Exploring Novel Aspects of Cannabis Use Patterns and Their Associations with Anxiety and Cannabis Outcomes in Trauma-Exposed Cannabis Users

by

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Dalhousie University is in Mi'kma'ki, the ancestral and unceded territory of the Mi'kmaq. We are all Treaty people.

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ABSTRACT

Many Canadian adults who have experienced trauma are also using cannabis. While these individuals may be self-medicating with cannabis to reduce their post-traumatic stress (PTS) symptoms acutely, they may be putting themselves at a higher longer-term risk of developing cannabis use disorder (CUD) and/or exacerbating their anxiety symptoms. The current thesis examined two novel aspects of cannabis use patterns – cannabis use regimens and cannabis potency – along with their relationships with the adverse cannabis and anxiety outcomes that can result from such patterns of cannabis use. Study 1 of this thesis examined and provided support that cannabis use regimens including *pro re nata* (PRN) or, "as needed," use were more prevalent, more likely to be transitioned to over time, and associated with higher cannabis use frequency per month compared to regularly scheduled (RS) use regimens in a sample of N=94 trauma-exposed regular cannabis users. Study 2 identified that [THC] proportion (THC/[THC+cannabidiol[CBD]]), a new proposed measure of cannabis potency, was significantly positively related to both CUD and anxiety symptoms, and those relationships did not differ by gender, in a sample of N=199 trauma-exposed recent cannabis users. These two aspects of cannabis use among trauma-exposed cannabis users may contribute to the high rates of CUD in this population. Taken together, the results of these two studies may inform preventative and/or clinical interventions for those using cannabis to cope with traumatic experiences, as those using highly potent cannabis (HPC) and/or in a PRN manner may be at the highest risk of adverse cannabis and/or anxiety outcomes.

Keywords: cannabis, trauma, trauma sequelae, dosing regimen, pro re nata, PRN, regularly scheduled, cannabis dose, cannabis frequency THC, CBD, THC:CBD ratio, THC potency, dependence, gender.

LIST OF ABBREVIATIONS AND SYMBOLS USED

APA	American Psychiatric Association
BID	Twice daily
CBD	Cannabidiol
CUD	Cannabis Use Disorder
CUDIT-R	Cannabis Use Disorder Identification Test-Revised
CUQ	Cannabis Use Questionnaire
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
H1	Hypothesis 1
H2	Hypothesis 2
H3	Hypothesis 3
H4	Hypothesis 4
H5	Hypothesis 5
LEC-5	Life Events Checklist-5
M	Mean
N	Sample Size
p	Significance
PCL-5	Posttraumatic Stress Disorder Checklist-5
PRN	*Pro re nata* or “as needed” use regimen
PRN+	Both *pro re nata* and regularly scheduled
PTS	Posttraumatic Stress
PTSD	Posttraumatic Stress Disorder

RS	Regularly Scheduled
SD	Standard Deviation
THC	Δ9-tetrahydrocannabinol
TID	Three times daily

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Congratulations!

CHAPTER 1: GENERAL INTRODUCTION

Throughout our lifetimes, we may experience events that can trigger a traumatic response in our brains. These responses may alter our neurochemistry in both the shorter- and longer-term. Trauma exposure is the diagnostic Criterion A for posttraumatic stress disorder (PTSD), and is defined, in the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision* (DSM-5-TR), as an exposure to death, threatened death, actual or threatened serious injury, or threatened sexual violence (American Psychiatric Association [APA], 2022). Examples of traumatic events meeting this Criterion A definition include but are not limited to: physical and sexual assault, natural disasters, serious physical injury, and military combat. Trauma exposure can occur in multiple ways: i.e., through directly or indirectly experiencing, witnessing, and/or learning about a traumatic event (APA, 2022). Trauma exposure has been a recognized global health issue for over a century now, with documented cases of exposures going as far back as the "shell shock" phenomena in World War I soldiers (Smith & Pear, 1917) and the documentation of "rape trauma syndrome," in sexual assault victims (Burgess & Holmstrom, 1974). Worldwide, trauma exposure prevalence rates have been documented to be as high as 70.4% (Kessler et al., 2017). In a survey conducted amongst 2991 nationally representative Canadian adults, 76.1% of respondents had experienced at least one traumatic event meeting criterion A of a PTSD diagnosis across their lifetime (Van Ameringen et al., 2008). While many individuals who have been exposed to a traumatic event(s) may not develop a traumatic stress disorder, they may still experience many negative physical and mental health issues.

Individuals with histories of trauma exposure are unique in their risk for mental health issues. A significant issue amongst those with histories of trauma exposure is the increased risk of substance use problems and addiction (Kevorkian et al., 2015; Bassir Nia et al., 2023). One of

the first studies of the high rates of substance-related issues amongst those with trauma exposure was conducted by Keane and colleagues (1988), who found high rates of problematic alcohol, nicotine, and caffeine use amongst treatment-seeking combat Veterans, particularly those with PTS symptoms[1] . Others have found that individuals who have experienced trauma are 4.5x more likely to develop a substance use disorder (SUD) than those who have not, according to the National Comorbidity Survey (NCS: Kessler et al., 1995). Even more recently, in a survey study among Canadian adults, of those who had experienced a traumatic event, 41.3% had a comorbid SUD involving alcohol, nicotine, and/or cannabis (Van Ameringen et al., 2008). Additionally, those reporting trauma exposure showed a much higher prevalence of alcohol abuse/dependence and other substance abuse/dependence[2] compared to those without trauma exposure (27.8% vs. 14.4% and 25.5% vs. 7.2%, respectively). Indeed, psychological trauma has been commonly associated with substance use issues, including both the development and maintenance of addictions (Levin et al., 2021; Stewart et al., 1998). However, conversely, substance use issues may additionally exacerbate posttraumatic stress (PTS) symptoms that occur after trauma exposure (Jacobsen et al., 2001). Additionally, others (e.g., Stewart, 1996) have suggested that the link of trauma exposure and substance use issues may be specific to those trauma survivors with significant PTS symptoms. There is substantial evidence for this contention (Brady et al., 2000; Brown et al., 1998; Van den Brink, 2015). The high frequency of concurrent trauma exposure and SUDs has been associated with more severe PTS symptoms and negative treatment outcomes for both PTS and SUD symptoms (Brady et al., 2000). Additionally, trauma reminders have been associated with a higher risk of substance misuse, and substance withdrawal has been

[1]PTSD refers to the psychiatric diagnosis, while PTS symptoms refer to continuous measures of symptoms the disorder that do not necessarily meet the diagnostic threshold.
[2] Substance abuse and substance dependence were DSM-IV (APA, 1994) terminology used to describe what we now refer to as milder and more severe forms of substance use disorder (SUD), respectively, in DSM-5-TR (APA, 2022).

associated with more severe PTS symptoms (Brown et al., 1998). Indeed, the reciprocal relationship between trauma exposure and SUDs have shown worsened outcomes for patients.

The consequences of trauma exposure also extend further than PTS symptoms, PTSD, and substance use problems. There are also emotional impacts that can be linked to increased anxiety levels. Although it can be argued that many of the symptoms of PTSD involve maladaptive, anxious responses to trauma exposure (e.g., avoidance), trauma exposure is also related to trauma exposure is also related explicitly to anxiety disorders. Indeed, PTSD used to be classified as an anxiety disorder but was moved into a separate category given that the negative affect involved is broader than just anxiety (e.g., involving anger, guilt and shame). For example, in a meta-analysis examining associations between early psychological trauma and anxiety disorders, Fernandes and Osorio (2015) found that individuals with early psychological trauma were 1.9-3.6 times more likely to develop anxiety disorders and that early trauma was the main predictor for social anxiety disorder. Additionally, Kuzminskaite and colleagues (2021) found that childhood trauma was associated with significantly higher prevalence and chronicity of anxiety disorders amongst a longitudinal cohort of Dutch adults.

One explanation of the links between trauma exposure and substance use disorders is the self-medication hypothesis (SMH) in the context of posttraumatic stress disorder (PTSD: APA, 2022; Khantzian, 1997) and anxiety disorder symptoms. The SMH is a causal model that draws on both psychodynamic and learning theory principles (Blume, 2001) to posit that individuals with psychiatric symptoms are more prone to developing problematic substance use due to a pattern of learned behavior where a substance is used to cope with the negative internal experiences associated with said exposure (Khantzian, 1997). In the context of trauma-exposed individuals, substance use produces short-term negatively reinforcing consequences if it

alleviates PTS or anxiety symptoms (Blume, 2001). With repeated pairings of the behavior (substance use) and negatively reinforcing consequence (aversive symptom relief), an individual may develop this maladaptive coping strategy with a strong association forming between substance use and relief of symptoms in the presence of trauma cue reminders (discriminative stimuli). This learning makes trauma survivors more susceptible to escalating their substance use over time, leading to more severe substance use and ultimately putting them at risk for developing SUD (Khantzian, 1997). Additionally, the SMH posits that substance users often experience affective states in extremes and often also experience alexithymia (i.e., difficulties recognizing emotional states). Because of these factors, users may learn to engage in substance use to manage or alleviate those extreme states. The combination of issues with self-regulating emotional states, self-esteem issues, and an inability to recognize these emotional states creates a vulnerability for an SUD to develop (Khantzian, 1997). This is applicable to PTS as some of the symptoms include extreme affective states, particularly persistent negative affective states and angry outbursts. The SMH for trauma exposure sequelae has been examined with multiple different substances, but particularly in the context of trauma sequelae and problematic alcohol use (Leeies et al., 2010; Hawn et al., 2020; Luciano et al., 2022). For example, Leeies and colleagues (2016) assessed the prevalence and correlates of self-medication of PTSD with drugs and alcohol amongst a nationally representative Canadian sample (N = 34,653). They found that 20% of the subsample of 3953 with a PTSD diagnosis used either alcohol, cannabis, or another substance to self-medicate. Additionally, self-medication behavior was associated with substantially lower mental health-related quality of life. In a systematic review (Hawn et al., 2020) of 24 studies that reviewed SMH in the context of PTS and comorbid problematic alcohol

use, just under half (k=11) of the studies had findings supportive of the SMH that individuals were using alcohol to relieve their PTS symptoms.

An area of research that is generally lacking is how the SMH may apply to those with trauma exposure who use cannabis. Cannabis use has significantly increased amongst Canadian adults between the years of 2006-2021, with an additional increase amongst adults post-legalization (Hall et al., 2023).[3] Those with trauma exposure are at particularly high risk of cannabis-related issues. First, cannabis use rates are typically higher amongst those with trauma histories than those without (Bassir Nia et al., 2023; Kevorkian et al., 2015). Second, longer-term cannabis use in those with trauma histories is associated with more adverse psychological affects of trauma exposure (Wilkinson et al., 2015; Drost et al., 2017; Rehman et al., 2021; Metrik et al., 2022). Third, cannabis dose escalation may worsen anxiety symptoms in those with trauma histories (Bhattacharyya et al., 2010, 2017; Raymundi et al., 2020; Sharpe et al., 2020). Finally, those with trauma histories have elevated rates of cannabis use disorder (CUD),[4] suggesting that cannabis use can escalate and lead to higher rates of physical dependence in this group (Berenz & Coffey, 2012; Morris & Buckner, 2020). While these connections between trauma exposure and adverse cannabis outcomes have been established, there are aspects of cannabis use patterns that have been either understudied or not examined at all with anxiety and adverse cannabis outcomes in trauma-exposed samples. For example, the prevalences of different cannabis use regimens (i.e., the administration schedule or the way an individual uses their cannabis) and the

[3] Canada legalized recreational cannabis use federally in October 2018 for adults 19 years of age and older.
[4] Cannabis dependence refers to a maladaptive pattern of cannabis use, including the development of physical dependence, which involves tolerance and withdrawal symptoms (DSM-IV; APA, 1994). Cannabis dependence was also a term used to represent the more severe of two diagnoses in the DSM-IV (APA, 1994). CUD refers to a broader psychiatric condition that includes both what used to be referred to as cannabis abuse and dependence in the DSM-IV (APA, 1994), as well as cannabis craving symptoms (DSM-5-TR; APA, 2022). Cannabis problems refer to a set of negative consequences of cannabis use behavior, which can include the symptoms of CUD but can be even broader and are typically measured continuously.

associations between those regimens and frequency/quantity of cannabis use have yet to be examined. Additionally, the potency of cannabis used and its associations with anxiety and cannabis dependence levels have also been underexamined and require further exploration in trauma-exposed samples. These two aspects of cannabis use patterns are crucial in furthering our understanding of the relationship between cannabis use and trauma exposure. For one, the understanding of how an individual is using cannabis in their natural setting can allow for recommendations that limit the potential for both CUD development and potential PTS exacerbation. Similarly, further understanding of the associations between cannabis potency and cannabis dependence and anxiety levels can also allow for recommendations that limit the potential for both CUD development and potential PTS exacerbation. The current thesis consists of two studies that fill these gaps. The first study consists of a secondary analysis of both the prevalence and associations of different cannabis use regimens with monthly cannabis use frequencies and quantities, while the second study was a primary analysis of the associations of cannabis potency levels with anxiety and cannabis dependence levels. Both studies used trauma-exposed cannabis-using adults as participants. First, I will provide the relevant background information for Study 1 and, afterward, the relevant background information for Study 2.

Research on Benzodiazepine Use Patterns (Study 1)

The study of the effects of substance administration regimens has proven useful in an older, yet related, area of literature about the use of benzodiazepines in individuals with anxiety and related disorders (Busto & Sellers, 1986; Westra & Stewart, 2002a; Westra & Stewart, 2002b). In this literature, there is evidence suggesting that a "pro re nata" ("PRN") regimen, or as-needed use, in response to the occurrence of anxiety-related symptoms is more common yet associated with more adverse outcomes in individuals with panic and other anxiety-related

disorders compared to a regularly scheduled (RS) use regimen (i.e., use at specific times of day; e.g., twice a day [BID], three times a day [TID]; Westra & Stewart, 2002a; Westra & Stewart, 2002b). For example, a PRN administration regimen has been observed to be more commonly utilized amongst chronic benzodiazepine users than RS schedules; moreover, those originally prescribed benzodiazepines according to an RS schedule tend to shift towards using in a PRN manner over time (Romach et al., 1991). PRN regimens of administration are also often preferred by patients using benzodiazepines when prescribed an RS schedule of use for as little as one week (Dammen et al., 1994). A survey of physicians showed that PRN regimens are more commonly prescribed than RS regimens for the treatment of anxiety and related disorders, particularly by family physicians, in well-intended attempts to minimize patients' use levels (Westra & Stewart, 2002a). However, PRN regimens are paradoxically associated with higher use levels and greater psychological dependence (Westra & Stewart, 1998). This may be due to the greater potential for negative reinforcement learning to occur in the case of PRN than RS regimens (Busto & Sellers, 1991; Westra & Stewart, 2002a).

Learning Theory for Cannabis Use Patterns

This literature on benzodiazepine administration regimens in anxiety may be relevant for understanding cannabis administration regimens in the context of individuals who have suffered trauma. Indeed, cannabis has been frequently substituted by patients for anxiety-relieving medications, including benzodiazepines (Corroon et al., 2017; Piper et al., 2019; Charoenporn et al., 2023), and prescribed use of cannabis has shown to lead to significant reductions in benzodiazepine use over time (Piper et al., 2019; Purcell et al., 2019) suggesting individuals may learn to use cannabis for similar purposes as for which they have learned to use benzodiazepines. However, the contributions of the regimen of substance administration to various substance and

anxiety outcome metrics have yet to be investigated in relation to cannabis use among individuals with trauma histories.

