggesting that rates of CUD are comparable between MC patients and recreational cannabis users (Lin, Ilgen, Jannausch, & Bohnert, 2016). However, using Lin and colleagues' recent study as an example, the authors did not differentiate those who *exclusively* use cannabis for medical reasons from those who also use recreationally. Further, their data is based on the National Survey on Drug Use and Health (NSDUH), which employs questions that are very similar to those asked in the CUDIT-R, which is problematic as results from the current study demonstrate that these types of queries are

not valid for assessing CUD in MC patients. Problematic cannabis use is likely a unique construct among those using cannabis medically, and novel tools are therefore needed for this unique population of cannabis consumers.

An additional limitation is related to the fact that MC patients and recreational cannabis users were recruited for separate studies and are not matched on demographic variables. Although age, sex, and education were controlled for in comparisons between MC patients and recreational cannabis users, these populations had additional demographic differences that may have influenced study findings. Future studies comparing MC patients to recreational users should recruit both groups in parallel and ensure individuals are well-matched.

Conclusions

In the current study, MC patients generally exhibit low risk patterns of cannabis use, as average scores indicate they MC patients generally do not meet CUDIT-R criteria for hazardous use or possible CUD. Although some patients did surpass the threshold for CUD after initiation of MC use, these data likely do not reflect rates of CUD in MC patients given that analyses also suggest that the CUDIT-R is not a valid measure for assessing CUD in those who use cannabis for medical purposes. Taken together, development of new metrics is needed to assess CUD in MC patients, and future studies should examine these new tools in larger and more diverse samples, including those who may use cannabis for both medical and recreational purposes.

CHAPTER FIVE

Discussion

Recreational vs. Medical Cannabis Use: Explaining Cognitive Outcomes and Cannabis Use Disorder Findings

The three studies included in previous chapters explore the impact of cannabis use on cognition in recreational users and medical cannabis (MC) patients, as well as the potential for development of problematic cannabis use. Throughout these chapters it becomes clear that a number of factors can influence findings when assessing both recreational cannabis users and MC patients. Although null findings were observed for several hypotheses, most notably alterations in cognitive functioning were not observed in either recreational consumers (for which decrements were predicted) and MC patients (for which improvements were hypothesized), it is important to recognize methodological limitations of the current studies may have impacted results rather than conclude that cannabis use does not impact cognition. Further, in the MC patients, it is also important to acknowledge that while previous research has indicated decrements in recreational users, MC patients in the current study did not exhibit any significant declines in cognitive functioning. Stable performance is also notable given that many MC patients included in the current study were older adults, who may be vulnerable to age-related cognitive decline. Accordingly, the goal of the following discussion is to consider aspects of cannabis use that require further exploration and consideration based on both previous research as well as findings from previous chapters that were significant, albeit preliminary in some cases.

In the majority of research studies, recreational users, like those included in the previous chapters, are typically comprised of young individuals (adolescents, emerging adults, and young adults) who are using or began using cannabis regularly and heavily during critical neurodevelopmental phases of life. In fact, all cannabis users included in Chapter 2, regardless of whether they were classified as early or late onset, initiated regular use of cannabis during adolescence or emerging adulthood (between ages 11-23). As this study was underpowered, it is likely that subtle decrements in these recreational cannabis users exist but could not be detected with the current analytic approach. Comparing those who initiate recreational use during adolescence/emerging adulthood to those who begin using regularly in later adulthood will be important to address in future investigations.

As recreational users' main goal of cannabis use is to feel high or altered, products with high levels of THC are typically chosen by this cohort. In fact, studies have shown that THC potency continues to rise dramatically in recreational cannabis products, while CBD levels have fallen to virtually undetectable levels (Chandra et al., 2019; ElSohly et al., 2016). This trend is problematic given that higher doses of THC are associated with increased cognitive impairment (Kowal et al., 2015; Morgan et al., 2012; Ramaekers et al., 2006), whereas CBD may be able to prevent or limit these negative effects. This combination of being young and being exposed to high levels of THC while neurodevelopmentally vulnerable is likely problematic. Although this pattern was not observed in the current study of recreational users, many patients were recruited several years ago prior to such drastic increases in THC potency. Further, in general, recreational

users included in the current sample were highly educated and intelligent, which may serve as a protective factor against negative consequences associated with THC exposure. Although some studies have attempted to examine higher potency products, most observational studies to date have simply asked participants about their products' potency (Large & Nielssen, 2017; Rigucci et al., 2016). In fact, it appears that no studies thus far, other than acute challenge paradigms, have directly assessed the impact of the use of high potency products; this is a major gap in the literature that warrants additional research.

In contrast, MC patients are typically middle-aged to older adults who often times use products that are less intoxicating or even non-intoxicating. First, as adults, most of whom are well beyond the window of critical neurodevelopment, cannabis is likely to have a differential impact on the aging endocannabinoid system (ECS) and, subsequently, cognitive outcomes. Based on preclinical evidence, some postulate that due to age-related changes in the ECS, exogenous cannabinoids may actually exert *positive* effects on cognition in older individuals (Weinstein & Sznitman, 2020), many of whom have actually begun to experience age-related cognitive decline. In addition, MC patients, who are searching for symptom alleviation, often choose products with more varied cannabinoid profiles than recreational users. In the current study, for example, MC patients reported higher exposure to CBD relative to THC. In general, CBD is touted as being neuroprotective, and although THC is commonly associated with negative effects, emerging preclinical evidence suggests that THC may also have its own neuroprotective effects in older populations. Specifically, THC has been shown to improve cholinergic

transmission and inhibit the aggregation of amyloid-beta (Weinstein & Sznitman, 2020), a protein implicated in the development of Alzheimer's disease.

Differences in cognitive performance, although not observed in the current study, are widely documented in the literature and often involve decrements in executive/inhibitory function in recreational users (Crean et al., 2011; Sagar & Gruber, 2019). This executive dysfunction may, in turn, affect risk for cannabis use disorder (CUD). In young, recreational consumers, it is possible that the even mild executive function decrements, combined with high, premorbid levels of impulsivity could influence the potential for the development of CUD. As seen in Chapter 2, recreational cannabis users reported significantly higher levels of self-reported impulsivity relative to non-cannabis users on the Barratt Impulsiveness Scale (BIS-11). In fact, impulsivity is well documented among individuals who use substances and has been shown to be a risk factor and predictor of substance use disorders (Guy, Smith, & Bentler, 1994; Poulton & Hester, 2019). Among recreational cannabis users, one study found that individuals with higher levels of impulsivity held fewer negative expectancies related to cannabis use and, consequently, used cannabis more frequently than those with lower levels of impulsivity (Vangsness, Bry, & LaBouvie, 2005). In addition, inhibitory functioning assessed via objective, cognitive paradigms also plays an important role in predicting risk for substance use disorders. For example, one study reported that poorer performance on inhibitory tasks prior to the initiation of cannabis use predicted increased cannabis use by late adolescence (Squeglia et al., 2014). Taken together, this evidence suggests that impulsivity/inhibition may be an important moderator in the development CUD.

To date, no published studies have assessed impulsivity in MC patients. Although not reported in Chapters 3 and 4, MC patients included in the current analyses also completed the Barratt Impulsiveness Scale (BIS-11) as part of the ongoing longitudinal study. At baseline, prior to initiation of substance use, MC patients reported impulsivity levels (BIS-11 average total score: 58.39) which are quite similar to levels reported by healthy controls included in Chapter 2 (BIS-11 average total score: 56.12), and notably lower than that of the recreational cannabis users in Chapter 2 (BIS-11 average total score: 65.03). It is possible that lower baseline impulsivity could serve as a protective factor against development of CUD symptoms. For example, lower levels of impulsivity may allow MC patients to use cannabis to the point of symptom alleviation and then stop, rather than continuing to use more cannabis for the rewarding effects of euphoria or feeling high. Once appropriate and valid tools are developed for screening assessments of CUD, specifically in MC patients, research exploring the relationship between impulsivity and CUD symptoms in MC patients will be beneficial, as it is possible that baseline levels of impulsivity may moderate, and therefore predict, risk for CUD in MC patients as well.

In addition, recreational users by definition use cannabis to change their current state or get high, which is accomplished by using products high in THC. Accordingly, recreational cannabis users may be at increased risk for CUD due to the fact that cannabis with higher THC content produces stronger reinforcing effects (Curran et al., 2016; Justinova, Goldberg, Heishman, & Tanda, 2005). Importantly, theories of addiction posit that intoxication produces pleasurable feelings and therefore reinforcing effects, which

ultimately leads to repeated use in order to continue to achieve the rewarding effects produced by the drug. Ultimately, reinforcement is implicated in drug use transitioning from voluntary to compulsive (Everitt & Robbins, 2016). Further, use of cannabis with higher THC content has been shown to be associated with greater addiction severity (Freeman & Winstock, 2015b). In contrast, one study found that individuals who consumed cannabis with higher amounts of CBD were less likely to show an attentional bias to cannabis-related images (Morgan, Freeman, Schafer, & Curran, 2010). These findings support the idea that CBD may protect against the development of CUD, as attentional bias to drug-related stimuli is correlated with symptoms of substance use disorders. Given that MC patients in the current studies were shown to have higher CBD exposure relative to THC, product choice may also be related to a lower risk for the development of problematic cannabis use among MC patients.

