Determinants of analgesic responses following medical cannabis initiation among patients with chronic pain

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May 2021

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science in Dental Sciences

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This thesis is dedicated to the courageous individuals who suffer from chronic pain on a daily basis and have been a huge source of inspiration over the last 2 years.

Abstract

Background: Pain is one of the most common reasons for which patients visit healthcare providers. In Canada, chronic pain is a major health problem that affects about 20% of adults. Over the past two decades, there has been a rise in the use of cannabis for therapeutic purposes, and there is a growing body of research supporting the analgesic benefits of medical cannabis for patients with chronic pain. To date, however, little is known on the factors that contribute to the analgesic benefits of cannabis in these patients. Given that symptoms of anxiety and depression (i.e., negative affect) and sleep problems are linked to heightened clinical pain intensity, there is reason to believe that reductions in patients' negative affect and sleep problems resulting from cannabis use might indirectly contribute to reductions in pain intensity. It is possible that other patient-specific factors might also contribute to the analgesic benefits of medical cannabis, but these factors have remained largely unexplored.

Objectives: The first objective of the present thesis was to examine if medical cannabis use was associated with reductions in "average" pain as well as with clinically significant (i.e., ≥ 30%) reductions in clinical pain intensity among patients with chronic noncancer pain. The second objective of the present thesis was to examine whether the association between medical cannabis use and reductions in clinical pain intensity was attributable to concurrent changes in negative affect and pain-related sleep interference. The third objective was to examine whether patient-specific characteristics were associated with reductions in clinical pain intensity following initiation of medical cannabis.

Methods: In this longitudinal study, chronic noncancer pain patients (n = 2068) completed self-report measures assessing a host of sociodemographic, lifestyle, medical, and psychological variables. Measures assessing clinical pain intensity, negative affect, and pain-related sleep

interference were completed at baseline and every three months, for a duration of one year, following initiation of medical cannabis.

Results: Analyses first indicated that initiation of medical cannabis was associated with reductions in "average" pain intensity ($p < .05$). However, medical cannabis use was not significantly associated with clinically significant (i.e., ≥ 30%) reductions in pain intensity. Further analyses indicated that initiation of medical cannabis was associated with reductions in negative affect and pain-related sleep interference (both p's < .05). Interestingly, reductions in pain intensity following the initiation of medical cannabis remained significant even after controlling for concurrent reductions in negative affect and pain-related sleep interference ($p < .05$). Analyses subsequently showed that patient characteristics such as age and sex were significant predictors of reductions in average pain intensity following initiation of medical cannabis (both p's < .05).

Conclusion: Findings from this thesis provide valuable new insights into our understanding of factors that may contribute to reductions in pain among patients with chronic pain who are using medical cannabis. Our results suggest that reductions in pain intensity following medical cannabis initiation are likely to be explained, in part, by concurrent reductions in negative affect and pain-related sleep interference. However, our findings indicated that reductions in pain following cannabis use cannot be entirely attributable to concurrent changes (i.e., reductions) in these variables. Finally, our findings indicated that the association between medical cannabis use and reductions in pain intensity was more pronounced among certain subgroups of patients, such as women and older patients. From a clinical point of view, our results could have implications for clinicians involved in the management of patients who might be considering medical cannabis as a therapeutic avenue.

Résumé

Contexte: Au Canada, la douleur chronique est un problème de santé majeur qui touche environ 20 % des adultes. Au cours des dernières années, il y a eu une augmentation de l'usage du cannabis à des fins thérapeutiques, et un nombre croissant d'études ont démontré les bienfaits analgésiques potentiels du cannabis médical pour les patients souffrant de douleur chronique. À ce jour, cependant, les facteurs qui contribuent aux bienfaits analgésiques du cannabis chez ces patients demeurent peu connu. Puisque que les symptômes d'anxiété et de dépression (affect négatif) et les problèmes de sommeil sont associés à une douleur plus élevée, la réduction de l'affect négatif et des problèmes de sommeil pourrait possiblement contribuer indirectement à la réduction de la douleur liée à l'usage de cannabis médical. D'autres facteurs spécifiques aux patients pourraient aussi contribuer aux bienfaits potentiels liés à l'usage de cannabis médical, mais ces facteurs demeurent peu étudiés.

Objectifs: Le premier objectif de la présente thèse était d'examiner si l'usage de cannabis médical est associé à la réduction de l'intensité de la douleur clinique « moyenne » ainsi qu'avec une réduction cliniquement significative (≥ 30 %) de la douleur chez les patients en douleur chronique. Le deuxième objectif était d'examiner si l'association entre l'usage de cannabis médical et la réduction de l'intensité de la douleur était attribuable à des changements concomitants de l'affect négatif et des problèmes de sommeil. Le troisième objectif était d'examiner si les caractéristiques des patients étaient associées à la réduction de l'intensité de la douleur suite à l'initiation du cannabis médical.

Méthodes: Dans cette étude longitudinale, des patients souffrant de douleur chronique non cancéreuse (n = 2068) ont complété des mesures évaluant des variables sociodémographiques, de

style de vie, médicales et psychologiques. Des mesures évaluant l'intensité de la douleur, l'interférence du sommeil lié à la douleur, et l'affect négatif ont été complétées avant le début du traitement ainsi qu'à tous les trois mois, pour une durée d'un an, suite à l'initiation du cannabis médical.

Résultats: Les analyses ont indiqué que l'initiation du cannabis médical a été associée à une réduction de l'intensité de la douleur "moyenne" ($p < .05$), mais n'a pas été associé à des réductions cliniquement significatives (i.e., $\geq 30\%$) de la douleur. Des analyses ont indiqué que l'usage de cannabis médical a été significativement associé à des réductions de l'affect négatif et des problèmes de sommeil ($p < .05$). Les réductions de l'intensité de la douleur après l'initiation du cannabis médical sont toutefois demeurées significatives même après avoir contrôlé pour les réductions concomitantes de l'affect négatif et des problèmes de sommeil des patients. Finalement, des caractéristiques des patients, telles que l'âge et le sexe, ont été significativement associées à la réduction de la douleur suite à l'initiation du cannabis médical.

Conclusion: La présente thèse apporte des connaissances nouvelles et utiles concernant notre compréhension des facteurs pouvant contribuer à la réduction de la douleur chez les patients utilisant du cannabis médical. Nos résultats suggèrent que la réduction de l'affect négatif et des problèmes de sommeil contribue aux bienfaits analgésiques du cannabis chez ces patients. Nos résultats indiquent toutefois que la réduction de la douleur en lien avec l'usage de cannabis n'est pas entièrement attribuable à des réductions concomitantes dans ces variables. Finalement, la réduction de la douleur liée à l'usage de cannabis médical pourrait être plus prononcée chez certains sous-groupes de patients, soit les femmes et les patients plus âgés. D'une perspective clinique, nos résultats pourraient avoir des implications pour les cliniciens impliqués dans la

gestion des patients souffrant de douleur chronique qui considèrent le cannabis médical comme avenue thérapeutique.

Acknowledgments

My graduate school journey would not have been possible without the constant support of many amazing people. While there are too many names to mention, I would like to especially thank a few of those who have made a huge impact on my life.

I wish to express my sincerest gratitude to my supervisor, **Dr. Marc Olivier Martel**, for his incredible support and guidance throughout my graduate experience. Thank you for sharing your enthusiasm, patience, motivation, and immense knowledge with me. Thank you for allowing me the opportunity to become involved in various research projects and for always providing me with constructive feedback. You have taught me so many invaluable lessons that I will carry on to my next adventures.

I am also grateful to my previous research mentors, **Dr. Parastou Eslami** (Harvard Medical School, Boston) and **Dr. Massieh Moayedi** (University of Toronto Faculty of Dentistry, Toronto). Thank you for the guidance you provided at the beginning of my journey as a researcher. Your dedication to your respective fields inspired me to continue down this path and become the person I am today.

Thank you to the Alan Edward Center for Pain Research and the associated scientists and clinicians from whom I learned a great deal over the last two years. The professional, personal, and academic wisdom I have gained from your expertise is beyond measure. I would also like to thank my thesis advisory committee: **Dr. Etienne Vachon-Presseau** and **Dr. Faleh Tamimi** for their insightful advice, perspective, and encouragement.

To my incredible lab members, fellow AECRP peers, and friends at the **Tran**, **Bedos**, **de Souza**, **Nicolau**, **Stone**, **Séguéla**, and **Tamimi** Labs – thank you for being a shoulder to rely on and making this experience memorable.

Thank you to the Faculty of Dentistry administrative team, **Crystal Noronha** and **Maria Palumbo**, for your assistance prior to and throughout the program. Your prompt answers to my questions and concerns are greatly appreciated.

To my close friends, **Delara**, **Benni**, and **Devangna** who supported me before and throughout this journey, thank you.

Finally, thank you to **my mother** for teaching me the art of dreaming big, to **my father** for teaching me hard work and resilience, to **my sister** for teaching me to do what I love, and to **my brother-in-law** for teaching me critical thinking. With your constant encouragement and unconditional love, "I have built a high palace that will never disappear. No rain, no wind will destroy it." **–** *Abolqasem Ferdowsi, Shahnameh: The Persian Book of Kings.*

Contribution of Authors

The MSc candidate (Miss Sotoodeh) conducted the literature search and was responsible for assembling study datasets. She also conducted all study analyses under the guidance of Dr. Martel, the candidate's supervisor. Miss Sotoodeh was involved in data interpretation as well as in the preparation of all study tables and figures. Miss Sotoodeh wrote the initial version of all sections of the present thesis. The supervisor (Dr. Martel) provided input on manuscript preparation and revisions. The findings reported in the present thesis represent original scholarship and new contributions to knowledge.

