

**CANNABIS AND PAIN: EXAMINING THE RELATIONSHIP BETWEEN FREQUENT  
CANNABIS USE AND PAIN SENSITIVITY**

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## Abstract

Recent years have seen an increase in the adoption of cannabinoid medicines and chronic pain has emerged as the most prominent condition treated. Although cannabinoid therapies have been shown to be modestly effective in the treatment of chronic pain across several randomized-controlled trials, the extent to which frequent cannabis use influences sensitivity to acute pain has not been systematically examined. Such a determination is clinically relevant given hypersensitivity to pain associated with prolonged use of other analgesics such as opioids and reports of increased pain sensitivity to experimentally induced pain during acute cannabis intoxication. The present study was the first to examine the effect of frequent cannabis use on pain sensitivity, relative to controls, in the absence of intoxication. Participants ( $N = 80$ ; 59% female) completed a cold-pressor task and a retrospective pain diary. Results demonstrated that frequent cannabis use was not associated with hyperalgesia as cannabis users ( $n = 40$ ) and non-users ( $n = 40$ ) were equally tolerant ( $OR = 1.01, p > .05$ ) and equally sensitive to pain ( $OR = 0.93, p > .05$ ) and reported no differences in pain intensity ( $OR = 1.00, p > .05$ ) or pain in the past-month ( $OR = 0.85, p > .05$ ), a finding that was consistent across gender. The failure to identify cannabis hyperalgesia represents an important advantage of therapeutic cannabis use for pain therapy.

## **Lay Summary**

Pain affects 1 in 5 Canadians and places a significant burden on the healthcare system and economy. Although opioids are widely prescribed for pain relief, they are controversial as they pose a risk for dependence and fatal overdose. Reports suggest opioid use may result in pain intolerance; several studies have identified increased pain sensitivity (i.e., hyperalgesia) among opioid using individuals. Cannabis use (CU) has been shown to be effective in the treatment of chronic pain however, experimental studies reported increased sensitivity to pain following cannabis intoxication. The present study was the first to examine the effect of frequent CU on pain sensitivity. Results indicated the groups did not differ across four domains of pain. These findings suggest that CU does not lead to hyperalgesia. Such a determination is clinically relevant as the apparent absence of a cannabis hyperalgesia represents a potential benefit of therapeutic CU for chronic pain.

## **Preface**

Ethics approval for this research was granted by The University of British Columbia's Behavioral Research Ethics Board (H17-00391). To date, the research included in this thesis has not been published. I was central in the design and development of this project, I conducted all participant recruitment, ran the experiment, and I was responsible for the analysis of the data.

## Table of Contents

<b>Abstract</b> .....	<b>iii</b>
<b>Lay Summary</b> .....	<b>iv</b>
<b>Preface</b> .....	<b>v</b>
<b>Table of Contents</b> .....	<b>vi</b>
<b>List of Tables</b> .....	<b>viii</b>
<b>List of Figures</b> .....	<b>ix</b>
<b>Acknowledgements</b> .....	<b>x</b>
<b>Chapter 1: Introduction</b> .....	<b>1</b>
1.1 Pain .....	1
1.2 Opioid Analgesia.....	4
1.3 Opioid-Induced Hyperalgesia.....	4
1.4 Cannabis and Pain .....	5
1.5 Cannabis Hyperalgesia.....	8
1.6 Theoretical Perspective .....	10
1.7 Clinical Endocannabinoid Deficiency .....	11
<b>Chapter 2: Methods</b> .....	<b>12</b>
2.1 Methods and Results .....	13
2.2 Apparatus and Materials.....	13
2.3 Self-Report Measures.....	14
2.4 Participant Sampling and Characteristics.....	16
2.5 Procedure.....	16
2.6 Analytic Plan.....	17
<b>Chapter 3: Results</b> .....	<b>19</b>
3.1 Assumptions .....	19

3.2	Cannabis Use .....	20
3.3	Cold-Pressor Task .....	21
<b>Chapter 4: Conclusion.....</b>		<b>29</b>
4.1	Limitations .....	33
4.2	Implications.....	33
4.3	Future Directions .....	34
4.4	Conclusion .....	34
<b>Bibliography .....</b>		<b>36</b>

## List of Tables

Table 1. Intercorrelations .....	20
Table 2. Participant demographics .....	21
Table 3. Cold-pressor task .....	23
Table 4. Non-parametric comparison of cannabis users and non-users .....	24
Table 5. Regression analyses for pain sensitivity predicting cannabis use criterion .....	25
Table 6. Regression analyses for pain tolerance predicting cannabis use criterion .....	26
Table 7. Regression analyses for pain intensity predicting cannabis use criterion .....	27
Table 8. Regression analyses for past-month pain predicting cannabis use criterion .....	28



**List of Figures**

Figure 1. Standardized average experimental pain ratings for each group. ....24

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## **Chapter 1: Introduction**

Since the late 1990s, the Canadian courts have recognized the rights of patients to access cannabis for therapeutic purposes (CTP) and the latest statistics indicate that there are over 250, 000 CTP patients currently registered in the government program (Health Canada, 2018). The number of patients accessing CTP is steadily growing –October-December 2017 saw a 14% increase in registrants (Health Canada, 2018). As the number of patients accessing CTP continues to rise, estimates suggest that over a third of Canadians will use cannabis at least once in their lifetime (Statistics Canada, 2016). Cannabis may be used therapeutically for several different conditions, such as post-traumatic stress disorder and insomnia (Walsh et al., 2016; Gates, Albertella, & Copeland, 2014); however, pain relief has risen to prominence - a recent survey of Canadian medical cannabis patients reported that over-half (53%) used cannabis for pain relief (Lucas & Walsh, 2017). Despite high rates of CTP for pain relief important outcomes remain obscure.

### **1.1 Pain**

The subjective experience of pain encompasses biological, psychological, and social factors that influence and maintain it. One in five Canadians are encumbered by chronic pain and often report insufficient relief and reduced quality of life (Moulin, Clark, Speechley, & Morley-Forster, 2002; Schopflocher, Taenzer, & Jovey, 2011). Unmanaged pain can lead to compromised immune function and increased comorbidity of depression and anxiety (Canadian Psychological Association, 2007; Liebeskind, 1991). Furthermore, it is estimated that Canadian health care costs associated with pain exceed \$6 billion per year and the shortcomings of available treatment options have led to the call for the development of a national pain strategy (Lynch, 2011).

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or

described in terms of such damage” (IASP Task Force on Taxonomy, 1979), and can be classified as nociceptive, neuropathic, or central. Nociceptive pain represents the normal response to injury of tissue and is often characterized as aching or throbbing. Pain signals are carried by peripheral nerves to dorsal root ganglia, up the spinothalamic track to the thalamus, and then to the cortex (Koenig et al., 2015). This nociceptive pain signalling alerts the organism to potential or occurring tissue damage which serves an important survival function.

The other two pain systems occur as a dysfunction in signaling and interpretation of pain. Neuropathic pain is caused by injury to, or disease of, the central and/or peripheral nervous system – such as the pain that develops as a result of damaged nerves in diabetic neuropathy. The inaccurate pain signals that ensue are typically described as sharp or burning. Central pain, which is often refractory to treatment, occurs when the brain and spinal cord generate pain signals in the absence of provocation or when benign peripheral signals are amplified (Nagda & Bajwa, 2004) – for example, pain that may present following a stroke.

