SUBSTANCE USE AND THE PSYCHOSTIMULANT RESPONSE IN ADULT ADHD

SUBSTANCE USE AND THE POTENTIAL IMPACT ON THE PSYCHOSTIMULANT RESPONSE IN ADULT ADHD

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Master of Science

McMaster University MASTER OF SCIENCE (2024) Hamilton, Ontario (Neuroscience)

TITLE: Substance Use and the Potential Impact on the Psychostimulant Response in Adult ADHD

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NUMBER OF PAGES: xiv, 65

LAY ABSTRACT

Attention deficit and hyperactivity disorder (ADHD) has three main symptoms including inattention, hyperactivity and impulsivity. Substance use disorder is commonly associated with ADHD. The ADHD population is at a 3 times greater risk for developing a cannabis use disorder compared to the general population. Psychostimulants are used to treat ADHD but there is currently no data looking at how cannabis use may affect the treatment response. This study aims to compare the response to ADHD treatment in adults with ADHD between cannabis and non-cannabis users. The study recruited forty participants who filled out a study questionnaire over 3 study visits for a total study length of 8 weeks. Study findings did not report a difference between cannabis and non-cannabis users in their ADHD symptoms, clinical severity and clinical improvement throughout the study. Further studies should continue investigating populations with co-occurring ADHD and cannabis use in relation to treatment response.

ABSTRACT

Background: Attention deficit and hyperactivity disorder (ADHD) is a neurodevelopmental disorder presenting with three core symptoms: inattention, hyperactivity and impulsivity. The ADHD population is 3 times more susceptible to developing a cannabis use disorder compared to the general population. Psychostimulants are the first-line treatment for ADHD. There is currently no literature on the impact of cannabis on the psychostimulant response.

Objectives: To compare the response to psychostimulant treatment in adults with ADHD between cannabis and non-cannabis users

Methods: Sixty-five participants with a primary diagnosis of ADHD were recruited from the MacAnxiety Research Clinic and St. Josephs Psychiatric Community Clinic. Participants were assigned to the cannabis, or non-cannabis group based on their cannabis status at baseline. The study was 8 weeks long and included 3 visits. The first visit of the study was called "Baseline" and would occur prior to the start of stimulant medication. Participants would be seen at two additional time points 4- and 8-weeks post-baseline visit at which point they would be taking their stimulant medication. At each study visit all participants would fill out the self-reported assessment battery conducted through REDCap. The study psychiatrist would assign a CGI-S score at the end of each visit and a CGI-I score at the end of week 4 and week 8.

Results: Cannabis and non-cannabis users did not differ statistically in their BAARS-IV, CGI-S and CGI-I scores over the study. Secondary outcomes investigating CUD, stimulant type, stimulant dosage, comorbidities and responder rate did not produce significant outcomes.

Conclusions: There was no difference in the treatment response to psychostimulants in adults with ADHD between cannabis and non-cannabis users. Further studies should continue exploring treatment response in populations with co-occurring adult ADHD and cannabis use.

Keywords: Cannabis; Substance use disorder; ADHD; Psychostimulants; Treatment

Dedicated to Guadalupe and Luis Francisco Romero

Acknowledgments

I would like to thank my supervisor Dr. Michael Van Ameringen for giving me the opportunity two years ago to join the MacAnxiety team, my master's would not be possible without my supervisor and the MacAnxiety team supporting me.

I would like to express my gratitude to Dr. Barbara Santos for being an amazing co-worker and friend throughout the past two years. Your constant support and reassurance helped me navigate through stressful times.

I would like to thank the program administrator Sandra for all her help and quick responses throughout this program.

I would like to thank my committee members for their ongoing academic support.

Most of all I would like to thank my family for their unconditional love and support throughout this time. This has been the hardest academic venture so far and I can't express how grateful I am to my wonderful mom who has always been my biggest supporter and has been there for me whenever I needed a second opinion, words of encouragement or a hug. To my loving dad who didn't let me quit and kept encouraging me to push through because he knew I would succeed. To my brother Erick, who has always supported me.

To my loving boyfriend Graeme, I appreciate all the late-night calls where I practiced my presentations to you and spent hours explaining my thesis to you, I am forever grateful for your support through my ongoing education and understanding when I had to cancel plans to work on my thesis.

I would like to thank my cohort friends that I made through the neuroscience graduate program, without you guys my master's would not have been as enjoyable, I'm happy I found community and lifelong friends during this time. All the late-night drinks, study sessions and laughs I will look back on fondly.

Finally, I would like to thank my beloved dog Rocky for always staying up late with me in my room to work on my thesis.

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LIST OF ABBREVIATIONS

AARS	Adult ADHD Rating Scale
ADHD	Attention Deficit and Hyperactivity Disorder
AEA	Anandamide
AG-2	2-Arachidonoylglycerol
AMP	Amphetamine
B-MACQ	Brief Marijuana Consequence Questionnaire
BAARS-IV	Berkley Adult ADHD Rating Scale
CB1R	Cannabinoid 1 Receptor
CB2R	Cannabinoid 2 Receptor
CBD	Cannabidiol
CBT	Cognitive Behavioral Therapy
CGI-I	Clinician Global Impression- Improvement
CGI-S	Clinician Global Impression- Severity
CUD	Cannabis Use Disorder
CUDIT-R	Cannabis Use Disorder Identification Test- Revised
DAT1	Dopamine Transporter 1
DRD4	Dopamine D4 Receptor Gene
DRD5	Dopamine D5 Receptor Gene
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5
GABA	Gamma-Aminobutyric Acid
GAD-7	General Anxiety Disorder-7

HIREB	Hamilton Integrated Research Ethic Board
IR	Immediate Release
MINI	Mini-International Neuropsychiatric Interview
MMQ	Marijuana Motives Questionnaire
MPH	Methylphenidate
OCD	Obsessive Compulsive Disorder
PHQ-9	Patient Health Questionnaire -9
RCT	Randomized Controlled Trial
REDCap	Research Electronic Data Capture
SCID-IV	Structured Clinical Interview for DSM- IV
SDS	Sheehan Disability Scale
SMD	Standard Mean Difference
SNAP25	Synaptosomal Associated Protein 25
SUD	Substance Use Disorder
THC	Delta-9-tetrahyrocannabinol

DECLARATION OF ACHIEVEMENT

Giovana Romero, BSc- Took over study in 2022 and was responsible for editing consent, protocol and assessment battery forms, lead in submitting amendments to ethic boards, lead in participant recruitment, lead in data analysis, lead in thesis write up and review. Responsible for the completion of the study.

Dr. Barbara Santos, MD, PhD- Study Psychiatrist at the main location (MacAnxiety Research Clinic) who provided the participants for the study through patients under her care.

Dr. Carolina Goldman Bergmann, MD, MSc- Started the study in 2021 and was responsible for the creation of the research question, study design, consent forms, protocol documents and initial participant recruitment. Study Psychiatrist at the second location (St. Josephs Psychiatry Community Clinic) that assisted in providing participants for the study through patients under her care.

Dr. Michael Van Ameringen, MD, FRCPC- Supervisor that was involved in creating the research question and study design, reviewing edits from protocol, consent, assessment battery and thesis write up documents.

In addition to the contributions mentioned above, the results from this study were presented at three conferences from December 2023- May 2024. References are mentioned below.

Romero, G., Santos, B., Goldman Bergmann, C., Van Ameringen, M. (2023, December). *Cannabis Use and Potential Impact on Psychostimulant Response in Adult ADHD* [Poster Presentation]. McMaster Graduate Symposium, Hamilton, ON, Canada.

Romero, G., Santos, B., Goldman Bergmann, C., Van Ameringen, M. (2024, April). *Cannabis Use and Potential Impact on Psychostimulant Response in Adult ADHD* [Data Blitz Talk]. McMaster PNB Research Day, Hamilton, ON, Canada.

Romero, G., Santos, B., Goldman Bergmann, C., Van Ameringen, M. (2024, May). *Cannabis Use and Potential Impact on Psychostimulant Response in Adult ADHD* [Poster Presentation]. Mohawk College Research and Psychiatry Day, Hamilton, ON, Canada.

1. Introduction

1.1 What is ADHD?

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that presents as three core symptom clusters: inattention, hyperactivity, and impulsivity. There are three subtypes of ADHD consisting of predominantly hyperactive/impulsive, predominately inattentive, and a combined subtype (Sharma & Couture, 2014). ADHD is a common childhood disorder but can often persist into adulthood and contribute to impairments in many facets of life. Interestingly a meta-analysis reported that ADHD has been shown to persist in around 15% of individuals who were diagnosed as children (Faraone et al., 2006), this finding is supported by a recent population based study reporting a similar prevalence of persistent ADHD from childhood into adulthood at around 14% (Barbaresi et al., 2018). A recent meta-analysis reports a prevalence of persistent adult ADHD (ADHD that continued from childhood) globally at 2.58% and symptomatic adult ADHD (ADHD first diagnosed as an adult but had childhood symptoms) globally at 6.76% (Song et al., 2021). These prevalence rates are consistent with other reported current ADHD prevalence rates of 4.4% (Kessler et al., 2006), 3.4% (Fayyad et al., 2007) and 2.5% (Simon et al., 2009). Out of the three subtypes of ADHD, 56% of adults make up the inattentive subtype, 22% make up the hyperactive/impulsive subtype and the remaining 22% make up the combined subtype (G. J. DuPaul et al., 2001) and in all subtypes the ratio of males to females is slightly higher in adults, with reported sex ratios of 2.1:1 in the inattentive subtype, 1.69:1 in the hyperactive/impulsive subtype and 2.73:1 in the combined subtype (Ramtekkar et al., 2010; Robison & Faraone, 2008). The etiology of ADHD is still unknown but most literature suggests a dysregulation of dopamine and norepinephrine signaling in the prefrontal cortex, cerebellum, and caudate nucleus which have functions in attention, decision-making, and emotion regulation (Sharma & Couture, 2014). Literature is divided on whether the dysregulation is due to a decreased or increased signaling of dopamine and norepinephrine. Neuroimaging studies have found that a location in the brain typically abundant in dopaminergic receptors called the caudate nucleus is smaller in ADHD individuals compared to non-ADHD individuals (Swanson et al., 2007). Others believe dysregulation is due to an overactive signaling of dopamine and norepinephrine due to polymorphisms and mutations (Sharma & Couture, 2014). Other theories for the etiology of ADHD include prenatal and birth factors, exposure to environmental toxins and familial heritability (Sciberras et al., 2017). Prenatal and birth risk factors for ADHD include low birth weight and maternal demographics such as age. One study reported findings that low birth weight may be a risk factor for ADHD; children born weighing less than 1500g were at a significant risk of developing ADHD (Halmøy et al., 2012). This is in contrast to the findings of another study that found no connection between birthweight and ADHD (Clements et al., 2015). Maternal age during pregnancy also seems to be a risk factor for ADHD. A recent study reported that younger maternal age (18-24 years old) may increase the risk of offspring developing ADHD (Gao et al., 2023), this finding is supported by another study reporting maternal age under 26 years old is associated with a higher risk of ADHD in offspring (Hvolgaard Mikkelsen et al., 2017). Environmental toxins such as polyfluoroalkyl a synthetic chemical have been found to be associated with an increased risk of ADHD (Hoffman et al., 2010) but data remains inconclusive with a lack of evidence in identifying which environmental toxins may play a role in ADHD etiology (Sciberras et al., 2017). Additionally there seems to be a genetic and heritability component to ADHD, etiology studies have reported heritability rates as high as 70% when

investigating through family and twin reports (Faraone & Larsson, 2019). Additionally, there has been an increasing research drive to try and pinpoint potential candidate genes implicated in ADHD etiology which reports have found implicated genes to be in the dopaminergic pathway such as Dopamine Transporter 1 (DAT1), Dopamine D4 Receptor Gene (DRD4), Dopamine D5 Receptor Gene (DRD5) and Synaptosomal Associated Protein 25 (SNAP25) (Faraone & Larsson, 2019; Kian et al., 2022). Therefore, the etiology of ADHD remains to be established. ADHD is more common in males compared to females (Ramtekkar et al., 2010) with ratios in childhood ADHD being 3:1 (Murray et al., 2019) and in adult ADHD ranging from 1:1 to 3:1(Faheem et al., 2022). Sex differences in adult ADHD is an area requiring more research as it is unclear why sex ratios attenuate from childhood into adulthood. Certain researchers believe the difference in sex ratios from childhood to adulthood could be due to females having a higher rate of ADHD persistence into adulthood compared to males but limited data is available to support this claim (Stibbe et al., 2020). Literature has mixed findings on whether impairment differs between the sexes. In relation to core ADHD symptoms in children three articles report that impairment is comparable between the sexes (Biederman et al., 2005; Graetz et al., 2005; Murray et al., 2019). Studies investigating sex differences in adult ADHD in relation to core symptoms are very limited, one article found females to have more inattention and hyperactivity symptoms compared to males (Fedele et al., 2012). Aside from core ADHD symptoms there may be differences in the prevalence of comorbidities and symptom severity between the sexes (Fedele et al., 2012). Females tend to have greater symptom severity in terms of emotional dysregulation compared to males (Robison & Faraone, 2008). Males have a higher comorbidity rate of conduct disorder and substance use disorder (SUD) compared to females. Females have a higher comorbidity rate of mood disorders and sleep-related symptoms compared to males (Anker et al., 2020; Fedele et al., 2012; Robison & Faraone, 2008).

1.2 Adult ADHD Functional Impairments and Comorbidities

Adult manifestations of ADHD are associated with poor socio-economic outcomes and complications in executive functioning tasks such as time management, multitasking, and organization (Katzman et al., 2017) which can lead to decreased success in occupational and academic domains. Young adults with ADHD are at an increased risk for drop-out and academic probation in college and university (G. DuPaul et al., 2009). Additionally, adults with ADHD struggle in the work environment starting from trouble initiating the job search , and attending less job interviews to job adherence potentially due to impairment in organizational skills (Adamou et al., 2013). Risk-taking behavior is prominent in adults with ADHD increasing the chances of interpersonal relationship problems and criminality which can result in higher divorce rates, more emergency room visits and higher rates of premature death compared to non-ADHD populations (Sharma & Couture, 2014; Zalsman & Shilton, 2016). Additionally, adults with ADHD commonly experience complications in emotional regulation such as low frustration tolerance, and emotional lability (Anker et al., 2020). The ADHD population is at a greater risk of developing a mood disorder and anxiety disorders, with studies reporting the probability being 4 times greater compared to non-ADHD populations (Choi et al., 2022; Perugi et al., 2019). Common mood disorders co-morbid with ADHD are depression and bipolar disorders. In the clinical ADHD population, the current prevalence rates of developing co-morbid depression are 25% (Fischer et al., 2007), and 18.6% in the general population (Binder et al., 2009). The prevalence of developing

comorbid bipolar disorders in the clinical ADHD population is 11-22% (Klassen et al., 2010; Skirrow et al., 2012). Anxiety-related disorders are also very common among the ADHD population with large prevalence rates in clinical population of 56% (Quenneville et al., 2022) and 37.9% in the general population (Choi et al., 2022; Mohammadi et al., 2021). Poor mood modulation in the ADHD population has been associated with an increased risk of substance use due to individuals potentially using substances to regulate mood (Wilens & Morrison, 2011). Furthermore, the prevalence of co-morbid substance use disorder and ADHD is highly prominent (Retz & Retz-Junginger, 2014; Zalsman & Shilton, 2016).

1.3 SUD and ADHD:

Substance use is known to be a common comorbidity of ADHD as having ADHD can make individuals 2-3 times more likely to develop a substance use disorder (Katzman et al., 2017; van Emmerik-van Oortmerssen et al., 2012). This comorbidity has been considerably studied with estimated prevalence rates ranging from 10-80% in clinical populations (Choi et al., 2022) and 35.95% in the general population (Chen et al., 2018). When ADHD is comorbid in substance use disorder the prevalence rates are lower with rates ranging from 21-40.9% (van de Glind et al., 2013; van Emmerik-van Oortmerssen et al., 2012). A Nigerian study reported that substance use comorbidity was greater in the hyperactive/inattentive subtype compared to other subtypes with a prevalence rate of 55.7% (Van Der Burg et al., 2019). Popular substances used when SUD is co-morbid with ADHD are alcohol, cannabis, cocaine and nicotine (Spera et al., 2020; van de Glind et al., 2013). Additionally, another study investigated patterns in modality use of substances in adult ADHD and found a prevalence of 60% lifetime and 6.9% currently using cannabis products, 40% lifetime and 2.8% currently using stimulants (ex. cocaine), 30% lifetime and 11.1% currently using alcohol, and less than 10% using benzodiazepines and opioids in both lifetime and current in their sample (Spera et al., 2020). Similarly, another article found that alcohol use and alcohol dependence were highly associated with the ADHD population (Capusan et al., 2019). It is unclear whether there is a preference for certain substances in ADHD or whether the individuals are using substances that are readily available in their communities. Most articles suggest there is no preference for specific substances in the ADHD population (Capusan et al., 2019; Clure et al., 1999; Faraone, Biederman, et al., 2007; Faraone, Wilens, et al., 2007). ADHD and SUD are thought to target similar neurotransmitters in the brain such as dopaminergic and serotonergic pathways leading researchers to believe that treating one condition could improve the other due to the bi-directional relationship (P.-J. Carpentier & Levin, 2017; Faraone, 2018). Both ADHD and SUD have abnormal regulations of dopaminergic pathways involved in reward and motivation, affecting areas of attention, and executive functions, all of which produce symptoms commonly experienced in both disorders (Van Der Burg et al., 2019). The high prevalence of SUD in the ADHD population could be for a variety of reasons that might include attempts at self-medication, the novelty/impulsivity of trying substances, social influence, familial history of SUD, and shared genetic risk (Zulauf et al., 2014).

1.4 Cannabis and ADHD:

Cannabis is a genus of plants that contain hundreds of cannabinoid components and terpenes. Terpenes in cannabis are mainly responsible for the smell and flavor while the multitude of cannabinoids contribute to different effects on the user based on the ratio found in the cannabis

consumed by the user (Haney, 2022). The two main cannabinoid components in cannabis are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Hunt et al., 2020). Just as there are exogenous cannabinoids there are also endogenous cannabinoids that are part of the endocannabinoid system. There are two main types of endogenous cannabinoids: anandamide (AEA) and 2-arachidonoylglycerol (2-AG) (Haney, 2022). The endocannabinoid system plays various roles in the brain such as contributing to the development of neural circuits, pain, immune function and motivations (Haney, 2022). Within the endocannabinoid system there are two main receptors Cannabinoid 1 Receptor (CB1R) and Cannabinoid 2 Receptor (CB2R) which exogenous and endogenous cannabinoids can bind to with varying affinities (Haney, 2022). CB1 receptors are concentrated in the brain and mediate the psychoactive effects and CB2 receptors are mainly expressed in the periphery and have functions in immunity (Haney, 2022). Endogenous cannabinoids bind to the CB1 or CB2 receptors through retrograde signaling (Henschke, 2019). The endocannabinoid system has been explored considerably for its potential therapeutic benefits, data has shown that an increase in exogenous cannabinoids can lead to neuroadaptations in the endocannabinoid system; chronic cannabis THC users could be impacting the therapeutic benefits the endocannabinoid system can provide due to neuroadaptations leading to a lower circulation of endogenous cannabinoids (Kearney-Ramos et al., 2023). Cannabis interacts with several neurotransmitters such as Gamma-Aminobutyric Acid (GABA), dopamine, and serotonin (Hunt et al., 2020). Cannabis acts to diminish GABA reuptake which can be helpful in the management of conditions such as epilepsy, but chronic cannabis use targeting GABA neurons can cause unwanted effects such as paranoia (Hunt et al., 2020). Cannabis has biphasic effects with dopamine. Dopamine has various functions including memory, and motivation. In low doses of cannabis containing THC, it can act as a partial agonist at CB1 receptors and increase the functions of dopamine but in high doses, it can act as an antagonist and reduce the functions of dopamine leading to impairment (Hunt et al., 2020). Similarly, cannabis has biphasic effects on serotonin. Serotonin has functions in arousal and feelings of anxiety, and depression. Low doses of cannabis containing THC can decrease serotonin function and high doses of THC can increase its functioning (Hunt et al., 2020). Cannabis is a widely used substance that has been commonly used for a variety of purposes such as medicinal, spiritual, and recreational reasons in countries that have legalized recreational cannabis use; the World Health Organization reports an annual prevalence of cannabis consumption at 2.5% globally (~147 million people) (World Health Organization, 2021). Since the legalization of recreational cannabis in Canada in 2018 there has been a rise in the prevalence of past 12-month cannabis use among adults over 25 years old (19% in 2018, 23% in 2023)(Government of Canada, 2022; Hall et al., 2023). The prevalence of current cannabis use is more prominent in the ADHD population (13.4%) compared to the general population (4.3%) (Brandt et al., 2018). The prevalence of lifetime cannabis use has been reported to be greater in the ADHD population compared to the general population with an odds ratio of 7.9 (Artigas et al., 2020; Dhamija et al., 2023). Popular cannabis products in Canada include joints, edibles, cannabis beverages, cannabis vapes/pens, and cannabis oils (Government of Canada, 2022). Cannabis is not a current approved treatment for ADHD and a recent review looking at cannabis and ADHD concluded that the literature does not recommend cannabis for ADHD treatment (Francisco et al., 2023). Despite these findings, it is not unusual for the ADHD population to self-medicate ADHD symptoms with cannabis because they believe it improves symptoms of inattention and mood (Francisco et al., 2023). One study reported the top two motivations for first cannabis use and continued use in adults with ADHD to be “getting high” and

"change mood" (Faraone, Wilens, et al., 2007). There are mixed results about whether cannabis does improve ADHD symptoms or not. Many factors mediate the effects of cannabis, such as product type, strain, potency of THC and CBD, and frequency of use. One study reported findings from an ADHD population that was surveyed on their perception of cannabis and its impact on their ADHD symptoms where they subsequently, found that 91.93% had reported cannabis positively impacted symptoms, 4.35% found cannabis to negatively impact symptoms and 3.73% found no difference on ADHD symptoms (Stueber & Cuttler, 2022). The same study found that frequency of cannabis use can influence the outcome of the users perception to symptoms (Stueber & Cuttler, 2022). Interestingly a majority of chronic cannabis users in this study perceived cannabis to be overall beneficial, reporting relief of most of their ADHD symptoms and stimulant adverse effects (Stueber & Cuttler, 2022). A review (Francisco et al., 2023) looking at cannabis and ADHD reported findings that only a couple case reports and series concluded positive effects for cannabis in ADHD symptomology, but this was in combination with standard treatment (Hupli, 2018; Mansell et al., 2022). Ultimately the majority of studies reported negative results for cannabis on ADHD symptoms including the only RCT available reporting no advantage for symptom reduction using cannabis over placebo (Cooper et al., 2017).