General Introduction

1.0. Pain

In many ways, pain is humanity's best teacher. This unpleasant sensation's presence is indicative of disease or injury to the body and discourages the repetition of harmful actions and behaviors [31]. Currently, the International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [3]. Pain is an internal personal experience that cannot be directly observed by others. It can be influenced by a number of biological, social, and psychological factors, which all contribute to its subjectivity [33, 133].

Pain is highly prevalent in North America and remains the number one reason for which patients seek medical attention. It impacts over 50 million individuals per year and can lead to an estimated cost of 70 billion dollars in loss of productivity and health care [60, 61]. Apart from the costs, pain causes considerable suffering through consequences such as physical disability, social isolation, and psychological distress [91].

Pain can be described by its location, cause of onset, and the affected organ. Also, the pathophysiology of pain can be classified into nociceptive, neuropathic, and nociplastic categories. Finally, pain can be classified as short-lasting (i.e., "acute") or longer-lasting ("chronic") based on its duration [127].

1.1. Acute pain

According to the IASP, acute pain lasts less than three months [30, 127]. Furthermore, it often implies the presence of "noxious pain", which refers to potential tissue damage or inflammation within the body [78, 102]. Common factors that contribute to the onset of acute pain include medical procedures, diseases, trauma, or physical labor. Although the degree of severity may vary across individuals experiencing acute pain, attempts to treat or remove the noxious stimulus often lead

to normal recovery. However, failure to properly treat acute pain may lead to chronic pain as a result of prolonged exposure to nociceptive input and changes to pathways within the central nervous system [78].

1.2. Chronic pain

The IASP defines chronic pain as pain that persists or recurs for more than 3 months [128]. At present, about 20-30% of the adult population in North America suffers from chronic pain [29, 137]. Compared to acute pain, which serves a protective function, chronic pain underlines a more serious problem. Chronic pain can be a major source of demoralization, distress, and functional impairment among patients [3, 129]. Although not always the case, chronic pain can develop following a disease diagnosis or an injury that remains unresolved during its accepted healing time [133]. In addition to its duration, chronic pain is labeled by its anatomical site and the affected organ systems. Common impacted sites include the back, neck, head, shoulder, hips, legs, and knees [113]. Over the past few decades, considerable research has been conducted to better understand the factors contributing to the development of chronic pain [3]. Due to the multifactorial nature of chronic pain, many factors may contribute to the onset of pain and its chronicity. This creates challenges from a diagnostic standpoint, and pain diagnoses can be challenging to make in clinical settings. Currently, healthcare providers can take advantage of the diagnostic codes within the latest International Classification of Diseases (ICD) that were put forward by the World Health Organization, as chronic pain was added to the 11th version of the ICD (i.e., ICD-11) in 2019. It is expected that the inclusion of chronic pain in the ICD-11 will serve to improve the classification of chronic pain as well as to increase the reliability of pain diagnoses. Importantly, the inclusion of chronic pain in the ICD-11 is expected to provide greater recognition of chronic pain as a disease, and to raise further awareness for this major health problem [127].

1.3. Conceptual models of pain

The search for the underlying causes of pain has spanned many centuries and resulted in the emergence of multiple conceptual models of pain. One of the first models that were put forward was the dualistic model by the 17th-century philosopher René Descartes [2]. The model viewed mind and body as two separate entities that operated independently of one another. Descartes deemed pain as a physical phenomenon directly related to the degree of tissue damage and independent of any psychological influence [2]. The theory's failure to account for subjective interindividual differences was heavily criticized and later led to major conceptual shifts and developments in our understanding of pain [73].

In 1965, The Gate Control Theory (GCT) by Ronald Melzack and Patrick Wall introduced the scientific community to the dynamic role played by the central nervous system (i.e., the brain and spinal cord) in pain perception and modulation of incoming nociceptive signals [92]. The theory also highlighted the contribution of psychological variables to the subjective experience of pain perception. In contrast to the dualistic model, the GCT viewed pain as multidirectional transmissions of pain signals between the periphery and the brain [92]. The GCT then gave rise to the biopsychosocial model of pain that was published in 1980. The biopsychosocial model was first introduced in medicine by George Engel highlighting the influence of psychosocial layers on the assessment and treatment of medical illnesses [49]. John Loeser then applied this idea to pain and put forth a conceptual model that emphasized the contribution of psychological, biological, and social factors to the subjective pain experience and behaviors [62, 134]. The biopsychosocial model has since been widely accepted and researched and had a major impact on the assessment and treatment of patients with pain.

1.4. Management of chronic noncancer pain using pharmacological and non-pharmacological interventions

Despite advances in our understanding of pain mechanisms and the risk factors associated with the development of chronic pain, the management of chronic pain remains a major challenge for clinicians involved in the care of these patients. Some of the most common pharmacological treatment approaches for the management of chronic pain include the use of nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, muscle relaxants, and opioids [26, 42, 56, 81]. Opioids are commonly prescribed for patients with moderate to severe pain and may be effective for some patients with chronic pain [23]. However, concerns have been raised concerning the misuse of opioids among patients with chronic pain, and research indicates that up to 10% of patients with chronic noncancer pain who are prescribed long-term opioid therapy meet diagnostic criteria for opioid use disorder [138]. Importantly, the broader societal harms associated with opioids are substantial. From 2016 to 2020, roughly 17,000 individuals died from apparent opioid toxicity in Canada, and close to 22,000 individuals were hospitalized due to opioid-related poisoning [105]. Furthermore, 97% of opioid-related deaths were reported as accidental and unintentional [105]. The majority of opioid-related deaths occurred among users of non-pharmaceutical opioids (e.g., illicitly manufactured fentanyl), indicating these deaths occurred primarily among illicit opioid users. However, opioid-related deaths also occurred among users of pharmaceutical opioids, which could have included a small subset of patients using opioids for chronic pain.

Other prescription drugs commonly used for the management of chronic pain include antidepressants as well as sedatives. Sedatives are commonly prescribed to relieve symptoms of anxiety and sleep problems in patients with chronic pain and include benzodiazepines, barbiturates, and sleep medications. The long-term use of sedative use has been associated with an increased likelihood of health problems [119], and research indicates that roughly 10% of chronic pain patients meet diagnostic criteria for sedative use disorder [79, 88, 98]. Furthermore, comorbid

heavy alcohol use is observed in 25% of chronic pain patients with benzodiazepine prescription [110], and the combination of sedatives, alcohol, and opioids has been identified as one of the root causes of opioid-related deaths [86, 146].

Several non-pharmacological treatment interventions are also commonly used for the management of patients with chronic noncancer pain. Some of these non-pharmacological interventions include physical therapy, manual therapy, as well a wide range of mind-body interventions [80, 132]. Psychological interventions are also commonly offered to patients suffering from chronic pain, and most of them are based on principles from behavioral therapy (BT), cognitive-behavioral therapy (CBT), or acceptance and commitment therapy (ATC). Psychological interventions have a long history for the management of patients with chronic pain and have traditionally been used with the aim of reducing patients' levels of pain, psychological distress, and pain-related disability (for reviews, see [75, 131, 147]). A systematic review of the literature indicated that psychological interventions such as cognitive-behavioral treatment (CBT) interventions as well as ACT/mindfulness-based interventions may be effective complementary approaches for the management of patients with chronic noncancer pain [75, 147]. While some of these interventions may have a direct impact on pain reduction, these interventions have primarily been found to be effective for the reduction of psychological distress and to improve patients' overall levels of daily life functioning [147]. Despite the potential utility and effectiveness of psychological interventions, some patients do not respond favorably to these interventions and may continue to experience high levels of pain-related psychological distress.

1.5. Consideration of cannabis for the management of chronic pain

Cannabis is a plant-based or botanical product with millennia of experience [17]. Over the past 6,000 years, cannabis has been widely used and explored for its therapeutic potential by

different cultures. In 2737 BC, the Chinese used cannabis to help alleviate the symptoms of rheumatism [100]. Moreover, Indian Vedic texts from 1500 BC point to the anxiolytic benefit of cannabis [59]. Later in 1025 AD, the prominent Iranian physician and father of early modern medicine, Avicenna, published "The Canon of Medicine" in which he included cannabis within his long list of anti-inflammatory and analgesic substances [76, 83, 95].

Recent legalizations of cannabis in North America have led to an increase in its use for therapeutic purposes. Currently, around 2.1 million people in the United States and 370,000 people in Canada hold medical cannabis licenses [1, 18]. In a recent review examining the prevalence and reasons for medical cannabis use, about 30-87% of patients across different populations reported using medical cannabis for pain or chronic pain relief [103]. Since 2001, the Canadian federal government has allowed access to cannabis for medical purposes under the Medical Marihuana Access Regulations (MMAR). In April 2014, this was replaced by the Marihuana for Medical Purposes Regulations (MMPR), and subsequently by the Access to Cannabis for Medical Purposes Regulations (ACMPR) in 2016. The ACMPR allows the production, sales, and distribution of dried (i.e., herbal) cannabis, oils, and capsules. Before the legalization of cannabis in Canada in October 2018, it was mandatory for Canadian physicians to authorize a certain limit of medical grams equivalent to dry cannabis products. This authorization also included limitations on tetrahydrocannabinol (THC) content across any type of medical cannabis products.

1.6. Cannabis formulations and mechanisms of action

Endocannabinoids are chemical ligands found within the body and are involved in maintaining homeostasis [17]. By binding to the endogenous receptors found on the internal organs, glands, connective tissues, immune cells, and the nervous systems, endocannabinoids play a role in the pathology of many diseases including pain. Similarly, the plant cannabis contains

exogenous cannabinoids, which can bind to the receptors in the body [17]. Exogenous cannabinoids vary in chemical structures, formulations, and types. The two most commonly used exogenous cannabinoids include tetrahydrocannabinol (THC) and cannabidiol (CBD). Pharmacokinetic properties and route of administration of exogenous cannabinoids may impact the body's metabolism processes including the duration of response, strength, and speed of onset [17].

