Chronic pain and its management among Canadian Veterans and non-Veterans. Digital Health Interventions as a viable solution.

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Abstract:

Since the number of physically and mentally injured Canadian Veterans is very high, there is a growing need to support Veterans and assist them in coping with their challenges. Veterans are more prone to suffer from certain medical issues (chronic pain, post-traumatic stress disorder (PTSD)) that are related to their military experience. Veterans with chronic pain are more likely to have comorbid conditions, including mental health issues. They experience more disability from chronic pain and rates of PTSD incidence are 10 times greater than the general population. Cannabis is widely being utilized by Canadian veterans to treat chronic pain and other medical conditions. However, little research has been conducted to investigate patterns and effectiveness of cannabis usage, particularly among veterans.

Published results have demonstrated that earlier online health promotion program (OHPP) versions can engage individuals to improve their healthy lifestyle habits (HLH) (exercise, stress management, healthy eating, etc.), provide measurable health benefits over up to 2 years (reduced stress, fatigue, insomnia, etc.) and reduce pain symptoms. Developing Innovative Digital Interventions to Manage Chronic Pain could be a viable solution for veterans suffering from chronic pain and comorbid mental health problems and may reduce or regulate medical cannabis (MC) consumption.

Résumé:

Étant donné que le nombre de vétérans canadiens blessés physiquement et mentalement est très élevé, il y a un besoin croissant de soutenir les vétérans et de les aider à faire face à leurs défis. Les vétérans sont plus susceptibles de souffrir de certains problèmes médicaux (douleur chronique, trouble de stress post-traumatique (SSPT)) liés à leur expérience militaire. Les vétérans souffrant de douleur chronique sont plus susceptibles d'avoir des conditions comorbides, y compris des problèmes de santé mentale. Ils souffrent davantage d'incapacités dues à la douleur chronique et ont des taux d'incidence de TSPT 10 fois plus élevés que la population générale. Le cannabis est largement utilisé par les anciens combattants canadiens pour traiter la douleur chronique et d'autres conditions médicales. Cependant, peu de recherches ont été menées pour étudier les tendances et l'efficacité de la consommation de cannabis, en particulier chez les anciens combattants.

Les résultats publiés ont démontré que les versions antérieures de l'OHPP (programme de promotion de la santé en ligne) peuvent engager les individus à améliorer leur HLH (mode de vie sain) (exercice, gestion du stress, alimentation saine), fournir des avantages mesurables pour la santé jusqu'à 2 ans (réduction du stress, de la fatigue et de l'insomnie) et réduire les symptômes de la douleur. Le développement d'interventions numériques innovantes pour gérer la douleur chronique pourrait être une solution viable pour les anciens combattants souffrant de douleur chronique et de problèmes de santé mentale comorbides et pourrait réduire ou réguler la consommation de cannabis médical (MC).

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Contribution of Authors

This Thesis was designed and written by Gunel Valikhanova. No editorial help was provided in the thesis.

Dr. Steven Grover reviewed the work presented in the 1st and 3rd chapters of the thesis.

Work presented in the 2nd chapter of the thesis has been submitted for publication.

The contribution of co-authors in the 2nd chapter of the thesis is listed below:

- Gunel Valikhanova wrote the manuscript initially, conducted data analyses on R statisticalsoftware and Python version 3.10.
- Yuka Kato conducted data analysis on R statistical software.
- Agnes Cheung collected the data.
- Ilka Lowensteyn created the questionnaire and collected the data.
- Mary-Ann Fitzcharles, Mark Ware, and Deborah Da Costa reviewed the manuscript and provided helpful comments.
- Steven Grover designed the study concept, created the questionnaire, provided insightful comments, and supervised the study.