The potential connection between PRN cannabis use and increased adverse outcomes may be explained by operant conditioning and negative reinforcement principles. Drawing from past research on benzodiazepine regimens and anxiety (Busto & Sellers, 1991; Westra & Stewart, 1998), if an individual uses cannabis on a PRN basis, particularly to cope with the negative effects of trauma cue exposure (e.g., for relief from anxiety or PTS symptoms), they may be more likely to develop strong associations between trauma cues, anxiety and/or PTS symptoms (antecedents), cannabis use (behavior), and relief outcomes (consequence). This suggests that those engaging in PRN cannabis use may escalate their cannabis use frequency and/or quantity relative to someone using cannabis in an RS regimen, where such antecedent cues are less likely to be present and where negative reinforcement learning is less likely (Blume et al., 2001; Romero-Sanchiz et al., 2022; DeGrace et al., 2023). This pattern of self-medication aligns with Khantzian's (1997) SMH and has been highlighted in patients with PTSD using alcohol, as reviewed earlier (Hawn et al., 2020; Luciano et al., 2022). This negative reinforcement learning process could also apply to those with trauma exposure who self-medicate with cannabis. Romero-Sanchiz et al. (2022) and DeGrace et al. (2023; in press) have shown evidence of trauma cue-elicited cannabis craving in cannabis users with trauma histories, where the presentation of a personalized trauma cue elicits cannabis craving. This craving presumably involves a learned strong desire to use cannabis to relieve the negative affect associated with reminders of the trauma, arising through a combination of classical and operant conditioning. This ties into cannabis use regimens because with PRN use comes an additional risk of cue-induced craving when cannabis administration is more closely related to trauma cue exposure and to experiencing

PTS symptoms. Understanding whether cannabis use regimens in trauma-exposed individuals are associated with cannabis outcome metrics such as frequency and quantity of use is crucial for identifying riskier patterns of cannabis administration and developing strategies to improve patient outcomes.

Historical Changes In Cannabis Potency (Study 2)

Cannabis use regimens among individuals with trauma histories represent an under-explored aspect of cannabis use patterns that might contribute to the higher rates of cannabis use and cannabis-related problems in those with trauma histories. Another underexplored yet potentially impactful component of cannabis use patterns concerns the potency of the cannabis products being used by this population. The primary index of cannabis product potency is the concentration of Δ9-tetrahydrocannabinol (THC), the main psychoactive compound in cannabis. THC potency is typically reported as a percentage of the cannabis product's weight. Over the past 50 years, the THC content of cannabis products has increased substantially across the global market (Cascini et al., 2012; Chandra et al., 2019; ElSohly et al., 2021; Freeman et al., 2021). Health Canada (2019) reported that THC levels in cannabis flower have increased from an average of 3% in the 1980s to 15% in recent years. Legal cannabis dispensaries in Canada now sell cannabis with average THC levels ranging from 14.4% to 18.2%, with THC-dominant strains constituting over 80% of the legal market (Mahamad et al., 2020). Clearly, cannabis potency has significantly increased over the years.

While mean THC concentrations have been rising, the concentrations of cannabidiol (CBD), a non-psychoactive cannabinoid (Russo, 2011), may have also increased but at a less substantial rate compared to THC concentrations in Canadian, U.S., and European markets (Chandra et al., 2019; Health Canada, 2023). Some research even suggests no change in CBD

concentrations over time. A meta-analysis of eight studies from 1975 to 2017 found no significant changes in CBD concentrations in U.S. and European herbal cannabis samples (Freeman et al., 2021). These smaller proportional increases (or lack of increases) in CBD relative to THC are concerning, given that CBD may moderate or buffer adverse THC effects (Russo & Guy, 2006; Russo, 2011). Unsurprisingly, the THC:CBD ratios in cannabis products have risen dramatically from 23:1 in 2008 to 104:1 in 2017 in U.S. samples and from 0.5:1–5:1 in 2009 to 5:1–31:1 in 2016 in French samples (Chandra et al., 2019). Recently, Health Canada (2023) reported that 20% of cannabis users were using CBD-predominant products, a 5% increase from 2022, while 35% preferred THC-predominant products, which are the most potentially harmful. CBD-predominant products were primarily used for medical purposes (51%), whereas THC-predominant products were used more for non-medical purposes or a combination of medical and non-medical purposes (35% and 41%, respectively; Government of Canada, 2023).

Adverse Consequences of Increases in Cannabis Potency

While the use of THC-predominant cannabis is more common, understanding the potential clinical impact of CBD on psychiatric disorders, such as those involving anxiety, is crucial. The anxiety-inducing effects of THC are well-documented (Bhattacharyya et al., 2010, 2017; Raymundi et al., 2020), but these anxiogenic effects may be attenuated when THC and CBD are administered together (Hutten et al., 2022; Zuardi et al., 1982). However, when THC ratios are high (i.e., high THC, low CBD), the protective effects of CBD on THC's anxiogenic effects are limited (Raymundi et al., 2020). Evidence from both pre-clinical trials and randomized controlled trials (RCTs) suggests that CBD administration may improve disorders such as generalized anxiety disorder (GAD; Blessing et al., 2015; Skelley et al., 2020).

Additionally, CBD administration has also been shown to reduce both substance cue-induced craving and anxiety levels in heroin users with opioid use disorder (Hurd et al., 2019). Further investigation is needed to understand the effects of CBD in mitigating the negative outcomes of cannabis use, as findings on the protective effects of CBD on other psychiatric conditions, such as cannabis use disorder (CUD), have been mixed (Englund et al., 2022; McKee et al., 2021).

The THC:CBD ratio in cannabis may be crucial for understanding its effects on users. This ratio is often used as a measure of cannabis product potency and serves as a guide in product choice for medicinal purposes, where both THC and CBD proportions are considered (Zeyl et al., 2020). The THC:CBD ratio may impact cannabinoid metabolism and the medicinal effects perceived by users (Freeman & Winstock, 2015; Pierre, 2017; Zeyl et al., 2020). There are potential negative consequences associated with using cannabis products containing high THC concentrations. As with many other drugs, the risk of adverse mental health outcomes increases with the consumption of higher-potency cannabis (HPC; Pierre, 2017). HPC use has been frequently associated with higher severity of cannabis dependence and greater risk of CUD (Arterberry et al., 2019; Freeman & Winstock, 2015; Stuyt, 2018; Petrilli et al., 2022), with frequent HPC use predicting greater dependence severity, particularly in younger users (Freeman & Winstock, 2015). Longitudinal data suggests that for each one percent increase in national average THC consumption (indexed by THC%), users are 1.41 times more likely to progress from cannabis initiation to CUD (Arterberry et al., 2019). Moreover, individuals initiating cannabis use with HPC have 2.97 times the risk of developing CUD within one year compared to those initiating use with lower potency cannabis (Arterberry et al., 2019). One reason posited for the increased likelihood of dependence with HPC use is the heightened risk of withdrawal symptoms (Bonnet & Preuss, 2017). Regular consumption of HPC can lead to withdrawal upon

cannabis discontinuation and relief from withdrawal symptoms upon resuming HPC use. Associations between HPC use and relief from withdrawal promote further HPC use through negative reinforcement learning, potentially leading to the development of CUD (Blume, 2001).

Gender and Cannabis Use

While these various adverse effects of HPC have been well-documented, gender identity has received little attention as a factor influencing HPC use or as a potential moderator of HPC effects on adverse outcomes (e.g., cannabis dependence and anxiety). Historically, there have been notable differences between men's and women's cannabis use. Typically, there is a higher prevalence of cannabis use in men, and men report more frequent and higher dose cannabis use than women (Cuttler et al., 2016; Greaves & Hemsing, 2020; Matheson & Le Foll., 2023). Men are also twice as likely to develop CUD as women (Cooper & Craft, 2018; Hemsing & Greaves, 2020), while women have demonstrated a "telescoping" effect of more rapid progression to CUD from first use (Cuttler et al., 2016; Greaves & Hemsing, 2020). There is evidence that these historical substance-use patterns were rooted in social norms of traditional masculinity and femininity. For instance, Mahalik and colleagues (2015) examined gender typicality and cannabis use behaviors in a longitudinal study examining a sample of adolescents who progressed into adulthood during the study; they found that both male and female participants who demonstrated higher male typicality (i.e., higher adherence to masculine gender norms) showed greater cannabis use compared to those with lower male typicality. Additionally, Wilkinson and colleagues (2018) examined gender typicality and cannabis use and found, similarly, a stronger relationship between cannabis use and traditional gender norms for male participants. They also found that greater male typicality was associated with greater odds of high cannabis use frequency.

However, trends amongst recent cohorts suggest that men's and women's cannabis use prevalence and patterns of use are converging. Kerr and colleagues (2007) noted steep increases in women's cannabis use and significant declines in men's cannabis use between 1984 and 2000. Chapman and colleagues (2017) reported that of 22 studies examining cannabis use patterns between males and females, almost half (i.e., 10 studies) showed evidence for sex convergence of cannabis use among more recent cohorts due to increases in female cannabis use. The same study noted that between 1945 and 1995, overall cannabis use gender ratios (male:female) in American cannabis users dropped from 2.0:1 to 1.2:1 (Chapman et al., 2017). Similarly, the UNODC World Drug Report (2022) has also reported that between 2007 and 2020, the male:female ratio for past month cannabis use prevalence dropped from 2.13:1 to 1.25:1. Even more recently, a Canadian study by Bernusky et al. (2023) found that female first- and second-year undergraduate students reported significantly more frequent cannabis use than their male counterparts, which suggests not only convergence but a possible reversal of gender effects in younger cohorts.

With this past research in mind, it is important to mention that many of these studies have referred to this convergence of cannabis use by biological sex (Kerr et al., 2007; Chapman et al., 2017; Bernusky et al., 2023), while some have conflated biological sex with gender identity (Cuttler et al., 2016; Greaves & Hemsing, 2020; Matheson & Le Foll, 2023). Historically, these sex/gender differences may have been driven by biological factors (e.g., differences in metabolism and body weight) and some by sociocultural gender roles (e.g., expectations of acceptable behavior in men and women). However, in many of these studies, sex and gender have been aligned and little investigation of gender non-conforming individuals has been conducted in the context of cannabis potency. While the distinction between biological sex and

gender identity is important for clarity, the findings of convergence for cannabis use reported have been congruent regardless of whether researchers were examining sex or gender. With respect to research addressing gender as a potential moderator of THC effects on adverse outcomes, most research examining sex/gender differences in anxiety levels with cannabis use are conducted with rats, which have noted that higher doses of THC increase anxiety-like behaviors in female rats more so than in male rats (Harte-Hargrove & Dow-Edwards, 2012). One study noted gender differences in the anxiogenic effects of THC, where women experienced greater anxiety levels than men with the same THC dose (Sholler et al., 2021). However, there is a gap in the research on gender as a moderator of the impact of THC on cannabis dependence, and no studies have yet examined gender as a moderator of HPC or THC:CBD ratio effects specifically on various adverse psychological and behavioral outcomes.

The evidence suggesting gender convergence for cannabis use in recent studies (Chapman et al., 2017; Kerr et al., 2007; UNDOC, 2022) and in gender moderation of the anxiogenic effects of THC (Sholler et a., 2021) requires further investigation in various cohorts. One cohort where this is of particular interest is those with trauma histories since they are at higher risk than those without such histories, of cannabis use, cannabis dependence, CUD (Cougle et al., 2011; Kevorkian et al., 2015; Nia et al., 2023), and anxiety (Hong et al., 2024). Additionally, those with trauma exposure significant enough for a PTSD diagnosis are at greater odds of lifetime cannabis use and CUD than those without (Kevorkian et al., 2015). Extension of this line of research to trauma-exposed individuals would add to the literature and help determine whether gender convergence of cannabis use is affecting a diverse population of individuals in more recent cohorts.

Mathematical Issues with Current Potency Measures

The assessment of THC potency through the THC:CBD ratio presents a mathematical challenge, especially when the CBD value is reported as zero. Calculating the THC:CBD ratio entails dividing the THC concentration by the CBD concentration, creating significant issues when CBD is self-reported as zero. Despite all cannabis products containing at least trace amounts of CBD, participants may often report their CBD percentage as zero if they understand trace amounts of CBD as being effectively zero CBD content. Since division by zero is mathematically undefined (Kihara & Pauly, 2016) (i.e., not possible to calculate), this results in missing THC:CBD ratio values for any individual reporting CBD concentrations of zero. This issue is particularly pronounced among individuals using cannabis with high THC percentages and reporting zero CBD, as these individuals theoretically have the highest risk of dependence and anxiety due to high THC levels without any potential protective effects of CBD. Neglecting to address this issue may lead to reproducibility problems in the literature, as the correlation between the THC:CBD ratio and various outcomes could be underestimated in samples that include several users reporting 0% CBD. An alternative mathematical approach to assessing cannabis potency, which mitigates the risk of losing data from theoretically high-risk cannabis users, involves calculating the THC proportion. This index represents the ratio of THC to the cannabinoid content of both THC and CBD (i.e., THC/(THC+CBD)). This value consistently ranges from 0.000 to 1.000 and can accommodate any missing values that arise from the traditional THC:CBD calculation.

The Present Thesis

Accumulating research suggests that those who have experienced trauma are more likely to use cannabis and to be at risk for CUD (Bassir Nia et al., 2023; Kevorkian et al., 2015). The current project aims to address two areas of research on cannabis use patterns that have been

underexamined or not examined at all in trauma-exposed populations to date yet have been linked with adverse outcomes in other areas of substance use research and/or other populations. First, research on how cannabis use regimens may influence cannabis use levels in trauma-exposed individuals is lacking. This is a potentially important topic to investigate with respect to cannabis, given similar older literature showing links between regimen and use levels in the benzodiazepine field. This thesis aimed to first address this gap in the cannabis literature by examining the relative prevalence of three cannabis use regimens self-reported by trauma-exposed cannabis-using adults, as well as the shifts between their initial and current cannabis use regimen, and the relation of their current cannabis use regimen to their current cannabis use levels (i.e., frequency per month; quantity per use occasion in the last month). Second, the influence of cannabis potency measures on cannabis dependence and anxiety levels and how these relations may differ by gender in trauma-exposed cannabis users had also not been examined previously. Further investigations of the relationships between cannabis potency and cannabis dependence, as well as with anxiety levels, are necessary in the already at-risk sample of trauma-exposed cannabis users, given the rapid rises in THC percentages in commercially available cannabis products and prior research suggesting links between THC potency to these adverse outcomes. Moreover, exploring the main and interactive effects of gender on these relations is important, given recent evidence of gender convergence in cannabis use and of possible gender moderation of THC's adverse effects.

Outline

Study 1 is presented in Chapter 2. Chapter 3 provides a bridge between Studies 1 and 2 and discusses the purpose of additionally examining how cannabis potency is related to problematic cannabis use and anxiety levels. Additionally, it bridges the gaps between Studies 1

and 2. Study 2 is then presented in Chapter 4. Chapter 5 presents a general discussion of both studies in the context of the extant literature, an integration of the results from both studies, and an identification of the strengths and weaknesses from each study. Finally, Chapter 5 covers my thesis findings' theoretical, clinical, and practical implications.

CHAPTER 2: STUDY 1

This chapter presents the first of two manuscripts on which this thesis is based. Under the co-supervision of Dr. Sherry Stewart and Dr. Phil Tibbo, Thomas Snooks prepared the initial draft, incorporated feedback from his co-authors, and finalized it for submission for review for publication. Dr. Stewart and Tibbo were co-supervisors at the time. Given the untimely passing of Dr. Sean Barrett (original committee member), going into the defense, the committee composition was altered Dr. Stewart (supervisor) and Dr. Tibbo and Dr. Pamela Arenella (committee members). The manuscript is undergoing peer review at *Addictive Behaviors*. The manuscript was submitted on May 16th, 2024. The full reference is as follows: Snooks, T., Tibbo, P.G., Romero-Sanchiz, P., DeGrace, S., & Stewart, S.H. (under review). Cannabis use regimens in trauma-exposed individuals: Associations with cannabis use quantity and frequency. *Addictive Behaviors*.