Pain can also be understood in temporal terms - as acute or chronic - both of which are unique clinical entities. Acute pain is a biological and psychological response to injury of tissue or the nervous system. Chronic pain is a highly complex phenomenon, considered a disease state that serves little to no biological purpose (Grichnik & Ferrant, 1991), and is associated with physical and psychological impairment that may contribute to the development of comorbid mood disorders and substance use problems (Gatchel, Peng, Peters, Fuchs, & Turk, 2007). Several cognitive-behavioral factors contribute to the maintenance of chronic pain (Keefe, Dunsmore, & Burnett, 1992), and exacerbate the disruption of normal pain signaling. Ongoing activation of nociceptors can underlie the transition from acute to chronic pain (Voscopoulos & Lema, 2010). This persistent pain state activates secondary mechanisms in the central nervous system (CNS) and periphery beginning with upregulation of enzymes which sensitize first-order neurons. Subsequently, N-methyl-D-aspartic acid (NMDA) channels are activated and alter the

neuronal cell composition that disrupts normal functioning and sends messages to the brain alerting it of pain in the absence of injury (Voscopoulos & Lema, 2010).

Several mechanisms have been proposed regarding pain transmission. The gate control theory of pain proposed by Melzack and Wall (1965) describes a process of inhibitory pain modulation whereby neurological gates, in the spinal cord, determine whether pain signals reach the brain or not. Multiple sensory signals can be sent to the gates simultaneously and consequently non-noxious stimuli may override pain signals. Pain signal transmission can also be influenced by cognitive and emotional processes; for example, past experience or expectation of pain can modulate gate opening along with attention and affect. Projections from the periaqueductal grey and the rostroventromedial medulla on spinal neurons inhibit or promote nociceptive stimulation. These areas contain high concentrations of opioid and cannabinoid receptors. Exogenous and endogenous opioids as well as endocannabinoids and phytocannabinoids produce centrally acting analgesia by activating the pain pathway (Palazzo, Luongo, de Novellis, Rossi, & Maione, 2010). Although the exact mechanisms remain unclear the co-occurrence of these highly concentrated receptors suggests a shared mechanism of action.

The 'pain matrix' is a collection of brain areas (i.e., rACC, pCC, somatosensory cortex 1 and 2, insula, amygdala, thalamus) that are activated by noxious stimuli that, along with pain signaling, are implicated in cognition, emotion, and motivation (Reviewed by Ossipov, Dussor, & Porreca, 2010). Expectation, emotional context (e.g., stress, mood, fatigue), and distraction all engage with the pain matrix to modulate the experience of pain (Reviewed by Ossipov et al., 2010) and thus the subjective experience and subsequent treatment of pain varies greatly from one person to another even when the severity of injury is similar.

## **1.2 Opioid Analgesia**

The term opioid refers to all substances that bind to opiate receptors (i.e., mu, delta, and kappa); they largely produce their analgesic effect by binding specifically to the mu opioid receptor. The clinical effects of opioids can be attributed to their role in inhibiting neurotransmitter release in the primary afferent terminals in the spinal cord and activation of descending inhibitory controls in the midbrain (Chahl, 1996). Although they are viewed by many patients and clinicians as the most effective drug for pain relief (Portenoy et al., 2004) and commonly prescribed, opioids are the subject of considerable controversy as they pose a risk of abuse and potential for fatal overdose (Dhalla et al., 2009).

## **1.3 Opioid-Induced Hyperalgesia**

Many patients regard opioids as the best pharmacotherapy for pain relief; however, prior research has found that pain intolerance and sensitivity may develop from sustained opioid use (Compton, Charuvastra, & Ling, 2001). Cross-sectional data suggest a large effect size, indicating a 42-76% increase in sensitivity to experimental pain induction among opioid-dependent patients compared to matched controls (Doverty et al., 2001; Compton, Canamar, Hillhouse, & Ling, 2012; however, some argue that it is difficult to determine if increased sensitivity is attributable to the development of opioid tolerance or a unique clinical phenomenon (Raffa & Pergolizzi, 2012).

Several preclinical and clinical studies have sought to elucidate this matter. Although the clinical prevalence is unavailable, evidence for a state of nociceptive sensitization, referred to as opioid induced hyperalgesia (OIH), has been identified by many studies (Reviewed by Lee, Silverman, Hansen, Patel, & Manchikanti, 2011). Andrews offered one of the first descriptions of OIH in the literature in 1943 after observing reduced pain thresholds in opioid-dependent individuals following morphine administration (Andrews, 1943). Several mechanisms for the transition to OIH have since been proposed. The downregulation of glutamate reuptake

mechanisms and subsequent increase in activation of NMDA receptors leads to sensitization of spinal neurons (Mao, Sung, Ji, & Lim, 2002b). Other studies have suggested that pain signals being transmitted via the spinal cord become amplified due to the upregulation of excitatory peptide neurotransmitters (Reviewed by DuPen, Shen, & Ersek, 2007). Regardless of the mechanism it appears OIH persists for at least one month following detoxification from opioids (Pud, Cohen, Lawental, & Eisenberg, 2006) and resolves within 6-months (Hay et al., 2003). Paradoxically, some research has demonstrated that following a period of prolonged abstinence, individuals that had previously had an opioid use problem, demonstrated increased pain threshold and decreased pain sensitivity to cold-pressor pain in comparison to healthy controls (Liebmann et al., 1997).

Opioid induced hyperalgesia is difficult to clinically diagnose as such conclusions require knowledge of baseline pain or retrospective assessment subsequent to opioid cessation (Angst, Chu, & Clark, 2010). A recent review reported on the instances of acute OIH (Reviewed by Kim, Stoicea, Soghomonyan, & Bergese, 2014); adult patients who received remifentanil infusions prior to abdominal surgery reported substantially greater postoperative pain, required rescue medication earlier, and requested nearly twice as much morphine within 24-hours of surgery compared to the control group (Guignard et al., 2000). Increased pain sensitivity resulting from opioid use along with the dose increase that is necessary to maintain consistent analgesic effects represent a major short-coming of opioid therapy and has been proposed to contribute to accidental poisoning and death.

#### **1.4 Cannabis and Pain**

The recognized epidemic of opioid poisoning in Canada makes the identification of alternative treatments for pain a research priority, and cannabis has emerged as a promising alternative. Cannabis is a complex therapeutic agent that possesses psychoactive, analgesic, anti-inflammatory, and anxiolytic capabilities and it has been posited that cannabis not only

modulates pain signaling but may also improve psychological aspects implicated in pain perception, such as mood and sleep (Jiang et al., 2014; Reviewed by Gates, Albertella, & Copeland, 2014).

Cannabis has been used therapeutically for over two millennia (Russo, 2007) and has its roots in ancient medicine as documented by the 1<sup>st</sup> century Greece *materia medica* (Aggarwal, 2013). Before the American Medical Association removed cannabis from the 12<sup>th</sup> edition of the U.S Pharmacopeia in 1942 (Joy, Watson, & Benson, 1999), cannabis-based medicines were sold by major pharmaceutical companies such as Eli Lilly (Aggarwal, 2013) and marketed for a variety of conditions, including pain (Grinspoon & Bakalar, 1993).