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List of abbreviations:

AI:	Artificial Intelligence
CBD:	Cannabidiol
CBT:	Cognitive-behavioral therapy
DCP:	Digital Care Program
DHI:	Digital Health Intervention
DVPRS:	Defense and Veteran Pain Rating Scale
FDA:	Food and Drug Administration
FHP:	Forward Head Posture
GPR:	Global Postural Re-education
iACT:	Internet-based acceptance and commitment therapy
LASS:	Life After Service Studies
LBP:	Low Back Pain
MC:	Medical Cannabis
MBSR:	Mindfulness-based Stress Reduction
OA:	Osteoarthritis
OHPP:	Online Health Promotion Programs
PNS:	Parasympathetic Nervous System
PTSD:	Post-traumatic stress disorders
QOL:	Quality of Life
RA:	Rheumatoid Arthritis
RCT:	Randomized Controlled Trials
REM:	Rapid Eye Movement
SNS:	Sympathetic Nervous System
SSRI:	Selective Serotonin Reuptake Inhibitors

THC:	Tetrahydrocannabinol
VAC:	Veteran Affairs Canada

Chapter 1

1.1 Introduction

Chronic pain (CP) is a leading cause of distress, disability, loss of employment, and poor quality of life all across the globe [1]. Approximately one in five people experience pain at some point in their lives, and another one in ten is diagnosed with chronic pain every year [1, 2]. More than 25 million people experience pain every day; around 10 million experience high levels of pain most days; and 8 million have pain so severe that it interferes with their life [3].

The severity of pain is associated with declines in general health, mental health issues, disability, and increased healthcare costs [4]. Both the incidence and financial burden of chronic pain are far higher than cardiovascular diseases, cancer, and diabetes put together [5]. People who experience pain may, at various points throughout their lives, suffer from acute pain, chronic pain, intermittent pain, or a combination of all three [4]. Even though people of all ages, genders, socioeconomic backgrounds, races/ethnicities, and geographic locations experience pain, there are still significant disparities in pain assessment, management, and treatment. A significant number of individuals who experience chronic pain continue needlessly to suffer as a result of insufficient assessment, management, and treatment throughout their life [6, 7].

CP is the single most common health issue affecting Canadian Veterans. With over 40 % of veterans reporting chronic pain after leaving active service, this remains a primary reason for long-term disability and the need for prescribed medications [8]. There is a dire need to analyze the characteristics of chronic pain in Veterans, including the influences of military culture, mental

health comorbidities, presentation of symptoms, and use of medical and complementary interventions to understand Veterans better and help with their conditions.

`1.2 Literature review

CP is defined as physical pain typically lasting three months or more than the anticipated healing time of a particular injury or disease [10, 11, 12]. The intensity of chronic pain may fluctuate over time, with intervals of severe pain and periods of dull persistent discomfort [10]. Chronic pain can become psychological with time and be maintained by lifestyle changes caused by anxiety surrounding pain rather than the actual pain, thus reinforcing its debilitating qualities [14, 15].

The treatment of chronic pain is sophisticated. Opioid drugs were commonly administered to patients with pain in the early 2000s under the pretext of relative safety [16]. With the support of clinical studies, the Food and Drug Administration (FDA) confirmed the safety of medications prescribed to patients with chronic pain [17]. The FDA incorrectly concluded that opioid drugs provided safe and effective pain management in the general population [18]. However, no randomized clinical trials validated its long-term use. As more is learned about opioids and their side effects [17, 18, 19], it has become clear that these medications are not safe. The widespread epidemic of addiction is a direct result of extensive misinformation about the relative safety of opioids [19]. Overdoses from illegal opioid use caused about 190 deaths per day in the United States [17]. There has been a huge need in recent years to develop safe methods for treating chronic pain [17]. Cannabis products have been recommended as a viable alternative therapy option for various conditions, including chronic pain [20, 21]. Cannabinoid receptors have been shown to play a crucial role in a variety of physiological processes, including pain, inflammation, and immune function, according to studies [22, 23].

The medical cannabis (MC) use among Canadian veterans and non- Veterans was explored in depth in the next chapter.