Cannabinoids bind to receptors in the endocannabinoid systems such as CB1R and CB2R. CB1R and CB2R are transmembrane G-protein coupled receptors. CB1R is located within the central and peripheral nervous systems [7, 17, 82]. CB1R activation mediates the inhibition of adenylate cyclase, inactivation of calcium channels, and the stimulation of potassium channels which in turn hyperpolarizes post-synaptic neurons and inhibits neurotransmitter release [7]. On the other hand, CB2R is located within the immune cells and plays an anti-inflammatory role through cell migration and cytokine release [152]. Exogenous THC ligands mainly bond CB1 receptors. A potential theory explains that the THC-binding of the CB1R mimics endogenous agonist, anandamide, and activates the receptor, creating a psychotropic euphoric effect in the individual [7]. However, CBD, a non-psychoactive cannabinoid, seems to have negligible affinity for CB1R and CB2R and acts as an indirect antagonist. CBD has anti-epileptic, analgesic, anxiolytic, anti-inflammatory, anti-psychotic, and neuroprotective effects [139]. CBD and THC can be used separately or together in different combinations (i.e., dosages) to improve therapeutic benefits [17].

1.7. Evidence supporting the potential benefits of cannabis and cannabinoids for the management of patients with chronic noncancer pain

As noted earlier, symptoms of pain represent the most commonly endorsed reasons behind medical cannabis prescriptions [103]. In the past decade, there has been an increased use of cannabis for the management of patients with different kinds of pain conditions [122]. In studies conducted

among patients with chronic pain, medical cannabis has been found to be superior to placebo for the reduction of pain intensity (for a review, see [122]). In these studies, medical cannabis was shown to reduce various endpoints of pain intensity, including patient reports of “average” and “worst” pain intensity [122]. These pain intensity endpoints have commonly been used as primary efficacy/effectiveness outcomes in the chronic pain treatment literature [8, 25, 67]. "Average" pain refers to the stable representation of pain over a prolonged period. Contrastingly, “worst” pain intensity refers to peak pain that demonstrates a high correlation with functional interference measures [67]. In previous work, the association between medical cannabis and clinically significant reductions in pain intensity has been less convincing. Clinically significant reductions convey whether the effect experienced by patients following the use of cannabis is important [107]. A reduction of approximately 2 points or higher on a 0-10 scale or a reduction of approximately 30% is considered to represent a clinically significant difference in pain intensity [44]. A few studies have shown that medical cannabis use is associated with 30 % reductions in pain intensity (for a review, see [122]), but several studies have also failed to find such association [99, 115, 141]. Taken together, findings from previous studies suggest that medical cannabis use is associated with reductions in clinical pain intensity, even though treatment effects appear relatively small and evidence supporting the effectiveness of medical cannabis remains limited.

1.8. Potential benefits of cannabis and cannabinoids to improve chronic pain patients' psychological functioning and sleep quality

Given the high comorbidity (i.e., co-occurrence) between chronic pain and psychological distress, increased attention has been paid to the potential benefits of medical cannabis for improving patients' psychological functioning [37]. Although there is evidence indicating that repeated use of cannabis may contribute to worsening psychological functioning, this has been primarily observed among individuals exhibiting clinically significant cannabis use problems

and/or meeting diagnostic criteria for cannabis use disorder [22, 36]. Although a subset of patients with chronic pain who are using medical cannabis may be susceptible to developing cannabis use problems [142], it is expected that cannabis use under appropriate medical supervision might reduce the likelihood of these problems and possibly represent a useful avenue for improving patients' psychological and/or emotional functioning. The anxiolytic effects of cannabis have been well documented [32], and evidence indicates that cannabis use is accompanied by reductions in negative affect both among pain [9, 13,] and non-pain [34, 117] populations.

Increased attention has also been devoted to the potential benefits of medical cannabis for improving sleep quality among patients with chronic pain. The prevalence of sleep disorders is known to be very high among patients with chronic pain, with prevalence rates ranging between 30-70% across different chronic pain populations [52, 68, 118]. Studies conducted among non-pain populations have revealed that cannabis may be used to facilitate sleep among those who experience occasional sleep disturbances, but also clinically significant sleep problems such as insomnia [136]. In the context of chronic pain, there is a well-known bi-directional association between sleep disturbances and pain, with sleep problems exacerbating pain intensity and, in turn, pain symptoms contributing to the maintenance of sleep problems [52, 68, 118]. Observational studies and randomized control trials have demonstrated that pain-related sleep interference significantly decreases with the use of cannabis [10, 66, 96], but these studies have not examined the degree to which these sleep-related improvements contributed to the analgesic benefits of medical cannabis.

1.9. Gaps in knowledge

Despite the recent increase in the use of medical cannabis for its analgesic properties, questions remain concerning the potential benefits of medical cannabis for the management of

patients with chronic noncancer pain. Previous studies have examined the association between medical cannabis use and changes (i.e., reductions) in patients' levels of pain over time, but most of these studies were conducted in the context of randomized controlled trials (RCTs) that were not necessarily representative of patient populations seen in real-life clinical settings. For instance, several RCTs conducted in this area excluded patients with mental health problems, which are known to be highly prevalent among patients with chronic pain [38-41]. Most previous studies examining the association between medical cannabis use and reductions in pain have also focused on patients presenting with specific pain conditions/diagnoses while excluded those presenting with other pain symptoms or medical comorbidities [144, 148]. Finally, most of the previous studies conducted on medical cannabis and pain were fairly short, rarely exceeding more than 3 months [144, 148]. Calls have thus been made to examine the potential benefits of medical cannabis under more generalizable conditions and among patients that are more representative of those seen in primary care and tertiary care settings [104, 150]. Calls have also been made to better understand the factors that might contribute to the potential reductions in pain intensity after initiation of medical cannabis [24]. Given the strong influence of negative affect and pain-related sleep problems on patients' pain intensity [46, 131], there is reason to believe that reductions (i.e., improvements) in these variables might indirectly contribute to reductions in pain intensity following initiation of medical cannabis. It is also possible that medical cannabis use is independently associated with improvements in all these outcome domains, which could provide new insights into the multidimensional benefits of medical cannabis that can be potentially experienced by chronic pain patients [111, 120]. To date, most previous studies in this area have examined different outcome domains in isolation (for reviews, see [55, 121]), without examining whether reductions in pain intensity following initiation of medical cannabis can be attributable

to concurrent improvements in other pain-relevant outcome domains, such as negative affect or sleep. In previous studies, little attention has also been devoted to examining whether certain subgroups of chronic pain patients are more likely to respond favorably to medical cannabis. Like any other type of pain treatment, patients may present with certain sociodemographic, clinical, and/or psychological characteristics that could influence the degree to which they will benefit from medical cannabis. Most previous studies on medical cannabis and pain have examined cannabis benefits at the group (i.e., sample) level, which could have precluded the identification of patients characteristics and/or sub-groups of patients who might respond favorably to medical cannabis. Identifying these patient characteristics and/or sub-groups of patients is needed and could have important clinical implications.

1.10. Thesis objectives

The first objective of the present thesis was to examine the association between medical cannabis use and reductions in clinical pain intensity among patients with chronic noncancer pain. Analyses examined the association between medical cannabis use and reductions in "average" pain intensity as well as with clinically significant (i.e., ≥ 30%) reductions in pain. The second objective of the present thesis was to examine whether the association between medical cannabis use and reductions in clinical pain intensity was attributable to concurrent changes (i.e., reductions) in negative affect and pain-related sleep interference. The third objective was to examine whether patients' baseline characteristics were associated with reductions in clinical pain intensity following initiation of medical cannabis.

2.0. Methods

2.1. Participants and recruitment

Patients included in the present study were enrolled into the Quebec Cannabis Registry (QCR), a prospective, observational, non-comparative registry of adult patients who initiated medical cannabis, under the care of physicians, for a variety of clinical indications. Francophone and Anglophone patients were enrolled during the period of May 2015 to October 2018 and were recruited from 71 public or private outpatient clinics certified to authorize medical cannabis in the province of Quebec. Patients were recruited from physician-collaborators who practiced medicine in Quebec and who were authorized for medical cannabis in accordance with the regulatory directives from the Collège des Médecins du Québec (CMQ) and the federal Access to Cannabis for Medical Purposes Regulations (ACMPR). All eligible physician-collaborators completed a training program in the research methods of the QCR. Medical cannabis products were purchased from a Canadian licensed cannabis producer, as authorized by physicians.

Patients included in the QCR consisted of patients who were 1) initiating medical cannabis under the care of a physician, 2) ≥ 18 years old at the time of medical cannabis initiation, 3) able to provide informed consent, and 4) able to complete self-report questionnaires. For the purposes of the present thesis, only 5) patients experiencing chronic noncancer pain were included (see Figure 1).

2.2. Measures and procedures

The project was initially approved by the central research ethics committee of the Ministry of Health and Social Services (CCER). The CCER assumed the role of evaluating and monitoring the project for both private clinics and participating institutions which were part of the health and social services network. In 2019, the research ethics board (REB) committee of the McGill

University Health Centre (MUHC) took over the role of the CCER for the QCR. Although a research protocol based on the QCR has already been submitted for publication, this is our first report examining the factors associated with clinical responses to medical cannabis among patients with chronic noncancer pain.

All patients included in the QCR were asked to sign a consent form. Patients were assessed at baseline and were then followed for up to four years after initiation of medical cannabis. Patients were scheduled for follow-up assessment visits every three months for the first two years, and then once a year in the third and fourth years. For the purposes of the present thesis, data collected at baseline (see section 2.2.1) and follow-up visits within the first 12 months (see section 2.2.2) were reported.

2.2.1. Baseline assessment

Before the first cannabis authorization, physicians and patients completed standardized case report forms on paper (i.e., paper-and-pencil), which were then transmitted to the research coordinator electronically using REDCap (Research Electronic Data Capture). During baseline assessment, the following variables were assessed, in the clinic:

2.2.1.1. Medical comorbidities and primary symptoms: Physicians recorded the presence (i.e., yes/no) of any current/ongoing medical conditions as well as primary symptoms experienced by patients (e.g., pain, spasticity, insomnia, anxiety).