The therapeutic mechanism of cannabis remained largely unknown until the early 1990s when two types of endocannabinoid receptors were identified. Cannabinoid 1 (CB1) receptors are found primarily in the CNS and cannabinoid 2 (CB2) receptors are located in peripheral tissues and the immune system (Lee, 2010); both receptors can be activated by the body's own natural cannabinoids (e.g., anandamide) as well as by components of the cannabis plant (e.g., tetrahydrocannabinol). Exogenous and endogenous cannabinoids are neuromodulators that act by increasing or decreasing the effect of neurotransmitters (Mckim & Hancock, 2013). The endocannabinoid system has been referred to as the "master regulator" for its homeostatic role in the body's drive to "relax, eat, sleep, forget and protect" (Di Marzo, Melck, Bisogno, & De Petrocellis, 1998). Endocannabinoid tone reflects various levels of endogenous cannabinoids present throughout the body, their synthesis, catabolism, and relative density of cannabinoid receptors (Russo, 2016).

Cannabinoids are centrally acting analgesics that provide pain relief by mitigating sensitization and inflammation via activation of CB1 and CB2 receptors (Starowicz, Malek, & Przewlocka, 2013). Two of the most prominent endocannabinoids involved in pain signalling are anandamide and 2-arachidonoylsn-glycerol (2-AG) both of which are produced and recruited following tissue damage and provide a first response to nociceptive signals (Hill et al., 2017). 2-



AG acts by suppressing sensitization and inflammation while anandamide modulates nociceptive signals by activating CB1 receptors in the CNS. Phytocannabinoids can stimulate the production of these endogenous cannabinoids and also interact with the cannabinoid receptors implicated in pain signaling, thus providing a rationale for the analgesic effects of exogenous cannabinoids.

Neurons in pain centers become less responsive to noxious stimuli after administration of synthetic cannabinoids (Martin, Hohmann, & Walker, 1996) and animal models suggest that cannabinoids and opioids produce analgesia by modulating the pain circuit in such a similar way that they are not pharmacologically dissociable (Meng, Manning, Martin, & Fields, 1998). However, there are ten times more CB1 receptors than opioid receptors in the CNS and pain circuits (Aggarwal, 2013) which suggests the endocannabinoid system is highly engaged in the modulation of pain.

Studies have highlighted the ability of cannabis to reduce the perception of pain in some individuals (Russo & Hohmann, 2013). Cross-sectional and population-based studies provide further evidence of the analgesic application of cannabinoids. A survey of medical cannabis users in Colorado found that 94% of patients indicated “severe pain” as the condition that they were treating (Light, Orens, Lewandowski, & Pickton, 2014) and an analysis of prescription data from United States Medicare part D enrollees found a substantial reduction in prescription pain medication in states with access to medical cannabis (Bradford & Bradford, 2016). Moreover, a recent review concluded that there was modest evidence that cannabinoid therapies were effective in the treatment of chronic pain (Whiting et al., 2015).

The effect of cannabis on pain may extend beyond the analgesic properties. Cannabis may also modulate the experience of pain by facilitating better sleep, improving mood (Reviewed by Walsh et al., 2017), and reducing inflammation and muscle spasms (Savage et al., 2016). However, despite its low toxicity and therapeutic potential, the College of Family Physicians of Canada guidelines recommend CU as a last resort in light of a paucity of research

on the effectiveness and long-term consequences of using cannabis to treat pain (College of Family Physicians of Canada, 2014).

## **1.5 Cannabis Hyperalgesia**

Despite substantial evidence of the use of cannabis for pain, the literature reports inconsistent findings regarding the longer-term impacts of using cannabis to treat pain. Experimental pain studies with healthy volunteers have been conducted to examine the analgesic properties of cannabis. A few particularly germane studies examined the effect of acute cannabis intoxication on experimentally-induced acute pain and found that in certain cases cannabis may be associated with a hyperalgesic effect.

The first study, a randomized, double-blind, placebo-controlled crossover trial in 15 healthy volunteers (58% male), examined four different concentrations of tetrahydrocannabinol (THC), placebo (<1% THC), low (2% THC), medium (4% THC), and high (8% THC) in participants that had smoked cannabis within the past 6 months but had abstained within the past 30 days (Wallace et al., 2007). The pain scores for the medium and high doses differed significantly from placebo however, in different directions. At the medium dose, participants reported decreased sensitivity to acute pain (heat-capsaicin sensitization model) suggesting an analgesic mechanism of cannabis. In the high dose, however, participants reported increased perception of pain across all three pain measures: brush, von Frey, and VASPI (Wallace et al., 2007), this moderate effect suggests acute, transient hyperalgesia.

In a second study, 16 healthy habitual male cannabis users were hospitalized for three months while proceeding through three study stages, one-month pre-CU washout, one month of ad libitum cannabis smoking, and one-month post-CU washout. Participants were administered a thermal pain test every one-to-two weeks and smoked one cannabis cigarette (2% THC) before each testing session. A small effect was demonstrated whereby pain discriminability and subjective reports of pain increased during the one month smoking phase and persisted during

the post-smoking phase. The authors concluded that cannabis may have a hyperalgesic effect that may enhance the perception of pain and this effect may persist for at least three to four weeks following moderate CU (Clark, Janal, Zeidenberg, & Nahas, 1981). The generalizability of these findings is limited by study methodology, including the relatively low potency of the cannabis administered (Cascini, Aiello, & Di Tanna, 2012).

A third study to assess the analgesic effects of smoked cannabis (THC range 3.56-5.60%) used a double-blind, placebo-controlled, within-subjects design to evaluate the subjective pain ratings of 42 non-medical cannabis users (50% male). Volunteers abstained from CU for at least 8 hours prior to the experimental session where they were instructed to smoke at least 70% of a cannabis cigarette and then complete a cold-pressor task. Cannabis use was associated with a decrease in pain sensitivity among men but not women. Women experienced an initial increase in pain tolerance followed by a decrease relative to the inactive cannabis and the authors suggested women may be more susceptible to the hyperalgesic effects of cannabis (Cooper & Haney, 2016). Similar differential gender effects were reported in a study of OIH in which the authors found morphine produced hyperalgesia earlier in females and lasted longer compared to their male counterparts (Juni, Klein, Kowalczyk, Ragnauth, & Kest, 2008).

A fourth study examined the analgesic effects of orally administered cannabis (20 milligrams THC) in 18 healthy female volunteers without a history of CU. In this randomized, double-blind, active placebo-controlled (i.e., 5 milligrams diazepam), crossover study (Kraft et al., 2008), participants experienced two different pain models: intradermal capsaicin and sunburn. Orally administered cannabis did not produce the expected analgesic effect and instead, 160-minutes following drug administration, a small reduction in pain thresholds was documented suggesting a hyperalgesic effect.

## 1.6 Theoretical Perspective

Opioid-induced hyperalgesia may provide a model for understanding cannabis hyperalgesia and lends well to an argument by analogy. Both substances have been used therapeutically since pre-history (Schultes, Hoffman, & Ratsch, 1992), are effective analgesics widely used for chronic pain (Portenoy et al., 2004; Aggarwal, 2013), and modulate the pain circuit in a pharmacologically similar way (Meng et al., 1998). Studies of the acute administration of opioids have reported transient hyperalgesia (Guignard et al., 2000) and similar findings have been reported in studies of cannabinoids (Wallace et al., 2007). Naturalistic and experimental studies of opioids suggest that sustained use may result in a state of nociceptive sensitization (e.g., Compton et al., 2001; Doverty et al., 2001); therefore, it is logical to infer that a similar state of hyperalgesia may result from frequent CU and provides further rationale for the present study.