1.2.1 Chronic pain in Veterans:

Studies have shown that chronic pain is more common in some groups, including those with lower socioeconomic status, racial and ethnic minorities, Veterans, and seniors [26]. It is a dramatic disease that significantly influences the quality of life (QOL) of numerous Veterans with untreated or inadequately treated pain. According to the U.S. Department of Veterans Affairs, the prevalence of chronic pain is 40% higher among US Veterans than the general population, with 65% of combat Veterans reporting chronic pain [28]. Due to the diversity of the Veteran community, the exact comorbidity rates for different medical and psychiatric illnesses are unknown. However, symptoms such as a higher risk of depression, anxiety, substance use disorders, underemployment, and decreased quality of life emphasize the importance of effective pain management in the Veteran population [28]. The fact that 41% of Canadian Veterans reported consistent chronic pain and 25% suffered pain interference made it significant to investigate the particular experience of chronic pain in the Veteran community [29]. Apart from having a higher incidence of chronic pain compared to the general population, Veterans also experience increased rates of severe pain [30]. According to Veteran Affairs Canada (VAC), 41% of Veterans had chronic pain, roughly double the rate of 22% in the general Canadian population; 63% of Veterans with chronic pain had been diagnosed with mental issues [31]. Ninety-one percent of Veterans with mental health disorders also had a chronic physical health condition, 62% had chronic pain, and 57% had pain-restricted activities [31]. Activity impairments were 11 times more likely among veterans with chronic pain than those without pain [31]. Typically, VAC disability payments are granted for conditions related to pain [31]. Life After Service Studies (LASS) revealed that veterans with chronic pain are more

likely to be: 45-54 years old; female; 10-19 years of service; less educated; unemployed; and non-commissioned ranks [31].

Women veterans are more likely than men to experience activity restrictions due to pain [31].

1.2.2 Comorbid mental health problems:

Chronic pain is a frequent illness among patients who seek treatment in primary care facilities [32]. It is associated with a high load of comorbidities involving physical and mental health problems [32]. Furthermore, those who live with chronic pain are more likely to struggle with substance abuse and commit suicide [15]. Therefore, the presence of depression, substance abuse, and anxiety should be of major concern due to the strong correlation between these disorders and an increased risk of suicide [34]. Post-traumatic stress disorders (PTSD) and sleep disturbance are two other examples of co-occurring mental health issues [35].

Depression and pain frequently coexist, have similar symptoms, and worsen one another [36]. Fibromyalgia and spinal pain patients, for example, may have comorbidity rates as high as 50%, according to some studies [15]. In contrast, studies have shown that adults with clinically increased depression symptoms are three to four times more likely to experience chronic neck and spinal pain compared to non-depressed adults [34]. Similarly, there is a bidirectional relationship between the intensity of chronic pain and the intensity of depressive symptoms [36].

CP not only affects the severity of depression but also raises the chance of anxiety [15]. Generalized anxiety is caused by excessive anxiety that impairs occupational and social functioning [15]. Identical comorbidity rates are observed in individuals with anxiety and chronic pain and those with symptoms of depression [15]. As with depression, there is a two-way

interaction between anxiety and chronic pain [33]. When one condition is present and severe, it increases the likelihood that the other will also be present and severe [33].

Barke et al. (2016) found that, compared to healthy controls, those with chronic pain were more likely to show fear response type stimulation in the hippocampus and temporal gyrus when exposed to pain-inducing activities [37]. These data imply that pain is like an anxiety-provoking trigger. In people with chronic pain, pain perception boosted anxiety and fear-based behavioral responses [37].

Chronic pain is often associated with sleep problems [38]. When patients with chronic pain eliminate daily distractions to relax and sleep, their perception of pain worsens [39]. Consequently, chronic pain patients are frequently more aware of their pain during this period, which inhibits their ability to initiate or maintain sleep [38, 39]. In addition, once sleep is attained, pain patients frequently have difficulties reaching rapid eye movement (REM) sleep [39]. The absence of REM sleep is strongly connected with the inability to consolidate memory [39]. It also ensures homeostasis in the body [39]. The absence of REM can result in daytime hypersomnolence, which might be troublesome and cause functional and occupational difficulties that have a detrimental impact on the patient's daily life [38, 39]. In addition to chronic pain, several other causes related to chronic pain treatment frequently disturb sleep. Opioid medicines are commonly used to treat long-term chronic pain [39]. These drugs have several adverse effects, including sleep disruption due to altered sleep architecture [39]. As a result, individuals who take opioids to relieve pain are frequently vulnerable to altered sleep states that may miss the REM sleep cycles, which is necessary for restorative sleep [39].