1.5 ADHD Treatment:

Treatment plans for ADHD include pharmacological options, cognitive behavioral therapy (CBT), or a combination of both. Pharmacological options include psychostimulants (amphetamine and methylphenidate formulations) and non-stimulants (atomoxetine, guanfacine, bupropion, clonidine, modafinil) (Mechler et al., 2022). The first line treatment for adult ADHD is psychostimulants because of their previously established efficacy in improving core symptoms of ADHD (Gonon, 2009; Retz & Retz-Junginger, 2014). Moderate to large effect sizes for stimulants are expected in adult ADHD, five meta-analyses and one meta-review concluded an average effect size for stimulant treatment in adults to be around 0.5 (Bushe et al., 2016; Castells et al., 2011; Cunill et al., 2016; De Crescenzo et al., 2017; Koesters et al., 2009; Stuhec et al., 2019). There are two classes of psychostimulants: amphetamines and methylphenidates both of which have demonstrated similar efficacy in treating ADHD (Faraone, 2018). Amphetamines work to increase levels of catecholamines by blocking dopamine and norepinephrine transporters and decreasing the activity of monoamine oxidase (Faraone, 2018). Methylphenidate similarly targets the inhibition of dopamine and norepinephrine transporters which also increases the circulation of both neurotransmitters (Faraone, 2018). Despite stimulant treatment showing great efficacy, there is still 20-50% of adults who do not respond to medication (Torgersen et al., 2008). The efficacy of stimulants could be affected by the formulation. A meta-analysis found that the immediate release (IR) formulation of methylphenidate could be less efficacious compared to the long-acting bi-phasic release formulation because IR requires more administrations a day increasing the probability of individuals with ADHD to potentially forget doses throughout the day (Castells et al., 2011). Common side-effects of the stimulant medication include headaches, insomnia, gastrointestinal symptoms, and occasionally cardiovascular symptoms (Bejerot et al., 2010; Fredriksen et al., 2013). A recent meta-analysis found a pooled prevalence of headaches in pediatric ADHD to be 26.6%, during treatment period (P.-Y. Pan et al., 2022). Another meta-analysis done in pediatric populations reported a prevalence of insomnia as an adverse effect for stimulants at 17% , 30.3% for decreased appetite and 12% for headaches (Schachter et al., 2001). In one RCT for adult ADHD looking at methylphenidate efficacy, it was reported that participants

on the stimulant had higher reported adverse effects with 22% reporting loss of appetite, 33% reporting sleep disturbances, 16% complaining of headaches, 24% reporting dry mouth and 9% tachycardia (Kooij et al., 2004). Similarly another RCT investigating methylphenidate efficacy reported a prevalence of 26.3% of participants having headaches during the treatment period, 19.3% reporting decreased appetite and 17.5% reporting insomnia (T. J. Spencer et al., 2007). Amphetamines had alike side effects to those of methylphenidate. An RCT looking at lisdexamfetamine dimesylate efficacy in adult ADHD reported a prevalence of 31% of participants having dry mouth, 23% decreased appetite, and 21% insomnia (Adler et al., 2008). Another study that looked at treatment outcomes in both methylphenidate and amphetamines reported that the most common adverse event for both stimulants was dry mouth (46%) (Bejerot et al., 2010).There are currently no meta-analyses covering pooled prevalence of adverse side effects for both stimulants in adult ADHD. Cognitive behavioral therapy is also a treatment option for adult ADHD with large effect sizes (Lopez et al., 2018) supported by a recent meta-analysis concluding an effect size of 0.76 (Young et al., 2020). CBT used for ADHD is adapted to address specific symptoms, functional impairments and develop skills to improve functioning using specific psychotherapeutic modules (Cherkasova et al., 2020; Corbisiero et al., 2018; Jensen et al., 2016). Common components in the CBT modules used for the treatment of adult ADHD cover topics of psychoeducation, adaptive thinking and coping with specific ADHD symptoms such as inattention (Sprich et al., 2010). One RCT comparing CBT alone versus CBT and medication for adult ADHD found CBT alone to have significant reductions in ADHD symptoms but ultimately found a greater reduction in the group with combined treatment (Cherkasova et al., 2020). Although a combined treatment approach has shown to be more efficacious than CBT alone literature has mixed findings on whether combined treatment is more efficacious than stimulant medication alone. An RCT comparing combined treatment (CBT and MPH) and MPH alone found that stimulant treatment alone was superior to the combined treatment method although both groups showed a decrease in ADHD symptoms (Corbisiero et al., 2018). A recent meta-analysis found the opposite result and reported that combined treatment was superior to stimulant treatment alone but only until the 3-month checkup, the subsequent checkups at 6 and 9 months demonstrated comparable results between the groups (Li & Zhang, 2024). Similarly an RCT found that combined treatment was superior to stimulant medication alone at the first checkup (24 weeks) but this advantage seemed to plateau at the 36 week checkup (M.-R. Pan et al., 2022). Another RCT that looked at combined treatment (cognitive behavioral therapy and stimulant medication) found it to be more effective in reducing core symptoms compared to medication alone only in participants who don't respond fully to medication alone (Safren et al., 2005).

1.6 Predictors of psychostimulant treatment outcomes in ADHD-SUD/Cannabis populations:

The relationship between cannabis and ADHD is complex. Although it is well documented that stimulant treatment is effective in treating ADHD it is uncertain whether stimulants remain efficacious if individuals have co-occurring substance use disorder, furthermore, no studies have looked at the impact of cannabis and stimulant treatment outcomes in adult ADHD. The presence of co-morbid substance use disorder presents a challenge in treating ADHD as most literature reporting on treatment for ADHD has SUD as an exclusion criterion making it harder to find conclusive evidence. Lots of literature remains inconclusive but the majority believe it could be a predictor of negative stimulant treatment outcomes (Konstenius et al., 2010; Levin et al., 2006, 2007). Positive stimulant treatment outcomes are dependent on many factors including efficacy of

medication, tolerability, adherence, and presence of co-morbidities. The efficacy of stimulant medication has already been well documented with moderate effect sizes in adults and adequate reductions in core symptoms of ADHD (Buitelaar et al., 2011; Bushe et al., 2016; Castells et al., 2011; Cunill et al., 2016; De Crescenzo et al., 2017; Stuhec et al., 2019). Most studies report good tolerability with few side effects and few reports of serious adverse events taking place (Edvinsson & Ekselius, 2018; Fredriksen et al., 2013). Positive outcomes are dependent on whether an individual is taking the medication as prescribed. The average adherence rate for methylphenidate is around 40-60% (Retz & Retz-Junginger, 2014). Co-morbid substance use can be viewed as a negative predictor of treatment outcomes. One meta-analysis found that methylphenidate was efficacious in reducing core ADHD symptoms with a pooled effect size of 0.57, reported using the standard mean difference (SMD) but authors found that having comorbid SUD was consistent with a lower SMD (0.16) therefore, although they found that methylphenidate did reduce core symptoms , the reduction was minimal in the SUD population (Castells et al., 2011). Additionally, an RCT that compared methylphenidate to placebo in a population of cocaine dependent treatment seeking participants with adult ADHD found no advantage in using methylphenidate to reduce core ADHD symptoms (Levin et al., 2007). This study categorized a 30% reduction in Adult ADHD Rating Scale (AARS) scores to be indicative of treatment response and found that 47% of participants in the methylphenidate group and 55% of participants in the placebo group met criteria for treatment response suggesting that the efficacy of stimulant medication can be lower in SUD populations (Levin et al., 2007). Similarly, another RCT compared methylphenidate and bupropion to placebo in a population of methadone maintained participants with adult ADHD (Levin et al., 2006). This study found that all three groups (methylphenidate, bupropion and placebo) had improved from baseline in their ADHD symptoms (response was characterized by a 30% reduction in AARS scores) but ultimately found no difference between the treatment and placebo groups, therefore showing that pharmacological treatment did not have an advantage over placebo in a comorbid SUD population (Levin et al., 2006). Overall suggesting that stimulant treatment efficacy may be reduced in substance using populations. Additional studies also concluded mainly negative results with stimulant treatment in adult ADHD populations with co-occurring amphetamine dependence (Konstenius et al., 2010). In most studies, stimulant treatment, and placebo both produce reductions in ADHD symptomology but fail to show a clear advantage for stimulant treatment over placebo with standard doses in ADHD populations with co-morbid SUD. Only a few RCT studies found positive outcomes and reductions in ADHD core symptoms in substance-using populations when using higher doses of methylphenidate treatment and cognitive behavioral therapy which suggest that both higher doses and CBT may be necessary for favorable outcomes in populations with ADHD and SUD (Konstenius et al., 2014; Levin et al., 2015). The type of substance can also influence the efficacy of treatment. It has been found that nicotine dependence doesn't influence efficacy of stimulant treatment as much as when it is compared to other substances such as cocaine (P.-J. Carpentier & Levin, 2017) yet no studies have looked at cannabis and its influence on stimulant treatment. The Canadian ADHD Resource Alliance reported that they do not support the treatment of ADHD while patients are using cannabis due to inconclusive data on the efficacy of treatment with cannabis use (CADDRA, 2020). Although there haven't been any studies to date that have looked at the impact of cannabis on stimulant treatment response in adult ADHD there have been many studies that overall concluded a minimal response or none to standard doses for stimulant treatment within ADHD-SUD populations.

1.7 Research aims and hypotheses:

There is a lack of clinical knowledge on the impact of cannabis and the response to stimulant treatment in adult ADHD. Due to the lack of literature in this area the primary research question this study aims to answer is the following (1) is there a difference in the psychostimulant treatment response in adult ADHD between cannabis and non-cannabis users? This study hypothesizes that there will be a difference in the psychostimulant treatment response between cannabis and non-cannabis users and that cannabis users will have less of a response to treatment and would therefore have higher total ADHD symptoms scores, higher clinical severity and clinical improvement scores compared to non-cannabis users. The secondary research questions this study aims to answer are the following (2) Does having a cannabis use disorder impact the treatment response? This study hypothesizes that having a cannabis use disorder will negatively impact treatment response and participants with a cannabis use disorder will therefore have higher total ADHD symptoms scores, higher clinical severity and clinical improvement scores compared to non-cannabis users. (3) Does the stimulant formulation (methylphenidate vs amphetamine) impact the treatment response? This study hypothesizes that one formulation is not more advantageous than the other and that both methylphenidate and amphetamine formulations will produce comparable reductions in treatment outcomes measures and therefore not impact treatment response. (4) Does the dosage of stimulant (high vs low) impact the treatment response? This study hypothesizes that dosage of stimulants will not impact treatment response and both high and low doses will produce comparable reductions in treatment outcomes measures. (5) Does having additional comorbidities impact the treatment response? This study hypothesizes that having one or more comorbidities will negatively impact the treatment response and result in having higher total ADHD symptoms scores, higher clinical severity and clinical improvement scores. (6) Do cannabis and non-cannabis users differ in the rate of treatment responders? This study hypothesizes that there will be a difference in the rate of treatment responders and that cannabis users will have a lower rate of response compared to non-cannabis users.

2. Methods

2.1 Subjects

All participants recruited were seeking ADHD treatment through family doctor referrals to the MacAnxiety clinic and the St. Joseph's Healthcare Community Psychiatric Clinic in Hamilton, Ontario. The study was initiated in 2021, and the last participant was entered in 2024. The study screened a total of 71 participants, 65 participants started the study, and 40 participants completed the study.

Participants were first screened by the study psychiatrist who had a copy and was aware of the study's inclusion criteria. The research assistant approached potential participants who were flagged by the study psychiatrist and inclusion criteria were confirmed again by the research assistant. Study inclusion required participants to be above the age of 18 years or older and have a primary diagnosis of ADHD. The diagnosis of ADHD was established by the study psychiatrist in accordance with Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria during

a clinical interview. Potential participants with co-morbid anxiety disorders, depression, obsessive compulsive disorder, and post-traumatic stress disorder, were allowed to be included in the study. Potential participants that met initial criteria and were using concomitant antidepressant, mood stabilizer and anti-psychotic medication were included provided a stable dosing had been maintained for at least 8 weeks. Participants were excluded if they were (1) pregnant or breastfeeding, (2) had a diagnosis of any of the following mental disorders as defined by the DSM-5: lifetime history of schizophrenia or any other psychosis, organic medical disorders, cluster A, B, and C personality disorders, (3) had a medical contraindication to psychostimulants (untreated hypertension, allergy to psychostimulants, untreated hyperthyroidism, glaucoma, cardiac disease), and (4) had a history of greater than two adequately dosed failed trials in psychostimulants for adult ADHD.

2.2 Settings

Participants were treated and seen at the MacAnxiety Research Centre, Hamilton, Ontario, Canada and the St. Joseph's Healthcare Community Psychiatric Clinic Hamilton, Ontario, Canada.

2.3 Study procedures

The study was 8 weeks long and included 3 visits. All study data was captured and managed using the Research Electronic Data Capture (REDCap) software (Harris et al., 2009). Participants were seen by the study psychiatrist as part of their regular care and were informed of the study if they met inclusion criteria. If participants were eligible and interested the research assistant would collect a signed informed consent form. The first visit of the study was called "Baseline" and would occur prior to the start of stimulant medication. During this visit the participant would fill out the self-reported assessment battery conducted through REDCap. The study psychiatrist would assign a CGI-S score at the end of this visit. The participant would be seen at two additional time points 4- and 8-weeks post-baseline visit at which point they would be taking their stimulant medication. At both visits' participants would see the psychiatrist as part of their regular care and would fill out the self-reported assessments through Redcap. The psychiatrist would assign a new CGI-S score at each visit along with a CGI-I score. Participants who were seen online completed the assessment battery through a private personalized link to REDCap software. Although the study included only 3-time points participants were being seen by the study psychiatrist as part of their regular care every two weeks but were only assessed and asked to complete the study survey battery at the three study time points (baseline, week 4 and week 8). Dosing was increased gradually over the course of the study based on efficacy and tolerability up until the maximum tolerated dose. Both formulations of stimulants (methylphenidate and amphetamine) were prescribed for participants in the study. Psychostimulants prescribed in the study were the following including dose ranges: Concerta (18-72mg), Foquest (25-100mg), Biphentin (10-80mg), and Vyvanse (10-60mg). Psychostimulants in the study were chosen by the study psychiatrist based on what was most suitable for the patients. Adverse reactions were reported by participants as spontaneous reports and were documented in the participant file under the reason for withdrawal of study. The criteria for withdrawal for the study were defined as switching stimulants in the middle of the study, the cessation of psychostimulant medication, not being able to be contacted and therefore lost to follow-up.

2.4 Assessment tools

2.4.1 Demographics
Participants answered questions regarding age, sex, education, ethnicity, occupation, marital status, and past ADHD history. These questions were administered only at baseline.

2.4.2 ADHD Assessment
To examine ADHD symptoms the Barkley Adult ADHD Rating scale (BAARS-IV) (Barkley, 2011) was administered. This scale is a screening tool for ADHD in adult patients based on the DSM-5 criteria and is sensitive to change with treatment. The BAARS-IV is a self-report scale which includes 4 sections: inattention, hyperactivity, impulsivity, and sluggish cognitive tempo. The questions are rated on a 4-point Likert scale: (1) never or rarely, (2) sometimes, (3) often, and (4) very often. Total scores are calculated based on the sum of the inattention, hyperactivity, and impulsivity sections. This questionnaire was administered at all three time points of the study and was used as a measure of treatment response.

2.4.3 Anxiety Assessment
To examine anxiety symptoms the Generalized Anxiety Disorder scale (GAD-7) (Spitzer et al., 2006) was administered. This scale is a tool used to examine participants' levels of anxiety over the past two weeks. The GAD-7 questions are rated on a 4-point Likert scale: (1) never or rarely, (2) sometimes, (3) often, and (4) very often. Total scores are calculated based on the sum of all items (Spitzer et al., 2006). This questionnaire was administered at all three time points of the study and was used to investigate a secondary aim on the impact of comorbidities on treatment response.

2.4.4 Depression Assessment
To examine depression symptoms the Patient Health Questionnaire (PHQ-9) (Kroenke & Spitzer, 2002) was administered. This scale is a tool used to measure participants' levels of depressive symptoms over the past two weeks. The PHQ-9 questions are rated on a 4-point Likert scale: (1) never or rarely, (2) sometimes, (3) often, and (4) very often. Total scores are calculated based on the sum of all items (Kroenke & Spitzer, 2002). This questionnaire was administered at all three time points of the study and was used to investigate a secondary aim on the impact of comorbidities on treatment response.

2.4.5 Functional Impairment Assessment
To examine functional impairment the Sheehan Disability Scale (SDS) (Leon et al., 1997) was administered. This scale is a tool used to measure social life, family life and work disability. Each item was rated on a scale from 0-10, "0" (not at all), "1-5" (moderate), and "6-10" (severely). This questionnaire was administered at all three time points of the study and was used as a measure of functional impairment.

2.4.6 Cannabis Assessments

To examine cannabis use disorder the Cannabis Use Disorder Identification Test- Revised (CUDIT-R) (Adamson et al., 2010) was administered at all time points of the study . CUDIT-R is a tool used to measure cannabis use in the past 6-months. Total scores are calculated based on the sum of all items. Scores of 8 or more indicate hazardous cannabis use and scores of 12 or more indicate a possible cannabis use disorder (Adamson et al., 2010). This questionnaire was used to investigate a secondary aim of cannabis use disorder and treatment response.

To examine consequences of cannabis use the Brief Marijuana Consequences Questionnaire (B-MACQ) (J. S. Simons et al., 2012) was administered. B-MACQ is a tool used to measure marijuana -related problems. Each of the 21 items on the scale was rated either yes or no. This scale measured consequences in the domains of social-interpersonal problems, impaired cannabis control, self-perception, self-care, risk behaviours, academic/occupational problems, physical dependence and black out use. This questionnaire was administered at all three time points of the study and was used as a descriptor of cannabis related consequences.

2.4.7 Motivations Assessment

To examine motivations of cannabis use the Marijuana Motives Questionnaire (MMQ) (J. Simons et al., 1998) was administered. The MMQ is a tool used to measure 5 different categories of motivations: enhancement, conformity, expansion, coping and social. Each item on this scale has a 4-point response: (1) almost never/ never, (2) sometimes, (3) often, (4) almost always/always. This questionnaire was administered at all three time points of the study and was used as a descriptor of the samples' motivations for using cannabis.

2.4.8 Additional Substance Use Assessments

To examine frequency, amount, and methods of use for nicotine, cannabis, alcohol, and controlled drugs a set of unique questions crafted by the investigator was administered. Amount of cannabis use was measured in grams and a textbox was provided in which participants could respond with name and potency of cannabis. Amount of alcohol use was measured in the number of standard drinks in one session. Methods of use for nicotine, cannabis and controlled substances were measured in click all that apply style questions with various common modalities of use presented (ex. Joints, edibles, vapes). Frequency of use for all substances was measured using increasing time frequencies (less than once a month, once a month, 2-3 days a month, 1-2 days a week, 3-4 days a week, 5-7 days a week). These questionnaires were administered at all three time points of the study and were used as descriptors of the samples substance use characteristics.

2.4.9 Clinician Assessments

To examine the overall clinical severity of ADHD the Clinical Global Impressions- Severity (CGI-S) scale (Guy, 1976) was administered. Scores range from 1 (normal, not at all ill) to 7 (among the most extremely ill patients).

To examine the overall improvement in clinical symptoms and functioning the Clinical Global Impressions- Improvement (CGI-I) scale (Guy, 1976) was administered. Scores range from 1 (very much improved) to 7 (very much worse).