In light of these key differences between recreational users and MC patients, empirical studies directly comparing these two groups are warranted. However, it is difficult to statistically compare the current cohorts given the number of critical differences between the two groups, including age, duration of cannabis use, and presence of medical or psychiatric disorders. In addition, given that exposure to specific cannabinoids appears to mediate cognitive outcomes, it will be important for this type of data to be incorporated into any comparison of recreational users versus MC patients; unfortunately, cannabinoid exposure data based on laboratory analyses of products used is not available for the majority of recreational cannabis users in the current dataset, and is not included in most published studies to date. Prospective studies recruiting well-

matched recreational and medical cannabis-using cohorts are needed to further assess differential effects of cannabis on cognition in these unique populations.

Potential Public Health Considerations

Findings from this set of studies raise a number of important questions and although results are considered preliminary, results of these detailed in-person studies also raise potential considerations regarding cannabis-related public health and public policy. Although cognitive decrements were not observed in the recreational cohort, given results of previous studies, it would appear safest to avoid recreational cannabis use during the vulnerable window of neuromaturation. Additional data, however, are needed guide policymakers in proposing age restrictions. Public health efforts should focus on delaying cannabis use, given that the risk of cognitive insult is likely to be lower in adults who are neurodevelopmentally mature.

In forming public policy, lawmakers and health officials are encouraged to remember that not all cannabis confers the same risks or benefits; the impact of individual cannabinoids must be considered. For example, preliminary data from hypothesis-generating analyses raise the possibility that higher urinary THC levels may be related to poorer cognitive performance. Additionally, pilot data (see Chapter 2 Discussion) from a subsample of recreational users recruited for the most recent study provides additional evidence that recreational users may be using more potent products than in years prior, which could negatively affect cognition. Studies with larger sample sizes and additional data are needed given that the potential for negative effects related to potency could be additive with the negative effects typically associated with adolescent

onset of cannabis use. Nevertheless, it may be helpful to consider imposing limits on THC content in recreational products to mitigate potential risk and harm. Similarly, given potentially protective factors of CBD, it may also be helpful to set thresholds for minimum levels of constituents with potentially beneficial effects. For example, results from Chapter 4 suggest that higher CBD exposure may related to improvements in mood, anxiety, and quality of life. Results, however, are preliminary, and additional research will be critical in helping to guide decisions about limiting or setting minimums for individual cannabinoid content.

Cannabis use is currently widespread throughout the nation both recreationally and medically. As such, it is important to monitor whether changes in legalization ultimately influence rates of CUD. In addition, it will be important for researchers to assess whether specific patterns of use confer differential levels of risk for the development of problematic use or CUD (e.g., medical versus recreational goal of use; use of high potency products versus use of low-THC products that also contain other non-intoxicating and potentially beneficially cannabinoids). While a number of measures exist to assess CUD in recreational users, to accomplish this goal, it will be critical to develop valid tools specifically to assess CUD in those who use cannabis medically.

Finally, findings from the current studies also help to highlight important gaps in the literature which will need to be addressed in order to more thoroughly understand both the positive and the negative effects related to cannabis use. For example, it will be helpful to gather data on younger cohorts of MC patients, older cohorts of recreational users, and individuals who use cannabis *both* medically and recreationally. Despite these

research gaps, some institutions have begun to draft guidelines for cannabis consumers who are interested in minimizing risks. In general, recommendations include delaying use until after adolescence, choosing products with lower levels of THC, and limiting cannabis use overall (Fischer et al., 2017).

Clearly, although cannabis has been studied for decades, there is still much more to learn. Early research efforts treated cannabis as if it were a single, homogenous plant used for one reason – to get high. However, researchers and consumers alike have more recently begun to conceptualize cannabis as a heterogenous, complex plant that can be used in a variety of ways for a variety of reasons. This newer, yet more accurate view of cannabis has raised a number of important questions which make it difficult to draw straightforward, overarching conclusions about the impact of "cannabis," as the term cannabis refers to a multitude of different plants, products, and formulations. In order to answer the many questions about the impact of cannabis use, it is necessary to explore the various individual constituents of the cannabis plant as well as the unique factors which underlie recreational and medical cannabis use.

APPENDIX

Appendix A

Standard Metric of THC & CBD Use: Example Calculation

Tincture
CW extra strength, 100mL bottle, 1.2mL per dropper
Patient uses 2 droppers per day
Values from lab analysis (0.56mg/mL THC per mL and 17.43mg/mL CBD)

- mL per week: 1.2mL x 2 droppers x 7 days = 16.8mL per week
- THC per week: 16.8mL per wk x 0.56mg THC per mL = **9.41mg THC/week**
- CBD per week: 16.8mL per wk x 17.43mg CBD per mL = **292.82mg CBD/week**

Flower
Strain: Bubba Kush Hemp
Patient used 0.5g in 5 weeks
Values from lab analysis (0.71% Total THC and 18.52% Total CBD)

- g per week: 0.5g/5 weeks = 0.1g OR 100mg per week
- mg THC per week: 100mg x 0.0071 CBD = **0.71mg THC/week**
- mg CBD per week: 100mg x 0.1852 THC = **18.52mg CBD/week**

Concentrate – vape cartridge
500mg cartridge of Granddaddy Purple
One cartridge lasts 3 weeks
Values from product label (78.47% Total THC and 0.18% Total CBD)

- mg per week: 500mg/3 weeks = 166.67mg
- mg THC per week: 166.67 x 0.7847 THC = **130.79mg THC**
- mg CBD per week: 166.67 x 0.0018 CBD = **0.30mg CBD**

Edible
Jar of honey containing 23 servings of hemp
Product label: 0 mg THC, 5mg CBD per serving
Patient used 1 serving each morning with breakfast

- mg THC per week: 0mg THC x 7 servings = **0.00mg THC per week**
- mg CBD per week: 5mg CBD x 7 servings = **35.00mg CBD per week**

Overall product totals
THC = 9.41mg + 0.71mg + 130.79mg + 0.00mg =
CBD = 292.82mg + 18.52mg + 0.30mg + 35.00mg =

140.91mg TOTAL THC per week
346.64mg TOTAL CBD per week

Figure A.1. Standard Metric of THC and CBD Use: Example Calculation

BIBLIOGRAPHY

Abrams, D. I. (2016). Integrating cannabis into clinical cancer care. *Current Oncolology, 23*(2), S8-S14. doi:10.3747/co.23.3099

Adamson, S. J., Kay-Lambkin, F. J., Baker, A. L., Lewin, T. J., Thornton, L., Kelly, B. J., & Sellman, J. D. (2010). An improved brief measure of cannabis misuse: the Cannabis Use Disorders Identification Test-Revised (CUDIT-R). *Drug and Alcohol Dependence, 110*(1-2), 137-143. doi:10.1016/j.drugalcdep.2010.02.017

Adamson, S. J., & Sellman, J. D. (2003). A prototype screening instrument for cannabis use disorder: the Cannabis Use Disorders Identification Test (CUDIT) in an alcohol-dependent clinical sample. *Drug and Alcohol Review, 22*(3), 309-315. doi:10.1080/0959523031000154454

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Andre, C. M., Hausman, J. F., & Guerriero, G. (2016). Cannabis sativa: The Plant of the Thousand and One Molecules. *Frontiers in Plant Science, 7*, 19. doi:10.3389/fpls.2016.00019

Baron, E. P. (2018). Medicinal Properties of Cannabinoids, Terpenes, and Flavonoids in Cannabis, and Benefits in Migraine, Headache, and Pain: An Update on Current Evidence and Cannabis Science. *Headache, 58*(7), 1139-1186. doi:10.1111/head.13345

Bashford, J., Flett, R., & Copeland, J. (2010). The Cannabis Use Problems Identification Test (CUPIT): development, reliability, concurrent and predictive validity among adolescents and adults. *Addiction, 105*(4), 615-625. doi:10.1111/j.1360-0443.2009.02859.x

Battisti, R. A., Roodenrys, S., Johnstone, S. J., Pesa, N., Hermens, D. F., & Solowij, N. (2010). Chronic cannabis users show altered neurophysiological functioning on Stroop task conflict resolution. *Psychopharmacology, 212*(4), 613-624. doi:10.1007/s00213-010-1988-3

Beck, A. T., & Steer, R. A. (1990). *Manual for the Beck Anxiety Inventory*. San Antonio, TX: Psychological Corporation.

Beck, A. T., Steer, R. A., & Garbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review, 8*, 77-100.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*, 561-571.