Similarly, other drugs, such as selective serotonin reuptake inhibitors (SSRIs), may have an inhibitory effect on REM sleep, resulting in a sleep-deprived phase that can worsen the symptoms of other mental disorders [15, 39]. Understanding the connection between chronic pain, its treatment, and sleep is crucial for enhancing chronic pain patients' quality of life and overall wellbeing [38].

Chronic pain and PTSD co-occur, and studies suggest that these two disorders intensify one another, causing a larger influence on normal functioning in combination than independently [40]. It is estimated that 15-30% of individuals with PTSD also have chronic pain problems, such as osteopathic pain and fibromyalgia [41]. It has been hypothesized that the nervous system's reaction to traumatic incidents triggers the body to enter the survival mode that is associated with alterations in motor functioning, hearing, and vision [33]. When the body fails to relax owing to experiencing trauma due to the incapacity of the parasympathetic nervous system (PNS) to manage the sympathetic nervous system's (SNS) response to trauma, the body's capacity to heal is impaired, and immunological responses are suppressed [33]. Consequently, when SNS and PNS cannot operate synchronously, the risk of having chronic pain problems increases [33]. Despite the psychosocial adjustment, the altered stress response might persist across the whole life of the traumatized patient and get reactivated in response to new stressors [33]. Unless interventions are utilized to restore the nervous system's stress responses to an appropriate condition, this cycle persists and sometimes worsens chronic pain [33].

1.2.3 Conventional management of chronic pain:

Opioid drugs have proven to be problematic, as evidenced by the high prevalence of dependence and abuse observed in recent decades [17, 42]. For the treatment of pain, hydrocodone, oxycodone, fentanyl, and morphine are typical options [43]. However, there are significant side effects associated with these drugs, such as significantly increased risks of addiction, tolerance, and physical dependency [17, 42]. Furthermore, opioid drugs can rapidly become addictive, resulting in a surge in dung-seeking behaviors among patients [42]. Apart from opioids, muscle relaxants, anticonvulsants, antidepressants, facet joint and epidural injections, spinal cord, and nerve blocks are used to treat chronic pain; however, they are also not without limitations or adverse side effects [42]. For the pharmacological treatment of chronic pain, non-narcotic pain medications are also common and available and frequently contain stronger doses than ordinary over-the-counter drugs [44]. Despite the transition away from opioid treatment and the enhanced use of effective non-narcotic treatments such as higher doses of Tylenol or Tramadol or other related non-opioid medications, the number of opioid-related deaths is still increasing due to the addictive nature of the drugs and the increased chance of overdose [45]. These results emphasize the seriousness of the opioid crisis and the growing necessity for further study into alternative treatment options for all population groups, specifically for Veterans suffering from chronic pain.

1.2.4 Behavioral management of chronic pain:

Since pharmacological long-term pain therapy is frequently ineffective and accompanied by adverse consequences, nonpharmacological therapies are frequently recommended. The treatment of chronic pain needs institution-based interdisciplinary approaches, such as education on lifestyle habits, alteration of pain perception, self-management training, and individualized exercise

programs [46]. Physical activity may enhance daily function, block pain signals, contribute to greater balance and relaxation, decrease joint pressure and stiffness, and positively impact life quality [47].

Cognitive-behavioral therapy (CBT) is the most prevalent psychological treatment for chronic pain [48]. CBT focuses on enhancing cognitive and behavioural flexibility in order to respond more adaptively to problems [48]. CBT often comprises the following components when applied to chronic pain: psychoeducation on pain; cognitive restructuring of maladaptive pain-related thoughts; problem-solving; relaxation techniques; behavioural management; and pacing [48].