2.5 Outcomes

Cannabis Status Definitions:

(1) Cannabis users were defined in the study as participants using cannabis at least once in the last 12 months up to daily use.

(2) Non-cannabis users were defined as participants who have not used cannabis in the last 12 months or have never used cannabis in their lifetime.

Primary Research Question:

(1) To investigate if there was a difference between cannabis users and non-cannabis users in treatment response this study used the Barkley Adult ADHD Rating Scale (BAARS-IV) scores and Clinician Global Impression- severity and improvement scores (CGI-S & CGI-I). This study compared the BAARS-IV and CGI-S scores from baseline to endpoint between cannabis and non-cannabis users. This study also compared the week 8 CGI-I scores between cannabis users and non-cannabis users.

Secondary Research Questions:

(2) To investigate if having a cannabis use disorder impacted the response to treatment this study used the Barkley Adult ADHD Rating Scale (BAARS-IV) scores and Clinician Global Impression- severity and improvement scores (CGI-S & CGI-I). This study compared the BAARS-IV and CGI-S scores from baseline to endpoint and CGI-I scores at endpoint between cannabis users who met criteria for cannabis use disorder and non-cannabis users.

(3) To investigate if there was a difference in the rate of responders to treatment between cannabis and non-cannabis users this study defined response to treatment for this analysis as a 30% reduction in baseline BAARS-IV scores and a CGI-I score of “1” or “2”.

(4) To investigate if the type of stimulant formulation impacted treatment response this study compared participants using methylphenidate and amphetamine formulations in terms of their BAARS-IV, CGI-S, and CGI-I scores over the course of the study. This study compared the BAARS-IV and CGI-S scores from baseline to endpoint and CGI-I scores only at endpoint between methylphenidate and amphetamine formulation users.

(5) To investigate if the dosage of stimulant impacted treatment response this study compared participants on low and high dose in terms of their BAARS-IV, CGI-S, and CGI-I scores over the course of the study. This study compared the BAARS-IV and CGI-S scores from baseline to endpoint and CGI-I scores only at endpoint between high and low dose users. All participants were within standard doses of stimulants. This study defined “High dose” as Concerta (54-72mg), Foquest (70-100mg), Biphentin (60-80mg) and Vyvanse (50-60mg). This study defined “low dose” as any dose below “the high dose” range.

(6) To investigate if the presence of comorbidities impacted the treatment response this study compared the number of comorbidities participants had in terms of their BAARS-IV, CGI-S, and CGI-I scores over the course of the study. This study compared the BAARS-IV and CGI-S scores from baseline to endpoint and CGI-I scores only at endpoint. This study also investigated whether baseline anxiety and depressive scores impacted endpoint BAARS-IV scores in cannabis users, non-cannabis users and the whole sample.

2.6 Data analysis

Sample size was based on a power calculation. There is currently no published literature that has examined the impact of cannabis on the response to stimulants for the treatment of ADHD in either adults or adolescents. We estimated effect size to be moderate to large based on past literature examining the efficacy of stimulant treatment in adult ADHD populations. Five meta-analyses and one meta-review concluded an average effect size of stimulant treatment in adults is around 0.5 (Bushe et al., 2016; Castells et al., 2011; Cunill et al., 2016; De Crescenzo et al., 2017; Koesters et al., 2009; Stuhec et al., 2019). Using R studio Webpower package, setting the power at 0.8 and the level of significance at 0.05, an overall sample of 40 participants (20 in each group) would be sufficient to detect a difference between the two groups. Considering 30% attrition this study aims to recruit a sample size of 52 participants with 26 participants in each group.

The Marijuana Motive Questionnaire, investigator created substance use questions, and Marijuana consequence questionnaire data were used as descriptors of the sample and presented as percentages. Demographic questions such as age, sex, education level, marital status, ethnicity, occupational status and previous ADHD history data were averaged and presented as percentages of the sample.

Primary and secondary outcomes that compared BAARS-IV and CGI-S scores from baseline to endpoint between groups were examined using a Friedman test for within measures and the Kruskal Wallis test for between measures. The comparison of endpoint CGI-I scores between groups was examined using an independent t-test or Mann Whitney test.

The secondary outcome investigating rate of responders was evaluated using a chi-square test.

The secondary outcome investigating the impact of comorbidities on treatment response specifically anxiety and depression scores was evaluated using linear regression.

2.7 Ethics

This study was approved by the Hamilton Integrated Research Ethics Board (HIREB) and all participants were given a copy of the informed consent form to take home and signed an informed consent at the study location to be included in the study.

3. Results

3.1 Participant Flow

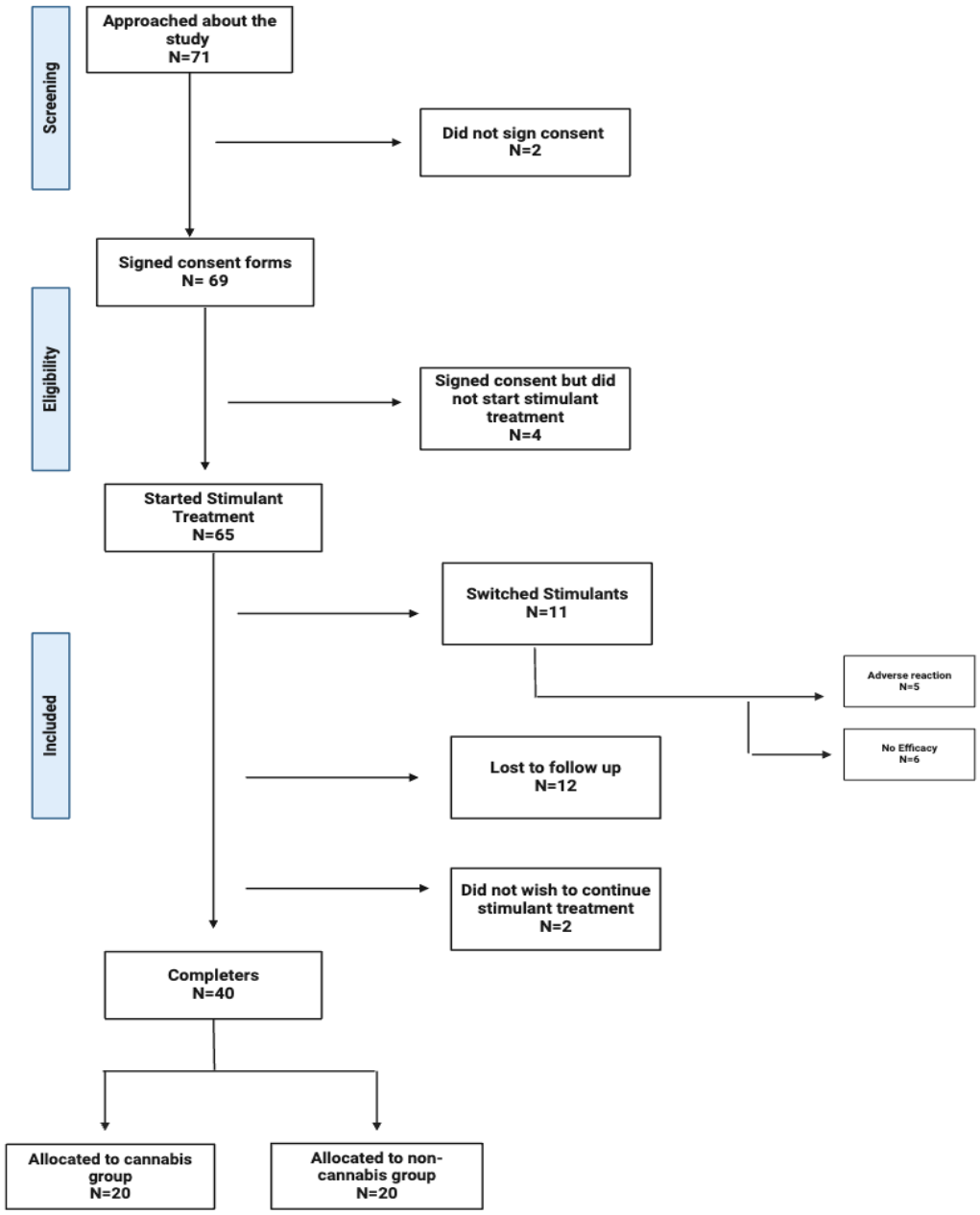

Figure 1: Participant Selection flowchart. This figure outlines the recruitment process from the number of participants approached about the study to the number of participants that received treatment and completed the study. This figure was created with *BioRender.com* and adapted from

template "Flow Chart (6 Levels, Vertical, Black and White)" (2024) Retrieved from https://app.biorender.com/biorender-templates.

3.2 Demographics

Table 1: Sample Characteristics

N=65		Whole Sample N=65 (%)	Cannabis Users N=33 (%)	Non-Cannabis Users N=32 (%)
Gender	Male	40	39	41
	Female	52	52	53
	Transgender	3	6	0
	Non-Binary	5	3	6
Marital Status	Single	54	45	62
	Married/ Common law	45	52	38
	Divorced/ Separated	1	3	0
Ethnicity	Caucasian	69	79	59
	South Asian	6	3	9
	Middle Eastern	3	0	6
	Latin/ Hispanic	5	6	3
	Black	6	3	10
	Asian/ Pacific Island	6	3	10
	Other	5	6	3
Occupational status	Work full-time	49	55	41
	Work part-time	14	12	16
	Student full-time	15	15	16
	Disability	9	9	9
	Sick	5	3	6
	Unemployed	6	3	9
	Homemaker	2	3	3
Education level	College/university graduate	46	55	37
	Some college/university	31	36	25
	Highschool graduate	12	3	22
	Post-graduate studies	11	6	16
Previous lifetime ADHD diagnosis	Yes	48	48	47
	No	52	52	53

Previous lifetime ADHD stimulant treatment	Yes	3	6	0
	No	97	94	100
		MEAN/SD	MEAN/SD	MEAN/SD
	MEAN AGE	30.18 ± 11.6	30.81 ± 9.9	29.5 ± 12.4

Table 2: Sample Characteristics of Study Completers

N=40		Total Completers Sample N=40 (%)	Cannabis Users N=20 (%)	Non-Cannabis Users N=20 (%)
Gender	Male	47.5	50	45
	Female	45	40	50
	Transgender	2.5	5	0
	Non-Binary	5	5	5
Marital Status	Single	42.5	35	50
	Married/ Common law	55	60	50
	Divorced/ Separated	2.5	5	0
Ethnicity	Caucasian	75	80	70
	South Asian	2.5	0	5
	Middle Eastern	2.5	0	5
	Latin/ Hispanic	2.5	5	0
	Black	2.5	0	5
	Asian/ Pacific Island	7.5	5	10
	Other	7.5	10	5
Occupational status	Work full-time	55	65	45
	Work part-time	7.5	5	10
	Student full-time	22.5	20	25
	Disability	5	0	10
	Sick	5	5	5
	Unemployed	2.5	0	5
	Homemaker	2.5	5	0
Education level	College/university graduate	47.5	60	35
	Some college/university	35	40	30
	Highschool graduate	7.5	0	15

	Post-graduate studies	10	0	20
Previous lifetime ADHD diagnosis	Yes	40	35	45
	No	60	65	55
Previous lifetime ADHD stimulant treatment	Yes	5	5	0
	No	95	95	100
		MEAN/SD	MEAN/SD	MEAN/SD
	MEAN AGE	31.3 ± 9.9	32.6 ± 9.9	30 ± 9.9

Table 3: Sample Characteristics of Study Dropouts

N=25		Total Dropout Sample N=25 (%)	Cannabis Users N=13 (%)	Non-Cannabis Users N=12 (%)
Gender	Male	24	23	25
	Female	68	69	67
	Transgender	4	8	0
	Non-Binary	4	0	8
Marital Status	Single	72	62	83
	Married/ Common law	28	38	17
	Divorced/ Separated	0	0	0
Ethnicity	Caucasian	60	76	42
	South Asian	12	8	17
	Middle Eastern	4	0	8

	Latin/ Hispanic	8	8	8
	Black	12	8	17
	Asian/ Pacific Island	4	0	8
	Other	0	0	0
Occupational status	Work full-time	36	38	33
	Work part-time	24	23	25
	Student full-time	4	8	0
	Disability	16	23	8
	Sick	4	0	8
	Unemployed	12	8	18
	Homemaker	4	0	8
Education level	College/university graduate	44	46	42
	Some college/university	24	31	17
	Highschool graduate	20	8	33
	Post-graduate studies	12	15	8
Previous lifetime ADHD diagnosis	Yes	60	69	50
	No	40	31	50
Previous lifetime ADHD stimulant treatment	Yes	0	0	0
	No	100	100	100
		MEAN/SD	MEAN/SD	MEAN/SD
	MEAN AGE	28.36 ± 12.8	28 ± 9.4	28 ± 16.2

Table 1 summarizes the participant characteristics and demographics for the entire sample. Majority of the sample was female (52%), single (54%) and of Caucasian decent (69%). With regards to education and occupational status majority of the sample had university/college degrees (46%) and were working full time (49%). Before the start of the study most of the sample did not have a previous ADHD diagnosis (52%) and did not have previous ADHD stimulant treatment (97%). The mean age of the sample was 30 years old (age range 19-79). These demographics are very comparable to the completers demographics as shown in *Table 2* with very minor differences. The majority of the completers sample was male (47.5), married/common law (55%) and of Caucasian decent (75%). With regards to education and occupational status majority of the sample had university/college degrees (47.5%) and were working full time (55%). Before the start of the

study most of the sample did not have a previous ADHD diagnosis (60%) and did not have previous ADHD stimulant treatment (95%). The mean age of the sample was 31 years old (age range 19-54). The completers sample has a slightly higher number of males (47.5 vs 40%), higher number of married participants (55 vs 45%), and a higher mean age (31 vs 30 years old) compared to the full sample. Additionally, the dropout sample (N=25) was analyzed and is similar to the completers sample with few differences. Alike to the completers sample, the dropouts were majority Caucasian (60 %), working full time (36 %), had college/university education (44 %), and didn't have previous ADHD stimulant treatment (100%). The dropouts differ slightly from the completers in the distribution of gender with a higher percent of females (68 vs 45%), higher number of single individuals (72 vs 42.5%), slightly lower mean age (28 vs 31 years old) and a higher percentage of individuals with a previous ADHD diagnosis (60 vs 40%). Overall, all samples analyzed are similar to each other in demographic measures. There were no statistical differences between cannabis users and non-cannabis users in the whole sample in terms of demographics. A Fisher's Exact test was used to determine the following differences, gender (p=0.707), marital status (p=0.26), occupational status (p=0.91), ethnicity (p=0.407), previous ADHD treatment (p=0.49), and education (p=0.053). A chi-square analysis was done to examine previous ADHD diagnoses which were also not statistically different between cannabis and non-cannabis users (x^2(1, N=65) =0.016, p=0.89).

3.3 Cannabis Descriptors of Sample

3.3.1 Cannabis Modality and Time of Use

When asked to provide information on what time(s) of the day participants would use cannabis and which modalities of cannabis use, there were 9 participants that were able to answer at baseline, 12 at follow-up one and 19 at endpoint. The number of participants answering this questionnaire varied based on whether participants stopped or started using cannabis at the follow-up assessments. Nighttime cannabis use (10pm-5am) was consistently the most popular at all time points of the study. The morning time from 6am-11am was at all time points in the study the least favoured for participants to use cannabis with only 12% reporting use during this time at baseline and dwindling to 6% the end of the study. Participants were able to click on multiple times of use and therefore it is possible participants were using at multiple times throughout the day, but overall, the most common time of use was at night. When investigating what modes of cannabis use were most popular among participants, 25 participants answered at baseline, 19 at follow up one and 15 at endpoint. This study found that joints and edibles were the most common modality of use accounting for (60%) of responses at baseline and continued being the most popular throughout the rest of the study. Throughout the study cannabis concentrates which are waxes or liquids containing high levels of THC or CBD were the least popular mode of use with only (5%) reporting this modality. Participants were able to click on multiple modalities of use, but overall, the most common modalities remained to be edibles and joints.

3.3.2 Cannabis Effects on ADHD Symptoms

Table 4: Perceptual effects of cannabis on ADHD symptoms (N=9)	
ADHD Symptom	Baseline
Cannabis has improved my sleep	44.4% Strongly agree 22.2% Agree 33.3% Neutral 0% Disagree 0% Strongly disagree
Cannabis has helped feelings of restless	55.6% Strongly agree 22.2% Agree 0% Neutral 22.2% Disagree 0% Strongly disagree
Cannabis has helped me slow down my thoughts	44.4% Strongly agree 11.1% Agree 22.2% Neutral 22.2% Disagree 0% Strongly disagree
Cannabis has helped me concentrate on tasks	0% Strongly agree 11.1% Agree 55.6% Neutral 33.3% Disagree 0% Strongly disagree
Cannabis has helped me make less impulsive decisions	0% Strongly agree 11.1% Agree 44.4% Neutral 44.4% Disagree 0% Strongly disagree
Cannabis has helped my organization	0% Strongly agree 0% Agree 44.4% Neutral 44.4% Disagree 11.1% Strongly disagree
Cannabis had helped working memory	0% Strongly agree 11.1% Agree 22.2% Neutral 55.6% Disagree 11.1% Strongly disagree

Table 4 summarizes the perceptual impact of cannabis on certain ADHD symptoms. It was reported that cannabis was not helpful in improving working memory as (55.6%) of participants disagreed and (11.1%) strongly disagreed with the statement that cannabis was helpful in

addressing this symptom. Working memory was defined as having the ability to hold onto information for a brief period of time such as remembering 2 or 3 simple instructions. Cannabis was found to be helpful for participants in dealing with feelings of restlessness with (55.6%) of participants clicking they strongly agreed and (22.2%) clicking they agreed with this statement. The remaining symptoms seemed to have mixed opinions on whether cannabis was helpful or not.

3.3.3 Cannabis Motivations and Consequences

Motivations for using cannabis were surveyed through the MMQ which covers 5 areas including conformity (using cannabis to fit in with a group), expansion (seeking personal or creative awareness using cannabis), coping (using cannabis to deal with personal circumstances), enhancement (using cannabis for enjoyment) and social (using cannabis to make social situations more enjoyable or less stressful). At baseline the most popular group of motivation for using cannabis among cannabis participants (N=10) was coping (40%) and enhancement (38%). The motivation at baseline most clicked as the reason for not using cannabis was conformity (94%).

Cannabis consequences were surveyed through the Brief Marijuana Consequence Questionnaire (B-MACQ) which measured consequences in 8 domains including social-interpersonal problems (cannabis use impacting relationships), impaired cannabis control (using more cannabis than originally planned), self-perception (unhappy with self-due to cannabis), self-care (physical well-being impacted by cannabis), risk behaviours (taking risks while using cannabis), academic/occupational problems (cannabis use impacting work and school), physical dependence (trouble cutting down on cannabis use) and black out use (not remembering periods of time due to cannabis use). At baseline participants using cannabis (N=33) reported the top consequence of using cannabis as blackout use (48%).

3.3.4 Cannabis Amount and Frequency

Three participants were able to provide potency information about their cannabis use and reported potencies ranging from 15-32.3% THC. Four participants were able to provide the amount of cannabis taken which ranged from 0.5g a day to 6g a day. Three participants were able to provide the name of the cannabis they were taking, which included “Redcan Reign drops”, “Bush Weed”, ‘Muskoka sugar cookie”, “pearl CBD gummies and “Sherbinksi’s mochi”.

In the entire sample out of 33 cannabis users this study had 23 recreational users and 10 regular cannabis users. A regular cannabis user was defined in the study as using cannabis 5-7 days a week. In the completers sample there were 12 recreational users and 8 regular cannabis users. Additionally, out of 25 dropouts, there were 13 participants that used cannabis, 2 of which used regularly and 11 that used recreationally. Recreational use varied from less than once a month up to 3-4 days a week. In the entire sample there were 5 participants using less than once a month, 2 participants using once a month, 8 participants using 2-3 days a month, 5 participants were using 1-2 days a week and 2 participants using 3-4 days a week. In the completers sample there were 4 participants using less than once a month, 1 participant using once a month, 3 participants using 2-3 days a month, 3 participants using 1-2 days a week and 1 participant using 3-4 days a week.

In the dropouts there was 1 participant using less than once a month, 1 participant using once a month, 6 participants using 2-3 days a month, 2 participants were using 1-2 days a week and 1 participant using 3-4 days a week. The frequency of cannabis use in the completers sample was comparable to the entire sample and the dropout sample.