The precise neurobiological mechanism underlying hyperalgesia resulting from substance use remains to be established. However, due to the complex interaction of biological, psychological, and social aspects of pain it is reasonable to assume the same complexity precipitates and perpetuates this state of increased sensitivity to noxious stimuli. From a broad perspective, based on the allostatic model of addiction (Koob & Le Moal, 1997, 2001), substance use may result in an opponent process that leads to a neurobiological sensitization to aversive stimuli while decreasing sensitivity to the effects of the psychoactive substance. Subsequently, the individual becomes increasingly more sensitive to punishment, pain, and other aversive stimuli while increases in substance use are required to achieve a hedonic equilibrium (Koob & Le Moal, 2008). In the case of cannabis hyperalgesia, it is possible that frequent and prolonged use may lead to a downregulation and sensitization of the endocannabinoid system. However, extant studies have identified hyperalgesia under acute

intoxication which may not lend well to this theory as it should be most pronounced in the absence of the substance.

## **1.7 Clinical Endocannabinoid Deficiency**

A theory proposed nearly two decades ago suggests that a clinical endocannabinoid deficiency (CED) may underlie several different hyperalgesic conditions such as fibromyalgia, irritable bowel syndrome, and chronic migraine syndrome (Russo, 2004). Viewing chronic pain through the lens of CED may explain in part why cannabinoid medicines are effective for chronic pain conditions. When endocannabinoid function is disrupted a lowered pain threshold, among other symptoms such as dysfunction in sleep, mood, and digestion, may manifest. Russo suggests that the cause of CED may be genetic, such as an attenuation of healthy functioning due to variability in endocannabinoid tone or acquired from injury or disease. Prolonged administration of THC to mice caused a downregulation of cannabinoid receptors apparent by the reduction in the number and signaling efficiency of CB1 receptors (Sim-Selley, 2003; Breivogel et al., 1999). Similar outcomes were seen in a study of daily cannabis smokers although the downregulation was reversed after ~4 weeks of abstinence (Hirvonen et al., 2012). The downregulation of CB1 receptors may create a situation which could be regarded an acquired endocannabinoid deficiency that may subsequently produce hyperalgesic symptoms consistent with CED.

## Chapter 2: Methods

Pain is reported to be the most prominent condition treated with cannabis and yet the effects of frequent CU on pain sensitivity have not been examined. Acute hyperalgesia has been demonstrated in several studies of cannabis intoxication (e.g., Kraft et al., 2008; Naef et al., 2003; Wallace et al., 2007; Clark et al., 1981; Cooper & Haney, 2016), however to my knowledge this is the first study to examine the effects frequent CU may have on pain sensitivity in men and women when compared to a non-using control group. The present study addressed this important outstanding issue, crucial to evaluating the therapeutic potential of cannabinoid medicines, by comparing sensitivity to acute pain between those that use cannabis and those that do not. We tested individuals that were not acutely intoxicated but whom consumed cannabis frequently to determine whether frequent CU resulted in hyperalgesia in response to experimental pain induction and self-reports of pain in the past-month thus further elucidating the complex relationship between cannabis and pain. Given the equivocal findings of the analgesic properties of cannabis this study will further elucidate this complex relationship and provide preliminary guidance to clinicians.

**Primary aim:** To determine the association between cannabis use and pain perception.

**Hypothesis 1a.** Individuals who report regular CU will demonstrate greater sensitivity to experimental pain-induction when compared to individuals with no past 6-month CU.

**Hypothesis 1b.** The increased sensitivity to pain induction will be moderated by gender such that the effects will be greater among females compared to males.

**Hypothesis 2a.** Individuals who report regular CU will demonstrate lower pain tolerance to experimental pain-induction when compared to individuals with no past 6-month CU.

**Hypothesis 2b.** The decrease in pain tolerance will be moderated by gender such that the effects will be greater among females compared to males.

**Hypothesis 3a.** Individuals who report regular CU will report greater pain intensity to experimental pain-induction when compared to individuals with no past 6-month CU.

**Hypothesis 3b.** The increase in pain intensity will be moderated by gender such that the effects will be greater among females compared to males.

**Hypothesis 4a.** Individuals who report regular CU will report greater pain in the past-month when compared to individuals with no past 6-month CU.

**Hypothesis 4b.** Greater reports of pain in the past-month will be moderated by gender such that the effects will be greater among females compared to males.

## **2.1 Methods and Results**

Data for the present study were collected as part of a two-part study. In Part 1, participants completed a survey pertaining to mental health (e.g., depression and anxiety) and substance use (e.g., alcohol and cannabis use). A total of 625 participants completed Part 1. Of these, 206 were deemed eligible for Part 2, based on CU patterns (i.e., 2-3x/week CU or no past 6-month CU), and contacted by email to participate. Eighty-three participants consented to participate in Part 2. Both groups in Part 2 underwent an experimental pain-induction (i.e., cold-pressor task). Cannabis users and non-users were compared on perceived pain scores. Supplementary analyses examined the potential moderating influences of psychosocial factors on pain (e.g., negative affect).

## **2.2 Apparatus and Materials**

A laboratory room at The University of British Columbia was used for Part 2 of this study. The room contained a desktop computer for the participant to complete questionnaires pre-and-post cold-pressor task. Participants were seated in an office chair with their back facing the researcher.

Several studies of OIH demonstrate modality-specific increases in pain sensitivity; hyperalgesia was detected with cold-pressor pain but absent in mechanically and thermally evoked pain models (Reviewed by Lee et al., 2011). The CPT involves voluntarily placing the hand and forearm in a container of cold water and ice (Edens & Gill, 1995). Pain of mild to moderate intensity builds until the individual withdraws their limb from the cold water. The CPT is desired both for its success inducing measureable levels of hyperalgesia in previous studies and meets criteria for experimentally induced pain (e.g., participant-stimulus autonomy, stimulus controllability, and reliability; Hirsch & Liebert, 1998).

The CPT was constructed with a drink cooler that contained a pump to circulate water through a cooling machine (Ecoplus 1/4 HP chiller) that regulated the temperature of 2 degrees Celsius (+/- 1). The CPT was retrofitted with a temperature probe that was partially submerged in the water to provide a digital temperature reading. Temperature readings following the CPT ranged from 3-4.9 degrees Celsius ( $M = 3.8$ ,  $SD = .55$ ).

## 2.3 Self-Report Measures

**Demographics.** A standard demographics questionnaire was developed to obtain demographic information on each participant. Questions pertaining to gender, ethnicity, and education were asked. Participants were asked to list any medications that they were on. Those in the CU condition were asked to report the time that they last used cannabis.

**Cannabis Use.** A CU frequency and quantity questionnaire was administered to screen for frequent CU (i.e., at least 2-3x/week) and non-use (i.e., no use within the past 6-months) and to quantify usage in grams.

**Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993).** The AUDIT is a 10-item measure designed to identify problematic levels of alcohol use, and screen for alcohol abuse and dependence. Of the 10 items, eight are rated on a 5-point scale that queries the frequency of alcohol use behaviors and feelings (e.g.,



“0-Never” to “4-Daily”), and two items are rated on a similarly constituted 3-point scale. The test has been shown to be internally consistent, reliable, and valid.