Mindfulness-based stress reduction (MBSR) is also another promising technique for the treatment of chronic pain. The MBSR program is an intervention in a group setting that focuses on developing awareness and acceptance of day-to-day events [49]. Increasing patients' awareness of their bodies, emotions, and thoughts, as well as developing self-regulation skills and adaptive behaviors to stress, are the core components of MBSR [49].

Since 2003, the Departments of Veterans Affairs and Defense have issued guidelines emphasizing non-opioid therapies as first-line options for managing chronic pain [50]. There is a need to identify nonpharmacological therapies, health promotion, psychosocial support, and coordination of care to manage pain in the Veteran population [51]. For example, experts propose educating veterans on the 1-10 Defense and Veteran Pain Rating Scale (DVPRS) in order to safely assess and treat their pain levels [51]. The implementation of the DVPRS eases self-reporting of pain intensity by patients and improves patient-healthcare provider dialogue [51].

Given the risks connected with opioid use, it is essential to recognise that nonpharmacological strategies may improve the QOL of veterans. In order to alleviate chronic pain and improve

veterans' quality of life, it is crucial to select the most effective nonpharmacological treatment approach.

1.2.5 Digital Therapeutics in the Management of CP:

Despite the supportive evidence regarding the benefits of behavioural management in pain treatment, this kind of therapy is not widely accessible, and the vast majority of chronic pain patients lack access to evidence-based care [52, 53]. Online treatment delivery is a viable method for increasing accessibility and reach.

A fundamental element of digital therapeutics is that they may boost a person's health and quality of life as effectively as conventional therapies and medications [54]. The purpose of digital therapeutics is to replace conventional interventions like face-to-face therapy, physical therapy, and even pharmaceutical or surgical treatments. Research on digital therapy for chronic pain dates back more than two decades but has lately advanced due to the increasing number of smartphones and the simplicity of developing apps. Numerous clinicians who treat patients with pain are investigating the use of digital therapeutics to manage and monitor patients with chronic pain.

When internet-delivered behavioural treatment (generally CBT) originally appeared, it was predominantly structured as a therapy based on self-help books, led by a therapist, and scheduled to mimic face-to-face therapy [55]. The majority of treatment components were offered as text on a website, and support was delivered via email [55]. Today, the majority of internet-delivered behavioural treatment still consists of written content, while video, audio, and animation content are gaining more popularity.

The benefits of online-delivered CBT is proven for a number of illnesses [56], has been shown to be cost-effective [56-58], and is a reasonable mean of increasing access to evidence-based therapy

[59]. Online-delivered interventions are proven to minimize the likelihood of therapist drift, which further promotes treatment accessibility by allowing less experienced therapists to present treatment content without compromising its quality [59]. Internet-delivered behavioural treatment has been found to be effective for psychiatric disorders, including anxiety disorders (specific phobias, general anxiety disorder, panic disorder, PTSD, obsessive-compulsive disorder, social phobia) and depression [60] and has demonstrated promising results for a range of different of somatic disorders including chronic pain [61]. Mobile and tablet internet use surpassed desktop use for the first time in 2016 [62]. That is why the adoption of smartphone applications may help better adjust to user needs and increase compliance. However, the use of smartphones for chronic pain treatment is nothing novel. Even as far back as 2011, researchers looked at 111 pain apps and found that "Pain apps appear to be able to offer relief without any consideration for the effectiveness of the product, or for the detrimental consequences of product use" [63].