3.4 Primary Research Question Outcomes

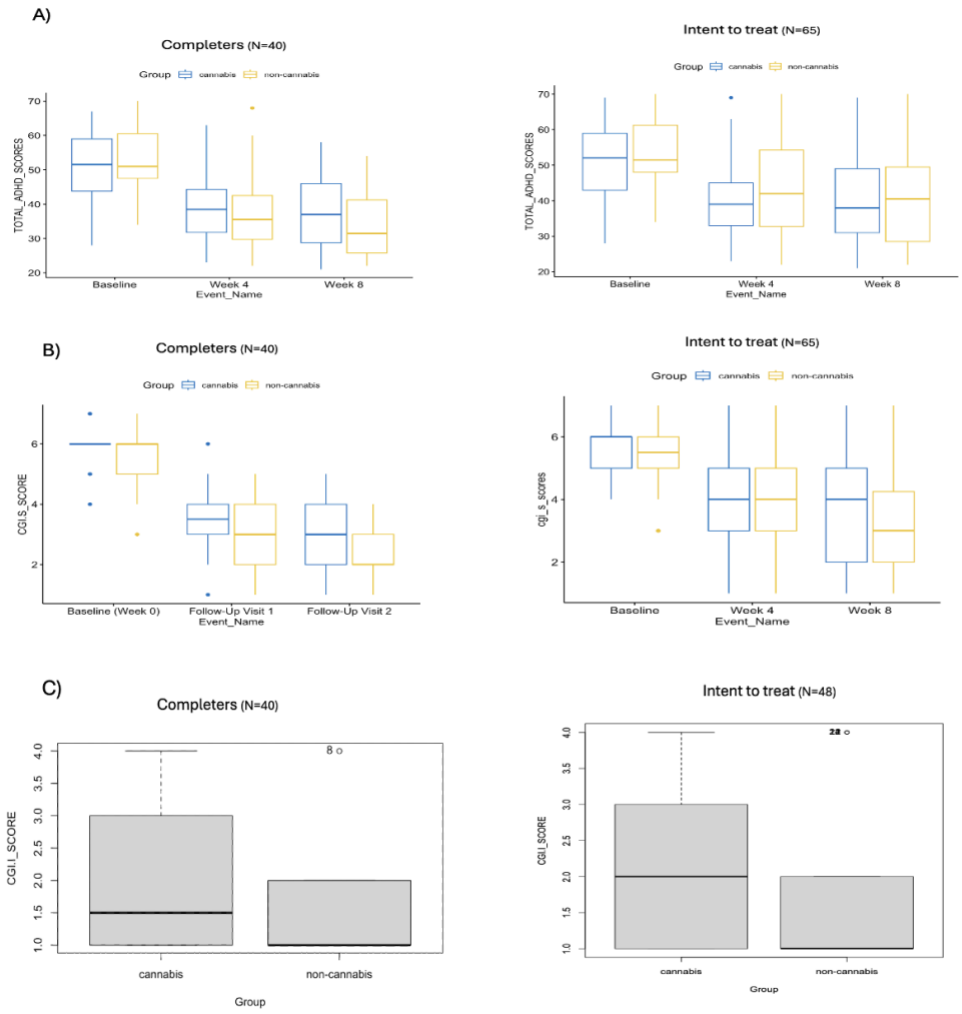

Figure 2: Primary Outcomes in completers and intent to treat sample between Cannabis and Non-Cannabis Users. (A) Comparing the average BAARS-IV scores between cannabis (blue) and non-cannabis users (yellow) at baseline, week 4 and week 8. On the left is the completers analysis and on the right side is the intent to treat analysis (B) Comparing the average CGI-S scores between cannabis (blue) and non-cannabis users (yellow) at baseline, week 4 and week 8. On the left is the completers analysis and on the right side is the intent to treat analysis (C) Comparing the average CGI-I scores between cannabis and non-cannabis users at endpoint. On the left is the completers analysis and on the right side is the intent to treat analysis. (Depicted figures were created using RStudio).

*Analysis is being depicted using boxplots which include the median represented as the dark solid line in the box, the upper box is representative of the upper quartile values and the lower limit of the box is representative of the lower quartile values. The lower whisker on the box plot represents the minimum data value and the upper whisker represents the maximum data value. Dots above or below the box plot represent outlier scores. Half box plots represent that the median is close to the lower or higher percentile scores, therefore both lines are very close to each other giving the illusion of half a box. Flat solid lines represent that the median was the only score and therefore is depicted as a line.

The primary outcomes comparing BAARS-IV, CGI-S and CGI-I scores between cannabis and non-cannabis users were nonsignificant for both the completers and intent to treat sample analyses despite 2 non-cannabis users starting to use cannabis after baseline and 5 cannabis users stopping their cannabis use after baseline. *Figure 2A* portrays visually the Kruskal-Wallis and Friedman test used to analyze the BAARS-IV scores over time between the two groups for both the completers and intent to treat analyses. As seen in *Figure 2A* in the completers analysis over time the BAARS-IV scores decreased from baseline to week 4 and baseline to week 8 *(CHI ^{2} [2] =45.7, p=1.17e-10)* but there is no difference between the groups *(H [1] =0.30, p=0.58)* despite cannabis users having slightly higher BAARS-IV scores. As depicted in *Figure 2A* on the right, the intent to treat analysis shows very similar results to those of the completers. Over the course of the study the BAARS-IV scores decreased from baseline to week 4 and baseline to week 8 *(CHI ^{2} [2] =57.8, p=2.84e-13)* but there is no difference between the groups *(H [1] =1.45, p=0.22),* interestingly non-cannabis users having slightly higher BAARS-IV scores in this analysis. When overall clinical severity including ADHD severity, comorbidities severity and functional impairment were compared using the CGI-S scale as depicted in *Figure 2B,* a similar pattern was seen for both the completers and intent to treat analyses where over time CGI-S scores decreased but there was no difference between cannabis and non-cannabis users. In the completers analysis the results of the Friedman test were significant showing that over time at all time points clinical severity scores were decreasing *(CHI ^{2} [2] =66.5, p=3.69e-15).* The Kruskal-Wallis test was not significant (H [1] =3.28, *p=0.069*) therefore, demonstrating that the clinical severity scores were comparable between cannabis and non-cannabis users, despite cannabis users having slightly higher severity scores. In the intent to treat analysis the results of the Friedman test were also significant showing that over time at all time points clinical severity scores were decreasing *(CHI ^{2} [2] =78.5, p=8.8e-18).* Similarly to the completers, the Kruskal-Wallis test was not significant for the intent to treat analysis (H [1] =2.58, *p=0.1*) therefore, demonstrating that the overall severity scores were comparable between cannabis and non-cannabis users, despite cannabis users having slightly higher CGI-S scores. Endpoint CGI-I scores were comparable between cannabis and non-cannabis users as the Mann-Whitney U test was not statistically significant for both the completers and intent to treat analyses. The Mann-Whitney U test for the completers *(1.85 $\pm$ 0.98, 1.4 $\pm$ 0.75, p=0.1235)* is shown in *Figure 2C* on the left. The Mann-Whitney U test for the intent to treat sample *(1.79 $\pm$ 0.93, 1.65 $\pm$ 1.02, p=0.277)* is shown in *Figure 2C* on the right

3.4.1 Spontaneous Adverse Reports

Table 5: Documentation of spontaneous adverse reports		
N=4		
Adverse symptom	Stimulant	Reported number of instances
Dry mouth	Lisdexamfetamine	1
Weight loss	Methylphenidate Hydrochloride Extended-Release Tablets	1
Dizziness	Methylphenidate Hydrochloride Extended-Release Tablets	1
Headaches	Lisdexamfetamine	1

3.5 Secondary Research Question Outcomes

3.5.1 Impact of Cannabis Use Disorder on Treatment Response

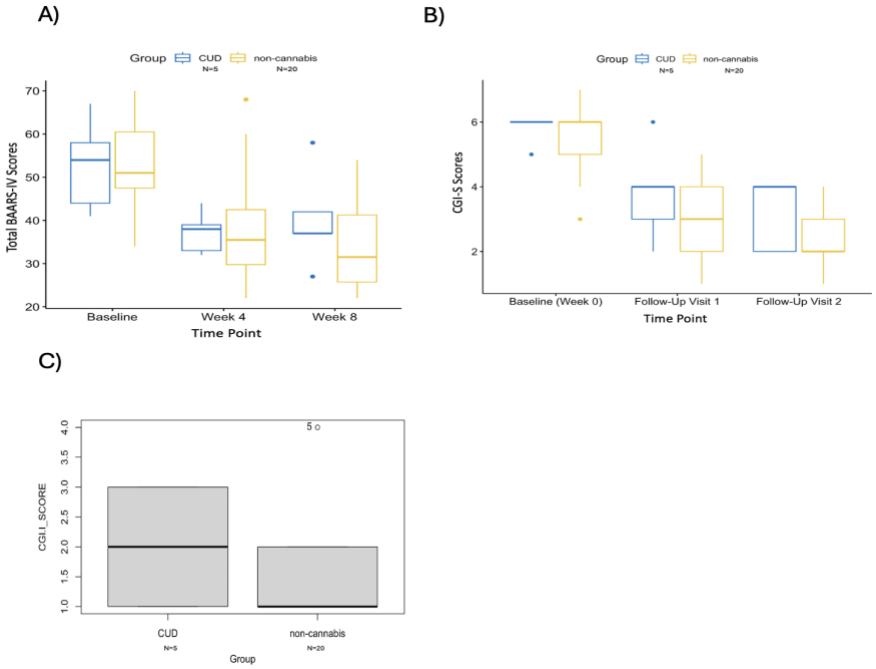

Figure 3: Secondary Outcomes between Cannabis users with potential cannabis use disorder (CUD) and Non-Cannabis Users in completers. (A) Comparing the average BAARS-IV scores between CUD and non-cannabis users at baseline, week 4 and week 8. (B) Comparing the average CGI-S scores between CUD and non-cannabis users at baseline, week 4 and week 8. (C) Comparing the average CGI-I scores between CUD and non-cannabis users at endpoint. (Depicted figures were created using Rstudio).
*Analysis is being depicted using boxplots which include the median represented as the dark solid line in box, the upper box is representative of the upper quartile values and the lower limit of the box is representative of the lower quartile values. The lower whisker on the box plot represents

the minimum data value and the upper whisker represents the maximum data value. Dots above or below the box plot represent outlier scores. Half box plots represent that the median is close to the lower or higher percentile scores, therefore both lines are very close to each other giving the illusion of half a box. Flat solid lines represent that the median was the only score and therefore is depicted as a line.

It was further examined whether having a cannabis use disorder impacted the response to treatment. CUDIT-R scores were analyzed for cannabis users and only users who had scores greater than 12 were categorized as users who met criteria for cannabis use disorder and were placed into the "CUD" group. Only 5 out of 20 cannabis users met criteria for potential cannabis use disorder and were placed in the "CUD" group as shown in panels *A-C*. When comparing BAARS-IV, CGI-S and CGI-I scores between CUD and non-cannabis users results were nonsignificant. *Figure 3A* highlights the Kruskal-Wallis and Friedman test used to analyze the BAARS-IV scores over time between the two groups. As seen in *Figure 3A* over time the BAARS-IV scores decreased from baseline to week 4 and baseline to week 8 *(CHI^2 [2] =35.7, p=1.81e-08)* but there is no difference between the groups *(H [1] =0.355, p=0.55)* despite CUD users having higher BAARS-IV scores. When overall clinical severity including ADHD severity, comorbidities severity and functional impairment were compared using the CGI-S scale as depicted in *Figure 3B,* CGI-S scores decreased over time but there was no difference between the groups. The results of the Friedman test were significant showing that over time at all time points clinical severity scores were decreasing *(CHI^2 [2] =41.6, p=9.26e-10).* The Kruskal-Wallis test was not significant *(H [1] =2.3, p=0.127)* therefore, demonstrating that the clinical severity scores were comparable between CUD and non-cannabis users, despite CUD users having slightly higher severity scores. Endpoint CGI-I scores presented in *Figure 3C* were comparable between CUD and non-cannabis users as the Mann-Whitney U test was not statistically significant *(2 ± 1, 1.4 ± 0.75, p=0.1508).*

3.5.2 Impact of Stimulant formulation on Treatment Response

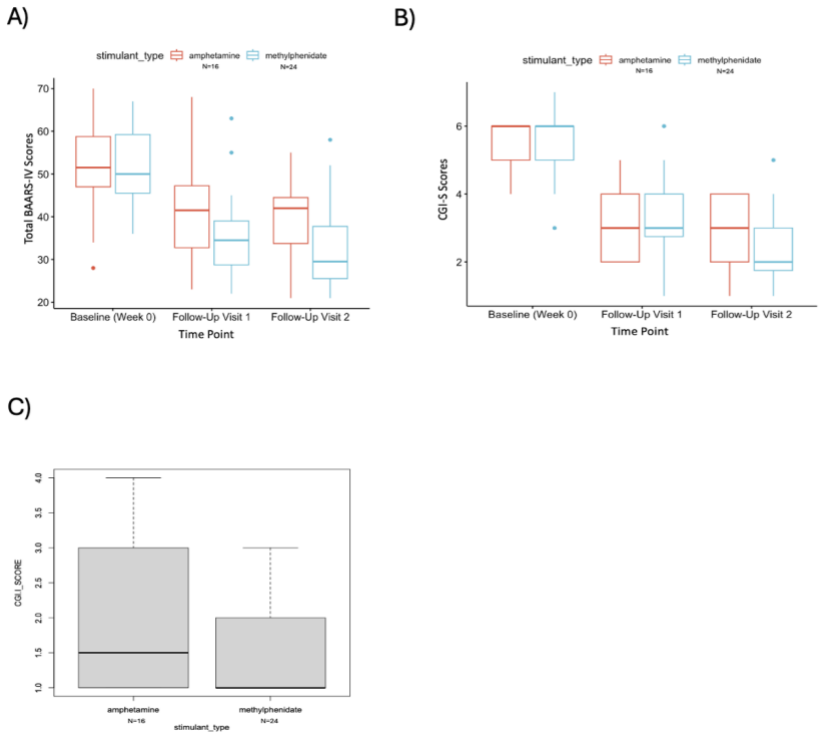

Figure 4: Stimulant analysis between methylphenidate and amphetamine Users in completers. (A) Comparing the average BAARS-IV scores between methylphenidate users and amphetamine users at baseline, week 4 and week 8. (B) Comparing the average CGI-S scores between methylphenidate users and amphetamine users at baseline, week 4 and week 8. (C) Comparing the average CGI-I scores between methylphenidate users and amphetamine users at endpoint. (Depicted figures were created using RStudio).
*Analysis is being depicted using boxplots which include the median represented as the dark solid line in box, the upper box is representative of the upper quartile values and the lower limit of the box is representative of the lower quartile values. The lower whisker on the box plot represents the minimum data value and the upper whisker represents the maximum data value. Dots above or below the box plot represent outlier scores. Half box plots represent that the median is close to the lower or higher percentile scores, therefore both lines are very close to each other giving the illusion of half a box.

All participants in the study were on different stimulant formulations therefore a stimulant analysis was conducted to see if the formulation had an impact on the response to treatment. Participants were split into methylphenidate and amphetamine groups. Within the methylphenidate group there were 24 participants total, 11 cannabis users and 13 non-cannabis users. Within the amphetamine group there were 16 participants total, 9 cannabis users and 7 non-cannabis users. When comparing BAARS-IV, CGI-S and CGI-I scores between methylphenidate and amphetamine users results were nonsignificant. *Figure 4A* shows the Kruskal-Wallis and Friedman test used to analyze the

BAARS-IV scores over time between the two groups. As seen in *Figure 4A* over time the BAARS-IV scores decreased from baseline to week 4 and baseline to week 8 *(CHI ^{2} [2] =45.7, p=1.17e-10)* but there is no difference between the groups *(H [1] =3.74, p=0.053)* despite amphetamine users having higher BAARS-IV scores. When overall clinical severity including ADHD severity, comorbidities severity and functional impairment were compared using the CGI-S scale as depicted in *Figure 4B,* CGI-S scores decreased over time but there was no difference between the groups. The results of the Friedman test were significant showing that over time at all time points clinical severity scores were decreasing *(CHI ^{2} [2] =66.5, p=3.69e-15).* The Kruskal-Wallis test was not significant (H [1] =0.081, *p=0.77*) therefore, demonstrating that the clinical severity scores were comparable between amphetamine and methylphenidate users, despite amphetamine users having slightly higher severity scores. Endpoint CGI-I scores presented in *Figure 4C* were comparable between the two groups as the Mann-Whitney U test was not statistically significant (*1.9 ± 1.12, 1.4 ± 0.6, p=0.1525).*

3.5.3 Impact of Stimulant Dose on Treatment Response

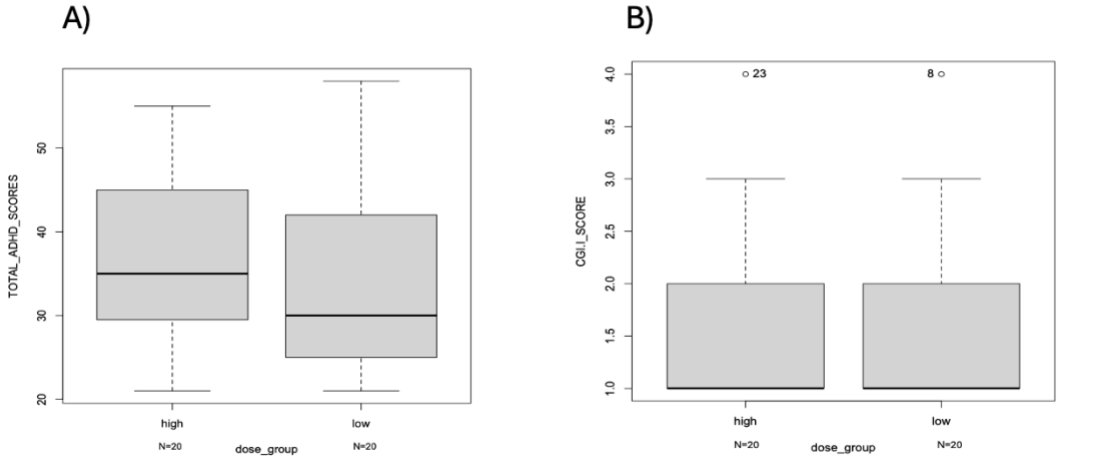

Figure 5: Dose analysis between high dose users and low dose Users in completers. (A)Comparing the average BAARS-IV scores between high dose users and low dose users at week 8. (B) Comparing the average CGI-I scores between high dose users and low dose users at endpoint. (Depicted figures were created using RStudio).
*Analysis is being depicted using boxplots which include the median represented as the dark solid line in box, the upper box is representative of the upper quartile values and the lower limit of the box is representative of the lower quartile values. The lower whisker on the box plot represents the minimum data value and the upper whisker represents the maximum data value. Dots above or below the box plot represent outlier scores. Half box plots represent that the median is close to the lower or higher percentile scores, therefore both lines are very close to each other giving the illusion of half a box.

In addition, to participants being on different stimulants, they were also all on different doses of stimulants. Participants were split into a high and low dose group based on their stimulant dosage at endpoint to see if having a certain dose impacts the response to treatment. This study defined "High dose" as Concerta (54-72mg), Foquest (70-100mg), Biphentin (60-80mg) and Vyvanse (50-60mg). This study defined "low dose" as any dose below the "high dose" range Within the high dose group there were 20 participants total, 11 cannabis users and 9 non-cannabis users. Within the low dose group there were 20 participants total, 9 cannabis users and 11 non-cannabis users. When comparing BAARS-IV and CGI-I scores between high dose and low dose users results were nonsignificant. *Figure 5A* shows the t- test used to analyze the BAARS-IV scores at endpoint between the two groups. As seen in *Figure 5A* the BAARS-IV scores are comparable as the t-test yielded a non-significant result *(37.35 ± 10.2, 33.6 ± 10.9, p=0.2701).* Endpoint CGI-I scores were comparable between the two groups as the Mann-Whitney U test was not statistically significant *(1.65 ± 1.03, 1.55 ± 0.78, p=0.7816)* presented in *Figure 5B.*

3.5.4 Impact of Comorbidities on Treatment Response

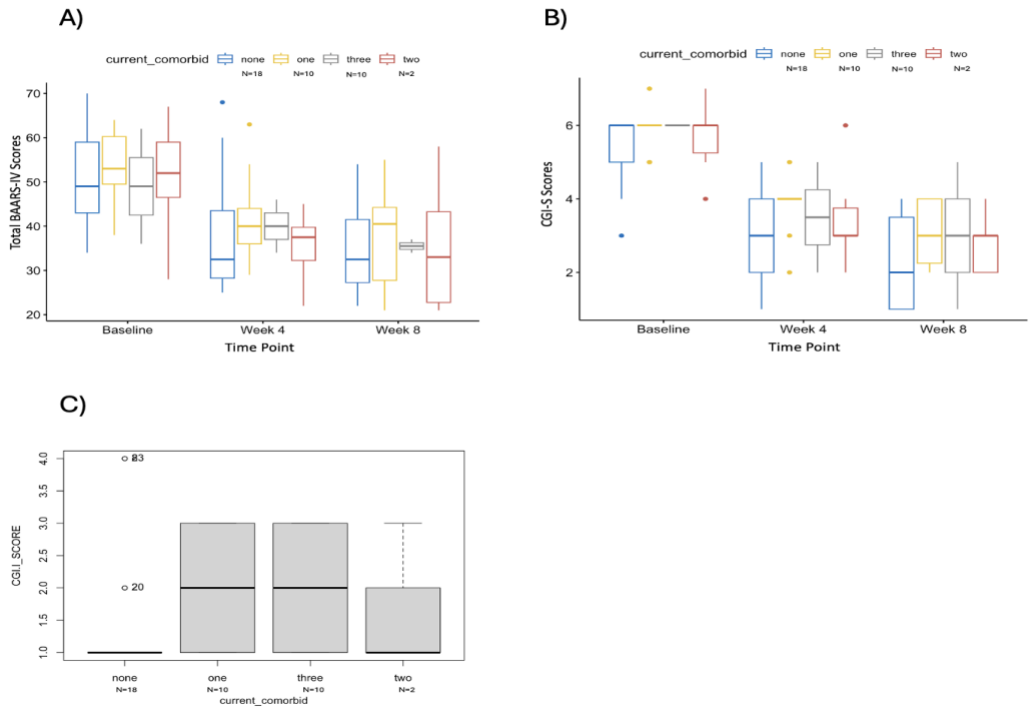

Figure 6: Comorbidities analysis in completers. (A) Comparing the average BAARS-IV scores between participants with none, one, two or three comorbidities at baseline, week 4 and week 8. (B) Comparing the average CGI-S scores participants with none, one, two or three comorbidities at baseline, week 4 and week 8. (C) Comparing the average CGI-I scores between participants with none, one, two or three comorbidities at endpoint. (Depicted figures were created using RStudio).
*Analysis is being depicted using boxplots which include the median represented as the dark solid line in box, the upper box is representative of the upper quartile values and the lower limit of the box is representative of the lower quartile values. The lower whisker on the box plot represents

the minimum data value and the upper whisker represents the maximum data value. Dots above or below the box plot represent outlier scores. Half box plots represent that the median is close to the lower or higher percentile scores, therefore both lines are very close to each other giving the illusion of half a box. Flat solid lines represent that the median was the only score and therefore is depicted as a line.