Abstract

People with trauma histories have increased odds of cannabis use. Little is known about the frequency or consequences of different cannabis use regimens in cannabis users with trauma histories. Individuals with anxiety disorders tend to administer benzodiazepines in a *pro re nata* (PRN; i.e., as needed) as opposed to regularly scheduled (RS, e.g., twice daily [BID], three times daily [TID]) manner. Although physicians tend to prescribe benzodiazepines on a PRN regimen to minimize use, this regimen is paradoxically associated with greater use levels. Indeed, PRN administration regimens may increase use via negative reinforcement processes. We extended this older benzodiazepine literature to cannabis by examining the regimen of cannabis use among 94 trauma-exposed cannabis users (mean age=35.1 years; 52.1% male; 23.4% with cannabis prescription). Participants reported their initial and current cannabis use regimen (PRN vs. RS vs. both ['PRN+']) and their past month cannabis use frequency (use occasions in last month) and quantity (grams/use occasion). Consistent with patterns in benzodiazepine research, PRN (47.1% of sample) and PRN+ (43.5% of sample) were more common than RS regimens (9.4% of sample). Also consistent with patterns seen with benzodiazepines, our sample moved toward PRN regimens from initial to current use: e.g., 100% of initial RS users switched to a regimen that included PRN use. Consistent with predictions emerging from learning theory, PRN and PRN+ cannabis users reported significantly higher cannabis use frequencies compared to RS users (p's < .01). Unexpectedly, there were no significant differences between cannabis use regimen groups for quantity of cannabis/occasion. While limited by their cross-sectional nature, with longitudinal replication, results may have implications for identifying cannabis use regimens that minimize frequency of use and thereby reduce risk for negative health outcomes.

Key Words: cannabis, trauma, trauma sequelae, dosing regimen, pro re nata, PRN, regularly scheduled, cannabis dose, cannabis frequency.

Introduction

Epidemiological studies suggest that cannabis is used at higher rates among people with than those without trauma histories (Bassir Nia et al., 2023; Kevorkian et al., 2015). The use of cannabis by those with traumatic histories is controversial with some arguing that it might be beneficial (Orsolini et al., 2019; Rehman et al. 2021), while others suggest potential harmful effects (Dagan & Yager, 2020). Their higher levels of use are thought to be motivated by the desire to cope with trauma-related sequelae like posttraumatic stress (PTS) symptoms (Blume et al., 2001; Romero-Sanchiz et al., 2022). Some emerging evidence supports the beneficial effects of cannabis in this regard. First, Walsh and colleagues (2023) found a medium-sized reduction in PTS symptoms between pre- and post-administration of vaporized cannabis with both balanced THC/CBD and high THC concentrations despite their small sample size (N=5 completers); analysis of placebo effects was not possible. Second, Bonn-Miller and colleagues (2021) found three different concentrations of smoked cannabis significantly improved PTS symptom severity in military Veterans after three weeks of treatment; however, no active treatment was significantly better than placebo. Cannabis has also demonstrated benefits for trauma-exposed individuals for immediate PTS symptom reduction in a study without a placebo control but no change in baseline symptomology was found over time (LaFrance et al., 2020). Additionally, cannabis has shown benefits for insomnia, nightmares, and PTS symptoms in an RCT conducted with a corrections population (Cameron et al., 2014), improved subjective sleep quality for individuals with combat-related PTSD in an uncontrolled naturalistic retrospective study (Nacasch et al., 2023), and reduced the association between PTS symptoms and suicidal ideation in an uncontrolled study (Lake et al., 2020).

Additionally, placebo effects of cannabis have been observed on stress and anxiety levels. CBD is a non-psychoactive cannabinoid found in cannabis. Experimental manipulation of CBD expectancy has been associated with blunted subjective stress in response to an acute lab-based stressor (Spinella et al., 2021; Zhekova et al., 2024). Moreover, those with strong a priori beliefs that CBD is anxiolytic have evidenced significantly blunted anxiety in response to a stress task when led to believe they were consuming CBD relative to when they were correctly informed about the content of their CBD-free oil (Spinella et al., 2021). These studies raise the possibility that in the uncontrolled studies of cannabis administration discussed earlier, effects of cannabis on PTS symptoms may be at least partly due to expectancy effects, pointing to the need for placebo-controlled studies. While there is a paucity of randomized controlled trial (RCT) data confirming the beneficial effects of cannabis in managing PTS symptoms, we need more high-quality evidence to suggest that cannabis significantly improves PTS symptom management (McKee et al., 2021).

There are reasons to be concerned about cannabis use in trauma-exposed individuals. First, longer-term use of cannabis in this population is associated with more severe PTS symptoms (Wilkinson et al., 2015; Drost et al., 2017; Rehman et al., 2021; Metrik et al., 2022). Second, while some evidence has suggested that higher doses of cannabis predict larger reductions in anxiety and intrusive PTS symptoms (LaFrance et al., 2020), escalating one's dose of cannabis can worsen anxiety symptoms (Bhattacharyya et al., 2010, 2017; Raymundi et al., 2020; Sharpe et al., 2020). Third, there are elevated rates of cannabis use disorder (CUD) among those with trauma histories (Berenz & Coffey, 2012) suggesting that use may lead to dose escalation and higher rates of dependence in this group. Despite the apparent risks of cannabis use among trauma-exposed individuals, little is known about the relative prevalence of various

cannabis administration regimens (i.e., patterns of cannabis use administration) or how these various use regimens relate to different cannabis outcome metrics in trauma-exposed cohorts.

The study of the effects of substance administration regimens has proven useful in an older yet related area of literature about the use of benzodiazepines in individuals with anxiety and related disorders (Busto & Sellers, 1986; Westra & Stewart, 2002a; Westra & Stewart, 2002b). In this literature, there is evidence suggesting that a "pro re nata" ("PRN") regimen, or as-needed use, in response to the occurrence of anxiety-related symptoms is more common, yet associated with more adverse outcomes in individuals with panic and other anxiety-related disorders compared to a regularly scheduled (RS) use regimen (i.e., use at specific times of day; e.g., twice a day [BID], three times a day [TID]; Westra & Stewart, 2002; Westra & Stewart, 2002b). For example, a PRN administration regimen has been observed to be more commonly utilized amongst chronic benzodiazepine users than RS schedules, and those prescribed initially benzodiazepines according to an RS schedule tend to shift towards using in a PRN manner over time (Romach et al., 1991). PRN regimens of administration are also often preferred by patients using benzodiazepines when prescribed an RS schedule of use for as little as one week (Dammen et al., 1994). A survey of physicians showed that PRN regimens are more commonly prescribed than RS regimens for the treatment of anxiety and related disorders, particularly by family physicians, in well-intended attempts to minimize patients' use levels (Westra & Stewart, 2002a). However, paradoxically, PRN regimens are associated with higher use levels and greater psychological dependence (Westra & Stewart, 1998). This may be due to the greater potential for negative reinforcement learning to occur in the case of PRN than RS regimens (Busto & Sellers, 1991; Westra & Stewart, 2002a).

This literature on benzodiazepine administration regimens in anxiety may be relevant for understanding cannabis administration regimens among individuals who have suffered trauma. Indeed, cannabis has been frequently substituted by patients for anxiety-relieving medications including benzodiazepines (Corroon et al., 2017) and prescribed use of cannabis is associated with significant reductions in benzodiazepine use over time (Purcell et al., 2019). The contributions of the regimen of substance administration to various substance outcome metrics have yet to be investigated with cannabis use among individuals with trauma histories or, indeed, anywhere in the cannabis literature. However, drawing from past theory and research in the field of benzodiazepine regimens and anxiety (Westra & Stewart, 1998; Busto & Sellers, 1991), if an individual uses cannabis on a PRN basis, particularly to cope with the negative sequelae of trauma cue exposure (e.g., for relief from anxiety or PTS symptoms), they may be more likely than others to develop strong associations between trauma cues, anxiety, and/or PTS symptoms (antecedents), cannabis use (behavior), and relief outcomes (consequence). This suggests that those who use cannabis in a PRN fashion may learn to escalate their cannabis use frequency and/or quantity relative to someone using cannabis in an RS regimen, where such antecedent cues are less likely to present for classical conditioning to occur and where the negative reinforcement of using cannabis to reduce PTS symptoms is thus less likely (Romero-Sanchiz et al., 2022; Blume et al., 2001). This has been previously posited in the self-medication hypothesis of substance use disorders, that substance use begins as an attempt to assuage painful feelings (Blume, 2001; Khantzian, 1985; Skinner, 1971), and has been highlighted for patients with PTSD using alcohol (Hawn et al., 2020; Luciano et al., 2022). This hypothesis of negative reinforcement could also apply to those with trauma-exposure self-medicating with cannabis. Understanding whether cannabis use regimens in cannabis users with trauma exposure histories

are associated with cannabis outcome metrics such as frequency and quantity of use is crucial for identifying more harmful patterns of cannabis administration and developing strategies for improving patient outcomes.

The purposes of the current study were to determine if regimens for cannabis administration among cannabis users with trauma histories follow similar patterns to those documented in research on benzodiazepines for the treatment of panic- and anxiety-related symptoms in terms of: a) the relative prevalence of different administration regimens, b) changes in administration regimen over time, and c) correlates of PRN use in terms of cannabis use frequency (use occasions in past month) and quantity (dose per use occasion). It was hypothesized that regimens involving PRN use would be more common than RS only regimens [H1] and that there would be movement toward PRN use regimens and away from RS only use regimens when examining changes in cannabis administration regimens over time [H2]. Finally, it was hypothesized that compared to RS use regimens, administration regimens involving PRN use would be associated with a greater cannabis use frequency (number of use occasions) in the last month [H3], and a greater quantity of cannabis use (in grams) per use occasion in the past month [H4], due to greater negative reinforcement learning opportunities with PRN than RS use regimens (Skinner, 1971; Blume, 2001; Khantzian, 1997).

Methods

Participants

Data for the present study were derived from a combined dataset originating from two previously published investigations by Romero-Sanchiz et al. (2022) and DeGrace et al. (2023). The primary aims of these studies were to scrutinize cannabis craving and emotional reactions to personalized trauma and control (cannabis and/or neutral) cues among trauma-exposed cannabis

users. The sample comprised 94 participants (52.1% male; M age = 35.1, SD = 13.5), who were recruited from the community in response to solicitations for a study on cannabis use among trauma survivors. Eligibility criteria, as outlined in the study advertisements, included regular cannabis use and experience of at least one-lifetime traumatic event. Of these participants, 51 were sourced from the study by Romero-Sanchiz et al. (2022), and 50 from the study by DeGrace et al. (2023). However, seven individuals from the DeGrace et al. (2023) study were excluded from the present analysis due to incomplete reporting of their current cannabis use regimen, resulting in a final sample size of N = 94. Participants were eligible for the parent studies if they met the following criteria: were aged between 19 and 65 years, reported at least one lifetime traumatic experience as per the Life Events Checklist-5 (LEC-5: Gray et al., 2004), and used at least one gram of cannabis per week in the last month (Romero-Sanchiz et al., 2022) or at least one gram in total in the past month (DeGrace et al., 2023).

Exclusion criteria included being under 19 years of age (the legal age for cannabis consumption in Nova Scotia), self-reporting a diagnosis of severe mental illness (i.e., psychosis or bipolar disorder), taking medication that could impact responses to trauma or substance cues, or being pregnant or nursing. No participants screened met these exclusionary criteria. Recruitment methods included social media platforms, Veterans' associations, local mental health clinical services, community flyers, and targeted online advertisements. Screening procedures encompassed sociodemographic information, the LEC-5, and the author-compiled cannabis measure. All procedures for the parent studies received approval from the Nova Scotia Health Authority's Research Ethics Board. Characteristics of the final combined sample (N = 94) are detailed in Table 1. The mean PTSD checklist (PCL-5) score for the sample was 34.8 (SD =

15.3), with 57.4% of participants scoring above an established clinical cutoff for PTSD (i.e., ≥33; Bovin et al., 2016).

Measures

Trauma Exposure: The Life Events Checklist (LEC-5) is a self-report instrument comprising 17 items that delineate potentially traumatic events in line with Criterion A of a DSM-5-TR (APA, 2022) PTSD diagnosis. The LEC-5 was employed to determine eligibility based on lifetime exposure to one or more traumatic events. It has demonstrated good test-retest reliability and strong convergence with established trauma measures such as the Posttraumatic Stress Disorder Checklist (PCL-5; Blevins et al., 2015).

Posttraumatic Stress Disorder Symptoms: The Posttraumatic Stress Disorder Checklist (PCL-5; Blevins et al., 2015) is a 20-item self-report measure assessing severity of DSM-5 PTSD symptoms (APA, 2022). PCL-5 items are rated on a 0-4 severity scale with 0 meaning, "not at all," and 4 meaning, "extremely", and scores are summed for a total score. The PCL-5 was utilized as a descriptive measure to report the proportion of the sample that met the criteria for a likely PTSD diagnosis (cut point = 33 and above).

Cannabis Use Dimensions: The Cannabis Use Questionnaire (CUQ) is an author-developed measure allowing participants to delineate various dimensions of their cannabis use, including regimen, frequency, quantity, and prescription status. Self-reported measures of psychoactive substance use are generally reliable and accurate when administered confidentially and without potential negative consequences for honest responses (Sobell & Sobell, 1990). These conditions were met in the original data collection (DeGrace et al., 2023; Romero-Sanchiz et al., 2022). Participants were presented with three regimen options—pro re nata (PRN), regularly

scheduled (RS), or both (PRN+)[5]—and asked to select the option that best represented their cannabis use regimen, both initially (when they first started using cannabis) and currently.

Cannabis use frequency and quantity were assessed in the past month. Participants reported the number of occasions they used cannabis per day, week (if less than daily), or month (if less than weekly) in an open-ended format, which was then converted to total monthly usage occasions for analysis. Dosage information was similarly reported and converted to total grams used in the past month. Cannabis dosage per use occasion (grams/occasion) was calculated by dividing the total grams used in the past month by the total number of use occasions.

Statistical Approach

Initially, we examined the validity of combining data from prescribed and non-prescribed users by testing the relationship between cannabis administration regimen and prescription status (yes/no) using a 2 x 3 chi-square analysis. Descriptive statistics were employed to document the prevalence of each cannabis use regimen for testing Hypothesis 1. Hypothesis 2 was tested using a McNemar test to determine proportional differences in regimen frequencies in the same individuals over time. For Hypotheses 3 and 4, independent sample t-tests were conducted to identify significant differences in mean past-month cannabis use levels (frequency and/or quantity) across each cannabis use regimen. A between-subjects design was adopted, with cannabis use regimen (PRN vs. PRN+ vs. RS) at the time of testing as the independent variable and past-month cannabis use occasions (frequency) and cannabis use dose in grams per occasion (quantity) as dependent variables. All analyses were performed using SPSS 25.0.

Results

[5] PRN+ was included as a regimen option based upon previous work in the benzodiazepine field (Westra & Stewart, 2002a,b) showing that many individuals use benzodiazepines in a combination of both PRN and RS manners.