**Beck Anxiety Inventory (BAI; Beck & Steer, 1990).** The BAI is a self-report measure of current generalized anxiety symptoms. The measure has 21-items on which participant’s rate how bothered they are by each symptom on a 4-point Likert scale ranging from “0-Not at all” to “3-Severely.” Total anxiety scores range from 0 – 63 and are summed with higher scores indicating greater symptoms of anxiety.

**Center for Epidemiologic Studies Depression Scale Revised (CESD-R; Eaton, Muntaner, Ybarra, Smith, Tien, 2004).** The CESD-R is a 20-item screening test for depression and major depressive disorder. This measure asks participants to rate each item on a 5-point Likert scale ranging from “0-Rarely or none of the time” to “4-Most or all of the time”. The total CESD-R score is calculated as a sum of responses to all 20-questions.

**Sensory Hypersensitivity Scale (SHS; Dixon et al., 2016).** The SHS is a 25-item self-report measure of sensory hypersensitivity. The scale assesses general and modality specific (e.g., touch, taste, and hearing) sensitivity on a 5-point Likert scale ranging from “1-Strongly Disagree” to “5-Strongly Agree”. Research suggests that an increased sensitivity to sensations is related to increased sensitivity to pain (Perkins, de Bruyne, & Giummarra, 2016). The SHS pain sensitivity factor was used as a measure of past-month pain.

**Visual Analogue Scale of Pain Intensity.** A visual analogue scale (VAS) was used as a unidimensional measure of pain intensity. Participants indicated the intensity of pain from “0-No pain” to “100-Worst pain imaginable” (Dannecker, George, & Robinson, 2007). The VAS is easy to use and is widely accepted as a reliable measure of pain intensity (Reviewed by Jensen Hjermstad et al., 2011).

## **2.4 Participant Sampling and Characteristics**

Participants were recruited from an online undergraduate subject pool at The University of British Columbia (UBC) Okanagan campus. Participants were informed of the study through a posting on the UBC Okanagan psychological research website (i.e., Sona) and by posters hung around campus. Participants were compensated with 1 course credit or 1 entry into a draw for an Amazon gift card (\$20 CAD) for each part of the study they completed. The exclusion criteria for Part 2 included (1) having an active acute (e.g., broken bone) or chronic pain condition, (2) acute cannabis intoxication (i.e., no CU within 8 hours of the experimental session). Previous studies have identified differences in experimental pain perception in that individuals with mood disorders are less likely than controls to perceive a stimulus as painful (Dickens, McGowan, & Dale, 2003); therefore, information regarding mental health history was collected to examine any differences in pain perception.

## **2.5 Procedure**

Participants were asked to refrain from consuming alcohol and pain medication (i.e., opioid and non-steroidal anti-inflammatory drugs) the day prior to the experimental session. The co-investigator ran participants individually. Both groups were asked to abstain from alcohol use and the use of analgesics for at least 8 hours prior to the experimental session. Cannabis users were asked to abstain from CU for at least 8 hours prior to their appointment.

Upon arrival to the appointment, the co-investigator explained the objectives of the study and explained that participants could discontinue at any point. Participants provided informed consent before taking part in all aspects of the study. Participants completed computer-administered questionnaires prior to the CPT. Participants were asked to submerge their non-dominant hand in room temperature water for 1-minute and then instructed to submerge that same hand in the cold-pressor. They were instructed to abstain from talking, to keep their immersed hand still during the task and to stop the task when they could no longer endure it.

Participants were instructed to report the first painful sensation and asked to tolerate the stimulus for as long as possible. Consistent with previous studies and to guard against negative consequences of exposure to cold, participants were instructed to remove their hand after 120 seconds (e.g., Cooper & Haney, 2016) had passed. Pain sensitivity was defined as the first report of pain (in seconds), tolerance as the duration that the hand was kept in the cold water (in seconds), and pain intensity was measured with a rating on a VAS (“0-No pain” to “100-Worst pain imaginable”).

Time was measured on a stopwatch held by the experimenter. Upon removing their hand from the water, the participant was given paper towel to dry their hand and then asked to resume the computerized questionnaires at their earliest convenience. The in-person component of the study took approximately 30-minutes to complete.

**Power analysis.** Using G\*Power 3 software (Faul, Erdfelder, Lang, & Buchner, 2007) I have estimated the appropriate sample size ( $N = 81$ ) I will need for sufficient statistical power (.80) to find an effect. Using logistic regression, a predetermined type 1 error rate ( $\alpha = .05$ ) and anticipated small to medium effect size ( $d = .33$ ) I expect to achieve sufficient statistical power.

**Missing Data.** Missing data were excluded from the analyses. Three participants were missing data necessary for an examination of covariates (i.e., AUDIT, BAI, CESDR) and were removed from the subsequent analyses.

## 2.6 Analytic Plan

Bivariate correlations (i.e., Pearson’s  $r$  and point-biserial) were used to examine the relationship between CU, pain, measures of affect, and alcohol use. The Mann-Whitney U non-parametric equivalent to independent samples t-test was used to examine differences between groups and to identify covariates that should be included in the subsequent binary logistic regressions.

**Hypothesis 1.** Binary logistic regression was used to model the association between pain sensitivity and cannabis user/non-user status. Alcohol use was added to the model as a covariate to determine if it was having a suppressor effect on the relationship between pain sensitivity and CU. An interaction term for gender was added to the third step to help identify a moderation effect.

**Hypothesis 2.** Binary logistic regression was used to model the association between pain tolerance and cannabis user/non-user status. Alcohol use was added to the model as a covariate to determine if it was having a suppressor effect on the relationship between pain tolerance and CU. An interaction term for gender was added to the third step to help identify a moderation effect.

**Hypothesis 3.** Binary logistic regression was used to model the association between pain intensity and cannabis user/non-user status. Alcohol use was added to the model as a covariate to determine if it was having a suppressor effect on the relationship between pain intensity and CU. An interaction term for gender was added to the third step to help identify a moderation effect.

**Hypothesis 4.** Binary logistic regression was used to model the association between past-month pain and cannabis user/non-user status. Alcohol use was added to the model as a covariate to determine if it was having a suppressor effect on the relationship between past-month pain and CU. An interaction term for gender was added to the third step to help identify a moderation effect.

## Chapter 3: Results

### 3.1 Assumptions

Following a visual examination of plotted data, the Shapiro-Wilk test of normality was used to check the distribution of scores. Results indicated that the variables were not normally distributed. Homogeneity of variance was assessed with Levene's test. The assumption was met for all variables except for pain intensity  $F(1, 78) = 5.80, p < .05$  and alcohol use  $F(1, 78) = 5.67, p < .05$ . Due to the data failing to meet the assumptions required for parametric tests, nonparametric equivalents were used.

**Correlations.** Intercorrelations were computed for all variables and are presented in Table 1. Values were examined to determine trends in the data, variables were correlated in a way that is consistent with prior research (e.g., anxiety correlated with depression) adding to our confidence in the data.