Becker, M. P., Collins, P. F., & Luciana, M. (2014). Neurocognition in college-aged daily marijuana users. *Journal of Clinical and Experimental Neuropsychology, 36*(4), 379-398. doi:10.1080/13803395.2014.893996

Befort, K. (2015). Interactions of the opioid and cannabinoid systems in reward: Insights from knockout studies. *Frontiers in Pharmacology, 6*, 6. doi:10.3389/fphar.2015.00006

Berg, E. A. (1948). A simple objective technique for measuring flexibility in thinking. *The Journal of General Psychology, 39*, 15-22. doi:doi:10.1080/00221309.1948.9918159

Bergamaschi, M. M., Queiroz, R. H., Chagas, M. H., de Oliveira, D. C., De Martinis, B. S., Kapczinski, F., . . . Crippa, J. A. (2011). Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. *Neuropsychopharmacology, 36*(6), 1219-1226. doi:10.1038/npp.2011.6

Bhattacharyya, S., Morrison, P. D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., . . . McGuire, P. K. (2010). Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology, 35*(3), 764-774. doi:10.1038/npp.2009.184

Bilkei-Gorzo, A., Albayram, O., Draffehn, A., Michel, K., Piyanova, A., Oppenheimer, H., . . . Zimmer, A. (2017). A chronic low dose of Delta(9)-tetrahydrocannabinol (THC) restores cognitive function in old mice. *Nature Medicine, 23*(6), 782-787. doi:10.1038/nm.4311

Blessing, E. M., Steenkamp, M. M., Manzanares, J., & Marmar, C. R. (2015). Cannabidiol as a Potential Treatment for Anxiety Disorders. *Neurotherapeutics, 12*(4), 825-836. doi:10.1007/s13311-015-0387-1

Bolognini, D., Rock, E. M., Cluny, N. L., Cascio, M. G., Limebeer, C. L., Duncan, M., . . . Pertwee, R. G. (2013). Cannabidiolic acid prevents vomiting in Suncus murinus and nausea-induced behaviour in rats by enhancing 5-HT1A receptor activation. *British Journal of Pharmacology, 168*(6), 1456-1470. doi:10.1111/bph.12043

Borrelli, F., Fasolino, I., Romano, B., Capasso, R., Maiello, F., Coppola, D., . . . Izzo, A. A. (2013). Beneficial effect of the non-psychotropic plant cannabinoid cannabigerol on experimental inflammatory bowel disease. *Biochemical Pharmacology, 85*(9), 1306-1316. doi:10.1016/j.bcp.2013.01.017

Bouso, J. C., Jimenez-Garrido, D., Ona, G., Woznica, D., Dos Santos, R. G., Hallak, J. E. C., . . . Farre, M. (2020). Quality of Life, Mental Health, Personality and Patterns of Use in Self-Medicated Cannabis Users with Chronic Diseases: A 12-Month Longitudinal Study. *Phytotherapy Research*. doi:10.1002/ptr.6639

Braga, R. J., Burdick, K. E., Derosse, P., & Malhotra, A. K. (2012). Cognitive and clinical outcomes associated with cannabis use in patients with bipolar I disorder. *Psychiatry Research, 200*(2-3), 242-245. doi:10.1016/j.psychres.2012.05.025

Bridgeman, M. B., & Abazia, D. T. (2017). Medicinal Cannabis: History, Pharmacology, And Implications for the Acute Care Setting. *Pharmacy and Therapeutics, 42*(3), 180-188.

Broyd, S. J., van Hell, H. H., Beale, C., Yucel, M., & Solowij, N. (2016). Acute and Chronic Effects of Cannabinoids on Human Cognition-A Systematic Review. *Biological Psychiatry, 79*(7), 557-567. doi:10.1016/j.biopsych.2015.12.002

Budney, A. J., Novy, P. L., & Hughes, J. R. (1999). Marijuana withdrawal among adults seeking treatment for marijuana dependence. *Addiction, 94*(9), 1311-1322. doi:10.1046/j.1360-0443.1999.94913114.x

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The pittsburgh sleep quailty index: a new instrument for psychiatric practice and research. *Psychiatry Research, 28*, 193-213.

Casey, B. J., Galvan, A., & Hare, T. A. (2005). Changes in cerebral functional organization during cognitive development. *Current Opinion in Neurobiology, 15*(2), 239-244. doi:10.1016/j.conb.2005.03.012

Chandra, S., Radwan, M. M., Majumdar, C. G., Church, J. C., Freeman, T. P., & ElSohly, M. A. (2019). New trends in cannabis potency in USA and Europe during the last decade (2008-2017). *European Archives of Psychiatry and Clinical Neuroscience, 269*(1), 5-15. doi:10.1007/s00406-019-00983-5

Colizzi, M., McGuire, P., Giampietro, V., Williams, S., Brammer, M., & Bhattacharyya, S. (2018). Modulation of acute effects of delta-9-tetrahydrocannabinol on psychotomimetic effects, cognition and brain function by previous cannabis exposure. *European Neuropsychopharmacology, 28*(7), 850-862. doi:10.1016/j.euroneuro.2018.04.003

Compton, W. M., Han, B., Jones, C. M., Blanco, C., & Hughes, A. (2016). Marijuana use and use disorders in adults in the USA, 2002–14: analysis of annual cross-sectional surveys. *The Lancet Psychiatry, 3*(10), 954-964. doi:10.1016/s2215-0366(16)30208-5

Cortes-Briones, J., Skosnik, P. D., Mathalon, D., Cahill, J., Pittman, B., Williams, A., . . . D'Souza, D. C. (2015). Delta9-THC Disrupts Gamma (gamma)-Band Neural Oscillations in Humans. *Neuropsychopharmacology, 40*(9), 2124-2134. doi:10.1038/npp.2015.53

Crane, N. A., Schuster, R. M., Fusar-Poli, P., & Gonzalez, R. (2013). Effects of cannabis on neurocognitive functioning: recent advances, neurodevelopmental influences, and sex differences. *Neuropsychology Review, 23*(2), 117-137. doi:10.1007/s11065-012-9222-1

Crawford, J. R., Stewart, L. E., & Moore, J. W. (1989). Demonstration of savings on the AVLT and development of a parallel form. *Journal of Clinical and Experimental Neuropsychology, 11*, 975-981.

Crean, R. D., Crane, N. A., & Mason, B. J. (2011). An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. *Journal of Addiction Medicine, 5*(1), 1-8. doi:10.1097/ADM.0b013e31820c23fa

Crippa, J. A., Derenusson, G. N., Ferrari, T. B., Wichert-Ana, L., Duran, F. L., Martin-Santos, R., . . . Hallak, J. E. (2011). Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. *Journal of Psychopharmacology, 25*(1), 121-130. doi:10.1177/0269881110379283

Curran, H. V., Freeman, T. P., Mokrysz, C., Lewis, D. A., Morgan, C. J., & Parsons, L. H. (2016). Keep off the grass? Cannabis, cognition and addiction. *Nature Reviews: Neuroscience, 17*(5), 293-306. doi:10.1038/nrn.2016.28

Dahlgren, M. K., Sagar, K. A., Racine, M. T., Dreman, M. W., & Gruber, S. A. (2016). Marijuana Use Predicts Cognitive Performance on tasks of Executive Function. *Journal on Studies of Alcohol and Drugs, 77*, 298-208.

Dahlgren, M. K., Sagar, K. A., Smith, R. T., Lambros, A. M., Kuppe, M. K., & Gruber, S. A. (2020). Recreational cannabis use impairs driving performance in the absence of acute intoxication. *Drug and Alcohol Dependence, 208*, 107771. doi:10.1016/j.drugalcdep.2019.107771

Daniller, A. (2019). Two-thirds of Americans support marijuana legalization. Retrieved from https://www.pewresearch.org/fact-tank/2019/11/14/americans-support-marijuana-legalization/

Day, A. M., Metrik, J., Spillane, N. S., & Kahler, C. W. (2013). Working memory and impulsivity predict marijuana-related problems among frequent users. *Drug Alcohol Depend, 131*(1-2), 171-174. doi:10.1016/j.drugalcdep.2012.12.016

de Mello Schier, A. R., de Oliveira Ribeiro, N. P., Coutinho, D. S., Machado, S., Arias-Carrion, O., Crippa, J. A., . . . Silva, A. C. (2014). Antidepressant-like and anxiolytic-like effects of cannabidiol: a chemical compound of Cannabis sativa. *CNS & Neurological Disorders Drug Targets, 13*(6), 953-960.

De Petrocellis, L., Ligresti, A., Moriello, A. S., Allara, M., Bisogno, T., Petrosino, S., . . . Di Marzo, V. (2011). Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. *British Journal of Pharmacology, 163*(7), 1479-1494. doi:10.1111/j.1476-5381.2010.01166.x

De Vita, M. J., Moskal, D., Maisto, S. A., & Ansell, E. B. (2018). Association of Cannabinoid Administration With Experimental Pain in Healthy Adults: A Systematic Review and Meta-analysis. *JAMA Psychiatry, 75*(11), 1118-1127. doi:10.1001/jamapsychiatry.2018.2503

Delis, D. C., Karmer, J. H., E., K., & Ober, B. A. (1987). *California Verbal Learning Test: Adult version.* San Antonio, TX: Psychological Corporation.