2.2.1.2. Pain conditions: Physicians recorded the presence (i.e., yes/no) of any pain condition (e.g., neuropathic pain, low back pain, complex regional pain syndrome, osteoarthritis, rheumatoid arthritis, neck pain, fibromyalgia) as well as the duration (in years) since the onset of pain.

2.2.1.3. Mental health problems: Physicians recorded the presence (i.e., yes/no) of any ongoing mental health problems (e.g., anxiety, depression, bipolar, insomnia, post-traumatic stress disorder) and any past (i.e., lifetime) history of trauma (i.e., physical or sexual abuse).

2.2.1.4. Concomitant medication use and cannabis treatment: Physicians recorded all medications (types and doses) taken by patients at the time of assessment. Physicians also recorded the therapeutic objectives for which medical cannabis was authorized. Medical cannabis directives were recorded by physicians in terms of authorized daily dose (i.e., grams/day), cannabis type (i.e., dry, oil, topical), the primary mode of administration (i.e., inhalation, oral, or a combination of the two modes), cannabinoid content ratio (i.e., THC dominant, CBD dominant, or balanced), and the number of cannabinoid products authorized.

In the clinic, through the standardized case report forms, patients provided sociodemographic information (i.e., age, sex, occupational status) and were then asked to provide information on the following variables:

2.2.1.5. Substance use: Patients were asked to report their frequency of alcohol use (i.e., units per week) and tobacco use status (i.e., current smoker, former smoker, never smoker). Patients were also asked to report any lifetime history of recreational drug use, including cannabis, using a binary (i.e., yes/no) response item, and to specify the type of recreational drug(s) used.

2.2.1.6. Pain intensity: Patients provided reports of pain intensity using items from the pain intensity subscale of the Brief Pain Inventory (BPI; [125]). On the BPI, patients were asked to rate the intensity of their pain "right now" and "on average" using 0-10 numeric rating scales (NRS) that ranged from 0 (no pain) to 10 (pain as bad as you can imagine). Several studies have

supported the reliability and validity of the BPI to assess pain intensity among patients with chronic noncancer pain [70, 125, 131].

2.2.1.7. Pain interference: The pain interference subscale of the Brief Pain Inventory (BPI; [125]) was used to assess pain interference. On the pain interference subscale, patients were asked to rate the degree to which pain has interfered with various domains of functioning over the past 24 hours on NRS that ranged from 0 (does not interfere) to 10 (completely interferes). The BPI pain interference subscale includes an item assessing the degree to which pain has interfered with patients' sleep over the past 24 hours. Several studies among patients with chronic noncancer pain have supported the reliability and validity of BPI items for assessing the interference of pain with daily life functioning and sleep quality [70, 125, 131].

2.2.1.8. Negative affect. Patients were asked to provide reports of depressive and anxiety symptoms using items from the Edmonton Symptom Assessment System (ESAS; [20]). Patients reported their current level of depressive symptoms on a 0-10 numeric rating scale that ranged from 0 (no depression) to 10 (worst possible depression). Patients also reported their current level of anxiety symptoms on a scale that ranged from 0 (no anxiety) to 10 (worst possible anxiety).

2.2.2. Follow-up assessments

Follow-up assessment visits were planned every three months after initiation of medical cannabis. During in-clinic follow-up visits, patients provided reports through the same standardized case report forms as those used at baseline for the assessment of *2.2.2.1) pain intensity, 2.2.2.2) pain-related sleep interference,* and *2.2.2.3) negative affect.*

At each of the follow-up assessment visits, physicians were also asked to record any changes in *2.2.2.4) medical cannabis therapeutic objectives, 2.2.2.5) medical cannabis directives* (i.e., daily dose, type, mode of administration, cannabinoid content ratio, or the number of

cannabinoid products authorized). Finally, physicians recorded *2.2.2.6*) any *changes in concomitant medication* (i.e., medication types and doses).

2.3. Data reduction and analysis

All analyses were conducted using IBM-SPSS 24. Descriptive data for continuous variables were presented as means and standard deviations. Data for categorical variables were presented as percentages. For all analyses, the alpha level of significance was set to 0.05. Unless otherwise specified, all statistical assumptions were deemed met.

Before conducting main study analyses, an index of "average pain intensity" was derived, separately for each of the assessment time points, by aggregating patients' ratings of "pain now" and "average pain" from the BPI [67]. In the present study, the internal reliability coefficient of the pain intensity index (Cronbach α across time points = .88) was excellent. An index of "clinically significant pain reduction" was also derived based on absolute (Δ) changes in patients' reports of average pain intensity across assessment visits. At each follow-up assessment visit, patients were coded as having experienced a clinically significant pain reduction if they reported any decrease of 30% (or more) in average pain intensity over the preceding visit. This cutoff is consistent with previously established operationalizations of clinically significant changes in clinical pain intensity among chronic pain populations [45, 50, 71]. Finally, consistent with past research [54, 63, 87], an index of negative affect was derived, separately for each of the assessment time points, by aggregating patients' ratings of depressive and anxiety symptoms on the ESAS. This was done due to the large shared variance between measures of depressive and anxiety symptoms among patients with chronic pain [74, 131]. In the present study, the internal reliability coefficient of the negative affect index (Cronbach α across time points = .85) was very good.

To examine the association between medical cannabis use and reductions in average pain intensity (Objective 1.1), multilevel analyses were used given the hierarchical (i.e. nested) data structure of this study, in which repeated measures (Level 1 units) were nested within participants (Level 2 units). Multilevel modeling is well suited to handle nested data structures and an unequal number of data points across participants. A multilevel analysis was first conducted using the average pain intensity index as the outcome, and "time" as the independent variable (IV). Time was treated as a categorical variable and corresponded to each of the study visits (i.e., baseline, 3m, 6m, 9m, 12m). To examine the association between medical cannabis use and clinically significant reductions in pain intensity (Objective 1.2), a multilevel logistic regression analysis was conducted using "time" as the independent variable and the "clinically significant pain reduction" index as the outcome.

A multilevel regression analysis was then conducted to examine whether the association between medical cannabis use and reductions in clinical pain intensity was attributable to concurrent changes (i.e., reductions) in negative affect and pain-related sleep interference (Objective 2). Prior to this analysis, the association between medical cannabis use ("time") and negative affect was first examined. The association between medical cannabis use and pain-related sleep interference was also examined. All these variables were then entered simultaneously in the multilevel regression model as time-variant (i.e., Level 1) independent variables. A significant main effect of "time" would suggest that the association between medical cannabis use and reductions in clinical pain intensity cannot be entirely attributable to changes (i.e., reductions) in negative affect and/or pain-related sleep interference following medical cannabis initiation.

To examine if patients' baseline characteristics were associated with reductions in clinical pain intensity following initiation of medical cannabis, a series of multilevel analyses were conducted using the "average" pain intensity index as the outcome. In these analyses, 2-way interaction terms between "time" (i.e., Level 1) and each of the patients' baseline (i.e., Level 2) characteristics were specified, after the inclusion of appropriate main effects. Interaction terms were specified for each of the Level 2 variables (i.e., sociodemographic characteristics, medical comorbidities, concomitant medication use, pain conditions, history of mental health problems, history of substance use) in separate multilevel models. Any significant two-way interaction effect would suggest that the magnitude of reductions in pain intensity following initiation of medical cannabis was influenced by patients' baseline characteristics [69].

All the multilevel models described above involved specifying a random intercept and fixed effects for independent variables (IVs). All multilevel models were carried out using maximum-likelihood (ML) estimation and included a first-order autoregressive variance-covariance matrix (AR1) to account for the autocorrelations between repeated measures over time. As recommended, all Level 1 independent variables were centered within-person and Level 2 independent variables were centered to the grand-mean before being entered in multilevel models [48, 97].

3.0. Results

3.1. Descriptive statistics

Descriptive statistics for the study sample are presented in Table 1. The sample included 52 % of women and the average age of patients was 51.4 (SD = 15.1) years. The most common pain conditions experienced by patients included low back pain (15.4 %), fibromyalgia (14.9 %), osteoarthritis (10.7%), and neuropathic pain (10.7%). In terms of concomitant medication use,

the most commonly used medications included opioids (32%), antidepressants (26.2%), benzodiazepines (23.7%), anticonvulsants (20%), and NSAIDs (17.6%).

Cannabis treatment characteristics included the use of THC dominant and CBD dominant formulations by 15 % and 33.6 % of patients, respectively. Cannabis treatment involving a combination of THC and CBD was used by 51.4 % of patients. The average daily THC dose used by patients was 1.38 grams/day (SD = 9.5). The different types of cannabis products and routes of administration are presented in Table 2.

3.2. Association between medical cannabis use and reductions in pain intensity

A multilevel analysis was first conducted using the average pain intensity index as the outcome, and "time" as the IV. Results revealed a significant effect of "time" on pain intensity ($F = 142.8$, $B = -1.30$, 95% CI = -1.41, -1.19, $p < .001$), as patients' levels of pain intensity decreased from baseline to follow-up. As can be seen from Figure 2, the decrease in patients' pain intensity levels was most pronounced between the baseline and 3-month follow-up assessment visit, with a mean decrease of 1.23 points on a 0-10 scale (95 % CI = 1.10, 1.37). Multilevel logistic regression was subsequently conducted to examine if medical cannabis use was associated with clinically significant (i.e., ≥ 30%) reductions in pain intensity. For this analysis, "time" was used as the IV, and the "clinically significant pain reduction" index was the outcome. Results indicated that the main effect of "time" on clinically significant pain reductions was not significant ($p > .05$).