Cannabis Use Regimen by Cannabis Prescription Status

The 2 (prescription: yes vs. no) by 3 (regimen: RS vs. PRN vs. PRN+) chi-square was not significant, indicating no significant difference in current cannabis use regimen by cannabis prescription status, $\chi^2(df = 2) = .133$, $p = .936$. This result allowed the merging of the data across prescription status (prescribed vs. not prescribed) in the remaining hypothesis tests.

Proportion of PRN, PRN+, and RS cannabis regimens

Regarding the prevalence of the three cannabis use regimens, approximately half (52.1%) of the participants indicated their current regimen was purely PRN, 39.4% listed their regimen as both PRN and RS (i.e., PRN+). In contrast, only 8.5% listed their regimen as purely RS. Thus, consistent with H1, PRN and PRN+ administration regimens were much more common than RS administration regimens at the testing time.

Change in Cannabis Use Regimen Over Time

Two participants failed to report their initial cannabis use regimen and were not included in this analysis. For H2, the McNemar test revealed a significant difference between the distribution of initial and current cannabis use regimens, $\chi^2(df = 2) = 97.169$, $p < .001$. Figure 1 in Appendix A illustrates the movement patterns from initial to current cannabis use regimens.

Consistent with H2, 100% (9/9) of individuals who began as RS users moved on to a regimen that included PRN use (PRN or PRN+). Additionally, only 7.1% of PRN only users moved to RS only use (5/70) and only 15.4% of those who were PRN+ users moved to RS only use (2/13) which was also consistent with H2. Interestingly, the largest proportion of the sample began and remained as PRN users (40.2% of the total sample or 52.7% of those who were originally PRN users (37/70)). Additionally, a substantial proportion of users whose initial

cannabis regimen was PRN only switched to using PRN+ (29.3% of the full sample or 38.6% of those who were originally PRN users (27/70)).

Cannabis Use Frequency and Quantity by Cannabis Use Regimen

Independent t-tests were used to examine differences in frequency of cannabis use in the last month (H3) and grams of cannabis used per occasion in the last month (H4) across each current cannabis use regimen (PRN, RS, and PRN+). See Table 2 for the means (and SDs) for each cannabis use variable and associated t-values for each comparison.

Consistent with H3, those using cannabis with a PRN-only regimen used cannabis significantly more often in the last month than those using cannabis on an RS-only regimen. Also consistent with H3, those using cannabis on a PRN+ regimen used cannabis significantly more often per month than those using cannabis on an RS-only regimen. Additionally, although not initially hypothesized, individuals on a PRN+ regimen used cannabis significantly more frequently than those using cannabis on a PRN-only regimen (see Table 2, top panel).

Inconsistent with H4, participants on PRN-only regimens and RS-only regimens did not differ significantly in their cannabis dosage (i.e., grams of cannabis used per occasion). Also inconsistent with H4, participants on PRN+ regimens and RS-only regimens did not significantly differ in their cannabis dosage either. Finally, PRN-only users and PRN+ users did not significantly differ in their cannabis dosage (see Table 2, bottom panel).

Discussion

The purposes of the current study were to determine if regimens for cannabis use among cannabis users with trauma histories follow similar patterns to those shown in the literature on benzodiazepine administration for the treatment of panic- and anxiety-related symptoms. This was examined both in terms of the relative prevalence of different regimens when participants

present for testing, changes in self-reported cannabis use regimens over time (initial to current use), and relations to measures of cannabis use frequency and quantity in the past month.

First, the results of the 2x3 chi-square showed no significant difference in the proportions of cannabis regimens by cannabis prescription status, which allowed prescribed and non-prescribed users to be combined during hypothesis testing. This was important to note as roughly one-quarter of all participants were prescribed cannabis, and there was initial concern that they had been more at risk of using cannabis in a PRN manner if cannabis prescription methods for trauma exposure were like those for benzodiazepines and anxiety-like disorders (Westra & Stewart 2002a; 2002b).

Consistent with patterns revealed in benzodiazepine regimen research (Westra & Stewart, 2002a; 2002b; Romach et al., 1991), and with H1, PRN regimens were much more common than an RS-only regimen at the time of testing. In terms of changes in use regimen over time, all those who initially used cannabis in an RS manner (100%) switched to a regimen that included PRN use (i.e., PRN or PRN+). Movement from PRN-related regimens to an RS-only regimen was rare: only 7.1% of those who were originally PRN-only users and only 15.4% of those who were originally PRN+ users moved to be RS-only users. As in previous findings with benzodiazepines in individuals with anxiety disorders (Romach et al., 1991), large proportions of individuals in the sample who began as PRN remained as such (52.7%). However, many PRN-only users unexpectedly switched to PRN+ use (38.6%). The movement from PRN to PRN+ could be a learned behavior of using cannabis as a prophylactic measure for PTS symptoms or other trauma sequelae (e.g., an individual with trauma-related nightmares takes cannabis PRN during the day to manage emergent anxiety/PTS symptoms but also learns to use it in an RS manner before bed to reduce the nightmares). Further research is needed to determine the differences (demographic,

motivational) between those who begin on PRN-only regimens and stay on them and those who begin on PRN-only regimens and transition to PRN+ regimens.

Consistent with learning theory predictions (Khantzian, 1997; Blume, 2001; Skinner, 1971), those using cannabis with a regimen that included a PRN portion used significantly more often over the span of a month than RS-only users; PRN and PRN+ users used cannabis approximately twice as often on average as RS users. These findings suggest that similarly to benzodiazepines (Westra & Stewart, 2002a), PRN use of cannabis (PRN only or a regimen that includes PRN use – i.e., PRN+) is associated with more frequent cannabis use in cannabis users with a history of trauma. This is also largely consistent with a previous finding that cannabis use to manage anxiety escalated in frequency over time in PTSD patients (LaFrance et al., 2020). Additionally, and unexpectedly, individuals using cannabis with a PRN+ regimen reported significantly higher frequency of use than those using with a PRN-only regimen. This might be explained by the additional opportunities to use cannabis on a combined schedule compared to one schedule alone. While these are cross-sectional data where temporality and causality cannot be established, they are consistent with learning theory predictions that PRN/PRN+ cannabis administration schedules may lead to increases in cannabis use frequency due to greater opportunities for negative reinforcement learning. More frequent cannabis use could potentially exacerbate trauma sequelae like PTS symptoms over time (Hinojosa et al., 2024) and could lead to the development of cannabis-related problems (i.e., dependence, CUD; Choi et al., 2023). Further research including measures such as the Cannabis Use Disorder Identification Test-Revised (CUDIT-R: Adamson et al., 2010) is needed to determine if cannabis use regimens including PRN components are associated with additional adverse outcomes such as cannabis-related harms or CUD symptoms/diagnoses.

However, inconsistent with other predictions drawn from learning theory, there were no significant differences between PRN or PRN+ regimens compared to RS only regimens in cannabis quantity (dose per occasion). Participants in our sample used an average of 0.79 grams of cannabis per usage occasion. In comparison to cannabis users in the general Canadian population surveyed in the 2022 Canadian Cannabis Survey (Government of Canada, 2022), the current sample was using almost half the cannabis in grams per occasion (0.79 grams to 1.3 grams, respectively) but was using more frequently per month (only 18% of general population participants used cannabis daily in the CCS versus 75.6% in the current sample).

These results suggest that regular cannabis users with trauma histories are using cannabis more often with lower quantities per usage occasion than cannabis users in the general Canadian population. The former finding is supported by previous research (Bassir Nia et al., 2023; Berenz & Coffey, 2012; Kervorkian et al., 2015). The latter finding, however, was unexpected as it has been reported that trauma-exposed individuals typically use larger quantities of cannabis compared to non-trauma-exposed individuals (Bassir Nia et al., 2023; Kevorkian et al., 2015). There are a few possibilities that could explain this discrepancy. First, the current sample could be using a higher cumulative cannabis dose per month compared to those surveyed in the 2022 CCS because of how much higher daily use was in the current sample compared to those in the 2022 CCS (i.e., More daily use = higher cumulative monthly dose). However, no comparison can be conducted because the CCS did not include a measure of cumulative cannabis dose per month in their survey. Another potential explanation for this discrepancy is that participants in the current study may be using less cannabis per occasion but using higher THC potency products compared to those surveyed in the 2022 CCS. There is previous evidence that higher THC concentrations may be associated with greater symptom relief with anxiety and trauma-related

disorders (Stith et al., 2019). THC concentrations in cannabis used have also been negatively related to the amount of cannabis used at a time (Freeman et al., 2014). The same study (Freeman et al., 2024) noted that daily cannabis users are 7.3 times more likely to accurately estimate the potency of THC in their cannabis use compared to non-daily users. Because of these associations, it could be that daily cannabis users may be using less cannabis per use occasion but consuming cannabis with higher THC levels compared to non-daily users as they have a greater understanding of how much cannabis they need to relieve symptoms related to their trauma exposure. However, participants in the current study were unfortunately not asked about the THC potency of their usual cannabis. Future research is needed to determine if the associations between cannabis use regimens and overall cannabis use frequency and quantity are moderated by cannabis potency in cannabis users with trauma histories.

Limitations

Several potential limitations to the present study should be considered when interpreting our results. First, RS use was defined as "at a regularly scheduled time." Several types of regimens can be defined as RS use, including use at similar times twice a day (BID), three times a day (TID), only upon waking up, before falling asleep, etc. Previous studies on benzodiazepine administration schedules elaborated on the definition of RS regimen by providing examples (Westra & Stewart, 2002a; Westra & Stewart, 2002b). Because the definition of RS use was not elaborated upon in our study, participants may have found this criterion to be too strict and not representative of their actual cannabis use, leading them to select the PRN+ regimen of administration. This could have contributed, at least in part, to the small proportion of participants who listed their current cannabis use regimen as RS only (8.5%). Second, there was no reported time frame between the initial and current cannabis regimen which makes it difficult

to determine the length of time that may have passed before each participant switched regimens (if they did) or whether greater passages of time between initial use and current assessment were associated with a greater probability of switching regimens; however, in the benzodiazepines and anxiety field, patients have reported a desire to switch to a PRN use regimen after as little as one week on an RS administration schedule (Romach et al., 1991).

Third, the independent variable for analysis of the cannabis use regimen was coded and measured as a categorical rather than as a continuous variable. Past evidence from benzodiazepine research has shown that many patients use their medication in a combination of as needed and regularly scheduled ways; this suggests that the construct of administration regimens may be more continuous than categorical (Westra & Stewart, 2002a). This possibility is also consistent with the current study's relatively high proportion of reported PRN+ regimens. Future studies should consider conceptualizing and measuring cannabis use regimens as a continuous variable to allow for a greater range of response options and more statistical power in data analysis. Finally, the current study did not include any data on motives for use, such as if the individual used cannabis more for recreational or medicinal purposes (Roy-Byrne et al., 2015) which may have differed by cannabis regimens. Future studies should include an examination of the motives that individuals have for their cannabis administration regimen.

Conclusion

The current findings may have implications for helping to identify the regimen of cannabis administration that minimizes overall cannabis use frequency and thereby reduces the risk for CUD and other adverse health consequences of cannabis use (e.g., adverse consequences to lung health; Kaplan, 2021; Winhusen et al., 2019) among trauma-exposed cannabis users. By increasing understanding of the correlates of cannabis administration regimen in terms of

cannabis use frequency gleaned from the current study, there may be important clinical implications emerging from these results. If replicated longitudinally and/or experimentally, the current findings provide insight for clinicians to determine how to best prescribe medicinal cannabis for those experiencing psychopathological symptoms related to trauma exposure (e.g., anxiety or PTS symptoms). Finally, the current results also may provide psychoeducational benefits for those who are self-administering cannabis without a prescription or without clinical oversight, as those who self-medicate for trauma exposure-related issues are more likely to use higher levels of cannabis than those with a prescription or doctor's aid (Bonn-Miller et al., 2007). Overall, the current study establishes an important direction for future research. Additional knowledge regarding the advantages and disadvantages of different cannabis administration regimens may ultimately aid in prescriber and user administration patterns that maximize the benefits and minimize the risks of this potentially therapeutic agent.

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Conflicts of Interest

No authors have any conflicts of interest to declare regarding this study.

Table 2.1 Descriptives and Clinical Characteristics of Final Sample [N=94]

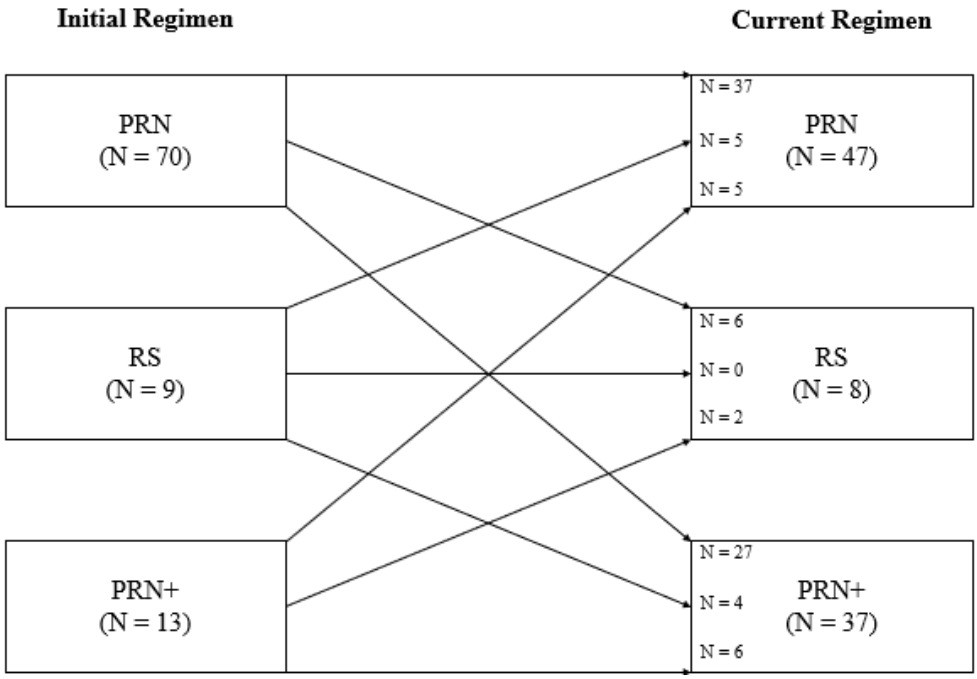
Demographic and Clinical Characteristics	*N(%)*/M(SD)
Gender	
Man	*49(52.1)*
Woman	*44(46.8)*
Non-Binary	*1(1.1)*
Age (in years)	35.1(13.5)
PCL-5 Score	34.8(15.3)
PSTD Cutoff (33)	
At or above	*54(57.4%)*
Below	*40(42.6%)*
Cannabis Prescription Status	
Prescription	*22(23.4)*
No Prescription	*72(76.6)*
Average Cannabis use in Grams per Occasion	.79(.64)

Table 2.2. Means, Standard Deviations, and T-Values for Regimen Comparisons

Variable	M(SD)	(df) t-value	p-level
Cannabis Frequency (occasions in past month)			
PRN	56.31(56.56)		
PRN+	88.43(70.60)		
RS	30.00(12.69)		
PRN vs. RS		(49.72*) = 1.301	< .01
PRN+ vs. RS		(42.67*) = 2.316	< .001
PRN vs. PRN+		(84) = -2.345	< .05
Cannabis Quantity (in grams/occasion)			
PRN	0.79(1.02)		
PRN+	0.63(0.47)		
RS	1.47(1.95)		
PRN vs. RS		(7.64*) = -0.966	.182
PRN+ vs. RS		(7.18*) = -1.209	.132
PRN vs. PRN+		(71.32*) = -0.295	.172

Notes. Cannabis frequency and cannabis quantity: author-compiled Cannabis Use Questionnaire (CUQ), * = adjusted degrees of freedom used for comparison due to significant Levene's test for equality of variance violations. All t-tests were one-tailed given directional predictions were made a priori.