Desrosiers, N. A., Ramaekers, J. G., Chauchard, E., Gorelick, D. A., & Huestis, M. A. (2015). Smoked cannabis' psychomotor and neurocognitive effects in occasional and frequent smokers. *Journal of Analytical Toxicology, 39*(4), 251-261. doi:10.1093/jat/bkv012

Di Forti, M., Marconi, A., Carra, E., Fraietta, S., Trotta, A., Bonomo, M., . . . Murray, R. M. (2015). Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. *The Lancet Psychiatry, 2*(3), 233-238. doi:10.1016/s2215-0366(14)00117-5

Di Marzo, V., & Piscitelli, F. (2015). The Endocannabinoid System and its Modulation by Phytocannabinoids. *Neurotherapeutics, 12*(4), 692-698. doi:10.1007/s13311-015-0374-6

Di Marzo, V., Stella, N., & Zimmer, A. (2015). Endocannabinoid signalling and the deteriorating brain. *Nature Reviews: Neuroscience, 16*(1), 30-42. doi:10.1038/nrn3876

Dougherty, D. M., Mathias, C. W., Dawes, M. A., Furr, R. M., Charles, N. E., Liguori, A., . . . Acheson, A. (2013). Impulsivity, attention, memory, and decision-making among adolescent marijuana users. *Psychopharmacology (Berl), 226*(2), 307-319. doi:10.1007/s00213-012-2908-5

Egerton, A., Allison, C., Brett, R. R., & Pratt, J. A. (2006). Cannabinoids and prefrontal cortical function: insights from preclinical studies. *Neuroscience & Biobehavioral Reviews, 30*(5), 680-695. doi:10.1016/j.neubiorev.2005.12.002

Ehrenreich, H., Kunert, H. J., Moeller, M. R., Poser, W., Schilling, L., Gigerenzer, G., . . . Rinn, T. (1999). Specific attentional dysfunction in adults following early start of cannabis use. *Psychopharmacology, 142*(3), 295-301. doi:10.1007/s002130050892

Elsaid, S., & Le Foll, B. (2020). The complexity of pharmacology of cannabidiol (CBD) and its implications in the treatment of brain disorders. *Neuropsychopharmacology, 45*(1), 229-230. doi:10.1038/s41386-019-0518-a

ElSohly, M. A., Mehmedic, Z., Foster, S., Gon, C., Chandra, S., & Church, J. C. (2016). Changes in Cannabis Potency Over the Last 2 Decades (1995-2014): Analysis of Current Data in the United States. *Biological Psychiatry, 79*(7), 613-619. doi:10.1016/j.biopsych.2016.01.004

Englund, A., Morrison, P. D., Nottage, J., Hague, D., Kane, F., Bonaccorso, S., . . . Kapur, S. (2013). Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. *Journal of Psychopharmacology, 27*(1), 19-27. doi:10.1177/0269881112460109

Epstein, H. T. (1999). Stages of increased cerebral blood flow accompany stages of rapid brain growth. *Brain and Development, 21*(8), 535-539. doi:10.1016/s0387-7604(99)00066-2

Everitt, B. J., & Robbins, T. W. (2016). Drug Addiction: Updating Actions to Habits to Compulsions Ten Years On. *Annual Review of Psychology, 67*, 23-50. doi:10.1146/annurev-psych-122414-033457

Fernandez-Ruiz, J., Sagredo, O., Pazos, M. R., Garcia, C., Pertwee, R., Mechoulam, R., & Martinez-Orgado, J. (2013). Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid? *British Journal of Clinical Pharmacology, 75*(2), 323-333. doi:10.1111/j.1365-2125.2012.04341.x

Field, A. (2013). *Discovering Statistics Using IBM SPSS, 4th Edition* (4th edition ed.). Los Angeles: SAGE

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, B. W. (1994). *Structured Clinical Interview for axis I DSM IV disorder, patient edition (SCID-I/P). Version 2.0.* New York, NY: Biometric Research Department, NY State Psychiatric Institute.

Fischer, B., Russell, C., Sabioni, P., van den Brink, W., Le Foll, B., Hall, W., . . . Room, R. (2017). Lower-Risk Cannabis Use Guidelines: A Comprehensive Update of Evidence and Recommendations. *American Journal of Public Health, 107*(8), e1-e12. doi:10.2105/AJPH.2017.303818

Fontes, M. A., Bolla, K. I., Cunha, P. J., Almeida, P. P., Jungerman, F., Laranjeira, R. R., . . . Lacerda, A. L. (2011). Cannabis use before age 15 and subsequent executive functioning. *British Journal of Psychiatry, 198*(6), 442-447. doi:10.1192/bjp.bp.110.077479

Freeman, T. P., & Winstock, A. R. (2015a). Examining the profile of high-potency cannabis and its association with severity of cannabis dependence. *Psychol Med, 45*(15), 3181-3189. doi:10.1017/S0033291715001178

Freeman, T. P., & Winstock, A. R. (2015b). Examining the profile of high-potency cannabis and its association with severity of cannabis dependence. *Psychological Medicine, 45*(15), 3181-3189. doi:10.1017/S0033291715001178

Fusar-Poli, P., Crippa, J. A., Bhattacharyya, S., Borgwardt, S. J., Allen, P., Martin-Santos, R., . . . McGuire, P. K. (2009). Distinct effects of delta-9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. *Archives of General Psychiatry, 66*(1), 95-105. doi:10.1001/archgenpsychiatry.2008.519

Gallily, R., Yekhtin, Z., & Hanuš, L. O. (2015). Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using Cannabis Extract Enriched in Cannabidiol. *Pharmacology & Pharmacy, 06*(02), 75-85. doi:10.4236/pp.2015.62010

Ganzer, F., Broning, S., Kraft, S., Sack, P. M., & Thomasius, R. (2016). Weighing the Evidence: A Systematic Review on Long-Term Neurocognitive Effects of Cannabis Use in Abstinent Adolescents and Adults. *Neuropsychology Review, 26*(2), 186-222. doi:10.1007/s11065-016-9316-2

Garcia-Arencibia, M., Molina-Holgado, E., & Molina-Holgado, F. (2018). Effect of endocannabinoid signalling on cell fate: life, death, differentiation and proliferation of brain cells. *British Journal of Pharmacology*. doi:10.1111/bph.14369

Gasnier, L. J. (Writer). (1936). Reefer Madness. In G. A. Hirliman (Producer).

Geffen, G. M., Butterworth, P., & Geffen, L. G. (1994). Test-retest reliability of a new form of the Auditory Verbal Learning Test (AVLT). *Archives of Clinical Neuropsychology, 9*, 303-316.

Gertsch, J., Pertwee, R. G., & Di Marzo, V. (2010). Phytocannabinoids beyond the Cannabis plant - do they exist? *British Journal of Pharmacology, 160*(3), 523-529. doi:10.1111/j.1476-5381.2010.00745.x

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., . . . Rapoport, J. L. (1999). Brain development during childhood and adolescence: a longitudinal MRI study. *Nature Neuroscience, 2*(10), 861-863. doi:10.1038/13158

Gogtay, N., Nugent, T. F., 3rd, Herman, D. H., Ordonez, A., Greenstein, D., Hayashi, K. M., . . . Thompson, P. M. (2006). Dynamic mapping of normal human hippocampal development. *Hippocampus, 16*(8), 664-672. doi:10.1002/hipo.20193

Gossop, M., Darke, S., Griffiths, P., Hando, J., Powis, B., Hall, W., & Strang, J. (1995). The Severity of Dependence Scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. *Addiction, 90*(5), 607-614.

Grella, C. E., Rodriguez, L., & Kim, T. (2014). Patterns of medical marijuana use among individuals sampled from medical marijuana dispensaries in los angeles. *Journal of Psychoactive Drugs, 46*(4), 267-275. doi:10.1080/02791072.2014.944960

Gruber, S. A., Dahlgren, M. K., Sagar, K. A., Gonenc, A., & Killgore, W. D. (2012). Age of onset of marijuana use impacts inhibitory processing. *Neuroscience Letters, 511*(2), 89-94. doi:10.1016/j.neulet.2012.01.039

Gruber, S. A., Dahlgren, M. K., Sagar, K. A., Gonenc, A., & Lukas, S. E. (2014). Worth the wait: effects of age of onset of marijuana use on white matter and impulsivity. *Psychopharmacology, 231*(8), 1455-1465. doi:10.1007/s00213-013-3326-z

Gruber, S. A., Sagar, K. A., Dahlgren, M. K., Olson, D. P., Centorrino, F., & Lukas, S. E. (2012). Marijuana impacts mood in bipolar disorder: a pilot study. *Mental Health and Substance Use, 5*(3), 228-239. doi:10.1080/17523281.2012.659751

Gruber, S. A., Sagar, K. A., Dahlgren, M. K., Racine, M., & Lukas, S. E. (2012). Age of onset of marijuana use and executive function. *Psychology of Addictive Behaviors, 26*(3), 496-506. doi:10.1037/a0026269

Gruber, S. A., Sagar, K. A., Dahlgren, M. K., Racine, M. T., Smith, R. T., & Lukas, S. E. (2016). Splendor in the Grass? A Pilot Study Assessing the Impact of Medical Marijuana on Executive Function. *Frontiers in Pharmacology, 7*, 355. doi:10.3389/fphar.2016.00355

Gruber, S. A., Silveri, M. M., Dahlgren, M. K., & Yurgelun-Todd, D. (2011). Why so impulsive? White matter alterations are associated with impulsivity in chronic marijuana smokers. *Experimental and Clinical Psychopharmacology, 19*(3), 231-242. doi:10.1037/a0023034

Guy, S. M., Smith, G. M., & Bentler, P. M. (1994). Consequences of adolescent drug use and personality factors on adults drug use. *Journal of Drug Education, 24*(2), 109-132.