3.3. Association between medical cannabis use and reductions in negative affect and pain-related sleep interference

Two separate multilevel analyses were conducted to examine whether medical cannabis use was associated with reductions in negative affect and pain-related sleep interference. Mean scores for these variables across all follow-up assessment time points are presented in Table 3.

Results revealed a significant main effect of "time" on negative affect (F = 98.9, B = -.96, 95% CI = -1.09, -.84, p < .001), indicating that patients' levels of negative affect decreased from baseline to follow-up. Results also revealed a significant main effect of "time" on pain-related sleep interference (F = 177.2, B = -2.0, 95% CI = -2.2, -1.93, p < .001), indicating that patients' pain-related sleep interference decreased from baseline to follow-up. Subsequent exploratory analyses indicated that reductions in negative affect and pain-related sleep interference following initiation of medical cannabis remained significant even after controlling for concurrent reductions in pain intensity (both p's < .001).

To examine whether the association between medical cannabis use and reductions in clinical pain intensity was attributable to concurrent changes (i.e., reductions) in negative affect and pain-related sleep interference, a multilevel regression analysis was conducted using the average pain intensity index as the outcome. In this analysis, the main effect of "time" was examined while simultaneously including negative affect (Level 1) and pain-related sleep interference (Level 1) as independent variables in the model. Results from this analysis indicated that the main effects for "time" (F = 33.5, B = -.64, 95% CI = -.75, -.53, p < .001), negative affect (F = 38.7, B = .11, 95% CI = .07, .15, p < .001), and pain-related sleep interference (F = 835.9, B = .32, 95% CI = .29, .34, p < .001) were all significant.

3.4. Patients' baseline characteristics and reductions in pain intensity following initiation of medical cannabis

To examine if patients' baseline characteristics were associated with reductions in pain intensity following initiation of medical cannabis, 2-way interaction terms between "time" (i.e., Level 1) and each of the patients' baseline (i.e., Level 2) characteristics were specified after inclusion of appropriate main effects. Interaction terms were first specified separately for each of the sociodemographic characteristics (i.e., age, sex, occupation). Results revealed a significant 2-

way (time X sex) interaction effect on pain intensity ($F = 3.6$, $p < .01$). As can be seen from Figure 3, data indicated that the reduction in pain intensity from baseline to the 3-month follow-up assessment time point was significantly greater for women than men. A significant 2-way (time X age) interaction effect on pain intensity was also found ($F = 4.5$, $p < .005$). Results indicated that the reduction in pain intensity from baseline to the 3-month follow-up assessment time point was significantly greater for older patients than younger patients (see Figure 4). None of the other Level 2 variables (i.e., medical comorbidities, concomitant medication use, pain conditions, history of mental health problems, history of substance use) significantly interacted with time (all p's > .05).

3.5. Sensitivity analyses

Sensitivity analyses were conducted to examine the influence of cannabis treatment characteristics (i.e., daily dose, cannabis type, mode of administration, cannabinoid content ratio, number of cannabinoid products authorized) on the main study outcome (i.e, pain intensity). Results revealed a significant interaction effect between time and "cannabis type" on pain intensity ($F = 2.9$, $p < .05$). Examination of data indicated that reductions in pain intensity from baseline to the 3-month follow-up assessment visit were significantly greater for patients using oil-based cannabis products than other types of cannabis. Results also revealed a significant interaction effect between time and "cannabis mode" on pain intensity ($F = 3.2$, $p < .05$), indicating that reductions in pain intensity from baseline to the 3-month follow-up assessment visit were significantly greater for patients using cannabis through the oral route than other types of routes of administration.

Given that cannabis "type" and " mode" were significantly associated with the magnitude of changes (i.e., reductions) in pain intensity following initiation of medical cannabis, sensitivity

analyses were conducted to examine if the two-way interactions involving sex and age remained significant even after controlling for these variables. Results indicated that two-way interaction effects involving sex ($F = 3.5$, $p < .01$) and age ($F = 4.5$, $p < .005$) both remained significant even after controlling for cannabis type and administration mode.

Finally, sensitivity analyses were conducted to examine if data missingness over the course of the 12-month study period was related to any of the main study variables (i.e., pain intensity, negative affect, pain-related sleep interference) that were assessed over time. For these analyses, patients' reports of pain intensity, negative affect, and pain-related sleep interference were averaged, separately, across all the follow-up assessment time points. In the present study, out of the initial sample at baseline ($n = 2,068$), data indicated that 72% completed the 3-month follow-up assessment and that 54%, 39%, and 24% of patients completed the 6, 9, and 12-month assessment time points, respectively. Analyses indicated that those who remained in the sample up to the 12-month assessment time point did not differ significantly from those who did not remain in the sample in terms of negative affect ($p > .05$). However, those who remained in the sample reported significantly lower levels of pain intensity ($p < .05$) and pain-related sleep interference ($p < .05$) than those who did not remain in the sample.

4.0. Discussion

The first objective of the present thesis was to examine the association between medical cannabis use and reductions in average pain intensity among patients with chronic pain. We also examined the association between cannabis initiation and clinically significant (i.e., ≥ 30%) reductions in pain intensity. The second objective was to examine the association between cannabis initiation and reductions in negative affect and pain-related sleep interference. We then examined whether the association between medical cannabis use and reductions in clinical pain

intensity remained significant after controlling for improvements in negative affect and pain-related sleep interference. The third objective of the present thesis was to examine the association between patients' baseline characteristics and reductions in pain intensity following initiation of medical cannabis.

4.1. Medical cannabis use and clinical pain intensity

In the present thesis, we first examined the association between medical cannabis initiation and clinical pain intensity. While previous studies have examined the association between medical cannabis use and pain severity, most of these studies were conducted in the context of randomized controlled trials that were not necessarily representative of patient populations seen in real-life clinical settings. Moreover, many of these studies were limited to patients presenting with specific pain conditions and excluded patients with predefined characteristics, such as mental health problems or complex medical comorbidities. Moreover, most of these studies were less than 3 months, which led to calls for the implementation of longer-term observational studies that could yield more generalizable results. In the present study, we found that there was a significant association between initiation of medical cannabis and reductions in clinical pain intensity. Results revealed that the decrease in patients' levels of pain intensity was most pronounced between the baseline and the 3-month follow-up assessment visit. More specifically, group-level analyses indicated that patients experienced a mean decrease of 1.23 points in pain on a 0-10 scale from baseline to the 3-month follow-up visit. Further examinations of patients' clinical pain intensity indicated that this decrease in pain remained fairly stable across all subsequent follow-up time points (i.e., at 6, 9, and 12 months). This finding is in line with those from other groups that have examined the association between medical cannabis use and reductions in pain intensity in the context of prospective longitudinal studies

among patients with chronic pain prescribed medical cannabis [9, 66, 93, 143]. Similar to the present study, these studies revealed that the use of medical cannabis was associated with significant improvements in pain intensity over time, but particularly during the first few weeks following initiation of cannabis use. Furthermore, the magnitude of pain intensity reductions (i.e., ranging from 0.92-1.25 points on a 0-10 NRS scale) in previous work was fairly similar to the magnitude of pain reduction observed in our study.

4.2. Clinically important reductions in pain intensity

As an extension of our first objective, other analyses were conducted to examine whether initiation of medical cannabis was associated with clinically important (i.e., ≥ 30%) reductions in pain intensity. This clinically significant cut-off was first identified by Farrar et al. in 2001 and has since been widely used when evaluating the clinical importance of chronic pain treatment outcomes [50]. Findings from the present study indicated that medical cannabis use was not associated with clinically important reductions in pain intensity. This finding is consistent with those from other studies that also failed to find an association between medical cannabis use and 30% reductions in clinical pain [93]. A number of previous studies, though, did find that medical cannabis use may lead to clinically significant reductions in pain [4, 47]. Some of the potential reasons that could explain discrepancies in findings observed across studies include the nature of study designs and study populations involved in these studies. For instance, most studies that have shown clinically significant reductions in pain intensity following initiation of medical cannabis were short-term randomized control trials comparing analgesic effects of medical cannabis to placebo drugs in specific pain populations, such as patients suffering from fibromyalgia or neuropathic pain [4, 116, 149]. The clinically important reductions in pain following initiation of medical cannabis may have thus been more pronounced due to the short time period

during which analgesic benefits of medical cannabis were measured, or due to the inclusion of patients presenting only with specific pain conditions. This contrasts with our study, which included patients presenting with many different types of chronic pain conditions. In our study, findings indicated that pain reductions following initiation of medical cannabis use were not particularly more pronounced for any specific pain condition, and this was somewhat surprising. However, it is possible that certain pain conditions do not respond favorably to cannabis, and the inclusion of patients presenting with such conditions could have contributed to decreasing the likelihood of observing clinically significant reductions in pain at the group (i.e., whole-sample) level following initiation of medical cannabis.

4.3. Medical cannabis use and negative affect

We were interested in examining whether medical cannabis was associated with changes or improvements in other variables known to be clinically relevant for patients with chronic pain. We thus examined the association between medical cannabis initiation and changes over time in patients' levels of negative affect (i.e., symptoms of anxiety and depression). Despite the high comorbidity between chronic pain and symptoms of negative affect [11, 12, 35, 131], surprisingly little research has been conducted so far to examine whether medical cannabis use among patients with chronic pain may be associated with changes in these symptoms. Results from the present study indicated that patients experienced significant reductions in negative affect following initiation of medical cannabis. More specifically, results indicated that patients experienced reductions of roughly 1 point on a 0-10 NRS in negative affect within the first 3 months following initiation of medical cannabis. Similar to pain intensity, improvements in negative affect were maintained across all subsequent assessment time points (i.e., up to 12 months). Our findings are consistent with the work of Aviram et al. [9], who also found a significant reduction in negative affect

following initiation of medical cannabis in the same population of patients. Interestingly, the magnitude of change in their study was similar to what was observed in our cohort. The association between medical cannabis use and reductions in negative affect observed in our study also parallels results from numerous survey studies that have found that patients with chronic pain tend to use substances (i.e, cannabis) to self-medicate symptoms such as anxiety and depression [37, 89]. The anxiolytic and/or mood-regulating effects of cannabis have long been documented [32], but particularly among non-pain populations [34, 117]. There is research showing that the repeated use of cannabis use may worsen psychological function, but this has been primarily observed among individuals exhibiting clinically significant cannabis use problems and/or meeting diagnostic criteria for cannabis use disorder [22, 36]. In our study, the reductions in patients' symptoms of anxiety and depression (i.e., negative affect) were maintained up to the 12-month assessment time point, suggesting that psychological functioning did not worsen over time. Reductions in negative affect over time following initiation of medical cannabis among patients with chronic pain could be due, in part, to the concurrent reductions in pain intensity that are being experienced, but could also be due to the feelings of pleasure and/or well-being that may accompany cannabis use [72].