1.3 Literature review (Digital interventions to manage chronic pain):

This section contains a comprehensive evaluation of existing online multidisciplinary interventions to address chronic pain, with an emphasis on physical exercise. This section aims to evaluate relevant randomized controlled trials (RCT) to determine the efficacy of digital health interventions in managing chronic pain. Google Scholar, PubMed, Up To Date, CINAHL Medline, PloS One, Science Direct, and other databases were searched. The purpose was to identify RCTs using digital health interventions, particularly physical exercise, for the treatment of chronic pain. Terms and phrases included in the review of the relevant literature were pain, chronic pain, physical activity, exercise, complementary alternative medicine, cognitive behavioral therapy, digital therapeutics, and e-health. The articles were selected according to their relevancy,

information source, and study purpose. The studies which were chosen included RCTs only. Eighteen studies were selected for further examination.

Almost the majority of studies concluded that behavioral interventions delivered online were beneficial for chronic pain management.

Raad Shebib et al. (2019) evaluated the effectiveness of a 12-week digital treatment program for LBP conducting two-armed RCT [65]. The digital care program (DCP) consisted of an app-delivered sensor-guided exercise program, education, CBT, health coaching, and activity and symptom tracking [65]. The control group was given only three digital education articles. The average improvement in pain results for individuals who completed the DCP ranged 52-64% ($p<0.01$), and the average improvement in disability results ranged 31-55% ($p<0.01$) [65].

H. S. Chhabra et al. (2018) conducted an RCT to assess the impact of a smartphone app (named Snapcare) on LBP patients' pain and function [66]. The application included daily exercises, daily activities, and progress. The physician prescribed the appropriate level of physical activity (including home workouts) to the control group. At 12 weeks, the pain score significantly decreased in both groups, however, it was not statistically significant ($p=0.23$) [66]. Additionally, the App group demonstrated a considerably higher drop in disability ($p=0.032$) [66]. Researchers concluded that health applications are viable methods for enhancing the health outcomes of people with chronic pain [66].

Jonathan D. Browne et al. (2022) investigated the PainNavigator platform's usefulness in the management of low back pain to guide future clinical trials [67]. The application contained preloaded medical education and wellbeing strategy content, such as CBT, mindfulness, yoga, and exercise [67]. The results demonstrated a 36% decrease in Pain, Enjoyment, and General Activity total scores, a 40% decrease in pain severity, and a 40% decrease in Patient Health Questionnaire

total scores ($p < 0.001$ for all) [67]. Researchers logically concluded that the PainNavigator app has therapeutic importance in the treatment of chronic low back pain and may be implemented to enhance patientcare [67].

Linda S. Ruehlman et al. (2011) evaluated the efficacy of a comprehensive, self-directed, and self-paced digital Chronic Pain Management Program [68]. The Pain Management Program included self-monitoring exercises, education, relaxation, and goal-directed behaviour implementation. For roughly six weeks, the intervention group was given unsupervised access to the program; the control group continued to receive their regular treatment. Utilization of the program was linked to significant reductions in pain intensity, pain-related interference and psychological burden, perceived impairment, catastrophizing, and pain-induced anxiety ($p<0.01$ for all) [68]. In addition, program participation resulted in significant reductions in depression, stress, and anxiety [68].

Rachel K. Nelligan et al. (2021) assessed the benefits of a self-directed web-based exercise and physical activity program accompanied by algorithmic behavior-change text messages about knee pain and function in individuals with knee osteoarthritis (OA) [69]. The control group was provided access to a website that contained information about OA as well as the advantages of physical activity and exercise. The intervention group received a prescription for a self-directed strengthening program and assistance to enhance physical activity, as well as automated text messages promoting exercise adherence [69]. The intervention group demonstrated more considerable improvements in total knee pain ($p<0.001$) and physicalactivity ($p=0.002$) compared to the control group [69]. This study suggests that this unsupervised, free-to- access online intervention is an excellent choice for increasing patient access to approved OA exercises and may assist clinicians with the management of knee OA patients [69].