Han, B. H., & Palamar, J. J. (2020). Trends in Cannabis Use Among Older Adults in the United States, 2015-2018. *JAMA Internal Medicine*. doi:10.1001/jamainternmed.2019.7517

Han, B. H., Sherman, S., Mauro, P. M., Martins, S. S., Rotenberg, J., & Palamar, J. J. (2017). Demographic trends among older cannabis users in the United States, 2006-13. *Addiction, 112*(3), 516-525. doi:10.1111/add.13670

Hanson, K. L., Thayer, R. E., & Tapert, S. F. (2014). Adolescent marijuana users have elevated risk-taking on the balloon analog risk task. *Journal of Psychopharmacology, 28*(11), 1080-1087. doi:10.1177/0269881114550352

Harding, I. H., Solowij, N., Harrison, B. J., Takagi, M., Lorenzetti, V., Lubman, D. I., . . . Yucel, M. (2012). Functional connectivity in brain networks underlying cognitive control in chronic cannabis users. *Neuropsychopharmacology, 37*(8), 1923-1933. doi:10.1038/npp.2012.39

Hart, C. L., Ilan, A. B., Gevins, A., Gunderson, E. W., Role, K., Colley, J., & Foltin, R. W. (2010). Neurophysiological and cognitive effects of smoked marijuana in frequent users. *Pharmacology Biochemistry and Behavior, 96*(3), 333-341. doi:10.1016/j.pbb.2010.06.003

Hart, C. L., van Gorp, W., Haney, M., Foltin, R. W., & Fischman, M. W. (2001). Effects of acute smoked marijuana on complex cognitive performance. *Neuropsychopharmacology, 25*(5), 757-765. doi:10.1016/S0893-133X(01)00273-1

Hasin, D. S., Saha, T. D., Kerridge, B. T., Goldstein, R. B., Chou, S. P., Zhang, H., . . . Grant, B. F. (2015). Prevalence of Marijuana Use Disorders in the United States Between 2001-2002 and 2012-2013. *JAMA Psychiatry, 72*(12), 1235-1242. doi:10.1001/jamapsychiatry.2015.1858

Haug, N. A., Padula, C. B., Sottile, J. E., Vandrey, R., Heinz, A. J., & Bonn-Miller, M. O. (2017). Cannabis use patterns and motives: A comparison of younger, middle-aged, and older medical cannabis dispensary patients. *Addictive Behaviors, 72*, 14-20. doi:10.1016/j.addbeh.2017.03.006

Hazekamp, A., & Fischedick, J. T. (2012). Cannabis - from cultivar to chemovar. *Drug Testing and Analysis, 4*(7-8), 660-667. doi:10.1002/dta.407

Heaton, R. K., & PAR Staff. Wisconsin Card Sorting Test: Computer Version 4.

Hemp Farming Act, H.R.5485 C.F.R., (2018).

Hermann, D., Sartorius, A., Welzel, H., Walter, S., Skopp, G., Ende, G., & Mann, K. (2007). Dorsolateral prefrontal cortex N-acetylaspartate/total creatine (NAA/tCr) loss in male recreational cannabis users. *Biological Psychiatry, 61*(11), 1281-1289. doi:10.1016/j.biopsych.2006.08.027

Hill, M. N., & McEwen, B. S. (2010). Involvement of the endocannabinoid system in the neurobehavioural effects of stress and glucocorticoids. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 34*(5), 791-797. doi:10.1016/j.pnpbp.2009.11.001

Houston, S. M., Herting, M. M., & Sowell, E. R. (2014). The neurobiology of childhood structural brain development: conception through adulthood. *Current Topics in Behavioral Neurosciences, 16*, 3-17. doi:10.1007/7854_2013_265

Hudock, C. (2019). U.S. Medical Cannabis Patients. Retrieved from https://newfrontierdata.com/marijuana-insights/u-s-medical-cannabis-patients/

Hurd, Y. L., Spriggs, S., Alishayev, J., Winkel, G., Gurgov, K., Kudrich, C., . . . Salsitz, E. (2019). Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals With Heroin Use Disorder: A Double-Blind Randomized Placebo-Controlled Trial. *American Journal of Psychiatry*, appiajp201918101191. doi:10.1176/appi.ajp.2019.18101191

Hurd, Y. L., Yoon, M., Manini, A. F., Hernandez, S., Olmedo, R., Ostman, M., & Jutras-Aswad, D. (2015). Early Phase in the Development of Cannabidiol as a Treatment for Addiction: Opioid Relapse Takes Initial Center Stage. *Neurotherapeutics, 12*(4), 807-815. doi:10.1007/s13311-015-0373-7

Infante, M. A., Nguyen-Louie, T. T., Worley, M., Courtney, K. E., Coronado, C., & Jacobus, J. (2019). Neuropsychological Trajectories Associated with Adolescent Alcohol and Cannabis Use: A Prospective 14-Year Study. *Journal of the International Neuropsychological Society*, 1-12. doi:10.1017/S1355617719001395

Iseger, T. A., & Bossong, M. G. (2015). A systematic review of the antipsychotic properties of cannabidiol in humans. *Schizophrenia Research, 162*(1-3), 153-161. doi:10.1016/j.schres.2015.01.033

Izzo, A. A., Borrelli, F., Capasso, R., Di Marzo, V., & Mechoulam, R. (2009). Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends in Pharmacological Sciences, 30*(10), 515-527. doi:10.1016/j.tips.2009.07.006

Jacobus, J., Bava, S., Cohen-Zion, M., Mahmood, O., & Tapert, S. F. (2009). Functional consequences of marijuana use in adolescents. *Pharmacology Biochemistry and Behavior, 92*(4), 559-565. doi:10.1016/j.pbb.2009.04.001

Jacobus, J., Squeglia, L. M., Infante, M. A., Castro, N., Brumback, T., Meruelo, A. D., & Tapert, S. F. (2015). Neuropsychological performance in adolescent marijuana users with co-occurring alcohol use: A three-year longitudinal study. *Neuropsychology, 29*(6), 829-843. doi:10.1037/neu0000203

Jacobus, J., & Tapert, S. F. (2014). Effects of cannabis on the adolescent brain. *Current Pharmaceutical Design, 20*(13), 2186-2193.

Jernigan, T. L., & Gamst, A. C. (2005). Changes in volume with age--consistency and interpretation of observed effects. *Neurobiology of Aging, 26*(9), 1271-1274; discussion 1275-1278. doi:10.1016/j.neurobiolaging.2005.05.016

Jonaitis, E. M., Koscik, R. L., Clark, L. R., Ma, Y., Betthauser, T. J., Berman, S. E., . . . Johnson, S. C. (2019). Measuring longitudinal cognition: Individual tests versus composites. *Alzheimer's & Dementia, 11*, 74-84. doi:10.1016/j.dadm.2018.11.006

Justinova, Z., Goldberg, S. R., Heishman, S. J., & Tanda, G. (2005). Self-administration of cannabinoids by experimental animals and human marijuana smokers. *Pharmacology Biochemistry and Behavior, 81*(2), 285-299. doi:10.1016/j.pbb.2005.01.026

Katona, I., & Freund, T. F. (2012). Multiple functions of endocannabinoid signaling in the brain. *Annual Review of Neuroscience, 35*, 529-558. doi:10.1146/annurev-neuro-062111-150420

Kempel, P., Lampe, K., Parnefjord, R., Hennig, J., & Kunert, H. J. (2003). Auditory-evoked potentials and selective attention: different ways of information processing in cannabis users and controls. *Neuropsychobiology, 48*(2), 95-101. doi:10.1159/000072884

Kowal, M. A., Hazekamp, A., Colzato, L. S., van Steenbergen, H., van der Wee, N. J., Durieux, J., . . . Hommel, B. (2015). Cannabis and creativity: highly potent cannabis impairs divergent thinking in regular cannabis users. *Psychopharmacology, 232*(6), 1123-1134. doi:10.1007/s00213-014-3749-1

Kuhathasan, N., Dufort, A., MacKillop, J., Gottschalk, R., Minuzzi, L., & Frey, B. N. (2019). The use of cannabinoids for sleep: A critical review on clinical trials. *Experimental and Clinical Psychopharmacology, 27*(4), 383-401. doi:10.1037/pha0000285

Large, M., & Nielssen, O. (2017). Daily use of high-potency cannabis is associated with an increased risk of admission and more intervention after first-episode psychosis. *Evidence-Based Mental Health, 20*(2), 58. doi:10.1136/eb-2017-102630

Laspada, N., Delker, E., Blanco, E., Encina, P., Caballero, G., Delva, J., . . . Gahagan, S. (2019). Marijuana use associated with worse verbal learning and delayed recall in a sample of young adults. *Revista Medica de Chile, 147*(2), 206-211. doi:10.4067/s0034-98872019000200206

Lebel, C., & Deoni, S. (2018). The development of brain white matter microstructure. *NeuroImage, 182*, 207-218. doi:10.1016/j.neuroimage.2017.12.097

Legleye, S., Kraus, L., Piontek, D., Phan, O., & Jouanne, C. (2012). Validation of the Cannabis Abuse Screening Test in a sample of cannabis inpatients. *European Addiction Research, 18*(4), 193-200. doi:10.1159/000336553

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological Assessment (5th ed.)*. New York, NY: Oxford University Press.