Table 1

*Intercorrelations*

Variables	1	2	3	4	5	6	7
1. VAS	-						
2. Sensitivity	-.45*	-					
3. Tolerance	-.51*	.47*	-				
4. Past- Month. P	.12	-.21	-.33*	-			
5. BAI	.21	-.23*	-.17	.26*	-		
6. CESDR	.21	-.14	-.05	.14	.64*	-	
7. AUDIT	.08	.00	.10	-.14	.09	.18	-
<i>M</i>	57.74	18.14	61.35	8.23	13.14	13.08	16.39
( <i>SD</i> )	(25.78)	(23.27)	(42.77)	(3.13)	(12.53)	(13.81)	(5.31)
Cronbach's Alpha	-	-	-	-	.94	.94	.86

*Note.* VAS = visual analogue scale; Sensitivity = first report of pain in seconds; Tolerance = duration hand submerged in seconds; Past-month P = past-month pain; BAI = Beck Anxiety Scale; CESDR = Center for Epidemiologic Studies Depression Scale Revised; AUDIT = Alcohol Use Disorders Identification Test; *M* = mean; *SD* = standard deviation; \*  $p < .05$ .

### 3.2 Cannabis Use

Eighty participants were recruited from Study 1 (40 cannabis users, 40 non-using controls) – see Table 2 for participant demographics. Nearly half of the cannabis using group ( $n = 18$ , 45%) reported using cannabis at least once a day and used an average of 4.18 grams/per week ( $SD = 5.41$ ). The majority ( $n = 39$ , 97.5%) indicated that they used cannabis recreationally and 19 said they used cannabis for medical purposes.

Table 2

*Participant demographics*

	Full Sample	Cannabis Users	Control
<i>n</i> (%)	80 (100)	40 (50)	40 (50)
<i>M</i> <sub>age</sub> (SD)	23.24 (6.82)	24.11 (9.05)	22.37 (3.33)
Female (%)	47 (58.8)	23 (57.5)	24 (60)
Male (%)	33 (41.3)	17 (42.5)	16 (40)
Ethnicity (%)			
Caucasian	73.75	37.50	36.25
Asian	11.25	3.75	7.50
South Asian	6.25	1.25	5.00
Indigenous	5.00	1.25	3.75
Hispanic	3.75	3.75	0.00
Black	1.25	1.25	0.00

**3.3 Cold-Pressor Task**

Descriptive information for the cold-pressor task is presented in Table 3. All of the participants reported that they experienced pain during the CPT however, some participants ( $n = 4$ ) did not report pain intensity above a 0 on the VAS following the task – these four participants were in the control group. Twenty-three participants endured the task for the full two minutes ( $M = 61.35$ ,  $SD = 42.77$ ). Females reported lower pain tolerance ( $Mdn = 32.00$ ) relative to their male counterparts ( $Mdn = 68.00$ ),  $U = 452.50$ ,  $z = -3.20$ ,  $p < .01$ . Females reported greater pain intensity ( $Mdn = 70.00$ ) relative to their male counterparts ( $Mdn = 60.00$ ),  $U = 1035$ ,  $z = 2.54$ ,  $p < .05$ . Results of the Mann-Whitney test are presented in Table 4. The groups did not differ on any variable except for alcohol use. AUDIT scores were included as a covariate in

subsequent analyses. See Figure 1 for a graphical representation of group averages across each pain domain (i.e., intensity, tolerance, sensitivity, and past-month pain).



Table 3

*Cold-pressor task*

	Control			Female Control			Male Control			Cannabis Users			Female CU			Male CU		
N	40			24			16			40			23			17		
	Min	Max	M (SD)	Min	Max	M (SD)	Min	Max	M (SD)	Min	Max	M (SD)	Min	Max	M (SD)	Min	Max	M (SD)
Sensitivity	2	120	20.05 (27.31)	2	120	18.42 (27.50)	12	120	22.50 (27.73)	3	120	16.23 (18.54)	2	120	17.35 (23.54)	3	38	14.71 (8.48)
Tolerance	7	120	59.82 (45.04)	7	120	49.79 (44.34)	3	120	74.88 (43.10)	5	120	62.88 (40.90)	7	120	49.74 (36.98)	20	120	80.65 (40.16)
Pain																		
Intensity (0-100)	0	95	55.80 (29.69)	0	95	61.38 (29.78)	0	80	47.44 (28.40)	10	87	59.68 (21.41)	0	95	66.78 (13.30)	10	80	50.06 (26.52)

*Note.* Sensitivity = First report of pain in seconds; Tolerance = duration hand kept in water in seconds; Pain intensity = rating on visual analogue scale; CU = cannabis use; M = mean; SD = standard deviation

Table 4

*Non-parametric comparison of cannabis users and non-users*

Variable	Median CU	Median Non-CU	Mann-Whitney U	SE	Z
Intensity	66.00	66.00	804.00	103.87	0.04
Sensitivity	11.50	9.50	874.50	103.77	0.72
Tolerance	43.00	39.50	891.50	102.67	0.89
Past-month P.	7.50	9.00	684.00	103.32	-1.12
BAI	7.50	8.50	789.00	103.76	-0.11
CESDR	9.00	9.00	748.50	103.74	-0.50
AUDIT	18.00	13.00	1253.50*	103.52	4.38

*Note.* Intensity = rating on a visual analogue scale (0-100); Sensitivity = first report of pain in seconds; Tolerance = duration hand submerged in seconds; Past-month P = past-month pain; BAI = Beck Anxiety Scale; CESDR = Centre for Epidemiologic Studies Depression Scale Revised; AUDIT = Alcohol Use Disorders Identification Test; SE = standard error; \*  $p < .05$ .

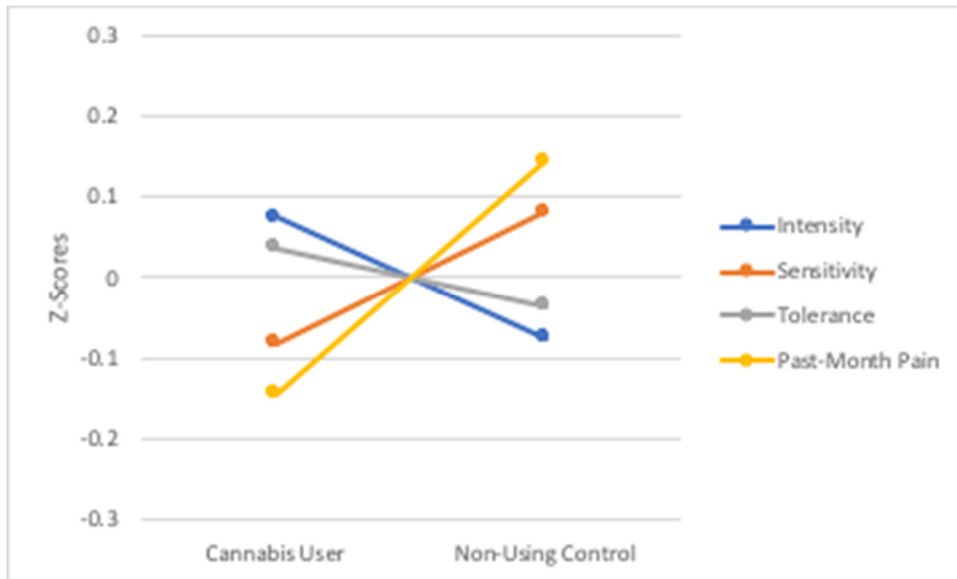


Figure 1. Standardized average experimental pain ratings for each group.

**Hypothesis 1.** Cannabis use was not associated with greater pain sensitivity. This effect was consistent when AUDIT scores were included in the model as covariates. The relationship was consistent across gender (Table 5).