For this secondary analysis participants were split into groups based on the number of current comorbidities ranging from none to three. Comorbidities were diagnosed by the study psychiatrist in accordance with DSM-5 criteria through clinical interview. Comorbidities present in this analysis are generalized anxiety disorder, social anxiety disorder, substance use dependence, major depressive disorder, obsessive compulsive disorder, and post-traumatic stress disorder. Generalized anxiety was present in 28% of the sample, 25% of cannabis users and 30% of non-cannabis users. Social anxiety disorder was present in 23% of the sample, 25% of cannabis users and 20% of non-cannabis users. Substance use dependence was present in 13% of the sample, 25% in cannabis users and 0% in non-cannabis users. Major depressive disorder was present in 5% of the sample, 10% of cannabis users and 0% of non-cannabis users. Obsessive compulsive disorder was present in 13% of the sample, 0% of cannabis users and 25% of non-cannabis users. Post-traumatic stress disorder was present in 3% of the sample, 5% of cannabis users and 0% non-cannabis users. Cannabis users and non-cannabis differed in the type of comorbidities present with a significant result on the fisher's exact test (p=0.0099). Cannabis users had a higher rate of MDD and SUD while non-cannabis users had a higher rate of OCD. Within the group with no comorbidities there were a total of 18 participants, 7 cannabis users and 11 non-cannabis users. Within the group with one comorbidity there were a total of 10 participants, 7 cannabis users and 3 non-cannabis users. Within the group with two comorbidities there were a total of 10 participants, 5 cannabis users and 5 non-cannabis users. Within the group with three comorbidities there were a total of two participants, 1 cannabis user and 1 non-cannabis users. When comparing BAARS-IV, CGI-S and CGI-I scores between the number of comorbidities the results were nonsignificant. *Figure 6A* shows the Kruskal-Wallis and Friedman test used to analyze the BAARS-IV scores over time between the groups. As seen in *Figure 6A* over time the BAARS-IV scores decrease from baseline to week 4 and baseline to week 8 *(CHI^2 [2] =45.7, p=1.17e-10) but* there is no difference between the groups *(H [1] =2.4, p=0.49)*. When overall clinical severity including ADHD severity, comorbidities severity and functional impairment were compared using the CGI-S scale as depicted in *Figure 6B*, CGI-S scores decreased over time but there was no difference between the groups. The results of the Friedman test were significant showing that over time at all time points overall clinical severity scores were decreasing *(CHI^2 [2] =66.5, p=3.69e-15).* The Kruskal-Wallis test was not significant *(H [1] =4.75, p=0.196)* therefore, demonstrating that the clinical severity scores were comparable between all comorbidity groups. Endpoint CGI-I scores presented in *figure 6C* were comparable between the groups as the Kruskal-Wallis test was not statistically significant *(H [1] =5.05, p=0.167)*.

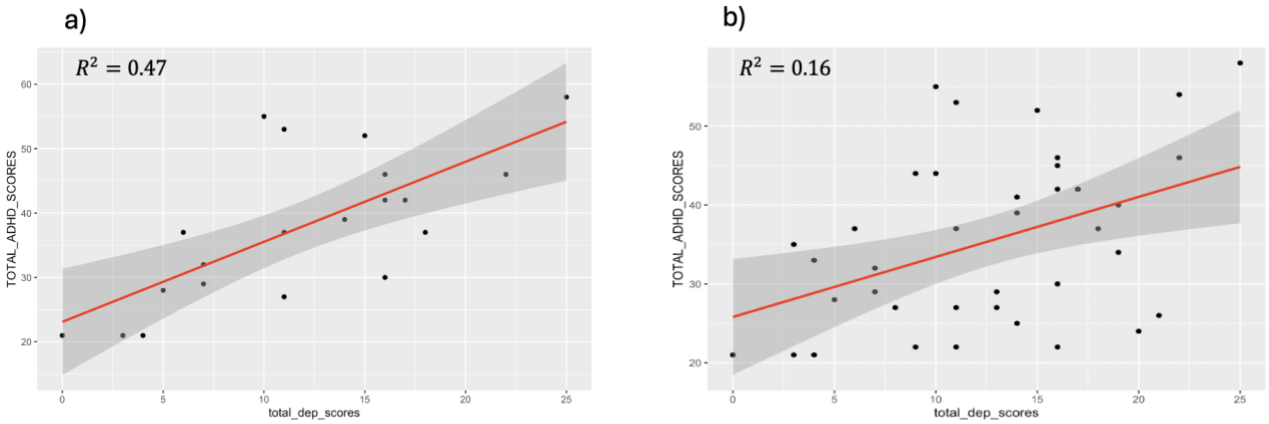

Figure 7: Depression Regression analyses in completers. (A)Linear regression with baseline PHQ-9 scores and endpoint BAARS-IV scores in only cannabis users. (B) Linear regression with baseline PHQ-9 scores and endpoint BAARS-IV scores in completers sample (including both cannabis and non-cannabis users). (Depicted figures were created using RStudio).

A linear regression was used to explore any correlation between baseline PHQ-9 scores and endpoint BAARS-IV scores within the sample, and then specifically in cannabis or non-cannabis users. Depicted in *figure 7A* is the regression using only cannabis users' which produced an r-squared value of 0.47 which suggests that 47% of the variance in cannabis users BAARS-IV scores was due to their baseline PHQ-9 scores. The beta-coefficient was 1.24 which showed that for every increase in PHQ-9 scores, the BAARS-IV score increases by 1.24 units. *Figure 7B* demonstrates the linear regression with the entire completers sample which produced an r-squared value of 0.16 which suggests that 16% of the variance in the samples BAARS-IV scores was due to their baseline PHQ-9 scores. The beta-coefficient was 0.76 which suggests that for every increase in PHQ-9 scores, the BAARS-IV score increases by 0.76 units. A linear regression was done using only non-cannabis users, but it produced a non-significant model result (p=0.139).

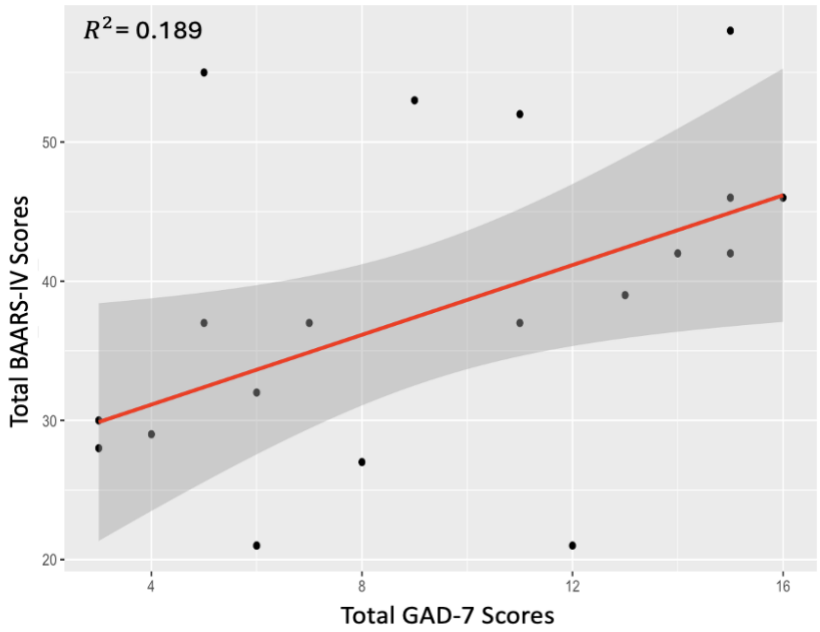

Figure 8: Anxiety Regression analysis in completers. Linear regression with baseline GAD-7 scores and endpoint BAARS-IV scores in cannabis users. (Depicted figures were created using RStudio).

A linear regression was used to explore any correlation between baseline GAD-7 scores and endpoint BAARS-IV scores within the sample, and then specifically in cannabis or non-cannabis users. Depicted in *Figure 8* is the regression using only cannabis users which produced an r-squared value of 0.189 which suggests that 19% of the variance in cannabis users BAARS-IV scores was due to their baseline GAD-7 scores. The beta-coefficient was 1.25 which showed that for every increase in GAD-7 scores the BAARS-IV score increases by 1.25 units. A linear regression was done using only non-cannabis users but produced a non-significant model result(p=0.297). Similarly, when performing the linear regression with the entire completers sample the model was also non-significant (p=0.064).

3.5.5 Responder Rate Between Cannabis and Non-cannabis Users

For this analysis response to treatment was defined as a 30% reduction in baseline BAARS-IV scores and a CGI-I score of "1" or "2". Overall, in the completers sample there was a 50% rate of response and overall, in the intent to treat sample there was a 32% responder rate. Within the response group of completers there were 35% cannabis users and 65% non-cannabis users. A chi-squared test was performed to determine if there was a difference between cannabis and non-cannabis users in terms of treatment responders. The analysis was non-significant (x^2(1, N=40) =3.6, p=0.06) therefore there was no statistical difference in the rate of treatment responders between cannabis and non-cannabis users.

4. Discussion

This study is the first to look at cannabis use and its impact on the psychostimulant treatment response in adult ADHD. This study sought out to answer the following questions (1) Is there a difference in the treatment response between cannabis and non-cannabis users (2) Does having a cannabis use disorder impact the treatment response (3) Do different psychostimulant formulations impact the response to treatment (4) Does the dosage of psychostimulants impact the response to treatment (5) Do additional comorbidities impact the response to treatment (6) Is there a difference in rate of responders between cannabis and non-cannabis users.

When investigating the primary research aim of whether there was a difference in treatment response between cannabis and non-cannabis users it was hypothesized that cannabis users would have a lower response to psychostimulant treatment compared to non-cannabis users and would subsequently have higher BAARS-IV, CGI-S and CGI-I scores compared to participants not using cannabis. Previous literature has reported unfavorable outcomes in populations with co-occurring ADHD and SUD in relation to psychostimulant treatment for adult ADHD (Castells et al., 2011; Levin et al., 2006, 2007). Contrary to previous literature and our hypothesis this study found that cannabis users did not differ statistically from non-cannabis users in treatment response measures of ADHD symptoms, overall clinical severity including severity of ADHD, comorbidities and functional impairment and overall clinical improvement covering improvement in clinical symptoms and functioning. This finding was evident in both the completers and the intent to treat analyses. In the completers analysis, it was found that both cannabis and non-cannabis participants were improving over time as time was significant for the analysis of BAARS-IV *(CHI^2 [2] =45.7, p=1.17e-10)* and CGI-S *(CHI^2 [2] =66.5, p=3.69e-15)* scores but there was no difference between groups when comparing BAAR-IV scores *(H [1] =0.30, p=0.58),* CGI-S scores (H [1] =3.28, *p=0.069*) and CGI-I scores *(1.85 $\pm$ 0.98, 1.4 $\pm$ 0.75, p=0.1235)* therefore suggesting that there was no difference between cannabis and non-cannabis users in the response to psychostimulant treatment since both groups were comparable in their ADHD symptoms, clinical severity, and clinical improvement over the course of the study. Similarly in the intent to treat analysis both groups were improving over time in terms of their BAARS-IV scores*(CHI^2 [2] =57.8, p=2.84e-13)* and CGI-S scores *(CHI^2 [2] =78.5, p=8.8e-18)* but there was no difference across the groups when comparing their BAARS-IV scores *(H [1] =1.45, p=0.22),* CGI-S scores (H [1] =3.28, *p=0.069*) and CGI-I scores*(1.79 $\pm$ 0.93, 1.65 $\pm$ 1.02, p=0.277)*. The findings from both analyses conclude that using cannabis does not affect treatment response differently compared to those who did not use cannabis. Several factors may have contributed to these unexpected findings, but we speculate this may be because participants were placed into groups based on their cannabis status at baseline instead of cannabis frequency. Our results with this grouping found no difference in ADHD symptoms, overall clinical severity and overall clinical improvement between the cannabis status and non-cannabis status groups. Similarly, results in the literature report a lack of significance when comparing ADHD symptoms in participants based on status instead of frequency. A recent study (Stueber & Cuttler, 2022) conducted a moderation analysis on ADHD symptoms using BAARS-IV scores, executive dysfunction and cannabis frequency, the study found cannabis frequency was able to moderate the relationship between total BAARS-IV scores and executive dysfunction. Notably, the study reported that when cannabis status was used instead

of frequency it was not a moderator in the relationship between total BAARS-IV scores and executive dysfunction (Stueber & Cuttler, 2022). Furthermore, the idea of dividing participants by frequency of cannabis use instead of status can be seen in the study by (MacDonald & Sadek, 2021) where they reported they found a significant difference between heavy cannabis users (using 3 or more times a week) and non-cannabis users (users below heavy use threshold or no use at all) when comparing total ADHD symptoms and impairment. The authors did not come to the same conclusion when participants were placed into groups based on SUD status instead of frequency (MacDonald & Sadek, 2021) therefore suggesting that the impact of cannabis is only clear when taking into consideration the frequency of cannabis use rather than the cannabis status. Therefore, our study may have not found a significant difference between the cannabis and non-cannabis groups due to the grouping of participants based on status instead of frequency. Additionally, in this study, the participants in the cannabis status group mostly had lower frequencies of cannabis use. In the entire sample of 33 cannabis users only 10 of these participants were using cannabis regularly therefore the remaining 70% of participants in the cannabis status group were using at a lower frequency with 22% of these participants using less than once a month and only 9% using at a frequency (3-4 days a week) close to daily use. The high number of participants using cannabis at lower frequencies may be indicative of why there was no difference in the treatment response between cannabis and non-cannabis users because the frequency of cannabis use is so low in the cannabis group that it is comparable to those who do not use cannabis. Another explanation for these results is that some participants switched cannabis status after baseline. Within the non-cannabis group 2 participants started using cannabis after baseline, 15 participants remained not using cannabis and 3 participants started using cannabis during the second visit but stopped using by the end of the study. Within the cannabis group, 5 participants stopped using cannabis after baseline, 7 participants remained using the same frequency of cannabis as described at baseline and 8 participants remained using cannabis but changed their frequency from what was reported at baseline. A reason why cannabis and non-cannabis users had comparable treatment responses could be because a quarter of the cannabis group stopped using cannabis and their scores might have been more reflective of those in the non-cannabis user group. The five cannabis participants who stopped using cannabis after baseline originally reported their motivation for using cannabis in the MMQ as using for coping reasons, suggesting that starting stimulant medication could have helped them address the symptoms cannabis was helping them cope with. The two non-cannabis users who started using cannabis reported their main motivation for using cannabis on the MMQ as enhancement which suggests participants started using for enjoyment since both participants reported using a small amount (10mg THC) and a low frequency (2-3 days a month). It is possible the constant questions referencing cannabis use in the study could have influenced these participants to start using but it is unclear. This study conducted an additional analysis between cannabis and non-cannabis users considering cannabis status at endpoint in order to take into account the individuals that switched their cannabis status after baseline. Interestingly as seen in *Supplementary Figure 9* when cannabis users are placed into groups based on endpoint cannabis status there is a difference in the treatment response across outcome measures. Cannabis users had higher BAARS-IV $(H\,[1] = 4.95,\ p = 0.026)$ and CGI-S $(H\,[1] = 5.19,\ p = 0.022)$ scores compared to non-cannabis users, their CGI-I scores were still comparable $(1.88 \pm 0.99,\ 1.43 \pm 0.78,\ p = 0.11)$. Additionally looking specifically at the cannabis participants who stopped using cannabis compared to the non-cannabis participants who started using cannabis their means for primary outcomes BAARS-IV and CGI-S scores were different from each other and their respective group

means as shown in S*upplementary Table 6 and 13*. The average BAARS-IV scores at endpoint for the cannabis group was 37.65 ± 11.5 which is higher than the mean of the cannabis users who stopped using cannabis with endpoint BAARS-IV scores of 32.2 ± 5.67. Similarly, the average BAARS-IV scores at endpoint for the non-cannabis group was 33.3 ± 9.3 which is lower than the mean of the non-cannabis users that started using cannabis with mean BAARS-IV scores of 44.5 ± 13.4. A similar pattern can be seen when looking at the CGI-S scores in the cannabis group. The mean CGI-S scores for the cannabis group at endpoint were 2.95 ± 1.2 compared to the mean of cannabis users that stopped using cannabis of 2.2 ± 1.6. These supplementary analyses provide a signal that cannabis use may impact the psychostimulant response when considering cannabis status at endpoint, and therefore reinforcing the idea that perhaps a difference was not detected in the primary outcomes due to participants switching cannabis use frequency and status throughout the study.

Previous literature reports that the a higher level of SUD severity can be a predictor of negative treatment outcomes in ADHD (Tamm et al., 2013) which is why as a secondary aim this study examined whether having a cannabis use disorder impacted the treatment response. This study did not find a significant difference between CUD and non-cannabis users when comparing BAARS-IV, CGI-S and CGI-I scores. Both groups were improving over time as time was significant for the analysis of BAARS-IV scores *(CHI ^{2} [2] =35.7, p=1.81e-08)* and CGI-S scores *(CHI ^{2} [2] =41.6, p=9.26e-10)* but there was no difference between the groups when comparing BAARS-IV scores *(H [1] =0.355, p=0.55)*, CGI-S scores *(H [1] =2.3, p=0.127)* and CGI-I scores *(2 ± 1, 1.4 ± 0.75, p=0.1508)* therefore suggesting that despite having a cannabis use disorder treatment response was similar to those who don't use cannabis. This study did not have a high level of CUD severity, therefore suggesting mild cannabis use may have no impact on the response to psychostimulant treatment as shown in this study and that negative outcomes may be tied to more severe CUD. The present study included users that were simply using cannabis within the last year and inclusion criteria did not require individuals to have a cannabis use dependence. This may provide an explanation as to why the study was able to achieve a comparable reduction in symptoms between cannabis and non-cannabis users given, they had less severe substance use, and majority of participants did not meet criteria for a cannabis use disorder. Previous studies with negative outcomes all had participants who met criteria for DSM-5 substance use dependence (Levin et al., 2006, 2007). The present study only had 5 participants out of 20 in the cannabis group that met criteria for potential cannabis use disorder based on CUDIT-R scores. The cannabis sub-group analysis was done with these individuals and compared to non-cannabis individuals to see if the response to psychostimulant medication was different when looking at individuals with a substance use disorder. Although there were no statistically significant differences found, CUD participants had higher BAARS-IV, CGI-S and CGI-I scores suggesting they could be trending towards significance but the sample size in the CUD group may be too small.