Figure 1. Stability and Change from Initial to Current Reported Cannabis Administration Regimens



Notes. PRN = As needed use, PRN+ = Both as needed and regularly scheduled use, RS = Regularly scheduled use. N = 2 participants were excluded due to missing data on initial use regimen.

CHAPTER 3: BRIDGING CHAPTER FROM STUDY 1 TO STUDY 2

In the previous chapter, we reviewed the results of my first thesis study (Study 1), which examined cannabis administration regimens in cannabis users with trauma histories. Specifically, we examined the relative prevalence of different administration regimens, as well as changes in administration regimen over time, and correlations of regimen of use with cannabis use frequency (use occasions in the past month) and quantity (dose per use occasion). From the results of Study 1, we learned that cannabis use regimens of both PRN-only and regimens including PRN-use (i.e., 'PRN+') were much more common than RS-only regimens. When movement between initial to current cannabis use regimens was assessed, all individuals who began as RS-only users switched, over time, to regimens that included PRN use. We also found that individuals who began as PRN-only users tended to remain as such over time, but one key unexpected finding was the large proportion of those who transitioned from PRN-only to PRN+ use. This could be an escalation of cannabis uses per month due to more opportunities to use cannabis compared to PRN-only. In terms of cannabis correlates of use regimen, we found that individuals using cannabis on PRN-only or PRN+ regimens were using cannabis significantly more frequently than those on RS-only schedules. However, we found no significant differences in the quantity of cannabis used per month between any of the regimens, including PRN use, compared with the RS-only regimen. It was concluded that PRN regimens are common, moved toward over time, and potentially risky, given their associations with greater cannabis use frequency.

While Study 1 focused on one potentially risky aspect of cannabis use patterns (i.e., PRN regimens of use) among cannabis users with trauma histories, Study 2 focused on another aspect of cannabis use patterns in the same population – namely, the potency of cannabis products used. By studying various relatively neglected aspects of cannabis use patterns in cannabis users with

trauma histories, it is hoped that we can identify modifiable aspects of their cannabis use patterns to help minimize this population's otherwise elevated risk for CUD (Bassir Nia et al., 2023; Kevorkian et al., 2015)

Increased Cannabis Potency May Introduce Additional Harm

One aspect of cannabis use patterns that was not assessed in our sample in Study 1 was cannabis potency, which was suggested as a potential explanation for our Study 1 findings that individuals using cannabis regimens, including PRN use, may be using cannabis more frequently but not in significantly higher quantities than those using RS regimens; specifically, it was suggested that perhaps the PRN users may be using higher potency products more frequently than RS-only users. Cannabis potency refers to the concentration of Δ^9-tetrahydrocannabinol (THC) in the product (Petrilli et al., 2022). The potency of THC in cannabis products has increased substantially over the past 50 years. In Canada alone, average THC concentrations (THC%) in cannabis flower has risen from 3% in the 1980's to 15% in 2018 (Health Canada, 2019). THC-dominant cannabis strains are the most ubiquitous among legal cannabis dispensaries, as they make up over 80% of the legal strains available to consumers (Mahamad et al., 2020). Cannabidiol (CBD, non-psychoactive cannabinoid) concentrations in cannabis products have remained more stable (Freeman et al., 2021), or risen less steeply than THC (Chandra et al., 2019; Health Canada, 2023), leading to substantially higher ratios of THC:CBD in current cannabis products. Higher cannabis potency has been associated with higher levels of cannabis dependence (Freeman et al., 2015; Matsumoto et al., 2020) and anxiety levels (Hines et al., 2020; Petrilli et al., 2022) in adult samples from the general population. For example, Freeman and colleagues (2015) found that frequent use of high-potency cannabis (HPC) was associated with greater cannabis dependence severity in adult users than low-potency cannabis.

Similarly, Matsumoto and colleagues (2020) found that HPC use was associated with a seven-times increased risk of dependence compared to low potency cannabis use in adult users. Regarding anxiety outcomes, Hines and colleagues (2020) found a significant association between HPC and anxiety levels and that the use of HPC was associated with twice the risk of a generalized anxiety disorder (GAD) compared to low-potency cannabis use in adult users. These relations remain to be studied in cannabis users with trauma histories who are already at risk for adverse cannabis outcomes and high levels of anxiety (Bassir Nia et al., 2023; Fernandes & Orsorio, 2015; Kevorkian et al., 2015).

Cannabis Dependence, Cannabis Use Disorder, and Anxiety

While there were many strengths to Study 1, there were several questions left unanswered about the impact of potentially problematic cannabis use patterns amongst those with self-reported trauma exposure. An important limitation of the outcomes examined in Study 1 is that we could only infer more problematic cannabis use from indications of risky cannabis use (higher use frequencies per month among the PRN/PRN+ vs. RS users). Key negative outcomes of cannabis use that were not examined included a measure of cannabis use disorder (CUD). In Study 2, we examined these potential adverse outcomes directly by including a measure of cannabis dependence levels as one of the two main outcomes. Cannabis dependence is the physiological adaptation to cannabis leading to tolerance and withdrawal symptoms upon cessation (APA, 2022). Dependence on cannabis does not have to be clinically significant based on psychiatric testing but can still cause physiological/psychological harm to its users which is why it is important to assess it in a continuous manner. CUD, on the other hand, is the diagnostic term to describe problematic cannabis use, which is based on the continued use of cannabis despite clinically significant adverse cognitive, behavioral, or physiological symptoms (APA,

2022). CUD includes dependence but is broader than just dependence. The use of cannabis and the prevalence of CUD amongst those with trauma histories is higher than among those with no trauma history (Bassir Nia et al., 2023; Kevorkian et al., 2015). Additionally, those with clinically diagnosed PTSD often experience comorbid CUD (Bilevicius et al., 2019; Kondov et al., 2020). Indeed, the overlap between trauma/PTS and cannabis dependence is a significant public health issue.

The higher prevalence of cannabis dependence among those with trauma histories assesses cannabis dependence a critical cannabis outcome to assess in studies of potentially problematic cannabis use patterns in cannabis users with trauma histories. To begin, trauma exposure has been repeatedly associated with increased anxiety in numerous different samples (Abraham et al., 2022; Shing Chiu et al., 2024**;** Suliman et al., 2009), and anxiety-related variables have been linked with cannabis in trauma-exposed populations. Moreover, frequent cannabis users have consistently higher prevalence of anxiety disorders and those with anxiety disorders show more frequent cannabis use than those without (Crippa et al., 2009). This suggests that cannabis use can worsen anxiety in the longer term amongst trauma-exposed individuals. Some cannabis use patterns may be more likely to have this adverse consequence, a possibility that was examined for the first time in trauma-exposed cannabis users in Study 2.

Where Does Gender Fit In?

While the connections of cannabis potency to cannabis dependence levels and anxiety levels continue to be explored, little work has investigated the role of gender in these relationships. Historically, there has been an emphasis on the negative aspects of cannabis use in men. For instance, men typically have a higher prevalence of cannabis use, higher dose frequency, and higher rates of CUD (Cuttler et al., 2016; Greaves & Hemsing, 2020; Matheson

& Le Foll., 2023) than women. However, recent evidence has suggested that cannabis use has been converging among men and women (Kerr et al., 2007; Chapman et al., 2017; UNDOC, 2022) and even some evidence has suggested that women may be using cannabis more often than men (Bernusky et al., 2023). These recent findings warranted further investigation, particularly whether the relationships between cannabis potency, cannabis dependence and anxiety differed among men and women.

Rationale For Study 2

While maintaining Study 1 interest in potentially risky aspects of cannabis use patterns and links with adverse outcomes, in Study 2, I shifted my focus to another neglected aspect of cannabis use patterns in this population and two other problematic outcomes. Specifically, the focus of Study 2 was to evaluate the relationships of various measures of cannabis potency to cannabis dependence and anxiety levels using a similar sample to Study 1 (i.e., adult, trauma-exposed cannabis users). An additional aim was to test whether these relationships differed by gender. Standardized, validated questionnaires on anxiety symptoms and cannabis dependence levels, as well as an author-compiled measure to assess cannabis potency, were administered to 199 Canadian adults who had experienced at least one lifetime traumatic event according to the LEC-5 (Gray et al., 2004) and who had used at least one gram of cannabis in the last month according to the Cannabis Timeline Followback (C-TFLB: Sobell & Sobell, 1992). First, correlational analyses were used to test for significant relationships between cannabis potency and both cannabis dependence and anxiety levels amongst the whole sample. Second, independent t-tests were used to determine if significant differences existed between men and women in cannabis potency, cannabis dependence, and/or anxiety levels. Finally, correlational analyses were used to determine significant relationships between cannabis potency and both

cannabis dependence and anxiety levels in each gender separately; these correlations were then compared across gender using Fisher's R-Z transformation (Meng, 1992) to determine if the correlations differed significantly between men and women.

My two thesis studies will increase our understanding of the relative riskiness of different aspects of cannabis use pattern (regimen, potency) in a population already at risk for adverse outcomes (trauma-exposed, cannabis-using adults). Additionally, my thesis findings may help identify risk reduction strategies and whom to target with preventive or early interventions.

CHAPTER 4: STUDY 2

This chapter presents the second of the two manuscripts on which this thesis is based. Under the co-supervision of Dr. Sherry Stewart and Dr. Phil Tibbo, Thomas Snooks prepared the initial draft and incorporated feedback from his co-authors. It was finalized for submission for review and publication. Dr. Stewart and Tibbo were co-supervisors at the time. Given the untimely passing of Dr. Sean Barrett (original committee member), going into the defense, the committee composition was changed to Dr. Stewart (supervisor) and Dr. Tibbo and Dr. Pam Arenella (committee members). The manuscript was prepared for submission into *Pharmacological Research's* special issue, "Sixty years from THC: Landscape and perspectives on the pharmacology of cannabinoids," and was submitted on July 12th, 2024. The full reference is as follows: Snooks, T., Stewart, S.H., Romero-Sanchiz, P., DeGrace, S., Barrett, S., Bernusky, H.C.R., & Tibbo, P.G. (under review). The Roles of Cannabis Potency and Gender in Cannabis Dependence and Anxiety in Recent Cannabis Users with Trauma Exposure Histories. *Pharmacological Research*.

Abstract

Over the past 20 years, levels of Δ9-tetrahydrocannabinol (THC) in cannabis have significantly increased, while levels of cannabidiol (CBD) have increased much less in comparison. Cannabis with higher THC potency (commonly assessed via THC:CBD ratio) may increase the risk for cannabis dependence and trigger/exacerbate anxiety. However, few studies of cannabis potency effects on cannabis dependence and anxiety have examined gender moderation. Additionally, there are issues with how cannabis potency is calculated via the THC:CBD ratio that may contribute to inconsistencies in the literature. N = 199 (55.8% women) recent cannabis users (≥1g in the past month) with trauma histories – a group at high risk for anxiety and cannabis dependence – completed an online survey including a measure of self-reported THC and CBD levels in participants' typically-used cannabis products. Cannabis potency was measured by THC:CBD ratio (THC%/CBD%) and by relative THC proportion (THC%/[THC%+CBD%]). The Cannabis Use Disorder Identification Test-Revised (CUDIT-R) and Generalized Anxiety Disorder-7 (GAD-7) assessed cannabis dependence and anxiety, respectively. Consistent with prior findings in the general population, cannabis potency was significantly positively correlated with cannabis dependence, p = .002, and anxiety levels, p = .020, but only when assessed via THC proportion and not THC:CBD ratio. Consistent with prior research, women reported significantly higher anxiety levels but also unexpectedly, higher THC:CBD ratios, than men. No significant gender differences were found in the associations of either potency measure with either outcome variable. Results are consistent with a convergence of previously reported gender differences in cannabis dependence and identify relative THC proportion as a superior predictor of adverse cannabis and anxiety outcomes than the THC:CBD ratio in both men and women.

Key Words: Cannabis, THC, CBD, THC:CBD ratio, THC potency, Dependence, Gender

Introduction

Cannabis potency, primarily measured by the concentration of Δ9-tetrahydrocannabinol (THC), has shown a significant upward trend over recent decades. This psychoactive compound has become increasingly potent, with the average THC content in cannabis flowers rising from around 3% in the 1980s to approximately 15% in recent years (Health Canada, 2019). Legal dispensaries in Canada now offer cannabis products with THC levels ranging between 14.4% and 18.2%, with THC-dominant strains comprising over 80% of available products (Mahamad et al., 2020). This escalation in THC levels is a global phenomenon, with similar trends reported in the US and European markets (Cascini et al., 2012; Chandra et al., 2019; ElSohly et al., 2021; Freeman et al., 2021). In stark contrast, the concentration of cannabidiol (CBD), a non-psychoactive cannabinoid known for its potential to mitigate the adverse effects of THC, has not experienced a parallel increase (Chandra et al., 2019). Health Canada (2023) reported an uptick in the use of CBD-predominant products across 2022. Nevertheless, THC-dominant products remain the most popular, particularly among non-medical users, raising concerns about the higher risk of adverse outcomes associated with high THC use (Stuyt, 2018).

The ratio of THC to CBD in cannabis products is crucial for understanding these products' effects on users. High THC:CBD ratios are linked with greater risks of anxiety and cannabis use disorder (CUD) (Raymundi et al., 2020; Freeman & Winstock, 2015). CBD can alleviate THC's anxiogenic effects, but this protective effect diminishes when THC levels are disproportionately high (Hutten et al., 2022). High-potency cannabis (HPC), characterized by elevated THC and low CBD, is associated with a higher severity of cannabis dependence and an increased risk of CUD (Arterberry et al., 2019; Stuyt, 2018).

Gender differences in cannabis use patterns and outcomes have historically shown men to have a higher prevalence and frequency of use, as well as a greater likelihood of developing CUD compared to women (Cooper & Craft, 2018; Hemsing & Greaves, 2020). However, recent data indicate a convergence in usage rates between genders in younger cohorts (Chapman et al., 2017; Kerr et al., 2007; Matheson & Le Foll, 2023). This convergence underscores the need to understand gender-specific responses to cannabis, especially considering the evolving composition and potency of cannabis products.

Given these developments, the traditional method of assessing cannabis potency via the THC:CBD ratio poses a mathematical challenge when CBD is self-reported as zero since it is not possible to divide by zero (Kilhary et al., 2016). Although all cannabis contains at least trace amounts of CBD, participants may self-report CBD% as zero if they are unaware of the exact amount of trace levels of CBD in their cannabis used. To address this, an alternative measure—THC proportion, calculated as THC/(THC+CBD)—is proposed to provide a more accurate representation of cannabis potency and its potential risks. This method avoids the pitfalls of loss of data when CBD concentrations are reported as zero and ensures that data from all users, including those at the highest risk (i.e., high THC and extremely low CBD), are included in analyses.