Jenny Rickardsson et al. (2020) studied the efficacy of a novel format of Internet-based acceptance and commitment therapy (iACT) that included daily micro-learning exercises [70]. iACT was designed with a micro-learning format that prompted short learning interactions with practical exercises and value-based exposure. Control group continued to get their usual chronic pain treatment. At post-assessment, iACT participants improved by more than 30% compared to control group for outcomes pain interference ($p = 0.047$) and pain intensity ($p = 0.01$), as well as process variables psychological inflexibility ($p = 0.002$) and value progress ($p = 0.01$) [70]. The study indicated that iACT as micro-learning has the potential to enhance a wide range of chronic pain outcomes, including quality of life, anxiety, depression, insomnia, and pain intensity [70].

Hannes Weise et al. (2022) aimed to compare the efficacy of a digital home exercise program to the standard of care for physiotherapy in terms of self-reported pain severity [71]. The interventional group was given mobile device access to the digital intervention. The control group underwent regular physiotherapy treatment. The application offered a self-directed home workout program based on movement therapy principles [71]. At 12 weeks, the mean difference of pain scores comparing the two groups was -2.44 ($P = 0.01$) in favour of the intervention group [71]. The research concluded that digital interventions are becoming a viable treatment option that can overcome the access and availability limitations of traditional healthcare delivery methods [71].

Daniel Pach et al. (2022) examined whether app-based relaxation activities, such as audio-based autogenic training, mindfulness, or guided imagery, are more beneficial than standard therapy alone in relieving chronic neck pain [72]. The mobile application comprised three forms of relaxation techniques: autogenic training, mindfulness, and guided imagery. Participants

from the control group downloaded the identical app. However, this app did not contain relaxation exercises. The mean intensity of neck pain decreased in both groups during three months, although no statistically significant difference was observed between the two groups ($p=0.23$) [72]. The study revealed that the study app did not effectively relieve chronic neck pain or maintain the users' self-care exercise engagement [72].

Pablo Rodrguez Sánchez-Laulhé et al. (2022) evaluated the short- and medium-term effectiveness of a digital app (CareHand) that includes a customized home exercise program, as well as educational and self-management guidelines, in comparison with standard care, for individuals with hand-related RA (rheumatoid arthritis) [73]. Individuals with RA who downloaded and used the CareHand app indicated better short- and medium-term hand function, work productivity, pain, and satisfaction outcomes than those who received standard care (all $p<0.05$) [73]. The results of this study indicate that a CareHand app is a helpful tool for providing exercise therapy and self-managementadvice to this population [73].

Tomomi Anan et al. (2021) investigated the impact of AI (artificial intelligence) – assisted health programs on musculoskeletal problems in workers with neck/shoulder stiffness/pain and LBP [74]. The AI-assisted chatbot was built to send messages to the participants with exercise instructions and recommendations on what they may do in their daily lives to alleviate the symptoms. Stretching, maintaining excellent posture, and mindfulness comprised the three components of the program. The control group received usual care. The intervention group participants demonstrated substantial reductions in the intensityof neck/shoulder pain/stiffness and low back pain compared to those in the control group (OR 6.36, 95% CI 2.57-15.73; $P<.001$) [74]. This study shows that in 12 weeks, the short exercises supplied by the AI-assisted health program reduced neck/shoulder pain and LBP [74].

Another study conducted by Ólöf Birna Kristjánsdóttir and colleagues (2013) assessed the long-term effects of a four-week smartphone intervention consisting of diaries and written feedback from therapists that was given after an inpatient chronic pain rehabilitation program [75]. The intervention included in-person individual sessions and four weeks of written communication through a smartphone. The written communication consisted of three daily diaries to induce pain-related feelings, thoughts, and activities, along with daily personalized written feedback centered on cognitive behavioural principles from a therapist. The control group did not receive a smartphone intervention. The outcomes of RCT over a longer period were inconclusive. At the 11-month follow-up, the researchers could not find any statistically significant differences between the groups on any study variables [75]. However, at 5-month follow-up, overall between-group effect sizes for pain acceptance (Cohen's d=0.54, P=.02) and catastrophizing (Cohen's d=0.74, P=.003) were moderate [75].