Lin, L. A., Ilgen, M. A., Jannausch, M., & Bohnert, K. M. (2016). Comparing adults who use cannabis medically with those who use recreationally: Results from a national sample. *Addictive Behaviors, 61*, 99-103. doi:10.1016/j.addbeh.2016.05.015

Lisdahl, K. M., Gilbart, E. R., Wright, N. E., & Shollenbarger, S. (2013). Dare to delay? The impacts of adolescent alcohol and marijuana use onset on cognition, brain structure, and function. *Frontiers in Psychiatry, 4*, 53. doi:10.3389/fpsyt.2013.00053

Lisdahl, K. M., Wright, N. E., Kirchner-Medina, C., Maple, K. E., & Shollenbarger, S. (2014). Considering Cannabis: The Effects of Regular Cannabis Use on Neurocognition in Adolescents and Young Adults. *Current Addiction Reports, 1*(2), 144-156. doi:10.1007/s40429-014-0019-6

Lloyd, S. L., & Striley, C. W. (2018). Marijuana Use Among Adults 50 Years or Older in the 21st Century. *Gerontology & Geriatric Medicine, 4*, 1-14.

Loflin, M., Babson, K., Browne, K., & Bonn-Miller, M. (2018). Assessment of the validity of the CUDIT-R in a subpopulation of cannabis users. *American Journal of Drug and Alcohol Abuse, 44*(1), 19-23. doi:10.1080/00952990.2017.1376677

Lovell, M. E., Akhurst, J., Padgett, C., Garry, M. I., & Matthews, A. (2019). Cognitive outcomes associated with long-term, regular, recreational cannabis use in adults: A meta-analysis. *Experimental and Clinical Psychopharmacology*. doi:10.1037/pha0000326

Lujan, M. A., Castro-Zavala, A., Alegre-Zurano, L., & Valverde, O. (2018). Repeated Cannabidiol treatment reduces cocaine intake and modulates neural proliferation and CB1R expression in the mouse hippocampus. *Neuropharmacology, 143*, 163-175. doi:10.1016/j.neuropharm.2018.09.043

Maccarrone, M., Bab, I., Biro, T., Cabral, G. A., Dey, S. K., Di Marzo, V., . . . Zimmer, A. (2015). Endocannabinoid signaling at the periphery: 50 years after THC. *Trends in Pharmacological Sciences, 36*(5), 277-296. doi:10.1016/j.tips.2015.02.008

MacLeod, C. M. (1991). Half a century of research on the Stroop effect: an integrative review. *Psychological Bulletin, 109*(2), 163-203. doi:10.1037/0033-2909.109.2.163

Majdan, A., Sziklas, V., & Jones-Gotman, M. (1996). Performance of healthy subjects and patients with resection from the anterior temporal lobe on matched tests of verbal and visuoperceptual learning. *Journal of Clinical and Experimental Neuropsychology, 18*, 416-430.

Masataka, N. (2019). Anxiolytic Effects of Repeated Cannabidiol Treatment in Teenagers With Social Anxiety Disorders. *Frontiers in Psychology, 10*, 2466. doi:10.3389/fpsyg.2019.02466

Mashhoon, Y., Sagar, K. A., & Gruber, S. A. (2019). Cannabis Use and Consequences. *Pediatric Clinics of North America, 66*(6), 1075-1086. doi:10.1016/j.pcl.2019.08.004

Medina, K. L., Hanson, K. L., Schweinsburg, A. D., Cohen-Zion, M., Nagel, B. J., & Tapert, S. F. (2007). Neuropsychological functioning in adolescent marijuana users: subtle deficits detectable after a month of abstinence. *Journal of the International Neuropsychological Society, 13*(5), 807-820. doi:10.1017/S1355617707071032

Minakawa, E. N., Wada, K., & Nagai, Y. (2019). Sleep Disturbance as a Potential Modifiable Risk Factor for Alzheimer's Disease. *International Journal of Molecular Sciences, 20*(4), pii: E803. doi:doi: 10.3390/ijms20040803

Morgan, C. J., & Curran, H. V. (2008). Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis. *British Journal of Psychiatry, 192*(4), 306-307. doi:10.1192/bjp.bp.107.046649

Morgan, C. J., Das, R. K., Joye, A., Curran, H. V., & Kamboj, S. K. (2013). Cannabidiol reduces cigarette consumption in tobacco smokers: preliminary findings. *Addictive Behaviors, 38*(9), 2433-2436. doi:10.1016/j.addbeh.2013.03.011

Morgan, C. J., Freeman, T. P., Schafer, G. L., & Curran, H. V. (2010). Cannabidiol attenuates the appetitive effects of Delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis. *Neuropsychopharmacology, 35*(9), 1879-1885. doi:10.1038/npp.2010.58

Morgan, C. J., Gardener, C., Schafer, G., Swan, S., Demarchi, C., Freeman, T. P., . . . Curran, H. V. (2012). Sub-chronic impact of cannabinoids in street cannabis on cognition, psychotic-like symptoms and psychological well-being. *Psychological Medicine, 42*(2), 391-400. doi:10.1017/S0033291711001322

Morgan, C. J., Schafer, G., Freeman, T. P., & Curran, H. V. (2010). Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study: naturalistic study [corrected]. *British Journal of Psychiatry, 197*(4), 285-290. doi:10.1192/bjp.bp.110.077503

Moriarty, O., McGuire, B. E., & Finn, D. P. (2011). The effect of pain on cognitive function: a review of clinical and preclinical research. *Progress in Neurobiology, 93*(3), 385-404. doi:10.1016/j.pneurobio.2011.01.002

NASEM. (2017). *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC.

National Academies of Sciences, E., and Medicine,. (2017). *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC.

National Institute on Drug Abuse. (2019). Monitoring the Future Survey: High School and Youth Trends. Retrieved from https://www.drugabuse.gov/publications/drugfacts/monitoring-future-survey-high-school-youth-trends

Nunberg, H., Kilmer, B., Pacula, R. L., & Burgdorf, J. (2011). An Analysis of Applicants Presenting to a Medical Marijuana Specialty Practice in California. *Journal of Drug Policy Analysis, 4*(1). doi:10.2202/1941-2851.1017

Olla, P., Rykulski, N., Hurtubise, J. L., Bartol, S., Foote, R., Cutler, L., . . . Erdodi, L. A. (2019). Short-term effects of cannabis consumption on cognitive performance in medical cannabis patients. *Applied Neuropsychology. Adult.*, 1-11. doi:10.1080/23279095.2019.1681424

Pamplona, F. A., da Silva, L. R., & Coan, A. C. (2018). Potential Clinical Benefits of CBD-Rich Cannabis Extracts Over Purified CBD in Treatment-Resistant Epilepsy: Observational Data Meta-analysis. *Frontiers in Neurology, 9*, 759. doi:10.3389/fneur.2018.00759

Park, J. Y., & Wu, L. T. (2017). Prevalence, reasons, perceived effects, and correlates of medical marijuana use: A review. *Drug and Alcohol Dependence, 177*, 1-13. doi:10.1016/j.drugalcdep.2017.03.009

Parsons, L. H., & Hurd, Y. L. (2015). Endocannabinoid signalling in reward and addiction. *Nature Reviews: Neuroscience, 16*(10), 579-594. doi:10.1038/nrn4004

Pawasarat, I. M., Schultz, E. M., Frisby, J. C., Mehta, S., Angelo, M. A., Hardy, S. S., & Kim, T. W. B. (2020). The Efficacy of Medical Marijuana in the Treatment of Cancer-Related Pain. *Journal of Palliative Medicine*. doi:10.1089/jpm.2019.0374

Pellati, F., Borgonetti, V., Brighenti, V., Biagi, M., Benvenuti, S., & Corsi, L. (2018). Cannabis sativa L. and Nonpsychoactive Cannabinoids: Their Chemistry and Role against Oxidative Stress, Inflammation, and Cancer. *BioMed Research International, 2018*, 1691428. doi:10.1155/2018/1691428

Piomelli, D., & Russo, E. B. (2016). The Cannabis sativa Versus Cannabis indica Debate: An Interview with Ethan Russo, MD. *Cannabis and Cannabinoid Research, 1*(1), 44-46. doi:10.1089/can.2015.29003.ebr

Piper, B. J., DeKeuster, R. M., Beals, M. L., Cobb, C. M., Burchman, C. A., Perkinson, L., . . . Abess, A. T. (2017). Substitution of medical cannabis for pharmaceutical agents for pain, anxiety, and sleep. *Journal of Psychopharmacology, 31*(5), 569-575. doi:10.1177/0269881117699616

Piyanova, A., Lomazzo, E., Bindila, L., Lerner, R., Albayram, O., Ruhl, T., . . . Bilkei-Gorzo, A. (2015). Age-related changes in the endocannabinoid system in the mouse hippocampus. *Mechanisms of Ageing and Development, 150*, 55-64. doi:10.1016/j.mad.2015.08.005

Poli, P., Crestani, F., Salvadori, C., Valenti, I., & Sannino, C. (2018). Medical Cannabis in Patients with Chronic Pain: Effect on Pain Relief, Pain Disability, and Psychological aspects. A Prospective Non randomized Single Arm Clinical Trial. *Clinica Terapeutica, 169*(3), e102-e107. doi:10.7417/T.2018.2062

Pollock, V., Cho, D. W., Reker, D., & Volavka, J. (1979). Profile of mood states: the factors and their physiological correlates. *Journal of Nervous and Mental Disease, 167*, 612-614.