The current study primarily aimed to examine the relationship between various indices of cannabis potency (THC:CBD ratio, THC proportion, %THC, and %CBD) and the levels of cannabis dependence and anxiety among recent cannabis users with trauma histories. A secondary aim was to assess if these variables and their relationships with cannabis dependence and anxiety varied by gender. We proposed five hypotheses: Based on the evidence of THC's adverse effects on anxiety and cannabis dependence in the general population (Arterberry et al.,

2019; Freeman & Winstock, 2015; Stuyt, 2018), we hypothesized that higher THC percentages and potencies (THC:CBD ratio and THC proportion) would correlate with increased anxiety and cannabis dependence levels in our trauma exposed sample of recent cannabis users. Considering mixed evidence for CBD's beneficial effects on cannabis and anxiety outcomes (Blessing et al., 2015; Englund et al., 2022; McKee et al., 2021; Skelley et al., 2020), we hypothesized that higher CBD percentages would be associated with lower anxiety and cannabis dependence levels. Extending literature on gender differences in cannabis dependence (Cuttler et al., 2016; Greaves & Hemsing, 2020; Matheson & Le Foll, 2023) and anxiety (Jalnapurkar et al., 2018; Matheson & Le Foll, 2023), we expected men to show higher THC:CBD ratios and THC proportions and greater cannabis dependence, while women would exhibit higher anxiety levels. Based on Sholler et al. (2021), we predicted stronger effects of cannabis potency on anxiety in women compared to men and explored whether this gender moderation extended to cannabis dependence. Finally, we hypothesized that the THC proportion (THC/(THC+CBD)) would be a better predictor of adverse outcomes (anxiety and cannabis dependence) than the THC:CBD ratio (THC/CBD) due to the latter's limitations in excluding high-risk participants from analysis.

Methods

Participants

The current study began with a sample of 202 participants (43.6% men, 98% sex-gender aligned, *M* age = 42.94 years, *SD* = 14.71, *M* PCL-5 score = 29.66, *SD* = 17.50) as part of a more extensive study (DeGrace et al., in press). Inclusion criteria were residing in Canada, being between the ages of 19-65 years, having experienced at least one lifetime traumatic event (Life Events Checklist [LEC-5]: Gray et al., 2004), and having used at least one gram of cannabis in

the past month (i.e., recent use). Participants were recruited through Qualtrics Panels, an online survey agency, to participate in a wellness survey and were compensated by Qualtrics.

Materials

Demographics: Participants self-reported their age, sex, and gender.

Trauma Exposure: The Life Events Checklist (LEC-5) is a self-report measure consisting of 17 items that describe potentially traumatic events (e.g., natural disaster, combat, assault) as outlined in Criterion A of a DSM-5-TR (APA, 2022) posttraumatic stress disorder (PTSD) diagnosis. The LEC-5 assessed study eligibility regarding lifetime exposure to one or more potentially traumatic events. The LEC-5 has demonstrated good test-retest reliability and strong convergence with other established trauma measures, such as the Posttraumatic Stress Disorder Checklist (PCL-5; Blevins et al., 2015).

Cannabis Use and Potency: The Cannabis Timeline Followback (C-TLFB; Sobell & Sobell, 1992) is a self-report measure used to examine past-month cannabis use and to determine eligibility for the current study (i.e., use of at least 1 g of cannabis in the past 30 days). The C-TLFB has demonstrated excellent test-retest reliability, construct validity (Hjorthøj et al., 2012**)**, and concurrent validity with the Marijuana Dependence Scale. Additionally, the C-TLFB's good psychometric properties have remained consistent when administered both in-person and online (Martin-Willet et al., 2019).

In an author-compiled measure, participants were asked to report the concentrations of THC and CBD, respectively, in the cannabis product they typically use. Participants reported concentrations as 0 to 100%. Items were presented to allow for only responses between 0-100. Self-report measures of cannabis potency have shown evidence of validity (Van Der Pol et al., 2013). Cannabis has been legal for recreational use in Canada since 2018. Canadian cannabis

retailers routinely include packaging that provides concentrations of THC and CBD. Because the surveys were completed online, those who did not know their concentrations of THC and CBD could check their packaging for this information. Additionally, preliminary ecological momentary assessment evidence from Wardell and colleagues (personal communication, May 8, 2024) is encouraging in that when participants have access to cannabis with THC/CBD% percentages indicated on the packaging, they self-report those percentages with 89-93% accuracy.

Cannabis Dependence: The Cannabis Use Disorder Identification Test-Revised (CUDIT-R; Adamson et al., 2010) is an 8-item self-report inventory used to measure the participant's severity of cannabis use disorder symptoms over the past six months. The CUDIT-R has demonstrated high internal consistency, test-retest reliability, discriminant validity, and high sensitivity and specificity in detecting cannabis dependence (Adamson et al., 2010). Total CUDIT-R scores were used as a continuous outcome measure of cannabis dependence but also broadly assess the symptoms of cannabis use disorder.

Anxiety: The Generalized Anxiety Disorder-7 (GAD-7; Spitzer et al., 2006) is a brief, 7-item self-report measure used to measure a participant's anxiety symptoms over the last two weeks. The GAD-7 has demonstrated strong reliability, criterion-related and construct validity, and high sensitivity in detecting generalized anxiety disorder (Spitzer et al., 2006; Plummer et al., 2016). Total GAD-7 scores were used as a continuous outcome measure of anxiety levels.

Procedure

Qualtrics Survey Panels first invited potential participants to complete a wellness survey. Respondents then completed screening measures (i.e., age, location of domicile, past month cannabis use (C-TFLB: Sobell & Sobell, 1992), and lifetime trauma history (LEC-5: Gray et al.,

2004)). Once screening measures were completed, respondents were automatically directed to the consent form and at the beginning of the survey if they were eligible or redirected out of the survey if they were ineligible. Once informed consent was provided, participants completed the author-compiled measure assessing percentages of THC and CBD in their cannabis, the CUDIT-R (Adamson et al., 2010) to evaluate their level of cannabis dependence, and the GAD-7 (Spitzer et al., 2006) to assess their anxiety symptoms. The Nova Scotia Health Authority Research Ethics Board approved all procedures for the current study.

Study Design

The current study used gender information gathered on the demographics survey to categorize participants into one of two gender groups (men and women). Three individuals whose sex and gender did not align were excluded since their numbers were too small to permit reliable comparisons for a third gender group, leaving $N = 199$ participants for analyses. Two measures of relative potency were used for analysis. The first was the traditional THC:CBD ratio calculated by dividing the THC percentage in cannabis used by the CBD percentage in cannabis used. The second was THC proportion, calculated by dividing THC% by the sum of THC% and CBD% in the cannabis used by participants. THC proportion was included as an additional metric of THC potency as the use of the traditional THC:CBD ratio resulted in the loss of a significant number of participants in cases when the CBD percentage in cannabis used was reported as 0 (in our case, $n = 32$, 16% of the total sample).

Hypotheses one and two were addressed using bivariate correlations (Pearson's r) for the whole cohort across THC%, CBD%, THC:CBD ratio, and THC proportion with cannabis dependence and anxiety scores. Hypothesis three was addressed using independent-sample t-tests to determine if there were significant differences between men and women for THC:CBD ratios,

THC proportions, total cannabis dependence (CUDIT-R: Adamson et al., 2010), and total anxiety scores (GAD-7: Spitzer et al., 2006). Hypothesis four was addressed using bivariate correlations (Pearson's *r*) between the two THC-CBD indices and cannabis dependence and anxiety scores in each gender separately. Fisher's R-Z transformations were then used to compare the correlations across gender to determine if the correlations were significantly different from each other (Meng et al., 1992). Finally, hypothesis five was addressed by examining the number of significant correlations between the two cannabis potency indices (THC:CBD ratio and THC proportion) with cannabis dependence and anxiety levels amongst the whole cohort and by gender.

Results

Bivariate Correlations for Whole Cohort

Bivariate correlations were used to examine the relationships between THC percentage, CBD percentage, THC:CBD ratio, and THC proportion with cannabis dependence and anxiety scores. For the correlations across the full sample, see Table 1 in Appendix A.

Partially consistent with H1, higher THC proportions were significantly associated with higher cannabis dependence, p =.002, and higher reported anxiety levels, p = .020. However, neither THC:CBD ratios, p = .493, nor THC levels alone, p = .445, were significantly related to cannabis dependence. Similarly, neither THC:CBD ratios, p = .439, nor THC levels alone, p = .251, were significantly related to anxiety levels. Partially consistent with H2, higher CBD levels alone in cannabis used were significantly related to lower cannabis dependence, p = .006, but were not significantly associated with anxiety levels, p = .106.

Independent T-Tests for Gender Differences

Independent samples t-tests were used to examine if differences existed between men and women in mean levels of the following variables: THC and CBD percentages, THC:CBD ratios,

THC proportions, cannabis dependence levels, and anxiety levels. For the means and standard deviations for each of these variables by gender, see Table 2 in Appendix B.

In partial support of H3, women demonstrated significantly higher anxiety than men, $t(197) = -2.058$, $p = .020$. Inconsistent with H3, there was no evidence that men scored higher than women in cannabis dependence levels, $t(197) = 1.509$, $p = .067$, THC percentages, $t(189.949) = -.953$, $p = .171$, CBD percentages, $t(191) = -.082$, $p = .467$, or THC proportions, $t(191) = -.555$, $p = .290$. Moreover, in direct contrast to H3, women reported using cannabis with significantly higher THC:CBD ratios compared to men, $t(114.735) = -1.717$, $p = .044$.

Bivariate Correlations by Gender and Fisher's R-Z Transformation

Results of the bivariate correlations by gender and Fisher's R-Z transformation appear in Table 3 in Appendix C. In direct contrast to H4, the relationship between THC proportion and anxiety levels was only significant for men and not for women. However, Fisher's R-Z transformation indicated that the relationship between THC proportion and anxiety levels did not vary significantly between men and women. The relationship between THC proportion and cannabis dependence levels was significant for both men and women. However, inconsistent with H4, Fisher's R-Z transformation indicated that the relationship between THC proportions and cannabis dependence levels did not vary significantly between men and women. No significant correlation was found between THC:CBD ratio and cannabis dependence levels for men or women and the magnitude of this relation did not vary by gender. Similarly, no significant correlation was found between THC:CBD ratio and anxiety levels for men or women, and the magnitude of this relation did not vary by gender.

Overall, a larger number of significant relationships were found using THC proportion as a comparative cannabis potency measure than THC:CBD ratios (5/6 correlations vs. 0/6

correlations, respectively). Specifically, there were significant relationships found between THC proportion and cannabis dependence and THC proportion with anxiety levels in the full sample as well as between THC proportion and anxiety levels in men and THC proportion and cannabis dependence in both men and women; none of these relations were significant when using THC:CBD ratio as the measure of cannabis potency. This pattern supports H5 that the THC proportion was a more sensitive index of cannabis potency than the THC:CBD ratio in detectin relations of cannabis potency to cannabis dependence and anxiety risk.

Discussion

The current study was designed to examine relationships between cannabis potency (and its constituent components) in the cannabis typically used by trauma-exposed recent cannabis users and their current levels of cannabis dependence and anxiety and to examine if these relationships varied by gender. The results for H1 and H2 were mixed. As hypothesized, THC proportion was significantly, positively related to both cannabis dependence and anxiety levels in this at-risk cohort. However, unexpectedly, neither THC% alone nor THC:CBD ratios were significantly related to either cannabis dependence or anxiety levels. The lack of significant findings between THC:CBD ratios and cannabis dependence or anxiety levels could be due to the mathematical flaws of this potency measure: 32 participants listed their CBD% as zero, meaning that missing values were produced for those individuals' THC:CBD ratio (i.e., THC%/0), which led to a loss of roughly 16% of the data from the whole cohort. The calculation for THC proportion included THC+CBD as the denominator and produced values between 0.000 and 1.000, which did not result in missing participant values when CBD values were reported as zero. While the results of our THC proportion index support previous findings of adverse effects of THC potency on both anxiety and cannabis dependence (Arterberry et al., 2019; Freeman &

Winstock, 2015; Stuyt, 2018), our results further suggest that THC% alone is not a sufficient index of the potential harm of cannabis. Indeed, while previous findings provide a mixed picture regarding CBD effects on cannabis-related and mental health outcomes (Englund et al., 2022; McKee et al., 2021), in our study CBD% alone was significantly, negatively associated with cannabis dependence levels, which could be because CBD appears to be devoid of positively reinforcing effects, meaning it would have little risk for those consuming it to develop dependence (WHO, 2018). These findings support previous findings that CBD may mitigate dependence risk (Morgan et al., 2010; Freeman et al., 2020). However, no relationship was found between CBD% alone and anxiety levels, which falls in line with prior findings on the mixed effectiveness of CBD as an anxiolytic (Englund et al., 2022; McKee et al., 2021). Overall, our findings suggest that the relationship between the two main cannabinoid constituents in cannabis may be a more important factor in cannabis' association with dependence and anxiety than THC alone and that CBD should be examined more extensively for its potential buffering role in the relationship between cannabis use and both cannabis dependence and anxiety.

Inconsistent with H3, women were using cannabis with significantly higher THC:CBD ratios than men, while no significant differences were found in THC proportion or cannabis dependence levels across the genders. The latter result was unexpected as men traditionally exhibit higher levels of cannabis dependence than women (Cuttler et al., 2016; Greaves & Hemsing, 2020; Matheson & Le Foll., 2023), but was more congruent with research conducted with recent cohorts where cannabis use levels and cannabis dependence rates are converging across genders (Chapman et al, 2017; Kerr et al., 2007; UNDOC, 2022) and even may be moving towards greater cannabis use in women than men (Bernusky et al., 2024). The finding of higher THC:CBD ratios in women vs. men were also in contrast with previous findings that women

preferred products with higher CBD levels (Goodman et al., 2022; Matheson et al., 2022). However, the finding of THC:CBD ratios being higher in women than men may have been due to missing values associated with the calculation of THC:CBD when CBD% was zero ($N = 21$ women vs $N = 11$ men). For instance, the average THC% used by men who were included in the THC:CBD ratio variable was 35.54% compared to 57% used by men who were treated as missing (i.e., those reporting their CBD% as zero). This pattern was not the same for women, as the average THC% used by women who were included in the THC:CBD ratio variable was 38.67% compared to 38.7% used by women who were treated as missing (i.e., those who self-reported CBD% of zero). In other words, it seems men with the riskiest cannabis use habits (higher THC and zero CBD reported) were inadvertently dropped as missing values on the THC:CBD ratio outcome creating an artificially lowered THC:CBD ratio in the remaining men. These missing values were accounted for in the calculation of THC proportion which may have been why there was no significant gender difference in THC proportion. Studies that have not accounted for this gender disparity in those being artificially eliminated due to the mathematical problem of being unable to divide by zero, might be creating misleading results with the current data being a good example.

Consistent with H3, anxiety scores among women were significantly higher than among men, which replicates the well-established gender difference in anxiety (Christiansen, 2015; Jalnapurkar et al., 2018). Additionally, it extends that finding to a sample at high risk of anxiety (recent cannabis users with trauma exposure, where both cannabis use (Kedzior & Laeber, 2014) and trauma exposure history (Hong et al., 2024) heighten risk of anxiety). In direct opposition to our hypothesis (H4) that the link of cannabis potency to anxiety would be more robust in women than men, the relationship between THC proportion and anxiety scores was significant only for

men and not for women. However, this gender difference in the magnitude of the THC proportion to anxiety relation was not itself significant when compared using Fisher's R-Z transformation. Additionally, no significant gender differences were found between relationships of THC proportion or THC:CBD ratios with anxiety. These results contrast those of Sholer et al. (2001), where women experienced higher anxiety levels than men when receiving the same dose of THC. Of course, Sholer et al.'s (2001) results are not directly comparable to ours as we assessed levels of generalized anxiety symptoms among cannabis users over the last two weeks whereas Sholer et al. (2001) assessed state anxiety reactions to acute THC administration.

Finally, H5, where THC proportion was predicted to have more significant associations with the dependent variables than THC:CBD ratio, was supported by the significant associations found between THC proportions with cannabis dependence and anxiety levels for the total cohort, along with the additional findings that THC proportions were significantly associated with cannabis dependence levels for both genders and for anxiety levels amongst men. The THC proportion measure was able to account for the missing values generated by the THC:CBD ratio measure and appears to have potentially yielded a more accurate representation of the relationships of cannabis potency to both cannabis dependence and anxiety.