Neurobiological explanations could also be invoked to explain the significant association between medical cannabis use and reductions in negative affect. For instance, there are some animal studies as well as human clinical trials indicating that cannabis may have an impact on neuronal systems that are involved in regulating mood such as the mesolimbic dopamine (DA) system [101, 108, 126]. Dopaminergic neurons are modulated by the endocannabinoid system where endogenous cannabinoid ligands stimulate dopamine release in the nucleus accumbens (NAc). Human and animal studies suggest that disruptions to these circuits are associated with mood

disorders. Interestingly, such disruptions are observed in chronic pain mouse models in which dopamine signaling is inhibited [101, 108]. Furthermore, a recent study has demonstrated that dopamine neuron activation in NAc is accompanied by antidepressant properties [15]. Taken with the fact that dopamine concentration levels increase in NAc following cannabis initiation in a CB1 receptor-dependent manner, it is possible that cannabis use leads to an improvement in negative affect through its impact on the neuronal DA system.

4.4. Medical cannabis use and pain-related sleep interference

Sleep quality represents another clinically relevant variable in the context of chronic pain given the high prevalence of sleep problems within this population [28, 68, 144, 145]. Although sleep problems such as insomnia can be caused by factors that are not directly related to pain (e.g., anxiety), the pain remains the reason most commonly reported by patients to explain difficulty falling asleep, sleep interruptions, or other types of sleep problems [68, 118]. In the present study, we examined the association between medical cannabis use and pain-related sleep interference. Results from our study indicated that patients experienced significant reductions in sleep-related pain interference after initiating medical cannabis. More specifically, results indicated an average reduction of 2 points on a 0-10 NRS in patients' reports of pain-related sleep interference on the Brief Pain Inventory (BPI) within the first 3 months after initiation of medical cannabis. Our findings were consistent with Safakish et al. who also observed significant improvements in pain-related sleep interference over time following initiation of medical cannabis in chronic pain patients [109]. It is possible that cannabis use indirectly led to reductions in pain-related sleep interference because patients experienced reductions in pain following initiation of medical cannabis. Given that pain is known to contribute to sleep problems [16, 118, 151], reductions in pain might have concurrently led to reductions in pain-related sleep problems. However, some of our

exploratory analysis indicated that reductions in pain-related sleep interference remained significant even after controlling for reductions in pain intensity, which suggests that improvements in sleep following cannabis initiation cannot be entirely explained by reductions in patients' levels of pain. There are other potential reasons that might explain why cannabis led to improvements in pain-related sleep interference. Given the high comorbidity between negative affect and sleep problems [21, 53, 106], reductions in negative affect might have concurrently led to reductions in pain-related sleep problems. Our exploratory analysis indicated that reductions in pain-related sleep interference remained significant even after controlling for changes in negative affect, but it is conceivable that reductions in patients' levels of anxiety and depressive symptoms (i.e., negative affect) contribute, to some extent, to the benefits of cannabis for improving sleep among patients with chronic pain [106, 140].

Given that the association between medical cannabis use and reductions in pain-related sleep interference remained significant after controlling for pain intensity and negative affect, a number of biological explanations could be invoked to account for this association. As noted earlier, exogenous cannabinoids such as CBD and THC have been shown to interact with the endocannabinoid system, which has been shown to influence the circadian sleep-wake cycle [135]. Many preclinical and clinical studies have shown that endocannabinoid (i.e., anandamide and 2-arachidonoylglycerol) concentrations are influenced by the circadian rhythm and vary throughout the cycle [64, 65]. During this circadian rhythm, humans experience an increase in 2-arachidonoylglycerol (2-AG) levels from mid-sleep to early afternoon. 2-AG is associated with sleep inhibition as observed in animal studies where REM sleep was reduced following the 2-AG increase in the brain [124]. Contrastingly, anandamide (AEA) is associated with sleep promotion and has been shown to promote slow-wave sleep via increases in sleep neurotransmitter,

adenosine. THC, like AEA, acts as a partial agonist against the CB1 receptor. As a result, THC may induce sleep through this direct pharmacological action. On the other hand, CBD has been shown to increase AEA concentrations through inhibition of the AEA degradative enzyme, fatty acid amide hydrolase [124]. Although speculative, these neurobiological systems could contribute to explaining the significant reductions in pain-related sleep interference following the initiation of medical cannabis.

4.5. Potential factors contributing to reductions in pain intensity following initiation of medical cannabis

Although previous studies that have examined the potential benefits of medical cannabis among patients with chronic pain have been informative, many questions have remained unaddressed concerning the factors that might contribute to cannabis analgesia in this population. In our study, given that medical cannabis was associated with reductions in negative affect as well as pain-related sleep interference, analyses examined whether the association between medical cannabis initiation and improvements in clinical pain intensity remained significant even after controlling for improvements in these variables over time. Results from a multilevel modeling analysis indicated that reductions in clinical pain intensity remained significant even after adjusting (i.e., controlling) for reductions over time in patients' levels of negative affect and pain-related sleep interference. These results suggest that the improvements in pain intensity following initiation of medical cannabis observed in our study cannot be entirely explained by improvements in patients' symptoms of anxiety, depression, and/or pain-related sleep interference. This raises interesting questions concerning the factors that might contribute to cannabis analgesia among patients with chronic pain. Although improvements in negative affect and sleep quality certainly represent important dimensions that could underlie the potential analgesic effects of cannabis among patients with chronic pain, there is reason to believe that

patient-specific characteristics might also influence patients' clinical responses to medical cannabis. For instance, like any other type of treatment, there is reason to believe that a host of sociodemographic, clinical, or psychological characteristics might influence the reductions in clinical pain intensity following initiation of medical cannabis.

4.6. Association between patients' baseline characteristics and reductions in pain intensity following initiation of medical cannabis

The third objective of the present thesis was to examine whether patients' baseline characteristics were associated with reductions in clinical pain intensity after initiation of medical cannabis. In our study, one of the patient characteristics that was significantly associated with improvements in pain intensity following initiation of medical cannabis was age. More specifically, results indicated that the effect of medical cannabis on pain was more pronounced among older patients than younger patients. These results may be explained by the fact that older adults, in general, are more likely to present with pain conditions that respond well to cannabis-based medicines. For instance, older adults are more likely to present with rheumatic conditions (e.g., osteoarthritis), and these conditions have been found to respond favorably to medical cannabis in some studies [57, 58, 90]. In the present study, we did not find any significant effect of patients' pain diagnoses on pain reductions following initiation of medical cannabis. However, the nature of patients' pain conditions needs to be considered when trying to interpret the association between age and pain reductions following medical cannabis use. Although speculative, the age-specific effects in our study could also be explained by the older adults' tendency to have an optimistic outlook on life and decreased tendency to worry [10, 41], which could have possibly contributed to augmenting the therapeutic effects of medical cannabis. Future studies will be needed to better understand why pain reductions following initiation of medical cannabis were more pronounced among older patients than younger patients.

The sex of patients is another patient characteristic that was found to be significantly associated with reductions in pain intensity following initiation of medical cannabis. Results indicated that pain reductions following initiation of medical cannabis were more pronounced among women than men. Medical cannabis use among women has been on the rise in recent years with pain relief being cited as the most common reason for use [6, 19]. Furthermore, women report higher levels of pain intensity than men and in turn have more room for improvements following analgesic treatments [51, 94]. The sex differences in pain reductions following medical cannabis initiation may also be explained by biological differences between the two sexes. For instance, some animal studies demonstrated that the potency of cannabis was higher in female rats due to differences in metabolism and effects of sex hormones [14, 84]. Based on these studies, there is thus reason to believe that interactions between cannabinoids and hormonal factors might contribute to explaining why pain reductions following initiation of medical cannabis in our study were more pronounced among women than men.

4.7. Clinical implications

Findings from the present thesis could have implications for clinicians involved in the management of patients with chronic pain who are considering medical cannabis as a therapeutic avenue. First, consistent with past research, our findings suggest that medical cannabis use may be associated with reductions in clinical pain intensity, but clinicians and patients should be cognizant that the magnitude of pain relief from medical cannabis use might not be perceived as clinically important or sufficient from a therapeutic standpoint. It is worth highlighting, though, that reductions in pain following initiation of medical cannabis were maintained over time, which represents a non-negligible therapeutic effect. From a clinical standpoint, our findings also suggest that medical cannabis could potentially have some utility as a complementary

intervention for the management of patients' symptoms of anxiety and depression. Despite the wide array of pharmacological and non-pharmacological approaches that have been put forward to help patients with chronic pain who struggle with symptoms of anxiety and depression, these psychological problems remain highly prevalent among these patients [27, 46, 131]. Similarly, our findings also suggest that medical cannabis could potentially have some utility for reducing patients' sleep problems, which are known to be predominant as part of chronic pain patients' symptom presentation [28, 68, 144, 145]. Over the years, considerable emphasis has been placed on the multidimensional nature of chronic pain and the importance of offering care that is not limited to pain reduction, but also targeting other dimensions of the chronic pain experience [43, 130, 150]. Although the reduction of patients' levels of pain will always remain a desirable pain management outcome, the need for interventions that could also contribute to improving patients' psychological/emotional functioning as well as sleep quality has been emphasized [43, 53, 130, 150]. Interestingly, findings from the present study indicated that reductions in patients' pain intensity, negative affect, and sleep problems following initiation of medical cannabis occurred partially independently from each other. Although preliminary, the concurrent but independent improvements observed across multiple outcome domains in our study following medical cannabis use certainly represent a clinically relevant finding.