This study found that stimulant formulation does not impact treatment response, therefore one stimulant formulation is not more advantageous than the other when comparing treatment outcome measures. This study found comparable reductions in ADHD symptoms *(H [1] =3.74, p=0.053)*, clinical severity scores (H [1] =0.081, *p=0.77*) and clinical improvement scores (*1.9 ± 1.12, 1.4 ± 0.6, p=0.1525)* with both stimulant formulations (methylphenidate and amphetamines)

therefore, stimulant formulation did not impact the treatment response. These results are in line with literature findings which report that both methylphenidate and amphetamine formulations in adults have shown comparable efficacy and reduction in ADHD symptoms (Faraone, 2018). This study is the first to investigate the impact of cannabis use on the psychostimulant treatment response in adult ADHD with participants who are all receiving treatment. Both the cannabis and non-cannabis groups were receiving stimulant treatment over the course of the study. Past literature in the field has compared populations with co-occurring ADHD and SUD on stimulant treatment to participants on placebo. In contrast to past literature that has reported little or no advantage to stimulant treatment over placebo in this population (Castells et al., 2011; Levin et al., 2006, 2007), this study found that cannabis users had comparable reductions in ADHD symptoms to non-cannabis users receiving stimulant treatment. These results suggest that even when using cannabis stimulant treatment is able to achieve reductions in ADHD symptoms and overall clinical severity although this may be as mentioned earlier due to the frequency of cannabis use in the sample being quite low. Additionally, the study investigated whether dosage of stimulants impacted the treatment response. The study found that high and low doses of stimulants both resulted in comparable scores in ADHD symptoms and clinical improvement when using standard doses. These findings are in contrast to previous studies which have found positive treatment outcomes in co-occurring ADHD and SUD populations only when using high doses of stimulants (Konstenius et al., 2014; Levin et al., 2015). One study (Konstenius et al., 2014) found that methylphenidate was efficacious in treating co-occurring SUD populations but only with high doses of MPH (180mg) compared to placebo. Another study (Levin et al., 2015) found that participants with cocaine use disorder were also responding to stimulant treatment with higher doses of mixed-salts amphetamines (60-80mg). In comparison to the present study, which found that high or low dose formulations in standard doses were able to report comparable BAARS-IV scores and CGI-I scores. Cannabis and non-cannabis users were evenly split into the low and high dose groups showing that cannabis users did not have to be on a high dose to achieve treatment response since cannabis users in the low dose group showed similar CGI-I scores *(1.65 $\pm$ 1.03, 1.55 $\pm$ 0.78, p=0.7816)* to those in a high dose group. A reason why previous literature only saw positive outcomes with high dose stimulants may be due to the level of SUD severity, all the participants in the (Konstenius et al., 2014) and (Levin et al., 2015) study had a substance use dependence compared to this study where the level of SUD severity was not high therefore suggesting why standard doses (high or low) were sufficient in the sample to see comparable reductions to non-cannabis users.

Our study found that regardless of the number of additional comorbidities the participants had comparable treatment response. The comorbidities analysis was not significant when comparing BAARS-IV scores *(H [1] =2.4, p=0.49)*, CGI-S *(H [1] =4.75, p=0.196)* and CGI-I scores *(H [1] =5.05, p=0.167)* which would suggest that the number of co-morbidities did not impact the response to ADHD treatment. Our study findings are in contrast to literature that suggests additional comorbidities can increase the risk of negative treatment outcomes and pose a challenge to treatment (Ingram et al., 1999; Reale et al., 2017). One study reported that participants with ADHD and at least one comorbidity showed better improvement when using a combined treatment approach suggesting that additional treatment approaches might be necessary to see better outcomes with participants with additional comorbidities (Reale et al., 2017). There is limited data investigating the impact of comorbidities on stimulant treatment response in adults with ADHD

(Torgersen et al., 2008) but the idea of multimodal treatment seems to be a common topic, some have suggested that in order to see more optimal treatment response for adults with ADHD and comorbidities , the comorbidities should be treated before starting ADHD treatment (Kooij et al., 2012). It is possible our results showed comparable reductions in symptoms and clinical severity regardless of how many comorbidities due to comorbidities being simultaneously treated but this remains to be seen due to lack of compliancy measures for comorbid medication in the study. Additionally, comorbidities were diagnosed through unstructured clinical interview which could have led to a reduced number of comorbidities being identified in participants and therefore again why this study did not find a difference across the number of comorbidities regarding ADHD symptoms, overall clinical severity and clinical improvement. It is also possible the severity of the comorbidities in our sample was low which is why it was found that regardless of how many comorbidities participants still all had comparable scores. This study additionally explored whether the type of co-morbidity impacted treatment outcomes using baseline depressive and anxiety scores to see if there is a correlation to endpoint BAARS-IV scores through a linear regression. When analyzing baseline depressive symptom scores (PHQ-9) with endpoint BAARS-IV scores in the entire sample it was found that 16% of the variability in the BAARS-IV scores of the sample was due to baseline depression scores. When looking only at cannabis users it was found that 47% of the variability in BAARS-IV scores were due to baseline depression scores. As seen in *Figure 7* higher baseline depressive scores were correlated with higher BAARS-IV scores at the end of the study. When analyzing baseline anxiety symptom scores (GAD-7) with endpoint BAARS-IV scores in cannabis users it was found that 19% of the variability in BAARS-IV scores was due to baseline anxiety scores. As seen in *Figure 8* higher baseline anxiety scores were correlated with higher BAARS-IV scores at the end of the study. Therefore, baseline depressive scores accounted for more variability in BAARS-IV scores than baseline anxiety scores in cannabis users. Despite both anxiety and depression accounting for variability in the BAARS-IV scores of cannabis users, their scores were still comparable to those of non-cannabis users at the end of the study. When looking at PHQ-9 and GAD-7 scores over the course of the study as shown in *Supplementary Figures 10 and 11* there is no difference between cannabis and non-cannabis users *(H [1] =0.013, p=0.9)*. Time was significant from baseline to week 4 and baseline to week 8 *(CHI ^{2} [2] =24.2, p=5.5e-06)* meaning that over the course of the study PHQ-9 and GAD-7 scores decreased but there are no differences between the groups and therefore, cannabis and non-cannabis users are comparable in their PHQ-9 and GAD-7 scores over the study. In terms of PHQ-9 scores both cannabis and non-cannabis users start at a moderate severity as described in *Supplementary Table 14* and by endpoint of the study both groups are at a mild severity. In regard to GAD-7 scores cannabis users start the study at a mild severity and at endpoint are still at a mild severity whereas non-cannabis users start the study at a moderate severity and end the study at a mild severity. Since both cannabis and non-cannabis users were able to improve in their PHQ-9 and GAD-7 scores over time it is possible that starting stimulant treatment helped their depressive and anxiety symptoms leading to a decrease in scores and severity over the study.

This study chose to analyze treatment response using total BAARS-IV scores, CGI-S and CGI-I scores but analyzing them separately. In literature other studies have chosen to analyze treatment response as a collection of criteria such as a 30% reduction in ADHD symptom scores from baseline and a final CGI-I score of "1" or "2"(Kooij et al., 2004; T. Spencer et al., 1995). To ensure one definition of treatment response was not a better indicator than another, one of the secondary

aims of this study was to investigate if there was a difference in treatment response between cannabis and non-cannabis users using rate of responders with treatment response defined as a collection of criteria (30% reduction in ADHD symptom scores from baseline and a final CGI-I score of "1" or "2"). This study did not find a difference between cannabis users and non-cannabis users in the treatment response when defining treatment response as a collective criterion (x^2(1, N=40) =3.6, p=0.06). Therefore, there was no statistical difference in the rate of treatment responders between cannabis and non-cannabis users. Although there was no statistical difference there was almost double the amount of non-cannabis users (65%) in the response group compared to cannabis users (35%). Interestingly from the participants that responded to treatment based on this criterion there were 7 cannabis users 4 of which reported they had stopped using cannabis after baseline therefore suggesting there may be an effect of cannabis on treatment response using this criterion, but it is being masked due to participants who stopped using cannabis but remained being marked as cannabis users due to group assignment at baseline. When the responder analysis was done using cannabis status at endpoint to account for the participants who switched their cannabis status throughout the study the Fisher Exact test revealed a statistically significant difference (p=0.001). This demonstrates that based on this combined criterion of response cannabis users have a lower response rate compared to non-cannabis users with (85%) non-cannabis users and (15%) cannabis users in the response group.

This study was adequately powered to detect a difference between groups, yet this study did not find a difference between cannabis and non-cannabis users in their response to treatment. These findings could be due to there being no difference or it is possible that confounders in the study have introduced variation to the results and no difference was detected. Interestingly when supplemental analyses were done to account for cannabis status at endpoint instead of baseline there was a signal indicating that cannabis users had a lower response to treatment compared to non-cannabis users. This study and its results carry significance because this is the first study to look at cannabis use and its impact on the psychostimulant response in adult ADHD contributing significantly to the limited knowledge in this field. This field of research is very important because often when testing efficacy or treatment response for stimulants populations with co-occurring SUD and ADHD are excluded and therefore this leads to a gap in literature and affects the treatment quality of these individuals (Tamm et al., 2013). Cannabis is very complex and heterogeneous and therefore pinpointing what aspects of cannabis affect treatment response is imperative.

This study gives an indication that cannabis use status at baseline may not impact the psychostimulant response but opens the field to further research on individual cannabis components and their impact due to a signal in supplemental analyses that cannabis may impact the treatment response based on frequency and endpoint cannabis status. The implications of the results of the study are important and require further development in this line of research in order to reach the end goal where clinicians can better advise their patients on the effects of cannabis use and ADHD stimulant treatment response so patients can make informed decisions about using cannabis with their medication. Future directions for this study would be to investigate the impact of cannabis use frequency on the psychostimulant response using the same measures as the current study. This new study would be meaningful due to the current study finding a signal that cannabis status at the end of the study accounting for changes in frequency over the study showed a

difference in the treatment response. This signal was originally missed in the primary results due to cannabis status being assigned at baseline therefore with a new study focusing on frequency of cannabis use the signal may be clearer and will add to the field about the impact of high and low frequency cannabis use on the treatment response.

4.1 Limitations

Despite our best efforts there were some limitations to the study. This study assigned participants to the cannabis or non-cannabis group based on their cannabis use at baseline. As the study progressed some participants stopped using cannabis or started using cannabis and therefore were in a group that was not representative of their cannabis status.

Another limitation is the heterogeneity of the cannabis group and cannabis components. This study did not give participants any cannabis, participants were using cannabis from the community and therefore it was difficult to standardize the frequency, amount, potency, time and modality of use within the cannabis group. The cannabis group also was not even in the amount of regular and recreational participants, there were more recreational users and within those using recreationally the frequency varied. Additionally, participants were not asked when in their lifetime they started using cannabis as the impact on treatment response could vary for participants who have been using cannabis for longer periods of time compared to participants who only recently started using cannabis.

This study allowed comorbid anxiety, depression, OCD and post-traumatic stress disorder but failed to have a compliancy measure for the concomitant medication. Individuals with additional co-morbid disorders may be at a higher risk of negative treatment outcomes (Ingram et al., 1999) especially if concomitant medication is not being taken as prescribed.

This study made clinical diagnoses based on the study psychiatrist using an unstructured clinical interview, but this study failed to use any structured clinical tools used such as the Structured Clinical Interview for DSM-IV (SCID-IV) or the International Neuropsychiatric Interview (MINI).

This study did not have an unbiased blinded independent rater. The study psychiatrist was not blinded to which group participants were placed into (cannabis status vs non-cannabis status) and this could have influenced the rating of severity and improvement scores.

This study did not track or have any questionnaires pertaining to individuals with a menstrual cycle which may have been a factor impacting treatment response.

4.2 Conclusion

In summary this study found no evidence of a difference in BAARS-IV, CGI-S or CGI-I scores between cannabis and non-cannabis users in the primary research question suggesting that cannabis did not impact the response to psychostimulant medication in adults with ADHD but

supplementary analyses considering cannabis status at endpoint were able to find a signal for an impact of cannabis on treatment response in adult ADHD. Thus, it is important that further studies replicate with a larger sample to confirm the results of this study and further work needs to be done to evaluate the impact of specific cannabis components on the response to psychostimulant medication for adult ADHD.

5. Supplementary Figures and Tables

Table 6: Means and Standard Deviations of BAARS-IV, CGI-S, and CG-I Scores in Cannabis and Non-Cannabis Users of the Completer Sample

N=40	BAARS-IV Scores						CGI-S Scores						CGI-I Scores	
	Baseline		Week 4		Week 8		Baseline		Week 4		Week 8		Week 8	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cannabis (N=20)	50.9	10.4	38.35	10.1	37.65	11.5	5.85	0.6	3.5	1.2	2.95	1.2	1.8	0.9
Non-cannabis (N=20)	52.3	9.6	38.05	11.8	33.3	9.3	5.35	0.9	3.0	1.1	2.3	0.9	1.4	0.7

Table 7: Means and Standard Deviations of BAARS-IV, CGI-S, and CG-I Scores in Cannabis and Non-Cannabis Users of the Intent to Treat Sample

N=65	BAARS-IV Scores						CGI-S Scores						CGI-I Scores	
	baseline		Week 4		Week 8		baseline		Week 4		Week 8		Week 8	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cannabis (N=33)	50.2	10.7	40.3	10.9	39.8	11.8	5.75	0.8	4.0	1.5	3.68	1.6	1.79	0.9
Non-Cannabis (N=32)	53.3	9.1	43.4	12.9	40.1	13.2	5.34	0.9	3.7	1.4	3.2	1.6	1.65	1.0

Table 8: Means and Standard Deviations of BAARS-IV, CGI-S, and CG-I Scores in CUD and Non-Cannabis Users

N=25	BAARS-IV Scores						CGI-S Scores						CGI-I Scores	
	Baseline		Week 4		Week 8		Baseline		Week 4		Week 8		Week 8	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
CUD (N=5)	52.8	10.5	37.2	4.8	40.2	11.3	5.8	0.4	3.8	1.4	3.2	1.0	2.0	1.0
Non-Cannabis (N=20)	52.3	9.6	38.05	11.8	33.3	9.3	5.35	0.9	3.0	1.1	2.3	0.9	1.4	0.7

Table 9: Means and Standard Deviations of BAARS-IV, CGI-S, and CG-I Scores in Methylphenidate and Amphetamine Users

N=40	BAARS-IV Scores						CGI-S Scores						CGI-I Scores	
	baseline		Week 4		Week 8		baseline		Week 4		Week 8		Week 8	
	Mean	SD	Mean	Mean	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
MPH (N=24)	52.0	8.9	35.5	9.5	32.5	10.1	5.6	0.9	3.2	1.3	2.4	1.1	1.4	0.6
AMP (N=16)	50.9	11.6	42.2	11.7	39.8	10.0	5.5	0.7	3.1	0.9	2.9	1.0	1.9	1.9

Table 10: Means and Standard Deviations of BAARS-IV and CG-I Scores in High and Low Dose Users at Endpoint

N=40	BAARS-IV Scores		CGI-I Scores	
	Week 8		Week 8	
	Mean	SD	Mean	SD
High dose (N=20)	37.35	10.21	1.65	1.03
Low dose (N=20)	33.6	10.96	1.55	0.78

Table 11: Means and Standard Deviations of BAARS-IV, CGI-S, and CG-I Scores in Number of Comorbidities Groups														
N=40	BAARS-IV Scores						CGI-S Scores						CGI-I Scores	
	baseline		Week 4		Week 8		baseline		Week 4		Week 8		Week 8	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
None (N=18)	50.8	10.4	37.6	12.8	34.6	9.9	5.2	0.9	2.8	1.2	2.2	1.2	1.2	0.70
One (N=10)	50.7	8.7	40.6	12.0	40.8	10.0	5.9	0.5	3.8	0.7	3.1	0.8	2.0	0.8
Two (N=10)	51.5	10.9	35.1	7.6	34.4	12.7	5.8	0.9	3.3	1.1	2.8	0.7	1.5	0.7
Three (N=2)	49.0	18.3	40.0	8.4	35.5	2.1	6.0	0	3.5	2.1	3.0	2.8	2.0	1.4

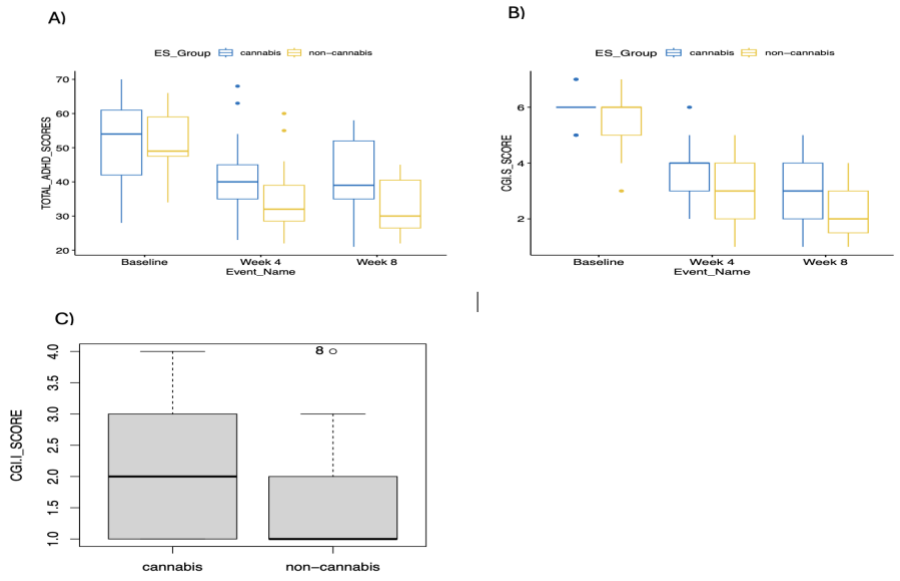

Figure 9: Primary Outcomes in Cannabis and Non-Cannabis Users Using Cannabis Status at Endpoint. (A) Comparing the average BAARS-IV scores between cannabis (blue) and non-cannabis users (yellow) at baseline, week 4 and week 8. (B) Comparing the average CGI-S scores between cannabis (blue) and non-cannabis users (yellow) at baseline, week 4 and week 8 (C) Comparing the average CGI-I scores between cannabis and non-cannabis users at endpoint. (Depicted figures were created using RStudio).

*Analysis is being depicted using boxplots which include the median represented as the dark solid line in the box, the upper box is representative of the upper quartile values and the lower limit of the box is representative of the lower quartile values. The lower whisker on the box plot represents

the minimum data value and the upper whisker represents the maximum data value. Dots above or below the box plot represent outlier scores. Half box plots represent that the median is close to the lower or higher percentile scores, therefore both lines are very close to each other giving the illusion of half a box. Flat solid lines represent that the median was the only score and therefore is depicted as a line.

Table 12: Means and Standard Deviations of BAARS-IV, CGI-S, and CG-I Scores in Cannabis and Non-Cannabis Users Based on Endpoint Cannabis Status

N=40	BAARS-IV Scores						CGI-S Scores						CGI-I Scores	
	baseline		Week 4		Week 8		baseline		Week 4		Week 8		Week 8	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Cannabis (N=17)	51.9	12.1	42.4	11.3	40.0	12.3	5.94	0.5	3.76	1.0	3.0	1.1	1.88	0.99
Non-Cannabis (N=25)	51.35	8.2	35.0	9.5	32.0	7.83	5.3	0.9	2.8	1.2	2.3	1.1	1.43	0.78

Table 13: Means and Standard Deviations of BAARS-IV, CGI-S, and CG-I Scores in Cannabis Users that Stopped Using Cannabis and Non-Cannabis Users that Started Using Cannabis

N=7	BAARS-IV Scores						CGI-S Scores						CGI-I Scores	
	baseline		Week 4		Week 8		baseline		Week 4		Week 8		Week 8	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Stopped using Cannabis (N=5)	49.5	5.9	30.0	5.39	32.2	5.67	5.4	0.89	2.8	1.4	2.2	1.6	1.4	0.89
Started using Cannabis (N=2)	56.00	19.8	52.2	21.9	44.5	13.4	5.5	0.7	4.0	0	1.5	0.7	1.0	0

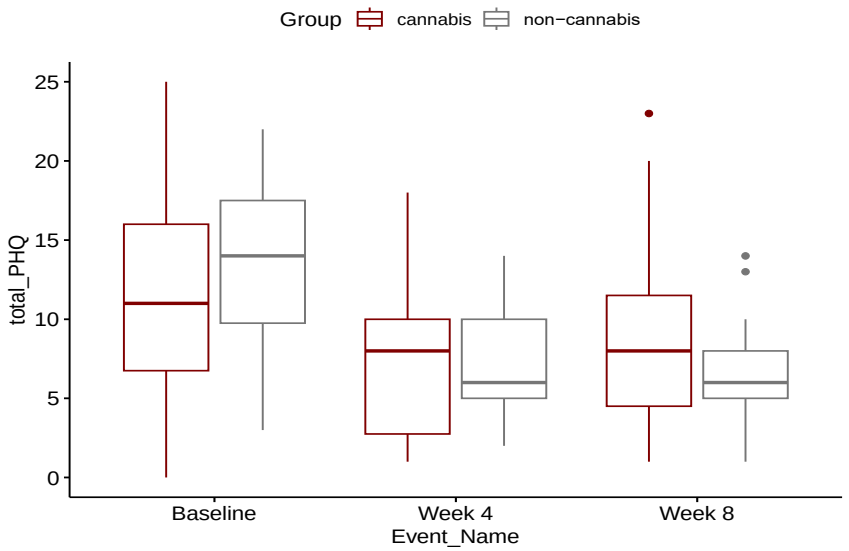

Figure 10: PHQ-9 Scores Over the Course of the Study in Cannabis and Non-Cannabis Users
Comparing the average PHQ-9 scores between cannabis (maroon) and non-cannabis users (grey) at baseline, week 4 and week 8.
*Analysis is being depicted using boxplots which include the median represented as the dark solid line in the box, the upper box is representative of the upper quartile values and the lower limit of the box is representative of the lower quartile values. The lower whisker on the box plot represents the minimum data value and the upper whisker represents the maximum data value. Dots above or below the box plot represent outlier scores. Half box plots represent that the median is close to the lower or higher percentile scores, therefore both lines are very close to each other giving the illusion of half a box. Flat solid lines represent that the median was the only score and therefore is depicted as a line.