Overall, the findings from the current study point to the importance of using the novel THC proportion measure [THC%/(THC%+CBD%)], rather than simply the THC:CBD ratio, as a variable for analyzing links of THC potency with anxiety and cannabis dependence, because it leads to far fewer missing values (and potentially less biased results). Understanding THC proportions present in cannabis products available to the public is also important, as cannabis with high THC and low CBD could be more detrimental to public health (Freeman & Winstock, 2015; Stuyt, 2018; Arterberry et al., 2019). THC proportion better accounts for those who are

using cannabis with the highest theoretical risk of harm (high THC, virtually no CBD) than THC:CBD ratio where such higher risk individuals are inadvertently excluded due to a mathematical paradox when respondents report the CBD concentration in their cannabis as zero. Additionally, given that the current study failed to see men greater than women gender differences on our cannabis indices that have been reported in past cohorts (Cuttler et al., 2016; Greaves & Hemsing, 2020; Matheson & Le Foll., 2023), the current findings are consistent with a variety of recent data suggesting gender convergence in various cannabis indices (Chapman et al., 2017; Kerr et al., 2007; UNDOC, 2022). Additionally, the findings that THC% and THC proportions did not differ between men and women also point to women using cannabis in an equally risky way to men, at least among a trauma exposed sample of recent cannabis users.

Limitations

Despite the interesting results, there are limitations to the current study that should be considered when interpreting the findings. The current study used a cross-sectional design. Because of this, the causal nature and temporal direction in the relationships of THC potency to anxiety and cannabis dependence cannot be determined. For example, it is possible that rather than HPC causing cannabis dependence, those with greater cannabis dependence may be selecting HPC products because they better alleviate their withdrawal symptoms. Second, the analysis of gender differences was limited to two categories and focused on individuals whose biological sex and gender identity aligned as there were too few participants to allow for a distinct group of gender non-conforming/non-binary individuals for reliable statistical comparison. This narrow focus on a binary conceptualization of gender in the present study is potentially problematic given that transgender and non-binary individuals have an increased risk of problematic cannabis use, CUD, and anxiety disorders (Connolly et al., 2020; Gonzalez et al.,

2017; Scheim et al., 2017). Additional studies with non-binary and/or other gender non-conforming individuals are warranted to explore if the current evidence of gender convergence of cannabis use exists beyond the gender binary.

There were also potential confounds for the measure of cannabis potency. The author-compiled questionnaire to assess cannabis potency in participants' usual cannabis was not assessed for reliability and validity prior to inclusion in the survey and was self-reported. For example, it may contain errors to the extent that participants are unaware of the THC or CBD content of their cannabis. Only 4/199 (2%) participants left one or more of the open-ended questions on cannabis potency blank or listed that they were unsure of the THC and CBD percentages in their cannabis use. However, self-report measures of cannabis potency have scarcely been examined in previous research, and evidence of accuracy has been mixed. One study found evidence of an association between subjective potency and actual THC concentration when participants self-reported categorically how "high," they felt (Van Der Pol et al., 2013), which may suggest that individuals can accurately report the potency of their cannabis when they do not have the exact THC/CBD information on the cannabis they use. Another study (Freeman et al., 2014) examined whether self-reported estimates of potency were predicted by higher THC concentrations actually used by 247 cannabis users. However, potency estimates were more accurate for daily users (25+ days a month) compared to recreational users (1-24 days a month). The sample used in the current study used cannabis on average about 13 days per month, meaning that in comparison to Freeman et al.'s findings (2014) for daily users, the current sample may be less accurate in their potency estimation. Canadian cannabis users have also previously demonstrated poor cannabis potency estimation, as less than one-third of 2354 participants were able to report the THC:CBD ratio in their cannabis, which is the task that we

asked our participants to do (Hammond & Goodman, 2022). However, all the studies mentioned (Van Der Pol et al., 2013; Freeman et al., 2014; Hammond & Goodman, 2022) were either conducted in the US and UK, where cannabis is not legal federally, or with Canadian participants before cannabis legalization in 2018. Post-legalization, cannabis products in Canada must be clearly marked with THC% and CBD%, which suggests that cannabis users are now regularly exposed to this information and should theoretically be able to accurately report those numbers or consult their packaging to obtain this information when completing an online survey. Additionally, preliminary ecological momentary assessment evidence from Dr. Jeffrey Wardell at York University (personal communication, May 8, 2024) is encouraging. Participants in that study were asked to self-report on their THC and CBD percentage of the product they were using that day and were also asked to submit a photo of the label. The self-reports showed 89-93% accuracy relative to the photo labels. Additional reliability and validity testing should be conducted in future studies to determine our scale's suitability for inclusion in future projects or to allow refinement of the measure to increase respondent accuracy.

There is also an issue with the missing values created by the THC:CBD ratio calculation when CBD% was reported as zero when technically, no cannabis is entirely devoid of CBD (Freeman et al., 2020). We considered correcting this by using a very small value to replace a CBD value of zero so a THC:CBD ratio value could still be generated (e.g., 0.1 was considered as an example), but this led to THC:CBD ratio values with new problems of extreme skew and kurtosis which precluded their use in correlational analysis. However, this points to the additional value of using THC proportion as a potency measure as the calculation still creates reportable values between 0.000-1.000 regardless of the value listed for CBD%.

The present study found no evidence of gender moderation. However, with a sample size of just under N=200, it is possible that we were underpowered to detect such gender moderation if the interaction with gender was small in magnitude. Nonetheless, if the gender differences are that small, they might not be of practical import. Finally, generalizability to the overall population may be limited as all individuals tested were recent cannabis users with trauma histories and these individuals are already at high risk of cannabis use, cannabis dependence (Kevorkian et al., 2015), and anxiety (Hong et al., 2024). However, it is important to examine these relationships in specific clinically relevant populations to allow for the translation of results to patient-centered care.

Conclusion

Overall, the current study's findings have important implications for understanding the role of cannabis potency in cannabis dependence and anxiety risk among recent cannabis users with trauma histories. The significant relationships found between CBD percentage and THC proportion with cannabis dependence levels suggest the importance of understanding the relative proportion of different cannabinoids going into current market cannabis. The results suggest that regulations on THC potency could be more accurately assessed through THC proportion and call for consideration of including higher relative CBD levels in commercial cannabis products. Because of these instances of similar risk between men's and women's cannabis use, therapeutic interventions must be gender-inclusive to ensure that women cannabis users are not dissuaded from seeking treatment for CUD or cannabis-induced anxiety by having treatments appear too oriented towards men. Cannabis dependence prevention messaging should also target both men and women. Additionally, the current results point to the importance of considering high THC potency as a risk for cannabis dependence in both men and women. It would also be beneficial

for future research to extend the study of cannabis potency and gender moderation of its effects to psychosis and psychotic disorders. The use of HPC products has been related to earlier onset of psychotic illness, up to 6 years earlier than the average age of onset (Di Forti et al., 2009; Di Forti et al., 2014). High THC in combination with low CBD in cannabis products is particularly concerning as CBD has demonstrated some attenuation of the effects of THC on psychosis (Schubart et al., 2011; Madras, 2019). Cannabis impacts on psychosis have also not had a sufficiently gendered focus on outcomes, which is important in determining specific treatment recommendations for patients (Crocker & Tibbo, 2018). Finally, more robust studies (i.e., longitudinal/experimental designs) on gender differences that include THC proportions, anxiety, and cannabis dependence levels are needed to further the understanding of gender moderation and the temporal and potentially casual nature of these relationships.

Ethical Considerations

All aspects of the research study from which the current manuscript was written were approved by the Nova Scotia Health Authority's (NSHA) Research Ethics Board.

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Table 4.1: Means, Standard Deviations (SDs), and Bivariate Correlations for THC%, CBD%, THC:CBD Ratio, and THC proportion with Cannabis Dependence and Anxiety Scores for the Full Cohort (n=199).

Variable	*M*	*SD*	Bivariate Correlations					
			1	2	3	4	5	6
1. THC%	35.86	33.52	-					
2. CBD%	15.90	22.55	.038	-				
3. THC:CBD	18.58	57.12	.204**	-.221**	-			
4. THC Prop	0.69	0.29	.408**	-.610**	.357**	-		
5. GAD-7	8.74	6.26	.048	-.090	.012	.149*	-	
6. CUDIT-R	11.40	6.30	.008	-.179**	-.001	.206**	.480**	-

Notes. *$p < .05$; *$p < .01$. THC%, CBD%, THC:CBD, THC Prop: author-compiled cannabis measure; CUDIT-R: Cannabis Use Disorder Identification Test-Revised (Adamson et al., 2010); GAD-7: Generalized Anxiety Disorder – 7 (Spitzer et al., 2006); THC:CBD (THC%/CBD%) ratio has missing values for *n* = 32 participants; THC Prop (THC%/THC%+CBD%).

Table 4.2 Means and Standard Deviations for THC and CBD percentages, THC:CBD ratios, THC proportions, Cannabis Dependence, and Anxiety Levels by Gender Identity.

Variable	Men (n = 88)		Women (n = 111)	
	M	SD	M	SD
1. THC%	33.36	27.94	37.84	37.45
2. CBD%	15.75	21.41	16.02	23.56
3. THC:CBD*	9.63	24.87	23.09	69.35
4. THC Prop	0.68	0.29	0.70	0.28
5. GAD-7*	7.73	6.02	9.55	6.35
6. CUDIT-R	12.15	6.80	10.80	5.78

Notes. THC%, CBD%, THC:CBD, THC Prop: author-compiled cannabis measure; CUDIT-R: Cannabis Use Disorder Identification Test-Revised (Adamson et al., 2010); GAD-7: Generalized Anxiety Disorder – 7 (Spitzer et al., 2006); THC:CBD ratio has missing values for $n = 32$ participants. *$p < .05$ (women > men).

Table 4.3 Bivariate Correlations and Fisher's R-Z Transformations for THC:CBD ratios, THC proportions, Cannabis Dependence, and Anxiety Levels by Gender Identity.

Relationship	Men (n = 88)		Women (n = 111)		Fisher's R-Z	
	r	p	r	p	Z	p
1. THC Prop – CUDIT-R	.229	.016*	.196	.023*	1.08	.140
2. THC Prop – GAD-7	.230	.016*	.075	.225	.24	.410
3. THC:CBD – CUDIT-R	.085	.231	-.012	.455	1.56	.059
4. THC:CBD-GAD-7	.120	.149	-.044	.399	1.04	.149

Notes. THC:CBD, THC Prop: author-compiled cannabis measure; CUDIT-R: Cannabis Use Disorder Identification Test-Revised (Adamson et al., 2010); GAD-7: Generalized Anxiety Disorder – 7 (Spitzer et al., 2006); THC:CBD ratio has missing values for $n = 32$ participants. *$p < .05$ (women > men).

CHAPTER 5: GENERAL DISCUSSION

Among a group of established high-risk cannabis users (i.e., those with a history of trauma exposure), questions remained about aspects of their patterns of cannabis use (i.e., their regimen of cannabis administration and how potent their cannabis is) and the relationships between those aspects of their cannabis use and negative outcomes. My thesis examined the prevalence of different cannabis use regimens, the movement towards different regimens over time, and the associations between cannabis use regimens with cannabis use frequency and quantity (Study 1). Additionally, I also examined the associations between cannabis potency measures with cannabis dependence and anxiety levels in both the total sample and by participant gender (Study 2). This chapter will summarize and discuss the findings of Studies 1 and 2 in relation to existing theory and findings, as well as provide an integration of the two sets of findings, their theoretical, methodological, and clinical implications, and the limitations of both studies and our general research design. Finally, I will conclude with the future directions that I believe this research can take and what we may be able to achieve with future investigations.

Study Summaries

Study 1

In Study 1, in a sample of regular cannabis users with a history of trauma, I found that PRN regimens of cannabis administration were much more common than an RS-only regimen at the time of testing. In terms of changes in use regimen over time, all individuals who initially used cannabis in an RS manner (100%) switched to a regimen that included PRN use (i.e., PRN or PRN+). Movement from PRN-related regimens to an RS-only regimen was rare: only 7.1% of those who were originally PRN-only users and only 15.4% of those who were originally PRN+ users moved to be RS-only users over time. Large proportions of individuals in the sample who

began as PRN remained as such (52.7%). However, many PRN-only users unexpectedly switched to PRN+ use (38.6%). Additionally, those using cannabis with a regimen that included a PRN portion used significantly more often over the span of a month than regularly scheduled users; PRN and PRN+ users used cannabis approximately twice as often on average as RS users. The individuals using cannabis with a PRN+ regimen also unexpectedly reported significantly higher frequency of use than those using with a PRN-only regimen. However, there were no significant differences between PRN or PRN+ regimens compared to RS regimens in cannabis quantity (dose per occasion).

Study 2

In the second study, we found that our new suggested measure of cannabis potency – THC proportion – was significantly, positively related to both cannabis dependence and anxiety levels in an at-risk sample of recent cannabis users with trauma histories. Moreover, CBD% alone was significantly, negatively associated with cannabis dependence levels. However, unexpectedly, neither THC% alone nor the traditional measure of cannabis potency – THC:CBD ratio – were significantly related to either cannabis dependence or anxiety levels. Consistent with H3, anxiety scores among women were significantly higher than among men, replicating the well-established gender difference in anxiety (Christiansen, 2015; Jalnapurkar et al., 2018). Inconsistent with H3, however, women were using cannabis with significantly higher THC:CBD ratios than men, while no significant differences were found in THC proportion or cannabis dependence levels across the genders. In direct opposition to our hypothesis (H4) that the link of cannabis potency to anxiety would be stronger in women than men, the relationship between THC proportion and anxiety scores was only significant for men and not women. However, the gender difference in the magnitude of the THC proportion to anxiety relation was not itself significant when compared using Fisher's R-Z transformation. Additionally, no significant

gender differences were found in the relationships of THC proportion or THC:CBD ratio with anxiety. These results contrast those of Sholer et al. (2001), where women experienced higher anxiety levels than men when receiving the same dose of THC. These results are not directly comparable, however, as I assessed levels of generalized anxiety symptoms among cannabis users over the last two weeks whereas Sholer et al. (2001) assessed state anxiety reactions to acute THC administration. Finally, H5 was supported by the five significant associations (our of six tests conducted) between THC proportion with cannabis dependence and anxiety levels vs no significant associations with these outcomes for THC:CBD ratio as the measure of cannabis potency. The THC proportion measure was able to account for the missing values generated by the THC:CBD ratio measures when CBD% was reported as zero and appears to have potentially yielded a more informative representation of the relationships of cannabis potency to both cannabis dependence and anxiety.

Integration of Findings

As the previous summaries have demonstrated, there are significant relations between cannabis use regimens and cannabis potency with adverse cannabis use outcomes, particularly with use frequency and dependence levels, as well as anxiety levels, amongst trauma-exposed, cannabis using adults. The two studies conducted as part of my thesis share many common elements. First, both studies examined relatively novel aspects of cannabis use patterns (regimen in Study 1; potency in Study 2) and their relationships with risky or adverse outcomes (frequency and quantity of cannabis use in Study 1; dependence and anxiety in Study 2). Both were conducted with samples drawn from a population at risk for CUD – namely, cannabis users with trauma histories. The idea was to find modifiable aspects of their cannabis use patterns that could be targeted for future interventions to reduce their elevated risk of CUD. With that idea in mind,

we found evidence that both novel aspects of cannabis use patterns were related to outcome variables representing a higher risk of developing CUD in those with trauma histories. First, our findings that PRN regimens (i.e., PRN alone or PRN+) were by far the most prevalent cannabis administration regimen similarly to previous findings with benzodiazapines and anxiety/panic disorders (Dammen et al., 1994; Westra & Stewart, 2002a). Additionally, the findings that 100% of initial RS users switched to a PRN-like regimen (Romach et al., 1991), and that PRN/PRN+ users were using cannabis significantly more often per month compared to RS users was also similarly found in benzodiazepine research (Westra & Stewart, 1998). All of these findings relate to risk for developing CUD as this form of self medication (i.e. PRN) is similarly common, similarly moved towards over time, and similarly associated with higher frequency of use amongst benzodiazepine users (Dammen et al., 1994; Romach et al., 1991; Westra & Stewart, 1998; Westra & Stewart, 2002a).