The identification of specific patient characteristics that are associated with the magnitude of pain relief following initiation of medical cannabis is another set of findings that could have some clinical relevance. Findings from the present study suggest that certain subgroups of patients may particularly benefit more from medical cannabis. More specifically, our results suggest that older patients, as well as female patients, may experience greater improvements in pain symptoms following initiation of medical cannabis than other patients. The risks associated

with cannabis use among older patients (e.g., confusion, falls) will always remain an important clinical consideration and pivotal to any decision related to the prescription of cannabis among this subgroup of patients [5]. Moreover, the difference in pain reduction following initiation of medical cannabis between younger and older patients was fairly small, raising questions regarding the clinical significance of this finding. More data from clinical settings are required to make a deduction regarding the clinical relevance of these results. Nonetheless, the possibility that this subgroup responds favorably to cannabis could be useful for clinicians involved in the care of older patients. Taken together, our findings that some patient characteristics (e.g., age, sex) may influence responses to medical cannabis could have implications for chronic pain patients and their physicians who are considering medical cannabis as a potential treatment avenue. In recent years, there has been considerable emphasis on the potential value of "personalized medicine" and the potential benefits of tailoring treatment based on patients' characteristics. In the context of cannabis treatment, this would require, in part, health care professionals' ability to identify which patients might respond more favorably to cannabinoids. Future work will be needed to replicate our findings and further identify whether other patient-specific characteristics are associated with improvements in pain intensity following initiation of medical cannabis. Future studies will also be needed to better understand the potential adverse effects of cannabis. Despite the potential benefits of cannabis for pain control, evidence shows that medical cannabis may present short-term adverse effects such as dizziness, drowsiness, or cognitive issues including confusion, perceptual disturbances, and memory impairments [122]. Often, these adverse effects have been viewed as "non-serious" [143], however they remain clinically important since they may interfere with patients' day-to-day functioning and lead to discontinuation of their medical cannabis treatment [143].

4.8. Limitations

A number of limitations must be taken into account when interpreting results from the present study. First, this was a longitudinal open-label observational study. Given that this was not a randomized controlled trial, it is not possible from the present study to draw firm conclusions regarding the effectiveness of medical cannabis for the reduction of patients' pain intensity. It is certainly possible that patients' expectations about pain relief and/or factors unrelated to cannabis contributed to reductions in patients' pain intensity over time. However, there is evidence from controlled studies supporting the effectiveness of cannabis among patients with chronic noncancer pain (for a review, see [121]), which is why the present study rather focused primarily on examining the factors that might contribute to the reductions in pain following initiation of medical cannabis. Second, the sample size decreased linearly over the course of the 12-month study period. The total sample size remained fairly large, but it is possible that patients who did not complete the entire 12-month study period benefited less from medical cannabis than those who remained in the study. This needs to be considered when interpreting the present findings. Another limitation of the present study was the relatively long time intervals in between follow-up assessment visits. The fact that patients completed self-report measures every 3 months, in the clinic, represents a methodological strength that allowed us to examine the association between medical cannabis use and concurrent changes in key outcome domains such as pain intensity, negative affect, and sleep. However, it is well-known that these variables may fluctuate over shorter time periods than 3 months [109, 112, 123], so future studies on cannabis should consider tracking changes in these variables over shorter periods of time (e.g., on a weekly or monthly basis). Third, symptoms of anxiety and depression (i.e., negative affect) were assessed solely based on self-reported questionnaires. Although self-report methods are commonly used

to assess symptoms of negative affect [77], future studies should consider complementing these self-report measures with additional assessment methods (e.g., clinical interviews). Fourth, future studies could benefit from using self-report measures that evaluate a broader range of sleep problems, and not only those only caused by pain [114]. Given that the present study assessed the interference of pain with sleep (using the BPI), the changes (i.e., reductions) in sleep that occurred following initiation of medical cannabis closely covaried with changes (i.e., reductions) in patients' levels of pain intensity. Finally, while the research involved a detailed characterization of patients, a number of demographic variables were not recorded. For example, factors such as ethnicity or education level might contribute to explaining why certain subgroups of patients experience larger or smaller improvements in pain from medical cannabis use [85]. Future studies should consider examining whether these patient characteristics influence responses to medical cannabis among patients with chronic pain.

4.9. Summary and future directions

In summary, the present thesis provides new insights into our understanding of symptom changes following the initiation of medical cannabis among patients with chronic pain. The present study has many strengths, including large sample size and the inclusion of patients presenting with many different pain conditions and comorbidities, which contributes to augmenting the generalizability of the findings that were reported. The present study also relied on a detailed assessment of patients' baseline characteristics, cannabis treatment characteristics, as well as on follow-ups clinic visits with treating physicians every three months. Importantly, findings from the present thesis provided new insights into the factors that might contribute to reductions in pain intensity among patients with chronic pain who were authorized for medical cannabis. One of the main findings of the present study is that reductions in pain intensity over

time following initiation of medical cannabis remained significant even after controlling for concurrent changes (i.e., reductions) in patients' levels of negative affect and pain-related sleep interference. This finding suggests that pain reductions following initiation of medical cannabis cannot be entirely attributable to the simultaneous improvements in negative affect and/or sleep quality that patients are experiencing from medical cannabis use. In addition to improving patients' psychological functioning and sleep quality, there is reason to believe that medical cannabis might have direct analgesic benefits, even if these benefits may not necessarily be clinically significant for all patients. Future research will be needed to identify the specific factors that might contribute to the analgesic benefits of medical cannabis among patients with chronic pain. The identification of patient characteristics and/or subgroups of patients who are likely to respond favorably to medical cannabis is another avenue that deserves attention in future research. Advances in this area might eventually lead to improved pain management outcomes among patients who are suffering from chronic pain and considering medical cannabis as a therapeutic avenue.

List of Tables and Figures

Table 1
Sample characteristics and descriptive statistics

Variables	Mean or %
Demographics	
Age (years)	51.4 ± 15.1
Sex (% women)	52.0 %
Occupational status	
Full-time	22.6 %
Part-time	7.10 %
Retired	23.6 %
Student	2.00 %
Short-term disability	9.90 %
Long-term disability	24.7 %
Pain conditions	
Neuropathic pain	10.7 %
Complex regional pain syndrome	3.10 %
Low back pain	15.4 %
Osteoarthritis	10.7 %
Rheumatoid arthritis	2.50 %
Fibromyalgia	14.9 %
Neck pain	3.00 %
Medical comorbidities	
Neurological	9.30 %
Gastroenterological	5.30 %
Infection	0.60 %
Other	5.30 %
Mental health	
Anxiety	6.80 %
Insomnia	3.10 %
Post-Traumatic Stress Disorder	2.70 %
Depression	3.40 %
Bipolar	0.30 %
Other	1.70 %
Substance use	
Alcohol (units per week)	1.41 ± 4.40
Tobacco (% current smokers)	51.1 %
Recreational drug use (% yes)	7.30 %
Recreational cannabis use (% yes)	4.70 %
Note: ± represents standard deviations	

Table 2
Medical cannabis treatment characteristics

Variables	Median or %
Type	
Dry	43.2 %
Oil	74.2 %
Oil/dry	22.1 %
Other	0.70 %
Mode	
Inhalation	47.0 %
Inhalation/oral	22.3 %
Oral	70.8 %
Topical	0.50 %
Other	0.40 %
Cannabinoid ratio	
THC dominant	15.0 %
CBD dominant	33.6 %
THC/CBD combination	51.4 %
Authorized dose	
THC (g/day)	1.38 (9.5)
Note: Values in parenthesis represent the interquartile range. [ł] Inhalation refers to smoking or vaping.	

Table 3

Mean scores for main study variables across follow-up assessment time points

Variables	Baseline	3 month	6 month	9 month	12 month
Pain intensity	5.8 (2.1)	4.5 (2.6)	4.3 (2.5)	4.5 (2.5)	4.5 (2.5)
Negative affect	3.6 (2.9)	2.7 (2.7)	2.7 (2.6)	2.8 (2.6)	2.8 (2.7)
Sleep interference	6.3 (3.0)	4.3 (3.4)	4.2 (3.3)	4.2 (3.3)	4.3 (3.2)

Note. Values in parentheses are standard deviations.