Poulton, A., & Hester, R. (2019). Transition to substance use disorders: impulsivity for reward and learning from reward. *Social Cognitive and Affective Neuroscience*. doi:10.1093/scan/nsz077

Power, B. D., Dragovic, M., Badcock, J. C., Morgan, V. A., Castle, D., Jablensky, A., & Stefanis, N. C. (2015). No additive effect of cannabis on cognition in

schizophrenia. *Schizophrenia Research, 168*(1-2), 245-251. doi:10.1016/j.schres.2015.06.026

Raber, J. C., Elzinga, S., & Kaplan, C. (2015). Understanding dabs: contamination concerns of cannabis concentrates and cannabinoid transfer during the act of dabbing. *Journal of Toxicological Sciences, 40*(6), 797-803. doi:10.2131/jts.40.797

Rabin, R. A., Barr, M. S., Goodman, M. S., Herman, Y., Zakzanis, K. K., Kish, S. J., . . . George, T. P. (2017). Effects of Extended Cannabis Abstinence on Cognitive Outcomes in Cannabis Dependent Patients with Schizophrenia vs Non-Psychiatric Controls. *Neuropsychopharmacology, 42*(11), 2259-2271. doi:10.1038/npp.2017.85

Ramaekers, J. G., Kauert, G., Theunissen, E. L., Toennes, S. W., & Moeller, M. R. (2009). Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. *Journal of Psychopharmacology, 23*(3), 266-277. doi:10.1177/0269881108092393

Ramaekers, J. G., Kauert, G., van Ruitenbeek, P., Theunissen, E. L., Schneider, E., & Moeller, M. R. (2006). High-potency marijuana impairs executive function and inhibitory motor control. *Neuropsychopharmacology, 31*(10), 2296-2303. doi:10.1038/sj.npp.1301068

Rigucci, S., Marques, T. R., Di Forti, M., Taylor, H., Dell'Acqua, F., Mondelli, V., . . . Dazzan, P. (2016). Effect of high-potency cannabis on corpus callosum microstructure. *Psychological Medicine, 46*(4), 841-854. doi:10.1017/S0033291715002342

Robinson, S. M., Sobell, L. C., Sobell, M. B., & Leo, G. I. (2014a). Reliability of the Timeline Followback for cocaine, cannabis, and cigarette use. *Psychology of Addictive Behaviors, 28*(1), 154-162. doi:10.1037/a0030992

Robinson, S. M., Sobell, L. C., Sobell, M. B., & Leo, G. I. (2014b). Reliability of the Timeline Followback for cocaine, cannabis, and cigarette use. *Psychology of Addictive Behaviors, 28*(1), 154-162. doi:10.1037/a0030992

Ross, J. M., Ellingson, J. M., Rhee, S. H., Hewitt, J. K., Corley, R. P., Lessem, J. M., & Friedman, N. P. (2019). Investigating the causal effect of cannabis use on cognitive function with a quasi-experimental co-twin design. *Drug and Alcohol Dependence*, 107712. doi:10.1016/j.drugalcdep.2019.107712

Russo, E. B. (2007). History of cannabis and its preparations in saga, science, and sobriquet. *Chemistry & Biodiversity, 4*(8), 1614-1648.

Russo, E. B. (2011). Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *British Journal of Pharmacology, 163*(7), 1344-1364. doi:10.1111/j.1476-5381.2011.01238.x

Ryan-Ibarra, S., Induni, M., & Ewing, D. (2015). Prevalence of medical marijuana use in California, 2012. *Drug and Alcohol Review, 34*(2), 141-146. doi:10.1111/dar.12207

Ryberg, E., Larsson, N., Sjogren, S., Hjorth, S., Hermansson, N. O., Leonova, J., . . . Greasley, P. J. (2007). The orphan receptor GPR55 is a novel cannabinoid receptor. *British Journal of Pharmacology, 152*(7), 1092-1101. doi:10.1038/sj.bjp.0707460

Sagar, K. A., Dahlgren, M. K., Gonenc, A., Racine, M. T., Dreman, M. W., & Gruber, S. A. (2015). The impact of initiation: Early onset marijuana smokers demonstrate altered Stroop performance and brain activation. *Developmental Cognitive Neuroscience, 16*, 84-92. doi:10.1016/j.dcn.2015.03.003

Sagar, K. A., Dahlgren, M. K., Racine, M. T., Dreman, M. W., Olson, D. P., & Gruber, S. A. (2016). Joint Effects: A Pilot Investigation of the Impact of Bipolar Disorder and Marijuana Use on Cognitive Function and Mood. *PloS One, 11*(6), e0157060. doi:10.1371/journal.pone.0157060

Sagar, K. A., & Gruber, S. A. (2018a). Interactions between recreational cannabis use and cognitive function: lessons from functional magnetic resonance imaging. *Annals of the New York Academy of Sciences*. doi:10.1111/nyas.13990

Sagar, K. A., & Gruber, S. A. (2018b). Marijuana matters: reviewing the impact of marijuana on cognition, brain structure and function, & exploring policy implications and barriers to research. *International Review of Psychiatry*, 1-17. doi:10.1080/09540261.2018.1460334

Sagar, K. A., & Gruber, S. A. (2019). Interactions between recreational cannabis use and cognitive function: lessons from functional magnetic resonance imaging. *Annals of the New York Academy of Sciences, 1451*(1), 42-70. doi:10.1111/nyas.13990

Sagar, K. A., Lambros, A. M., Dahlgren, M. K., Smith, R. T., & Gruber, S. A. (2018). Made from concentrate? A national web survey assessing dab use in the United States. *Drug and Alcohol Dependence, 190*, 133-142. doi:10.1016/j.drugalcdep.2018.05.022

Schmidt, M. (2016). *Rey Auditory Verbal Learning Test* Torrance, CA: Western Psychological Services.

Schneider, M. (2008). Puberty as a highly vulnerable developmental period for the consequences of cannabis exposure. *Addiction Biology, 13*(2), 253-263. doi:10.1111/j.1369-1600.2008.00110.x

Schwartz, R. H., Gruenewald, P. J., Klitzner, M., & Fedio, P. (1989). Short-term memory impairment in cannabis-dependent adolescents. *American Journal of Diseases of Children, 143*(10), 1214-1219. doi:10.1001/archpedi.1989.02150220110030

Scott, J. C., Slomiak, S. T., Jones, J. D., Rosen, A. F. G., Moore, T. M., & Gur, R. C. (2018). Association of Cannabis With Cognitive Functioning in Adolescents and Young Adults. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2018.0335

Scullin, M. K., & Bliwise, D. L. (2015). Sleep, cognition, and normal aging: integrating a half century of multidisciplinary research. *Perspectives on Psychological Science, 10*(1), 97-137. doi:10.1177/1745691614556680

Shannon, S., Lewis, N., Lee, H., & Hughes, S. (2019). Cannabidiol in Anxiety and Sleep: A Large Case Series. *The Permanente Journal, 23*, 18-041. doi:10.7812/TPP/18-041

Shannon, S., & Opila-Lehman, J. (2015). Cannabidiol Oil for Decreasing Addictive Use of Marijuana: A Case Report. *Integrative Medicine, 14*(6), 31-35.

Shi, L., Chen, S. J., Ma, M. Y., Bao, Y. P., Han, Y., Wang, Y. M., . . . Lu, L. (2018). Sleep disturbances increase the risk of dementia: A systematic review and meta-analysis. *Sleep Medicine Reviews, 40*, 4-16. doi:10.1016/j.smrv.2017.06.010

Shinjyo, N., & Di Marzo, V. (2013). The effect of cannabichromene on adult neural stem/progenitor cells. *Neurochemistry International, 63*(5), 432-437. doi:10.1016/j.neuint.2013.08.002

Shoop, S. J. W. (2015). Should we ban the use of 'Last Observation Carried forward" analysis in epidemiological studies? *SM Journal of Public Health & Epidemiology, 1*(1), 1004.

Shover, C. L., Davis, C. S., Gordon, S. C., & Humphreys, K. (2019). Association between medical cannabis laws and opioid overdose mortality has reversed over time. *Proceedings of the National Academy of Sciences of the United States of America*. doi:10.1073/pnas.1903434116

Smart, R., Caulkins, J. P., Kilmer, B., Davenport, S., & Midgette, G. (2017). Variation in cannabis potency and prices in a newly legal market: evidence from 30 million cannabis sales in Washington state. *Addiction, 112*(12), 2167-2177. doi:10.1111/add.13886

Sneider, J. T., Gruber, S. A., Rogowska, J., Silveri, M. M., & Yurgelun-Todd, D. A. (2013). A preliminary study of functional brain activation among marijuana users during performance of a virtual water maze task. *Journal of Addiction, 2013*, 461029. doi:10.1155/2013/461029

Sobell, L. C., Sobell, M. B., Leo, G. I., & Cancilla, A. (1988). Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. *British Journal of Addiction, 83*(4), 393-402.

Solowij, N., & Battisti, R. (2008). The chronic effects of cannabis on memory in humans: a review. *Current Drug Abuse Reviews, 1*(1), 81-98.