Second, our findings that THC proportions were significantly related to higher cannabis dependence and anxiety levels (Arterberry et al., 2019; Freeman & Winstock, 2015; Stuyt, 2018), suggest that those who are using HPC are at a heightened risk of developing CUD. Inversely, CBD% alone was associated with lower cannabis dependence levels (Morgan et al., 2010; Freeman et al., 2020), which suggests that CBD content in cannabis used may have be protective of the anxiogenic effects of THC that are well established (Hutten et al., 2022; Sharpe et al., 2020; Zuardi et al., 1982). Our discoveries indicate that the interplay among cannabinoid components in cannabis could wield a more significant influence on cannabis dependence and anxiety outcomes than THC alone. Furthermore, our research underscores the necessity for a thorough exploration of CBD's potential in mitigating the possible negative influence of cannabis consumption on both cannabis dependence and anxiety levels. Additionally, no significant

gender differences (men vs women) were found between the relationships of the cannabis potency indices (THC:CBD ratio and THC proportion) with cannabis dependence and anxiety levels in Study 2. This lack of gender moderation suggests that cannabis potency poses a similar risk for men and for women in terms of cannabis dependence and anxiety outcomes, which extends to cannabis potency, other findings suggesting a similar risk across genders of other aspects of cannabis use with various adverse outcomes (Bernusky et al., 2023; Chapman et al., 2017; Kerr et al., 2007; UNDOC, 2022).

Taking these two sets of findings together, we can suggest that a PRN regimen of cannabis use coupled with the use of a cannabis product with high THC and low CBD is likely to be most risky for the development of CUD and/or exacerbation of PTS/anxiety-related symptoms in trauma-exposed adult cannabis users and that these particular cannabis potency risks are relatively equal amongst men and women. With these findings, we may be able to help explain the elevated risk of CUD amongst those with trauma histories (Bassir Nia et al., 2023; Kevorkian et al., 2015). Since our studies used only those cannabis users with trauma histories, future studies could compare cannabis users with and without trauma histories to examine group differences in these aspects of cannabis use patterns to determine if those with trauma histories use higher THC potency cannabis and/or are more likely to use their cannabis in a PRN regimen.

Theoretical Integration

The current thesis has important theoretical contributions. Much of Study 1's theoretical basis was derived from operant conditioning theory and negative reinforcement principles (Blume, 2001; Skinner, 1971) and from the broader self-medication hypothesis (SMH; Khantzian, 1997). For instance, the application of both theories posits that cannabis acts as a short-term negative reinforcement that alleviates aversive and painful psychiatric symptoms like,

in this context, PTS symptoms. In Study 1, those using cannabis in a PRN manner were theoretically more likely to develop strong associations between trauma cues, PTS/anxiety symptoms, and relief outcomes, which may lead to more frequent use and potential dependence development. Consistent with predictions emerging from application of these two theoretical models, PRN and PRN+ cannabis users reported significantly higher cannabis use frequency over the past month compared to RS users, suggesting regimen of use may be an important addition to these theoretical models. However, it is essential to note that the SMH is derived from psychodynamic principles and thus has additional components not included in the operant conditioning model. For example, the SMH posits that self-medication occurs in vulnerable individuals who have: (a) difficulties in regulating affective states, particularly negative affective states, which they are motivated to reduce; (b) impairments in identifying emotional states (i.e., alexithymia); (c) broader difficulties in regulating interpersonal relationships; and (d) low self-esteem (Khantzian, 1997). Future research should test whether PRN/PRN+ cannabis users (vs. RS cannabis users) exhibit higher levels of these broader emotional and relational vulnerabilities by including measures of difficulties with emotional regulation, alexithymia, relationship functioning, and self-esteem. This would help determine whether the current Study 1 results are best viewed from a narrower learning history perspective or the broader lens of the SMH.

While negative reinforcement learning may explain the findings of Study 1, positive reinforcement learning principles may be able to help explain our results from Study 2. Indeed, we found that higher THC proportions, a novel measure of cannabis potency, were significantly associated with higher levels of cannabis dependence in trauma-exposed cannabis users. This may be due in part to the positive reinforcement (reward outcomes) of using higher-potency cannabis products. In theory, cannabis with a higher THC:CBD ratio has more inherently

reinforcing effects on trauma-exposed individuals due to the perception of a better high and stronger subjective effects, especially with the absence of CBD, which may dampen these rewarding effects. There is evidence of this already, as Freeman and Winstock (2015) found that higher potency cannabis, despite its negative effects (like its association with anxiety in my Study 2), was also considered to produce the best high and was the preferred type of cannabis amongst an adult population of cannabis users. Combine this with the fact that trauma-exposed individuals are already at a higher risk of developing CUD than the general population (Bassir Nia et al., 2023; Kevorkian et al., 2015), and you have a high likelihood of trauma-exposed individuals using HPC and a high risk of developing CUD. Theoretically, combining the positive reinforcement effects of highly potent cannabis (i.e. the ability to re-experience positive affect while using cannabis) with the negative reinforcement effects of a PRN or PRN+ regimen of use, and you have a very detrimental pattern of cannabis use that puts already at-risk individuals at an even higher risk of developing CUD and of exacerbating their PTS/anxiety symptoms.

Methodological Implications

In the current thesis, I have proposed a novel cannabis potency measure that may be superior to how cannabis potency is often assessed in the extant literature (i.e., THC% or THC:CBD ratio, or subjective potency). In Study 2, cannabis potency was only found to be significantly related to cannabis dependence and anxiety levels when using our novel THC proportion measure, which could have occurred due to the inclusion of the missing values that occurred for THC:CBD when participants self-reported CBD% as zero. This new measure could be utilized in future studies to explain the discrepancies found previously regarding the influence of the THC:CBD ratio on various adverse outcomes (e.g., cannabis dependence and anxiety outcomes; Englund et al., 2022; McKee et al., 2021).

Clinical Implications

While these two combined studies examined different aspects of cannabis use patterns (regimens of cannabis use vs. cannabis potency), each independent variable showed some statistically significant links with potentially problematic cannabis use outcomes in terms of both high frequency of use (for PRN regimens in Study 1), which was consistent with previous benzodiazepine research (Westra & Stewart, 2002a,b), and higher levels of cannabis dependence (for cannabis potency in Study 2) which was consistent with previous research investigating the impacts of HPC in the general population (Arterberry et al., 2019; Freeman & Winstock, 2015; Stuyt, 2018). These two aspects of cannabis use patterns should be considered crucial for those with trauma exposure. Using cannabis on a PRN schedule could lead to the development of CUD with repeated pairings of PTS/anxiety symptoms or trauma cues (antecedents) and relief (consequence) with cannabis use (behavior) (Mowrer, 1951; Stasiewicz & Maisto, 1993). If coupled with the use of HPC, PRN use could lead to PTS/anxiety symptom exacerbation and the development of CUD amongst those with trauma exposure. Cannabis use would maintain anxiety through avoidance of symptoms which would prevent the habituation of anxiety and maintain anxiety through negative reinforcement associated with cannabis use and relief of symptoms. This would additionally reinforce cannabis use, potentially leading to CUD development. Future studies should also examine links between cannabis use regimens with PTS and anxiety symptom severity.

This thesis has three main clinical implications if replicated and extended longitudinally. First, clinicians treating PTS sequelae in those who are regular cannabis users should prescribe or recommend to patients a cannabis use regimen based on RS rather than PRN principles to help ensure that cannabis use does not escalate in frequency, thereby limiting the potential for CUD to

develop (Westra & Stewart, 2002a,b). Second, cannabis prescribed should be lower in THC and higher in CBD to additionally mitigate the potential risk of dependence development and to ensure that there is some potential for CBD to attenuate some of the less desirable effects of THC (Blessing et al., 2015; Skelley et al., 2020). CBD is not without risk either, though, as recent findings suggest that CBD may damage liver function (Chen et al., 2024). Finally, therapeutic interventions must be gender-inclusive to ensure that women cannabis users are not dissuaded from seeking treatment for CUD or cannabis-induced anxiety. Women have shown higher withdrawal intensity than men despite similar cannabis use levels (Sherman et al., 2017). Women also have shown greater lifetime panic disorder rates than men (which can be triggered by cannabis use: Crippa et al., 2009; Hathaway et al., 2003) despite similar cannabis use levels in men and women (Sherman et al., 2017). Moreover, chronic pain is more treatment-resistant to cannabis intervention in women than men when the same dose is administered across genders (Sherman et al., 2016, 2017). Given that we found higher cannabis potency to be related to higher CUD symptoms and anxiety, an integrated treatment approach targeting both cannabis use and anxiety/stress disorders that could lead to more desirable treatment outcomes and could improve treatment for both men and women. Additionally, messaging about cannabis dependence prevention should be included in all legal cannabis retailers across Canada that mention the importance of monitoring both consumers' THC consumption and regimen of use to mitigate their risk of developing frequent cannabis use, CUD, or cannabis-related anxiety.

Strengths

The current thesis has multiple strengths that reassure us of its quality and potential impact. First, we were able to gather two relatively large samples ($N = 93$ for Study 1 and $N = 199$ in Study 2) of a vulnerable population (i.e., cannabis users with trauma histories). This data

was gathered both in person in Nova Scotia (Study 1) and online across Canada (Study 2), which allowed us to gather an extensive snapshot of current cannabis use patterns amongst Canadian cannabis users with trauma histories. Because of this, we can generalize many of the results of my thesis to trauma-exposed cannabis users in both the province of Nova Scotia and at a national level. Second, many of the measures used were reliable and validated including: the LEC-5 for trauma exposure (Gray et al., 2004) for selecting trauma-exposed participants in Studies 1 and 2, and the CUDIT-R and GAD-7 for cannabis dependence and anxiety level outcomes (Adamson et al., 2010; Spitzer et al., 2006) in Study 2. Using these established, standardized measures enhances the validity of our findings. Additionally, the development and initial validation of the novel cannabis potency measure in Study 2 is a strength for the current thesis as this measure could be a more accurate measure for cannabis potency compared to traditional THC:CBD ratios with further reliability and validity testing. Overall, these numerous strengths demonstrate that the current thesis has the potential to positively impact the field of cannabis research generally and to enhance understanding of specific cannabis risks amongst individuals with traumatic experiences.

Limitations

While the current thesis has many strengths, it also has limitations that may impact our findings. First, both Studies 1 and 2 utilized a cross-sectional design. Thus, we cannot determine causality or even temporality amongst our independent and dependent variables. This means that we cannot conclusively say that PRN and PRN+ cannabis use regimens themselves are the reason why individuals using these regimens were using at significantly higher cannabis frequencies than those using under RS regimens in Study 1 or that PRN regimens preceded (rather than followed) higher cannabis use frequencies. Similarly, we cannot conclusively say

that higher cannabis potency (assessed by THC proportion) was the cause of higher cannabis dependence and anxiety levels in Study 2 or even that higher THC proportion preceded (rather than followed) cannabis dependence or anxiety. Second, the samples in Studies 1 and 2 did not necessarily have clinical diagnoses of PTSD and only had to meet criterion A of a PTSD diagnosis for inclusion in either study. Although many participants in Studies 1 and 2 were above the clinical cutoff score (33) for the PCL-5 (Blevins et al., 2015), not all participants met or were above this cutoff score. The rates of likely PTSD diagnoses were determined by self-report, which is subject to user error and additionally limits our ability to generalize these results to PTSD populations. Future studies should examine these novel cannabis use behaviors with samples of cannabis users who have a clinical diagnosis of PTSD made with a validated structured interview like the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2018). Third, all our data was collected through self-report measures that were conducted retrospectively. All variables reported were based on recollection, which may be problematic as many of our participants were heavy cannabis users who may have issues with memory impairment (Prini et al., 2020). Moreover, our novel measures of cannabis use patterns (regimen in Study 1; THC potency in Study 2) were not validated before use in the current thesis studies. Because of this, self-reporting errors may have been introduced that may have influenced our findings. Additional testing on the reliability and validity of both author-compiled measures of cannabis use regimens and cannabis potency should be conducted to determine if revisions to each scale should be made before their use in future studies. However, many of the outcome measures in the current thesis described previously (i.e., the GAD-7 and CUDIT-R) have demonstrated high validity with trauma-exposed cannabis users despite being utilized retrospectively (Bentley et al., 2021; Myers et al., 2023) and our measure of cannabis frequency

and quantity was structured and administered using principles recommended for increasing accuracy of substance use self-reports (Sobell & Sobell, 1990). Additional testing on the reliability and validity of both author-compiled measures of cannabis use regimens and cannabis potency should be conducted to determine if revisions to each scale should be made before their use in future studies. Nonetheless, the fact that these measures were related to many of the theoretically hypothesized outcomes in the expected directions in the current thesis provides some initial evidence of their validity.

Fourth and finally, the current thesis did not address the impacts of the novel measures of the two aspects of cannabis use patterns (regimen and potency) on PTS symptoms in trauma-exposed individuals. This research gap will be important to address in the future as we would predict that additional frequency of cannabis use amongst those with a PRN cannabis use regimen and those using cannabis containing higher THC proportions should experience PTS exacerbation via anxiety increases (Choi et al., 2023; Hinojosa et a., 2024).

Conclusion

The findings of my thesis hold significant implications for understanding various aspects of cannabis use among trauma-exposed individuals and for interventions and prescribing practices and safer marketing with this population. Firstly, by shedding light on the relationship between cannabis administration regimen and use frequency, this research contributes to the potential identification of optimal usage patterns that may mitigate the risk of CUD and other adverse health outcomes linked to cannabis consumption, such as lung health issues (Kaplan, 2021; Winhusen et al., 2019). Understanding these relations could guide prescribing clinicians in tailoring medicinal cannabis treatments for individuals experiencing PTS symptoms, thus optimizing therapeutic outcomes and minimizing risks (Bonn-Miller et al., 2007).

Moreover, the study underscores the importance of considering cannabis potency, particularly the relative proportions of THC and CBD, in understanding dependence and anxiety risks among recent cannabis users with trauma histories. The observed relationships between CBD percentage and THC proportion with cannabis dependence levels highlight the significance of cannabinoid composition in market cannabis products. Regulatory efforts aimed at assessing THC potency should include considerations of THC proportion, and our findings are consistent with calls for incorporating higher relative CBD levels in commercial cannabis products to potentially mitigate dependence and anxiety risks (Schubart et al., 2011; Madras, 2019). Additionally, the study emphasizes the both men and women are at risk of CUD and anxiety when using high THC potency products, suggesting the need for gender-focused research on cannabis outcomes. Future studies employing robust methodologies, such as longitudinal or experimental designs, are crucial for further elucidating the temporal and causal nature of these relationships and whether these relationships do vary by gender over time. Overall, these insights pave the way for guiding more informed prescriber and user practices regarding cannabis use patterns that may maximize therapeutic benefits while minimizing risks associated with cannabis use in those who have previously experienced trauma.

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