Table 14: Means and Standard Deviations PHQ-9 Scores in Cannabis and Non-Cannabis users

N=40	PHQ-9 Scores					
	Baseline		Week 4		Week 8	
	Mean	SD	Mean	SD	Mean	SD
Cannabis (N=20)	11.7	6.57	7.25	5.19	8.65	5.98
Non-Cannabis (N=20)	13.7	5.39	7.35	3.77	6.6	3.25

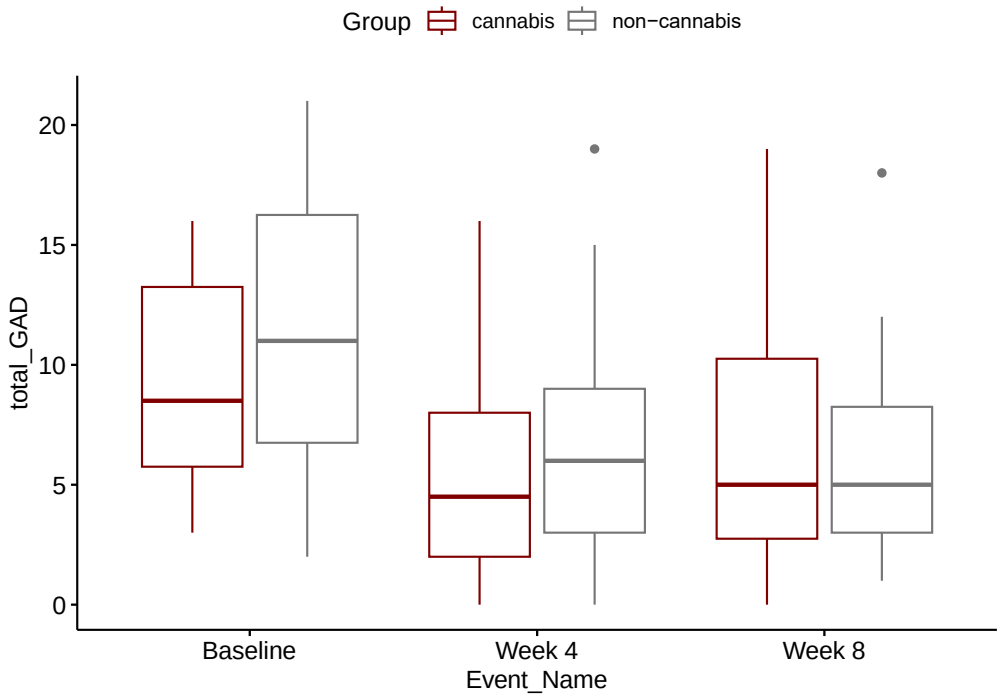

Figure 11: GAD-7 Scores Over the Course of the Study in Cannabis and Non-Cannabis Users
Comparing the average GAD-7 scores between cannabis (maroon) and non-cannabis users (grey) at baseline, week 4 and week 8.
*Analysis is being depicted using boxplots which include the median represented as the dark solid line in the box, the upper box is representative of the upper quartile values and the lower limit of the box is representative of the lower quartile values. The lower whisker on the box plot represents the minimum data value and the upper whisker represents the maximum data value. Dots above or below the box plot represent outlier scores. Half box plots represent that the median is close to the lower or higher percentile scores, therefore both lines are very close to each other giving the illusion of half a box. Flat solid lines represent that the median was the only score and therefore is depicted as a line.

Table 15: Means and Standard Deviations GAD-7 Scores in Cannabis and Non-Cannabis Users

N=40	GAD-7 Scores					
	baseline		Week 4		Week 8	
	Mean	SD	Mean	SD	Mean	SD
Cannabis (N=20)	9.2	4.44	5.8	4.54	6.7	5.73
Non-Cannabis (N=20)	11.1	6.03	6.6	4.89	6.15	4.05

Table 16: Means and Standard Deviations PHQ-9 Scores in Cannabis Users that Stopped Using Cannabis and Non-Cannabis Users that Started Using Cannabis

N=7	PHQ-9 Scores					
	baseline		Week 4		Week 8	
	Mean	SD	Mean	SD	Mean	SD
Stopped using Cannabis (N=5)	10.2	5.35	3.0	2.9	4.2	3.11
Started using Cannabis (N=2)	12.5	13.4	8.5	7.7	8.5	7.77

Table 17: Means and Standard Deviations GAD-7 Scores in Cannabis Users that Stopped Using Cannabis and Non-Cannabis Users that Started Using Cannabis Users

N=7	GAD-7 Scores					
	baseline		Week 4		Week 8	
	Mean	SD	Mean	SD	Mean	SD
Stopped using Cannabis (N=5)	6.0	4.63	3.8	5.26	3.6	4.39
Started using Cannabis (N=2)	10.0	9.89	5.0	4.24	6.0	5.65

6. Bibliography:

Adamou, M., Arif, M., Asherson, P., Aw, T.-C., Bolea, B., Coghill, D., Guðjónsson, G., Halmøy, A., Hodgkins, P., Müller, U., Pitts, M., Trakoli, A., Williams, N., & Young, S. (2013). Occupational issues of adults with ADHD. *BMC Psychiatry*, *13*(1), 59. https://doi.org/10.1186/1471-244X-13-59

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. https://doi.org/10.1016/j.drugalcdep.2010.02.017

Adler, L. A., Goodman, D. W., Kollins, S. H., Weisler, R. H., Krishnan, S., Zhang, Y., & Biederman, J. (2008). Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Lisdexamfetamine Dimesylate in Adults With Attention-Deficit/Hyperactivity Disorder. *The Journal of Clinical Psychiatry*, *69*(9), 1364–1373. https://doi.org/10.4088/JCP.v69n0903

Anker, E., Haavik, J., & Heir, T. (2020). Alcohol and drug use disorders in adult attention-deficit/hyperactivity disorder: Prevalence and associations with attention-deficit/hyperactivity disorder symptom severity and emotional dysregulation. *World Journal of Psychiatry*, *10*(9), 202–211. https://doi.org/10.5498/wjp.v10.i9.202

Artigas, M. S., Sánchez-Mora, C., Rovira, P., Richarte, V., García-Martínez, I., Pagerols, M., Demontis, D., Stringer, S., Vink, J., Børglum, A., Neale, B. M., Franke, B., Faraone, S. V., Casas, M., Ramos-Quiroga, J. A., & Ribasés, M. (2020). Attention-Deficit/Hyperactivity Disorder and lifetime cannabis use: Genetic overlap and causality. *Molecular Psychiatry*, *25*(10), 2493–2503. https://doi.org/10.1038/s41380-018-0339-3

Barbaresi, W. J., Weaver, A. L., Voigt, R. G., Killian, J. M., & Katusic, S. K. (2018). Comparing Methods to Determine Persistence of Childhood ADHD Into Adulthood: A Prospective, Population-Based Study. *Journal of Attention Disorders*, *22*(6), 571–580. https://doi.org/10.1177/1087054715618791

Barkley, R. A. (2011). *Barkley Adult ADHD Rating Scale-IV (BAARS-IV)* (pp. x, 150). The Guilford Press.

Bejerot, S., Rydén, E. M., & Arlinde, C. M. (2010). Two-Year Outcome of Treatment With Central Stimulant Medication in Adult Attention-Deficit/Hyperactivity Disorder: A Prospective Study. *The Journal of Clinical Psychiatry*, *71*(12), 13597. https://doi.org/10.4088/JCP.09m05168pur

Biederman, J., Kwon, A., Aleardi, M., Chouinard, V.-A., Marino, T., Cole, H., Mick, E., & Faraone, S. V. (2005). Absence of Gender Effects on Attention Deficit Hyperactivity Disorder: Findings in Nonreferred Subjects. *American Journal of Psychiatry*, *162*(6), 1083–1089. https://doi.org/10.1176/appi.ajp.162.6.1083

Binder, C., McIntosh, Kutcher, S., Levitt, Rosenbluth, & Fallu. (2009). Adult ADHD and comorbid depression: A consensus-derived diagnostic algorithm for ADHD. *Neuropsychiatric Disease and Treatment*, 137. https://doi.org/10.2147/NDT.S4720

Brandt, A., Rehm, J., & Lev-Ran, S. (2018). Clinical Correlates of Cannabis Use Among Individuals With Attention Deficit Hyperactivity Disorder. *Journal of Nervous & Mental Disease*, *206*(9), 726–732. https://doi.org/10.1097/NMD.0000000000000877

Buitelaar, J. K., Kooij, J. J. S., Ramos-Quiroga, J. A., Dejonckheere, J., Casas, M., van Oene, J. C., Schäuble, B., & Trott, G.-E. (2011). Predictors of treatment outcome in adults with

ADHD treated with OROS® methylphenidate. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *35*(2), 554–560. https://doi.org/10.1016/j.pnpbp.2010.12.016

Bushe, C., Day, K., Reed, V., Karlsdotter, K., Berggren, L., Pitcher, A., Televantou, F., & Haynes, V. (2016). A network meta-analysis of atomoxetine and osmotic release oral system methylphenidate in the treatment of attention-deficit/hyperactivity disorder in adult patients. *Journal of Psychopharmacology (Oxford, England)*, *30*(5), 444–458. https://doi.org/10.1177/0269881116636105

Capusan, A. J., Bendtsen, P., Marteinsdottir, I., & Larsson, H. (2019). Comorbidity of Adult ADHD and Its Subtypes With Substance Use Disorder in a Large Population-Based Epidemiological Study. *Journal of Attention Disorders*, *23*(12), 1416–1426. https://doi.org/10.1177/1087054715626511

Carpentier, P.-J., & Levin, F. R. (2017). Pharmacological Treatment of ADHD in Addicted Patients: What Does the Literature Tell Us? *Harvard Review of Psychiatry*, *25*(2), 50–64. https://doi.org/10.1097/HRP.0000000000000122

Castells, X., Ramos-Quiroga, J. A., Rigau, D., Bosch, R., Nogueira, M., Vidal, X., & Casas, M. (2011). Efficacy of Methylphenidate for Adults with Attention-Deficit Hyperactivity Disorder. *CNS Drugs*, *25*(2), 157–169. https://doi.org/10.2165/11539440-000000000-00000

Chen, Q., Hartman, C. A., Haavik, J., Harro, J., Klungsøyr, K., Hegvik, T.-A., Wanders, R., Ottosen, C., Dalsgaard, S., Faraone, S. V., & Larsson, H. (2018). Common psychiatric and metabolic comorbidity of adult attention-deficit/hyperactivity disorder: A population-based cross-sectional study. *PLoS ONE*, *13*(9), e0204516. https://doi.org/10.1371/journal.pone.0204516

Cherkasova, M. V., French, L. R., Syer, C. A., Cousins, L., Galina, H., Ahmadi-Kashani, Y., & Hechtman, L. (2020). Efficacy of Cognitive Behavioral Therapy With and Without Medication for Adults With ADHD: A Randomized Clinical Trial. *Journal of Attention Disorders*, *24*(6), 889–903. https://doi.org/10.1177/1087054716671197

Choi, W.-S., Woo, Y. S., Wang, S.-M., Lim, H. K., & Bahk, W.-M. (2022). The prevalence of psychiatric comorbidities in adult ADHD compared with non-ADHD populations: A systematic literature review. *PLOS ONE*, *17*(11), e0277175. https://doi.org/10.1371/journal.pone.0277175

Clements, C. C., Castro, V. M., Blumenthal, S. R., Rosenfield, H. R., Murphy, S. N., Fava, M., Erb, J. L., Churchill, S. E., Kaimal, A. J., Doyle, A. E., Robinson, E. B., Smoller, J. W., Kohane, I. S., & Perlis, R. H. (2015). Prenatal antidepressant exposure is associated with risk for attention deficit-hyperactivity disorder but not autism spectrum disorder in a large health system. *Molecular Psychiatry*, *20*(6), 727–734. https://doi.org/10.1038/mp.2014.90

Clure, C., Brady, K. T., Saladin, M. E., Johnson, D., Waid, R., & Rittenbury, M. (1999). Attention-Deficit/Hyperactivity Disorder and Substance Use: Symptom Pattern and Drug Choice. *The American Journal of Drug and Alcohol Abuse*, *25*(3), 441–448. https://doi.org/10.1081/ADA-100101871

Cooper, R. E., Williams, E., Seegobin, S., Tye, C., Kuntsi, J., & Asherson, P. (2017). Cannabinoids in attention-deficit/hyperactivity disorder: A randomised-controlled trial. *European Neuropsychopharmacology*, *27*(8), 795–808. https://doi.org/10.1016/j.euroneuro.2017.05.005

Corbisiero, S., Bitto, H., Newark, P., Abt-Mörstedt, B., Elsässer, M., Buchli-Kammermann, J., Künne, S., Nyberg, E., Hofecker-Fallahpour, M., & Stieglitz, R.-D. (2018). A Comparison of Cognitive-Behavioral Therapy and Pharmacotherapy vs. Pharmacotherapy Alone in Adults With Attention-Deficit/Hyperactivity Disorder (ADHD)—A Randomized Controlled Trial. *Frontiers in Psychiatry*, *9*. https://doi.org/10.3389/fpsyt.2018.00571

Cunill, R., Castells, X., Tobias, A., & Capellà, D. (2016). Efficacy, safety and variability in pharmacotherapy for adults with attention deficit hyperactivity disorder: A meta-analysis and meta-regression in over 9000 patients. *Psychopharmacology*, *233*(2), 187–197. https://doi.org/10.1007/s00213-015-4099-3

De Crescenzo, F., Cortese, S., Adamo, N., & Janiri, L. (2017). Pharmacological and non-pharmacological treatment of adults with ADHD: A meta-review. *Evidence Based Mental Health*, *20*(1), 4–11. https://doi.org/10.1136/eb-2016-102415

Dhamija, D., Bello, A. O., Khan, A. A., Gutlapalli, S. D., Sohail, M., Patel, P. A., Midha, S., Shukla, S., & Mohammed, L. (n.d.). Evaluation of Efficacy of Cannabis Use in Patients With Attention Deficit Hyperactivity Disorder: A Systematic Review. *Cureus*, *15*(6), e40969. https://doi.org/10.7759/cureus.40969

DuPaul, G. J., Schaughency, E. A., Weyandt, L. L., Tripp, G., Kiesner, J., Ota, K., & Stanish, H. (2001). Self-Report of ADHD Symptoms in University Students: Cross-Gender and Cross-National Prevalence. *Journal of Learning Disabilities*, *34*(4), 370–379. https://doi.org/10.1177/002221940103400412

DuPaul, G., Weyandt, L., O'Dell, S., & Varejao, M. (2009). College Students With ADHD: Current Status and Future Directions. *Journal of Attention Disorders*, *13*(3), 234–250. https://doi.org/10.1177/1087054709340650

Edvinsson, D., & Ekselius, L. (2018). Long-Term Tolerability and Safety of Pharmacological Treatment of Adult Attention-Deficit/Hyperactivity Disorder: A 6-Year Prospective Naturalistic Study. *Journal of Clinical Psychopharmacology*, *38*(4), 370. https://doi.org/10.1097/JCP.0000000000000917

Faheem, M., Akram, W., Akram, H., Khan, M. A., Siddiqui, F. A., & Majeed, I. (2022). Gender-based differences in prevalence and effects of ADHD in adults: A systematic review. *Asian Journal of Psychiatry*, *75*, 103205. https://doi.org/10.1016/j.ajp.2022.103205

Faraone, S. V. (2018). The Pharmacology of Amphetamine and Methylphenidate: Relevance to the Neurobiology of Attention-Deficit/Hyperactivity Disorder and Other Psychiatric Comorbidities. *Neuroscience and Biobehavioral Reviews*, *87*, 255–270. https://doi.org/10.1016/j.neubiorev.2018.02.001

Faraone, S. V., Biederman, J., & Mick, E. (2006). The age-dependent decline of attention deficit hyperactivity disorder: A meta-analysis of follow-up studies. *Psychological Medicine*, *36*(2), 159–165. https://doi.org/10.1017/S003329170500471X

Faraone, S. V., Biederman, J., Wilens, T. E., & Adamson, J. (2007). A naturalistic study of the effects of pharmacotherapy on substance use disorders among ADHD adults. *Psychological Medicine*, *37*(12), 1743–1752. https://doi.org/10.1017/S0033291707000335

Faraone, S. V., & Larsson, H. (2019). Genetics of attention deficit hyperactivity disorder. *Molecular Psychiatry*, *24*(4), 562–566. https://doi.org/10.1038/s41380-018-0070-0

Faraone, S. V., Wilens, T. E., Petty, C., Antshel, K., Spencer, T., & Biederman, J. (2007). Substance Use among ADHD Adults: Implications of Late Onset and Subthreshold Diagnoses. *The American Journal on Addictions*, *16*(s1), 24–34. https://doi.org/10.1080/10550490601082767

Fayyad, J., Graaf, R. D., Kessler, R., Alonso, J., Angermeyer, M., Demyttenaere, K., Girolamo, G. D., Haro, J. M., Karam, E. G., Lara, C., Lépine, J.-P., Ormel, J., Posada-Villa, J., Zaslavsky, A. M., & Jin, R. (2007). Cross-national prevalence and correlates of adult attention-deficit hyperactivity disorder. *The British Journal of Psychiatry*, *190*(5), 402–409. https://doi.org/10.1192/bjp.bp.106.034389

Fedele, D. A., Lefler, E. K., Hartung, C. M., & Canu, W. H. (2012). Sex Differences in the Manifestation of ADHD in Emerging Adults. *Journal of Attention Disorders*, *16*(2), 109–117. https://doi.org/10.1177/1087054710374596

Fischer, A. G., Bau, C. H. D., Eugenio H. Grevet, Salgado, C. A. I., Victor, M. M., Kalil, K. L. S., Sousa, N. O., Garcia, C. R., & Belmonte-de-Abreu, P. (2007). The role of comorbid major depressive disorder in the clinical presentation of adult ADHD. *Journal of Psychiatric Research*, *41*(12), 991–996. https://doi.org/10.1016/j.jpsychires.2006.09.008

Francisco, A. P., Lethbridge, G., Patterson, B., Goldman Bergmann, C., & Van Ameringen, M. (2023). Cannabis use in Attention – Deficit/Hyperactivity Disorder (ADHD): A scoping review. *Journal of Psychiatric Research*, *157*, 239–256. https://doi.org/10.1016/j.jpsychires.2022.11.029

Fredriksen, M., Halmøy, A., Faraone, S. V., & Haavik, J. (2013). Long-term efficacy and safety of treatment with stimulants and atomoxetine in adult ADHD: A review of controlled and

naturalistic studies. *European Neuropsychopharmacology*, *23*(6), 508–527. https://doi.org/10.1016/j.euroneuro.2012.07.016

Gao, L., Li, S., Yue, Y., & Long, G. (2023). Maternal age at childbirth and the risk of attention-deficit/hyperactivity disorder and learning disability in offspring. *Frontiers in Public Health*, *11*. https://doi.org/10.3389/fpubh.2023.923133

Gonon, F. (2009). The dopaminergic hypothesis of attention-deficit/hyperactivity disorder needs re-examining. *Trends in Neurosciences*, *32*(1), 2–8. https://doi.org/10.1016/j.tins.2008.09.010

Government of Canada. (2022, December 16). *Canadian Cannabis Survey 2022: Summary* [Surveys]. https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/research-data/canadian-cannabis-survey-2022-summary.html

Graetz, B. W., Sawyer, M. G., & Baghurst, P. (2005). Gender Differences Among Children With *DSM-IV* ADHD in Australia. *Journal of the American Academy of Child & Adolescent Psychiatry*, *44*(2), 159–168. https://doi.org/10.1097/00004583-200502000-00008

Guy, W. (1976). *ECDEU assessment manual for psychopharmacology*. U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs.