Table 5

*Regression analyses for pain sensitivity predicting cannabis use criterion*

	Full Sample					
	B	SE	$\chi^2$	OR	95% CI	<i>d</i>
<i>Step 1</i>						
Pain sensitivity	-0.01	0.01	0.53	0.99	[0.97, 1.01]	-0.01
<i>Step 2</i>						
Pain sensitivity	-0.01	0.01	0.83	0.99	[0.97, 1.01]	-0.01
Alcohol use	0.29*	0.08	14.27	1.34	[1.15, 1.55]	0.16
<i>Step 3</i>						
Pain sensitivity	-0.07	0.09	0.64	0.93	[0.78, 1.11]	-0.04
Alcohol use	0.29*	0.08	13.94	1.34	[1.15, 1.57]	0.16
Gender	-0.58	0.88	0.43	0.56	[0.10, 3.16]	-0.32
Pain sensitivity X gender	0.03	0.05	0.50	1.03	[0.94, 1.13]	0.02

*Note.* SE = standard error; OR = odds ratio; CI = confidence interval; \*  $p < .05$ .

**Hypothesis 2.** Cannabis use was not associated with lower pain tolerance. This effect was consistent when AUDIT scores were included in the model as covariates. The relationship was consistent across gender (Table 6).

Table 6

*Regression analyses for pain tolerance predicting cannabis use criterion*

	Full Sample					
	B	SE	$\chi^2$	OR	95% CI	<i>d</i>
<i>Step 1</i>						
Pain tolerance	0.00	0.01	0.10	1.00	[0.99, 1.01]	0.00
<i>Step 2</i>						
Pain tolerance	0.00	0.01	0.00	1.00	[0.99, 1.01]	0.00
Alcohol use	0.29*	0.08	14.13	1.33	[1.15, 1.54]	0.16
<i>Step 3</i>						
Pain tolerance	0.01	0.02	0.28	1.01	[0.97, 1.06]	0.01
Alcohol use	0.29*	0.08	14.10	1.33	[1.15, 1.54]	0.16
Gender	0.46	1.08	0.18	1.58	[0.19, 12.98]	0.25
Pain tolerance X gender	-0.01	0.01	0.34	0.99	[0.97, 1.02]	-0.01

*Note.* SE = standard error; OR = odds ratio; CI = confidence interval; \*  $p < .05$ .

**Hypothesis 3.** Cannabis use was not associated with greater pain intensity. This effect was consistent when AUDIT scores were included in the model as covariates. The relationship was consistent across gender (Table 7).

Table 7

*Regression analyses for pain intensity predicting cannabis use criterion*

	Full Sample					
	B	SE	$\chi^2$	OR	95% CI	<i>d</i>
<i>Step 1</i>						
Pain intensity	0.01	0.01	0.46	1.01	[0.99, 1.02]	0.01
<i>Step 2</i>						
Pain intensity	0.00	0.01	0.13	1.00	[0.98, 1.02]	0.00
Alcohol use	0.28*	0.08	13.99	1.33	[1.14, 1.54]	0.16
<i>Step 3</i>						
Pain intensity	0.00	0.04	0.01	1.00	[0.94, 1.08]	0.00
Alcohol use	0.28*	0.08	13.76	1.33	[1.14, 1.54]	0.16
Gender	-0.16	1.35	0.01	0.86	[0.06, 11.95]	-0.08
Pain intensity X gender	0.00	0.02	0.00	1.00	[0.96, 1.04]	0.00

*Note.* SE = standard error; OR = odds ratio; CI = confidence interval; \*  $p < .05$ .

**Hypothesis 4.** Cannabis use was not associated with greater pain in the past-month.

This effect was consistent when AUDIT scores were included in the model as covariates. The relationship was consistent across gender (Table 8).

Table 8

*Regression analyses for past-month pain predicting cannabis use criterion*

Full Sample						
	B	SE	$\chi^2$	OR	95% CI	<i>d</i>
<i>Step 1</i>						
Past-month pain	-0.10	0.07	1.65	0.91	[0.79, 1.05]	-0.05
<i>Step 2</i>						
Past-month pain	-0.07	0.09	0.69	0.93	[0.79, 1.10]	-0.04
Alcohol use	0.28*	0.08	13.75	1.33	[1.14, 1.54]	0.16
<i>Step 3</i>						
Past-month pain	-0.17	0.32	0.29	0.85	[0.46, 1.57]	-0.09
Alcohol use	0.29*	0.08	13.64	1.33	[1.14, 1.55]	0.16
Gender	-0.50	1.58	0.10	0.61	[0.03, 13.28]	-0.27
Past-month pain X gender	0.06	0.18	1.10	1.06	[0.74, 1.52]	0.03

*Note.* SE = standard error; OR = odds ratio; CI = confidence interval; \*  $p < .05$ .

## **Chapter 4: Conclusion**

Cannabis has been used for the treatment of pain for millennia and analgesia remains the most commonly cited contemporary application of medical cannabis. However, past research has demonstrated an association between CU and increased sensitivity to acute pain. The present study sought to elucidate the association between CU and pain by examining frequent cannabis user's response to pain in the absence of intoxication. Findings from the present study suggest that frequent CU is not associated with differences in retrospective reports of pain nor does it lead to a noticeable change in acute pain sensitivity, pain tolerance, or pain intensity. These results suggest that hyperalgesia does not occur as a result of frequent CU.

The first hypothesis predicted that greater pain sensitivity would be associated with frequent CU. This hypothesis was not supported. Cannabis use was not associated with differences in the duration between when the participant submerged their hand in the CPT and their first report of pain. The pattern of results was consistent after controlling for the effects of covariates (i.e., alcohol use and gender).

The second hypothesis predicted that lower pain tolerance would be associated with frequent CU. This hypothesis was not supported. There were no group differences in the duration in which participants had their hand submerged in the CPT. The results remained consistent after controlling for the effects of covariates (i.e., alcohol use and gender).

The third hypothesis predicted that greater pain intensity would be associated with frequent CU. This hypothesis was not supported. Participants in both groups rated pain intensity, following the CPT, in ways that were almost statistically indistinguishable. The pattern of results was consistent after controlling for the effects of covariates (i.e., alcohol use and gender).

The fourth hypothesis predicted that greater past-month pain would be associated with frequent CU. This hypothesis was not supported, and the pattern of results was consistent after controlling for the effects of covariates (i.e., alcohol use and gender). Despite not reaching significance, cannabis users did trend towards slightly lower past-month pain compared to the control group.

Our findings diverge from those which found that following cannabis consumption, some participants reported increases in pain sensitivity (Wallace et al., 2007; Kraft et al., 2008; Cooper & Haney, 2016). This may be due in large part to the differences in study design. The Wallace Study (Wallace et al., 2007) reported an increase in intradermal-capsaicin pain intensity 45-minutes after smoking “high dose” cannabis (8% THC). Pain intensity was unchanged 5-minutes following CU in the high dose condition and remained unchanged in the low and medium dose cannabis. The authors proposed that there is an “analgesic window” in which cannabis is effective and that cannabis hyperalgesia is associated with higher dose cannabis. Given the fundamental differences in study design (e.g., cannabis administration and pain stimuli) it is not surprising that our findings are not consistent with the Wallace study (Wallace et al., 2007).