Figure 1

Study inclusion flowchart

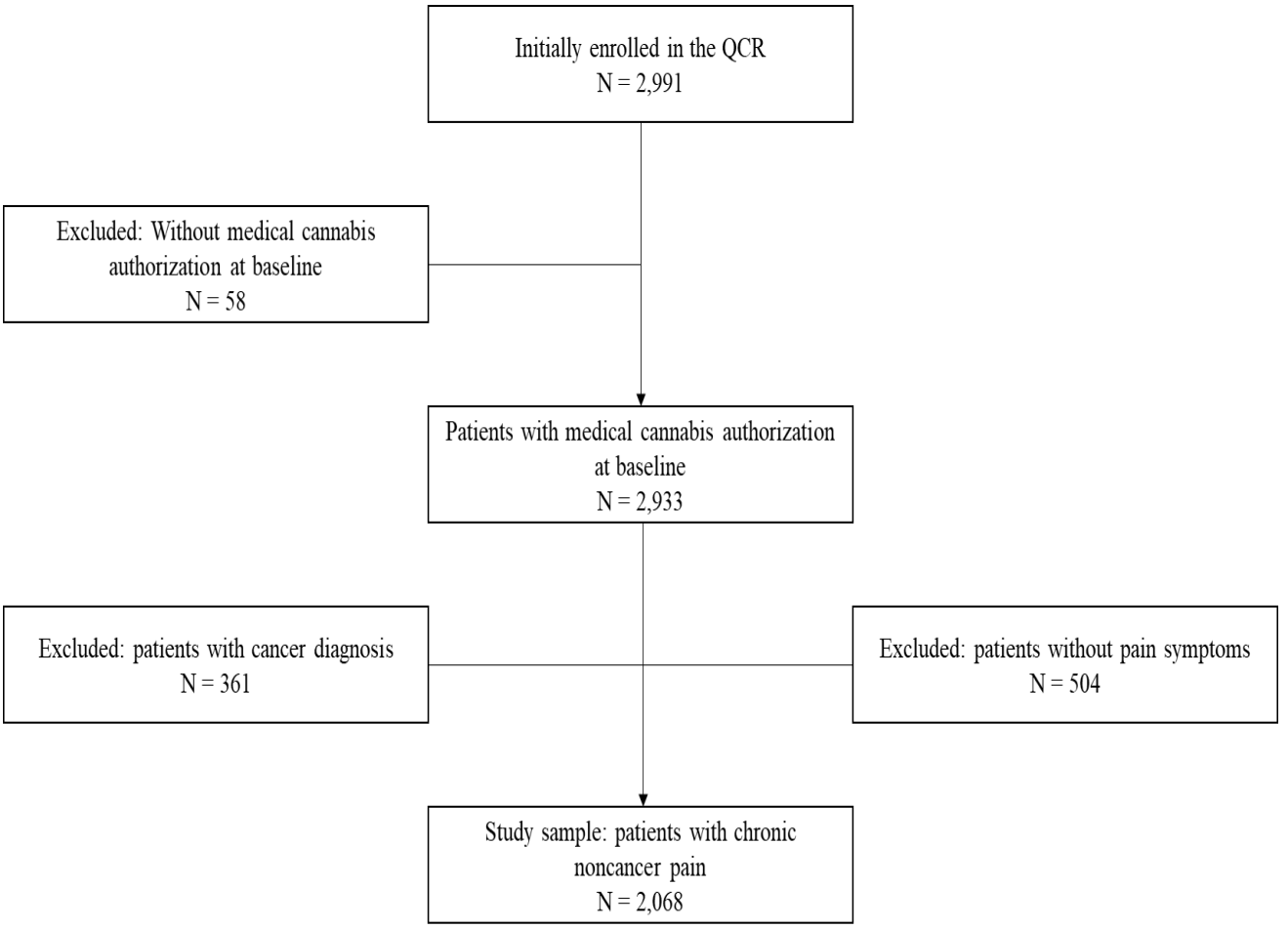

Figure 2

Reductions in pain intensity following initiation of medical cannabis among patients with chronic pain as a function of time

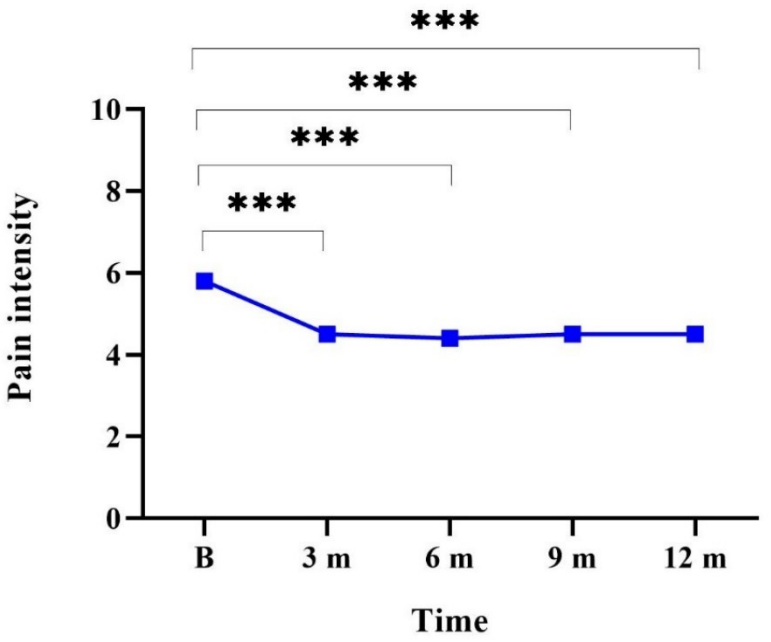

Figure 1 shows patients' average pain intensity levels (0-10) as a function of time (i.e., across all follow-up assessment time points). *** $p < 0.001$.

Figure 3

Reductions in pain intensity following initiation of medical cannabis as a function of sex

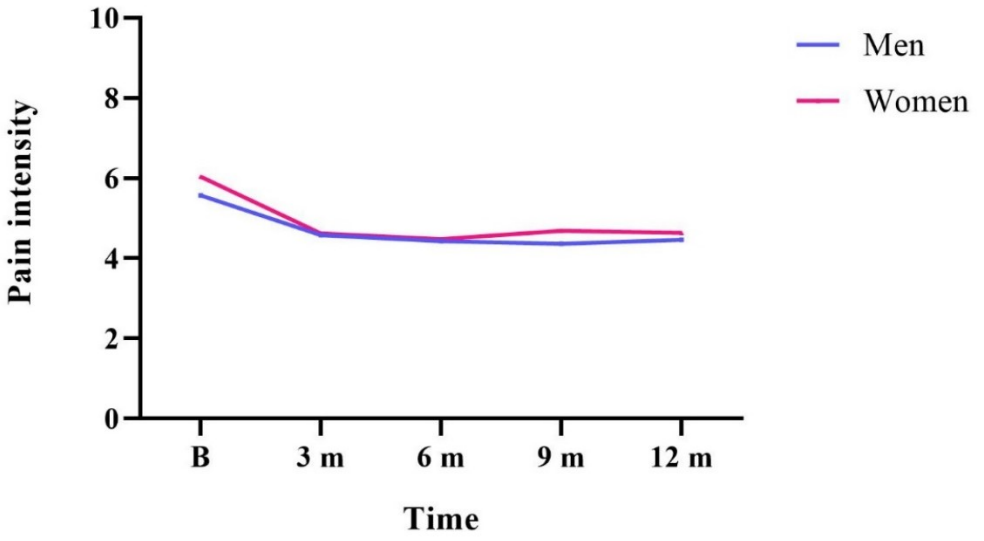

Figure 2 shows patients' average pain intensity levels (0-10) across all follow-up assessment time points, separately for men and women.

Figure 4

Reductions of pain intensity following initiation of medical cannabis as a function of time and age

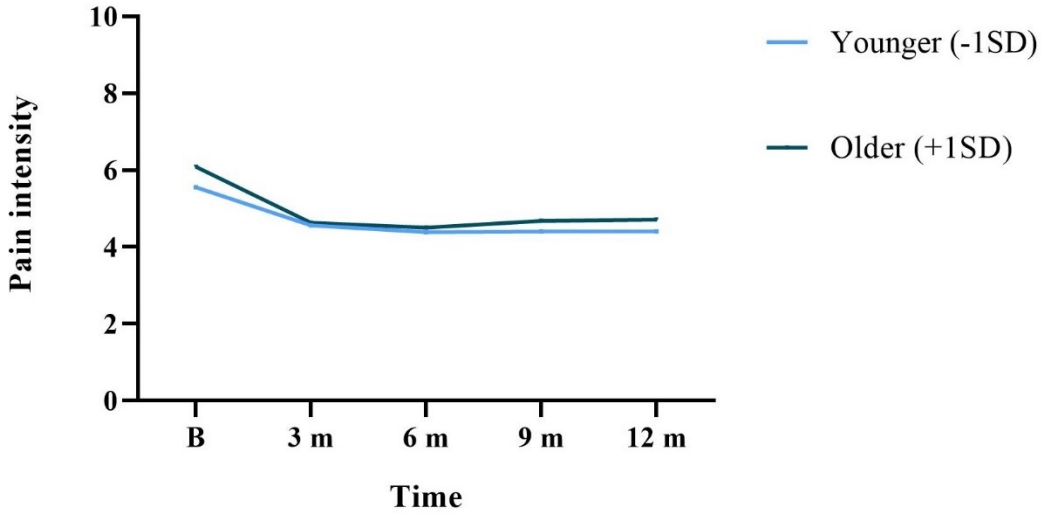

Figure 3 shows patients' average pain intensity levels (0-10) across all follow-up assessment time points and as a function of patient age. SD: Standard deviation. For data visualization purposes, patients who were -1SD and +1SD from the sample mean age at baseline were categorized as "younger" and "older", respectively.

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5.0. Appendices
5.1. IRB Ethics Approval

Centre universitaire de santé McGill — McGill University Health Centre

Annual renewal submission

Protocol title: **A Database on the Use of Cannabis for Medical Purposes Established for Research Purposes**

Principal investigator: **Antonio Vigano**

Submit date: **2020-04-01 09:23**

Submitted by: **Ellasus, James**

Project's REB approbation date: **2019-05-03**

Nagano identifier: **RCQ**

Project number(s): **MP-37-2020-5568**

Form: **F9-55900**

Form status: **Approved**

Administration

1. **MUHC REB Panel & Co-chair(s):**
   Cells, tissues, genetics & qualitative research (CTGQ)
   Co-chair: Marie Hirtle

2. **REB Decision:**
   Approved - REB delegated review

3. **Comments on the decision:**

   Re-approval valid for the following sites:
   - MUHC
   - CHUM

4. **Renewal Period Granted:**
   From 2020-05-04 Until 2021-05-03

5. **Date of the REB final decision & signature**
   2020-04-02
   Signature

   James Ellasus
   MUHC REB Coordinator
   for MUHC Co-chair mentioned above