Hall, W., Stjepanović, D., Dawson, D., & Leung, J. (2023). The implementation and public health impacts of cannabis legalization in Canada: A systematic review. *Addiction*, *118*(11), 2062–2072. https://doi.org/10.1111/add.16274

Halmøy, A., Klungsøyr, K., Skjærven, R., & Haavik, J. (2012). Pre- and Perinatal Risk Factors in Adults with Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry*, *71*(5), 474–481. https://doi.org/10.1016/j.biopsych.2011.11.013

Haney, M. (2022). Cannabis Use and the Endocannabinoid System: A Clinical Perspective. *American Journal of Psychiatry*, *179*(1), 21–25. https://doi.org/10.1176/appi.ajp.2021.21111138

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, *42*(2), 377–381. https://doi.org/10.1016/j.jbi.2008.08.010

Henschke, P. (2019). Cannabis: An ancient friend or foe? What works and doesn't work. *Seminars in Fetal and Neonatal Medicine*, *24*(2), 149–154. https://doi.org/10.1016/j.siny.2019.02.001

Hoffman, K., Webster, T. F., Weisskopf, M. G., Weinberg, J., & Vieira, V. M. (2010). Exposure to Polyfluoroalkyl Chemicals and Attention Deficit/Hyperactivity Disorder in U.S. Children 12–15 Years of Age. *Environmental Health Perspectives*, *118*(12), 1762–1767. https://doi.org/10.1289/ehp.1001898

Hunt, D. A., Keefe, J., Whitehead, T., & Littlefield, A. (2020). Understanding Cannabis. *The Journal for Nurse Practitioners*, *16*(9), 645–649. https://doi.org/10.1016/j.nurpra.2020.07.007

Hupli, A. M. M. (2018). Medical Cannabis for Adult Attention Deficit Hyperactivity Disorder: Sociological Patient Case Report of Cannabinoid Therapeutics in Finland. *Medical Cannabis and Cannabinoids*, *1*(2), 112–118. https://doi.org/10.1159/000495307

Hvolgaard Mikkelsen, S., Olsen, J., Bech, B. H., & Obel, C. (2017). Parental age and attention-deficit/hyperactivity disorder (ADHD). *International Journal of Epidemiology*, *46*(2), 409–420. https://doi.org/10.1093/ije/dyw073

Ingram, S., Hechtman, L., & Morgenstern, G. (1999). Outcome issues in ADHD: Adolescent and adult long-term outcome. *Mental Retardation and Developmental Disabilities Research Reviews*, *5*(3), 243–250. https://doi.org/10.1002/(SICI)1098-2779(1999)5:3<243::AID-MRDD11>3.0.CO;2-D

Jensen, C. M., Amdisen, B. L., Jørgensen, K. J., & Arnfred, S. M. H. (2016). Cognitive behavioural therapy for ADHD in adults: Systematic review and meta-analyses. *ADHD Attention Deficit and Hyperactivity Disorders*, *8*(1), 3–11. https://doi.org/10.1007/s12402-016-0188-3

Katzman, M. A., Bilkey, T. S., Chokka, P. R., Fallu, A., & Klassen, L. J. (2017). Adult ADHD and comorbid disorders: Clinical implications of a dimensional approach. *BMC Psychiatry*, *17*(1), 302. https://doi.org/10.1186/s12888-017-1463-3

Kearney-Ramos, T., Herrmann, E. S., Belluomo, I., Matias, I., Vallée, M., Monlezun, S., Piazza, P. V., & Haney, M. (2023). The Relationship Between Circulating Endogenous Cannabinoids and the Effects of Smoked Cannabis. *Cannabis and Cannabinoid Research*, *8*(6), 1069–1078. https://doi.org/10.1089/can.2021.0185

Kessler, R. C., Adler, L., Barkley, R., Biederman, J., Conners, C. K., Demler, O., Faraone, S. V., Greenhill, L. L., Howes, M. J., Secnik, K., Spencer, T., Ustun, T. B., Walters, E. E., & Zaslavsky, A. M. (2006). The prevalence and correlates of adult ADHD in the United States: Results from the National Comorbidity Survey Replication. *The American Journal of Psychiatry*, *163*(4), 716–723. https://doi.org/10.1176/appi.ajp.163.4.716

Kian, N., Samieefar, N., & Rezaei, N. (2022). Prenatal risk factors and genetic causes of ADHD in children. *World Journal of Pediatrics, 18*(5), 308–319. https://doi.org/10.1007/s12519-022-00524-6

Klassen, L. J., Katzman, M. A., & Chokka, P. (2010). Adult ADHD and its comorbidities, with a focus on bipolar disorder. *Journal of Affective Disorders*, *124*(1), 1–8. https://doi.org/10.1016/j.jad.2009.06.036

Koesters, M., Becker, T., Kilian, R., Fegert, J., & Weinmann, S. (2009). Limits of meta-analysis: Methylphenidate in the treatment of adult attention-deficit hyperactivity disorder. *Journal of Psychopharmacology*, *23*(7), 733–744. https://doi.org/10.1177/0269881108092338

Konstenius, M., Jayaram-Lindström, N., Beck, O., & Franck, J. (2010). Sustained release methylphenidate for the treatment of ADHD in amphetamine abusers: A pilot study. *Drug and Alcohol Dependence*, *108*(1–2), 130–133. https://doi.org/10.1016/j.drugalcdep.2009.11.006

Konstenius, M., Jayaram-Lindström, N., Guterstam, J., Beck, O., Philips, B., & Franck, J. (2014). Methylphenidate for attention deficit hyperactivity disorder and drug relapse in criminal offenders with substance dependence: A 24-week randomized placebo-controlled trial. *Addiction, 109*(3), 440–449. https://doi.org/10.1111/add.12369

Kooij, J. J. S., Burger, H., Boonstra, A. M., Van der Linden, P. D., Kalma, L. E., & Buitelaar, J. K. (2004). Efficacy and safety of methylphenidate in 45 adults with attention-deficit/hyperactivity disorder. A randomized placebo-controlled double-blind cross-over trial. *Psychological Medicine, 34*(6), 973–982. https://doi.org/10.1017/s0033291703001776

Kooij, J. J. S., Huss, M., Asherson, P., Akehurst, R., Beusterien, K., French, A., Sasané, R., & Hodgkins, P. (2012). Distinguishing Comorbidity and Successful Management of Adult ADHD. *Journal of Attention Disorders*, *16*(5_suppl), 3S-19S. https://doi.org/10.1177/1087054711435361

Kroenke, K., & Spitzer, R. L. (2002). The PHQ-9: A New Depression Diagnostic and Severity Measure. *Psychiatric Annals*, *32*(9), 509–515. https://doi.org/10.3928/0048-5713-20020901-06

Leon, A. C., Olfson, M., Portera, L., Farber, L., & Sheehan, D. V. (1997). Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. *International Journal of Psychiatry in Medicine*, *27*(2), 93–105. https://doi.org/10.2190/T8EM-C8YH-373N-1UWD

Levin, F. R., Evans, S. M., Brooks, D. J., & Garawi, F. (2007). Treatment of cocaine dependent treatment seekers with adult ADHD: Double-blind comparison of methylphenidate and placebo. *Drug and Alcohol Dependence*, *87*(1), 20–29. https://doi.org/10.1016/j.drugalcdep.2006.07.004

Levin, F. R., Evans, S. M., Brooks, D. J., Kalbag, A. S., Garawi, F., & Nunes, E. V. (2006). Treatment of methadone-maintained patients with adult ADHD: Double-blind comparison of methylphenidate, bupropion and placebo. *Drug and Alcohol Dependence*, *81*(2), 137–148. https://doi.org/10.1016/j.drugalcdep.2005.06.012

Levin, F. R., Mariani, J. J., Specker, S., Mooney, M., Mahony, A., Brooks, D. J., Babb, D., Bai, Y., Eberly, L. E., Nunes, E. V., & Grabowski, J. (2015). Extended-Release Mixed Amphetamine Salts vs Placebo for Comorbid Adult Attention-Deficit/Hyperactivity

Disorder and Cocaine Use Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*, *72*(6), 593–602. https://doi.org/10.1001/jamapsychiatry.2015.41

Li, Y., & Zhang, L. (2024). Efficacy of Cognitive Behavioral Therapy Combined with Pharmacotherapy Versus Pharmacotherapy Alone in Adult ADHD: A Systematic Review and Meta-Analysis. *Journal of Attention Disorders*, *28*(3), 279–292. https://doi.org/10.1177/10870547231214969

Lopez, P. L., Torrente, F. M., Ciapponi, A., Lischinsky, A. G., Cetkovich-Bakmas, M., Rojas, J. I., Romano, M., & Manes, F. F. (2018). Cognitive-behavioural interventions for attention deficit hyperactivity disorder (ADHD) in adults. *The Cochrane Database of Systematic Reviews*, *2018*(3), CD010840. https://doi.org/10.1002/14651858.CD010840.pub2

MacDonald, B., & Sadek, J. (2021). Naturalistic exploratory study of the associations of substance use on ADHD outcomes and function. *BMC Psychiatry*, *21*(1), 251. https://doi.org/10.1186/s12888-021-03263-6

Mansell, H., Quinn, D., Kelly, L. E., & Alcorn, J. (2022). Cannabis for the Treatment of Attention Deficit Hyperactivity Disorder: A Report of 3 Cases. *Medical Cannabis and Cannabinoids*, *5*(1), 1–6. https://doi.org/10.1159/000521370

Mechler, K., Banaschewski, T., Hohmann, S., & Häge, A. (2022). Evidence-based pharmacological treatment options for ADHD in children and adolescents. *Pharmacology & Therapeutics*, *230*, 107940. https://doi.org/10.1016/j.pharmthera.2021.107940

Mohammadi, M.-R., Zarafshan, H., Khaleghi, A., Ahmadi, N., Hooshyari, Z., Mostafavi, S.-A., Ahmadi, A., Alavi, S.-S., Shakiba, A., & Salmanian, M. (2021). Prevalence of ADHD and Its Comorbidities in a Population-Based Sample. *Journal of Attention Disorders*, *25*(8), 1058–1067. https://doi.org/10.1177/1087054719886372

Murray, A. L., Booth, T., Eisner, M., Auyeung, B., Murray, G., & Ribeaud, D. (2019). Sex differences in ADHD trajectories across childhood and adolescence. *Developmental Science, 22*(1), e12721. https://doi.org/10.1111/desc.12721

Pan, M.-R., Zhang, S.-Y., Qiu, S.-W., Liu, L., Li, H.-M., Zhao, M.-J., Dong, M., Si, F.-F., Wang, Y.-F., & Qian, Q.-J. (2022). Efficacy of cognitive behavioural therapy in medicated adults with attention-deficit/hyperactivity disorder in multiple dimensions: A randomised controlled trial. *European Archives of Psychiatry and Clinical Neuroscience*, *272*(2), 235–255. https://doi.org/10.1007/s00406-021-01236-0

Pan, P.-Y., Jonsson, U., Çakmak, S. S. Ş., Häge, A., Hohmann, S., Norrman, H. N., Buitelaar, J. K., Banaschewski, T., Cortese, S., Coghill, D., & Bölte, S. (2022). Headache in ADHD as comorbidity and a side effect of medications: A systematic review and meta-analysis. *Psychological Medicine, 52*(1), 14–25. https://doi.org/10.1017/S0033291721004141

Perugi, G., Pallucchini, A., Rizzato, S., Pinzone, V., & De Rossi, P. (2019). Current and emerging pharmacotherapy for the treatment of adult attention deficit hyperactivity disorder (ADHD). *Expert Opinion on Pharmacotherapy*, *20*(12), 1457–1470. https://doi.org/10.1080/14656566.2019.1618270

Quenneville, A. F., Kalogeropoulou, E., Nicastro, R., Weibel, S., Chanut, F., & Perroud, N. (2022). Anxiety disorders in adult ADHD: A frequent comorbidity and a risk factor for externalizing problems. *Psychiatry Research*, *310*, 114423. https://doi.org/10.1016/j.psychres.2022.114423

R Core Team. (2023). *R: A Language and Environment for Statistical Computing* [R]. R foundation for Statistical Computing. https://www.R-project.org/

Ramtekkar, U. P., Reiersen, A. M., Todorov, A. A., & Todd, R. D. (2010). Sex and age differences in Attention-Deficit/Hyperactivity Disorder symptoms and diagnoses: Implications for DSM-V and ICD-11. *Journal of the American Academy of Child and Adolescent Psychiatry*, *49*(3), 217-28.e1-3.

Reale, L., Bartoli, B., Cartabia, M., Zanetti, M., Costantino, M. A., Canevini, M. P., Termine, C., Bonati, M., Conte, S., Renzetti, V., Salvoni, L., Molteni, M., Salandi, A., Trabattoni, S., Effedri, P., Filippini, E., Pedercini, E., Zanetti, E., Fteita, N., … on behalf of Lombardy ADHD Group. (2017). Comorbidity prevalence and treatment outcome in children and adolescents with ADHD. *European Child & Adolescent Psychiatry*, *26*(12), 1443–1457. https://doi.org/10.1007/s00787-017-1005-z

Retz, W., & Retz-Junginger, P. (2014). Prediction of methylphenidate treatment outcome in adults with attention-deficit/hyperactivity disorder (ADHD). *European Archives of Psychiatry and Clinical Neuroscience*, *264*(1), 35–43. https://doi.org/10.1007/s00406-014-0542-4

Robison, R. J., & Faraone, S. V. (2008). Gender Differences in 2 Clinical Trials of Adults With Attention-Deficit/Hyperactivity Disorder: A Retrospective Data Analysis. *J Clin Psychiatry*.

Safren, S. A., Otto, M. W., Sprich, S., Winett, C. L., Wilens, T. E., & Biederman, J. (2005). Cognitive-behavioral therapy for ADHD in medication-treated adults with continued symptoms. *Behaviour Research and Therapy*, *43*(7), 831–842. https://doi.org/10.1016/j.brat.2004.07.001

Schachter, H. M., Pham, B., King, J., Langford, S., & Moher, D. (2001). How efficacious and safe is short-acting methylphenidate for the treatment of attention-deficit disorder in

children and adolescents? A meta-analysis. *CMAJ: Canadian Medical Association Journal*, *165*(11), 1475–1488.

Sciberras, E., Mulraney, M., Silva, D., & Coghill, D. (2017). Prenatal Risk Factors and the Etiology of ADHD—Review of Existing Evidence. *Current Psychiatry Reports*, *19*(1), 1. https://doi.org/10.1007/s11920-017-0753-2

Sharma, A., & Couture, J. (2014). A review of the pathophysiology, etiology, and treatment of attention-deficit hyperactivity disorder (ADHD). *The Annals of Pharmacotherapy*, *48*(2), 209–225. https://doi.org/10.1177/1060028013510699

Simon, V., Czobor, P., Bálint, S., Mészáros, Á., & Bitter, I. (2009). Prevalence and correlates of adult attention-deficit hyperactivity disorder: Meta-analysis. *The British Journal of Psychiatry*, *194*(3), 204–211. https://doi.org/10.1192/bjp.bp.107.048827

Simons, J., Correia, C. J., Carey, K. B., & Borsari, B. E. (1998). Validating a five-factor marijuana motives measure: Relations with use, problems, and alcohol motives. *Journal of Counseling Psychology*, *45*(3), 265–273. https://doi.org/10.1037/0022-0167.45.3.265

Simons, J. S., Dvorak, R. D., Merrill, J. E., & Read, J. P. (2012). Dimensions and Severity of Marijuana Consequences: Development and Validation of the Marijuana Consequences Questionnaire (MACQ). *Addictive Behaviors*, *37*(5), 613–621. https://doi.org/10.1016/j.addbeh.2012.01.008

Skirrow, C., Hosang, G. M., Farmer, A. E., & Asherson, P. (2012). An update on the debated association between ADHD and bipolar disorder across the lifespan. *Journal of Affective Disorders*, *141*(2–3), 143–159. https://doi.org/10.1016/j.jad.2012.04.003

Song, P., Zha, M., Yang, Q., Zhang, Y., Li, X., & Rudan, I. (n.d.). The prevalence of adult attention-deficit hyperactivity disorder: A global systematic review and meta-analysis. *Journal of Global Health*, *11*, 04009. https://doi.org/10.7189/jogh.11.04009

Spencer, T. J., Adler, L. A., McGough, J. J., Muniz, R., Jiang, H., & Pestreich, L. (2007). Efficacy and Safety of Dexmethylphenidate Extended-Release Capsules in Adults with Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry*, *61*(12), 1380–1387. https://doi.org/10.1016/j.biopsych.2006.07.032

Spencer, T., Wilens, T., Biederman, J., Faraone, S. V., Ablon, J. S., & Lapey, K. (1995). A double-blind, crossover comparison of methylphenidate and placebo in adults with childhood-onset attention-deficit hyperactivity disorder. *Archives of General Psychiatry*, *52*(6), 434–443. https://doi.org/10.1001/archpsyc.1995.03950180020004

Spera, V., Pallucchini, A., Maiello, M., Carli, M., Maremmani, A. G. I., Perugi, G., & Maremmani, I. (2020). Substance Use Disorder in Adult-Attention Deficit Hyperactive Disorder Patients: Patterns of Use and Related Clinical Features. *International Journal of Environmental Research and Public Health*, *17*(10), 3509. https://doi.org/10.3390/ijerph17103509

Spitzer, R. L., Kroenke, K., Williams, J. B. W., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: The GAD-7. *Archives of Internal Medicine*, *166*(10), 1092–1097. https://doi.org/10.1001/archinte.166.10.1092

Sprich, S. E., Knouse, L. E., Cooper-Vince, C., Burbridge, J., & Safren, S. A. (2010). Description and Demonstration of CBT for ADHD in Adults. *Cognitive and Behavioral Practice*, *17*(1), 9–15. https://doi.org/10.1016/j.cbpra.2009.09.002

Stibbe, T., Huang, J., Paucke, M., Ulke, C., & Strauss, M. (2020). Gender differences in adult ADHD: Cognitive function assessed by the test of attentional performance. *PLoS ONE*, *15*(10), e0240810. https://doi.org/10.1371/journal.pone.0240810

Stueber, A., & Cuttler, C. (2022). Self-Reported Effects of Cannabis on ADHD Symptoms, ADHD Medication Side Effects, and ADHD-Related Executive Dysfunction. *Journal of Attention Disorders*, *26*(6), 942–955. https://doi.org/10.1177/10870547211050949

Stuhec, M., Lukić, P., & Locatelli, I. (2019). Efficacy, Acceptability, and Tolerability of Lisdexamfetamine, Mixed Amphetamine Salts, Methylphenidate, and Modafinil in the Treatment of Attention-Deficit Hyperactivity Disorder in Adults: A Systematic Review and Meta-analysis. *Annals of Pharmacotherapy*, *53*(2), 121–133. https://doi.org/10.1177/1060028018795703

Swanson, J. M., Kinsbourne, M., Nigg, J., Lanphear, B., Stefanatos, G. A., Volkow, N., Taylor, E., Casey, B. J., Castellanos, F. X., & Wadhwa, P. D. (2007). Etiologic Subtypes of Attention-Deficit/Hyperactivity Disorder: Brain Imaging, Molecular Genetic and Environmental Factors and the Dopamine Hypothesis. *Neuropsychology Review*, *17*(1), 39–59. https://doi.org/10.1007/s11065-007-9019-9

Tamm, L., Trello-Rishel, K., Riggs, P., Nakonezny, P. A., Acosta, M., Bailey, G., & Winhusen, T. (2013). Predictors of treatment response in adolescents with comorbid substance use disorder and attention-deficit/hyperactivity disorder. *Journal of Substance Abuse Treatment*, *44*(2), 224–230. https://doi.org/10.1016/j.jsat.2012.07.001

Torgersen, T., Gjervan, B., & Rasmussen, K. (2008). Treatment of adult ADHD: Is current knowledge useful to clinicians? *Neuropsychiatric Disease and Treatment*, *4*(1), 177–186. https://doi.org/10.2147/ndt.s1223

van de Glind, G., Van Emmerik-van Oortmerssen, K., Carpentier, P. J., Levin, F. R., Koeter, M. W. J., Barta, C., Kaye, S., Skutle, A., Franck, J., Konstenius, M., Bu, E., Moggi, F., Dom, G., Demetrovics, Z., Fatséas, M., Schillinger, A., Kapitány-Fövény, M., Verspreet, S., Seitz, A., … van den Brink, W. (2013). The International ADHD in Substance Use Disorders Prevalence (IASP) study: Background, methods and study population. *International Journal of Methods in Psychiatric Research*, *22*(3), 232–244. https://doi.org/10.1002/mpr.1397

Van Der Burg, D., Crunelle, C. L., Matthys, F., & Van Den Brink, W. (2019). Diagnosis and treatment of patients with comorbid substance use disorder and adult attention-deficit and hyperactivity disorder: A review of recent publications. *Current Opinion in Psychiatry*, *32*(4), 300–306. https://doi.org/10.1097/YCO.0000000000000513

van Emmerik-van Oortmerssen, K., van de Glind, G., van den Brink, W., Smit, F., Crunelle, C. L., Swets, M., & Schoevers, R. A. (2012). Prevalence of attention-deficit hyperactivity disorder in substance use disorder patients: A meta-analysis and meta-regression analysis. *Drug and Alcohol Dependence*, *122*(1), 11–19. https://doi.org/10.1016/j.drugalcdep.2011.12.007

Wilens, T. E., & Morrison, N. R. (2011). The intersection of attention-deficit/hyperactivity disorder and substance abuse: *Current Opinion in Psychiatry*, *24*(4), 280–285. https://doi.org/10.1097/YCO.0b013e328345c956

World Health Organization. (2021). *Cannabis*. https://www.who.int/teams/mental-health-and-substance-use/alcohol-drugs-and-addictive-behaviours/drugs-psychoactive/cannabis

Young, Z., Moghaddam, N., & Tickle, A. (2020). The Efficacy of Cognitive Behavioral Therapy for Adults With ADHD: A Systematic Review and Meta-Analysis of Randomized

Controlled Trials. *Journal of Attention Disorders*, *24*(6), 875–888. https://doi.org/10.1177/1087054716664413

Zalsman, G., & Shilton, T. (2016). Adult ADHD: A new disease? *International Journal of Psychiatry in Clinical Practice*, *20*(2), 70–76. https://doi.org/10.3109/13651501.2016.1149197

Zulauf, C. A., Sprich, S. E., Safren, S. A., & Wilens, T. E. (2014). The Complicated Relationship Between Attention Deficit/Hyperactivity Disorder and Substance Use Disorders. *Current Psychiatry Reports*, *16*(3), 436. https://doi.org/10.1007/s11920-013-0436-6