The Clark Study (Clark et al., 1981) was the most similar in design to the present study. Following a period of frequent CU, individuals ceased use but continued to report increased thermal pain intensity and pain discriminability, which suggest cannabis hyperalgesia remained even in the absence of intoxication. However, this study differed from ours in important ways. These differences included a component of ad libitum CU (2% THC; National Institute of Drug Abuse), the exclusion of female participants, and the repeated use of a thermal pain instrument. Most notable is the difference in THC concentration as a recent review demonstrated average-market THC concentrations close to 10% (Cascini, Aiello, & Di Tanna, 2012). Another significant difference is that participants experienced the thermal pain stimuli several times over the course of the 3-month experiment and likely developed expectations for the noxious stimuli. The



literature on pain suggests that expectations significantly influence the experience of pain and thus may hint at a possible explanation for the persisting increase in intensity (Atlas & Wagner, 2012).

The Cooper Study (Cooper & Haney, 2016) used a CPT protocol and temperature parameters that were consistent with the present study. However, it is not surprising that our study did not replicate their findings given that individuals experienced the CPT following cannabis administration. Following CU, females and males experienced an increase in pain tolerance; however, women subsequently experienced a decrease in pain tolerance, relative to placebo, two hours after cannabis administration. The sex-dependent temporal differences in cannabis analgesia are curious but present in the Kraft Study as well. The Kraft Study (Kraft et al., 2008) examined the analgesic effects of orally administered cannabis in cannabis-naïve females experiencing intradermal-capsaicin pain. Two hours following drug administration, a small reduction in pain threshold was reported.

The Kraft and Cooper studies demonstrated a delayed hyperalgesic effect among women that occurred two hours following cannabis administration. These findings may provide evidence in support of the opponent process theory which would suggest that as the subjective effects of cannabis diminish an individual may become more sensitive to noxious stimuli because of a change in their hedonic equilibrium (Koob & Le Moal, 2008). However, our findings are not consistent with an allostatic model of hyperalgesia. Although the opponent process theory has been put forward as a mechanism for opioid-induced hyperalgesia (Hill et al., 2017), the frequent use of cannabis does not appear to cause the same dysregulation of homeostasis that results in opioid-induced hyperalgesia.

Findings from the present study do not support the hypothesis that a downregulation of the endocannabinoid system and changes in CB1 receptor signaling that occur in response to repeated cannabis administration (Sim-Selley, 2003; Hirvonen et al., 2012) subsequently cause hyperalgesia. These findings are particularly interesting within the framework of CED which

suggests that some individuals experience hyperalgesic conditions due to a disruption in the endocannabinoid system. Findings from this study suggest that, despite a possible disruption to the endocannabinoid system following frequent CU, that symptoms consistent with CED do not emerge from sustained cannabis; our results do not provide support for an acquired endocannabinoid deficiency resulting from frequent cannabis use.

In three of the four aforementioned studies individuals were administered cannabis prior to the pain induction task; therefore, it is possible that the psychoactive effects of CU favor acute pain facilitation. Given the important contribution of cognition and affect to the experience of pain, there are several potential explanations for why the subjective effects of CU may lead to hyperalgesia. The psychoactive effects of cannabis include perceptual changes such that sensitivity to certain stimuli may be enhanced (National Academy of Sciences, 2017); such as, increased sustained attention (Hart et al., 2001), as well as physiological effects that can mimic anxiety (e.g., increased heart rate). Wallace and colleagues (2007) suggested that “emotional effects produced by cannabinoids (e.g., dysphoria), could counteract the analgesic effects of cannabis” (p. 792). However, the present study design does not test this assertion and more generally does not speak to the acute effects of cannabis intoxication on pain perception. However, our results nonetheless do suggest that the longer-term effects of frequent CU do not include lasting hyperalgesia.

In the present study, CU was associated with higher scores on a measure of alcohol use. Although not novel, these findings highlight the importance of examining the use of other drugs when conducting CU research. Consistent with prior research, women reported lower pain tolerance and greater pain sensitivity in response to the CPT, relative to males in the study (Hellstrom & Lundberg, 2000). Some explanations have been offered to explain this discrepancy. Women have been shown to demonstrate a lower pain tolerance when processed by a female experimenter (Tashani, Alabas, & Johnson, 2010), and due to cyclical variations in estrogen levels (Hellstrom & Lundberg, 2000). Interestingly, men and women did not differ on a

self-reported pain intensity rating. This rating was possibly subject to less response bias as the participant entered it on the computer out of the experimenter's view (Bowling, 2005).

#### **4.1 Limitations**

There are a number of limitations to the present study. First, the participants self-reported their CU and we did not confirm the presence of cannabis metabolites, therefore it is possible that some participants were assigned to the wrong group. Second, the ecological validity of the cold-pressor task is not universally recognized. Although it is widely used in pain research, it has been noted that such tasks may not accurately mimic acute pain as experienced in daily life; for example, participants have control over the intensity and duration of pain. Further, the CPT only induces one type of pain whereas a multi-model pain battery that covers multiple types of pain may have produced more comprehensive evaluation (Enggaard et al., 2001; Luginbuhl et al., 2001). Third, there are constraints to the generalizability of our findings beyond a sample of undergraduate students and thus may not extend to patients experiencing chronic pain.

#### **4.2 Implications**

Despite the limitations, this study has important implications. First, the present study addresses, in-part, a call from a recent review (Hill et al., 2017) that stated studies of the long-term use of exogenous cannabinoids would be necessary for determining "whether the same hyperalgesic response to cannabinoids that is currently observed with opioids would ensue." Second, the present study suggests that cannabinoids are distinct from opioids in that their frequent use does not lead to similar sensitization of the pain signaling system that can occur from opioid therapy. This is an important distinction that care providers and patients should consider when exploring different options for pain management. These findings are particularly

relevant in light of recent reports of opioid over-prescribing and high rates of pain in the population, as it suggests cannabis may not carry the same risk of hyperalgesia as opioids.

### **4.3 Future Directions**

With regard to future directions, ecological momentary assessment may help to provide more accurate estimates of pain in daily life and as such might increase confidence in the generalizability of effects. As the present study was conducted in healthy undergraduate students it is unclear if the effects will generalize to those with chronic pain therefore, the study of cannabis hyperalgesia should be undertaken with a clinical sample. Characterizing the analgesic effects of cannabis along with comparative effectiveness studies of opioids and cannabinoids will be essential to inform the role of these substances in pain therapy.

### **4.4 Conclusion**

Pain is a prominent complaint across cultures and pain management represents a substantial challenge to the health care professions. As such, finding suitable analgesic therapies remains a top priority in health research. Fundamental questions remain such as for who and at what dose does cannabis offer effective analgesia. Studies of the acute effects of cannabis are informative, but the identification of side-effects that persist beyond the acute effects remain paramount when considering the costs and benefits of CU. The failure to identify hyperalgesia among frequent cannabis users is especially salient for patients and health practitioners when determining the most suitable pain therapy. Hyperalgesia represents a major shortcoming of opioid therapy and in this regard, our study has failed to demonstrate a similar shortcoming of frequent CU. As drug policy in Canada experiences a major shift, the research landscape should become more conducive to studies on the therapeutic use of cannabinoids, ultimately better equipping patients and health care providers with the necessary information to make informed decisions about pain therapy. In the meantime, studies such as this one can

help to demystify the consequences of frequent CU in a healthy population and thus help to better characterize the risks and benefits of cannabis for therapeutic purposes.

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