Solowij, N., Jones, K. A., Rozman, M. E., Davis, S. M., Ciarrochi, J., Heaven, P. C., . . . Yucel, M. (2011). Verbal learning and memory in adolescent cannabis users, alcohol users and non-users. *Psychopharmacology, 216*(1), 131-144. doi:10.1007/s00213-011-2203-x

Sowell, E. R., Thompson, P. M., Tessner, K. D., & Toga, A. W. (2001). Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: Inverse relationships during postadolescent brain maturation. *Journal of Neuroscience, 21*(22), 8819-8829.

Spielberger, C., Gorsuch, R., Lushene, P., Vagg, P., & Jacobs, A. (1983). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.

Spira, A. P., Chen-Edinboro, L. P., Wu, M. N., & Yaffe, K. (2014). Impact of sleep on the risk of cognitive decline and dementia. *Current Opinion in Psychiatry, 27*(6), 478-483. doi:10.1097/YCO.0000000000000106

Squeglia, L. M., Jacobus, J., Nguyen-Louie, T. T., & Tapert, S. F. (2014). Inhibition during early adolescence predicts alcohol and marijuana use by late adolescence. *Neuropsychology, 28*(5), 782-790. doi:10.1037/neu0000083

Stern, Y., Arenaza-Urquijo, E. M., Bartres-Faz, D., Belleville, S., Cantilon, M., Chetelat, G., . . . Conceptual Frameworks, W. (2018). Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimer's & Dementia*. doi:10.1016/j.jalz.2018.07.219

Stogner, J. M., & Miller, B. L. (2015). Assessing the Dangers of "Dabbing": Mere Marijuana or Harmful New Trend? *Pediatrics, 136*(1), 1-3. doi:10.1542/peds.2015-0454

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests (3rd ed.)*. New York, NY: Oxford University Press.

Substance Abuse and Mental Health Services Administration. (2017). *Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health* (HHS Publication No. SMA 17-5044, NSDUH Series H-52). Rockville, MD.

Substance Abuse and Mental Health Services Administration. (2019). *Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health* (HHS Publication No. PEP19-5068, NSDUH Series H-54). Rockville, MD.

Sznitman, S. R., & Room, R. (2018). Rethinking indicators of problematic cannabis use in the era of medical cannabis legalization. *Addictive Behaviors, 77*, 100-101. doi:10.1016/j.addbeh.2017.09.026

Takakuwa, K. M., Hergenrather, J. Y., Shofer, F. S., & Schears, R. M. (2020). The Impact of Medical Cannabis on Intermittent and Chronic Opioid Users with Back Pain: How Cannabis Diminished Prescription Opioid Usage. *Cannabis and Cannabinoid Research*. doi:10.1089/can.2019.0039

Tanaka, C., Matsui, M., Uematsu, A., Noguchi, K., & Miyawaki, T. (2012). Developmental trajectories of the fronto-temporal lobes from infancy to early adulthood in healthy individuals. *Developmental Neuroscience, 34*(6), 477-487. doi:10.1159/000345152

Troutt, W. D., & DiDonato, M. D. (2015). Medical Cannabis in Arizona: Patient Characteristics, Perceptions, and Impressions of Medical Cannabis Legalization. *Journal of Psychoactive Drugs, 47*(4), 259-266. doi:10.1080/02791072.2015.1074766

Turna, J., Patterson, B., & Van Ameringen, M. (2017). Is cannabis treatment for anxiety, mood, and related disorders ready for prime time? *Depression and Anxiety, 34*(11), 1006-1017. doi:10.1002/da.22664

U.S. Department of Justice. (2019). Controlled Substances Schedules. Retrieved from https://www.deadiversion.usdoj.gov/schedules/

Uematsu, A., Matsui, M., Tanaka, C., Takahashi, T., Noguchi, K., Suzuki, M., & Nishijo, H. (2012). Developmental trajectories of amygdala and hippocampus from infancy to early adulthood in healthy individuals. *PloS One, 7*(10), e46970. doi:10.1371/journal.pone.0046970

Valdeolivas, S., Navarrete, C., Cantarero, I., Bellido, M. L., Munoz, E., & Sagredo, O. (2015). Neuroprotective properties of cannabigerol in Huntington's disease: studies in R6/2 mice and 3-nitropropionate-lesioned mice. *Neurotherapeutics, 12*(1), 185-199. doi:10.1007/s13311-014-0304-z

van der Pol, P., Liebregts, N., Brunt, T., van Amsterdam, J., de Graaf, R., Korf, D. J., . . . van Laar, M. (2014). Cross-sectional and prospective relation of cannabis potency, dosing and smoking behaviour with cannabis dependence: an ecological study. *Addiction, 109*(7), 1101-1109. doi:10.1111/add.12508

Vangsness, L., Bry, B. H., & LaBouvie, E. W. (2005). Impulsivity, negative expectancies, and marijuana use: a test of the acquired preparedness model. *Addictive Behaviors, 30*(5), 1071-1076. doi:10.1016/j.addbeh.2004.11.003

Vytal, K. E., Cornwell, B. R., Letkiewicz, A. M., Arkin, N. E., & Grillon, C. (2013). The complex interaction between anxiety and cognition: insight from spatial and verbal working memory. *Frontiers in Human Neuroscience, 7*, 93. doi:10.3389/fnhum.2013.00093

Wachtel, S. R., ElSohly, M. A., Ross, S. A., Ambre, J., & de Wit, H. (2002). Comparison of the subjective effects of Delta(9)-tetrahydrocannabinol and marijuana in humans. *Psychopharmacology, 161*(4), 331-339. doi:10.1007/s00213-002-1033-2

Wagner, S., Helmreich, I., Dahmen, N., Lieb, K., & Tadic, A. (2011). Reliability of Three Alternate Forms of the Trail Making Tests A and B. *Archives of Clinical Neuropsychology, 26*(4), 314-321. doi:10.1093/arclin/acr024

Walsh, D., Nelson, K. A., & Mahmoud, F. A. (2003). Established and potential therapeutic applications of cannabinoids in oncology. *Supportive Care in Cancer, 11*(3), 137-143. doi:10.1007/s00520-002-0387-7

Walsh, Z., Callaway, R., Belle-Isle, L., Capler, R., Kay, R., Lucas, P., & Holtzman, S. (2013). Cannabis for therapeutic purposes: patient characteristics, access, and reasons for use. *International Journal of Drug Policy, 24*(6), 511-516. doi:10.1016/j.drugpo.2013.08.010

Ware, J. E., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Medical Care, 30*, 473-483.

Wechsler, D. (1987). *Manual for the Wechsler Memory Scale-Revised*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: The Psychological Corporation.

Weinstein, G., & Sznitman, S. R. (2020). The implications of late-life cannabis use on brain health: A mapping review and implications for future research. *Ageing Research Reviews*, 101041. doi:10.1016/j.arr.2020.101041

Whiting, P. F., Wolff, R. F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A. V., . . . Kleijnen, J. (2015). Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA, 313*(24), 2456-2473. doi:10.1001/jama.2015.6358

WHO Assist Working Group. (2002). The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. *Addiction, 97*(9), 1183-1194.

Williams, A. R., Santaella-Tenorio, J., Mauro, C. M., Levin, F. R., & Martins, S. S. (2017). Loose regulation of medical marijuana programs associated with higher rates of adult marijuana use but not cannabis use disorder. *Addiction, 112*(11), 1985-1991. doi:10.1111/add.13904

Winward, J. L., Hanson, K. L., Tapert, S. F., & Brown, S. A. (2014). Heavy alcohol use, marijuana use, and concomitant use by adolescents are associated with unique and shared cognitive decrements. *Journal of the International Neuropsychological Society, 20*(8), 784-795. doi:10.1017/S1355617714000666

Yucel, M., Bora, E., Lubman, D. I., Solowij, N., Brewer, W. J., Cotton, S. M., . . . Pantelis, C. (2012). The impact of cannabis use on cognitive functioning in patients with schizophrenia: a meta-analysis of existing findings and new data in a first-episode sample. *Schizophrenia Bulletin, 38*(2), 316-330. doi:10.1093/schbul/sbq079

Yucel, M., Lorenzetti, V., Suo, C., Zalesky, A., Fornito, A., Takagi, M. J., . . . Solowij, N. (2016). Hippocampal harms, protection and recovery following regular cannabis use. *Translational Psychiatry, 6*, e710. doi:10.1038/tp.2015.201

Zeiger, J. S., Haberstick, B. C., Corley, R. P., Ehringer, M. A., Crowley, T. J., Hewitt, J. K., . . . Rhee, S. H. (2010). Subjective effects to marijuana associated with marijuana use in community and clinical subjects. *Drug and Alcohol Dependence, 109*(1-3), 161-166. doi:10.1016/j.drugalcdep.2009.12.026

Zuardi, A. W. (2008). Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Revista Brasileira de Psiquiatria, 30*(3), 271-280.

Zuardi, A. W., Cosme, R. A., Graeff, F. G., & Guimaraes, F. S. (1993). Effects of ipsapirone and cannabidiol on human experimental anxiety. *Journal of Psychopharmacology, 7*(1 Suppl), 82-88. doi:10.1177/026988119300700112

Zuardi, A. W., Shirakawa, I., Finkelfarb, E., & Karniol, I. G. (1982). Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology, 76*(3), 245-250.

CURRICULUM VITAE