Anita B. Amorim et al. (2019) carried out a pilot RCT with a blinded evaluation of the results [76]. The intervention group was provided with a booklet containing information on various forms of physical exercise, in addition to one in-person and 12 over-the-phone health coaching sessions. An application that was accessible via the internet and a fitness tracker were used to facilitate the intervention (Fitbit). Control group was given the physical activity instruction booklet and were advised to stay active. Although estimates did not reach statistical significance, there was a 38% decrease in the rate of care-seeking among participants in the intervention group compared to the regular care group (Incidence Rate Ratio: 0.62, 95% CI: 0.32 to 1.18, p = 0.14) [76]. The researchers came to the conclusion that the health coaching physical activity method that was tested in this study is viable, and has the potential to minimize care- seeking behaviour in patients with LBP after they are discharged from treatment [76].

Blair Irvine et al. (2015) assessed the effectiveness of a mobile-Web intervention named "FitBack" for assisting users in implementing self-tailored measures to treat and prevent LBP [77]. After initial assessments, participants were randomly assigned to one of three groups: the FitBack intervention, the alternative care group which received eight emails advising them to link to six Internet resources for LBP, or the control group that only was contacted to conduct assessments. The FitBack application gave users control over the cognitive and behavioural techniques they used to improve their LBP. At the 4-month follow-up, users of the FitBack program demonstrated better improvement than the control group in every assessment of critical physical, behavioural, and worksite outcome variables (all $p<0.01$) [77].

Thomas R. Toelle et al. (2019) conducted an RCT to examine the therapeutic impact of a multidisciplinary mHealth back pain app (Kaia App) [78]. The app includes three therapeutic modules: back pain-related education, physiotherapy/physical activity, and mindfulness and relaxation exercises. The control treatment comprised of six individual physiotherapy sessions, as well as online education. At the 12-week follow-up, the intervention group experienced much less painthan the control group ($p<0.05$) [78]. Researchers concluded that the Kaia App was a more effective therapyfor LBP patients than physiotherapy with online education [78].

Christine Rini et al. (2015) designed an 8-week, automated, Internet-based Pain coping skills training program called PainCOACH and assessed its potential effectiveness and tolerability in a small-scale, two-arm RCT [79]. The PainCOACH program included modules such as progressive muscle relaxation, mini-exercises, activity/rest cycling, problem-solving. Control group completed assessment only. Women who received the PainCOACH intervention reported much less pain than those in the control group following therapy (Cohen d = 0.33) [79]. It was not possible to examine the impact of interventions on men due to the limitedsample size and low

pain [79].

Fatemeh Abadiyan et al. (2021) assessed the impact of adding a smartphone app into an 8-week global postural re-education (GPR) program on neck pain, quality of life, endurance, and forward head posture (FHP) in patients suffering from chronic neck pain and FHP [80]. Random assignment was used to place people in one of three groups: group 1 (GPR with a smartphone app), group 2 (GPR alone), and group 3 (The control group). Both Group 1 and Group 2 received the experimental interventions for approximately 50 minutes per day, four days per week, for a total of 8 weeks. The first group also used an app on their phones to remind them to exercise at predetermined intervals. Compared to GPR alone, the GPR with a smartphone app group showedsignificant improvement in pain, endurance, FHP, and disability ($p=0.04$, $p=0.033$, $p=0.047$ accordingly) [80]. All results showed statistically significant differences between the GPR with a smartphone app and GPR groups versus the control group [80].

Gabriel Mecklenburg et al. (2018) evaluated the efficacy of a digital care program provided remotely for chronic knee pain [81]. Treatment group participants were registered in the Hinge Health digital care program. This was a home-based, 12-week program that was given remotely and involved sensor-guided exercise therapy, cognitive behavioural therapy, education, weight loss, and psychosocial support via a personal coach with team-based interactions [81]. The control group was given three pieces of self-care education regarding chronic knee pain. At the completion of the program, participants in the digital care program showed a significantly higher reduction in Knee Injury and Osteoarthritis Outcome Score Pain ($p=0.002$) and a significantly betterimprovement in physical function than the control group ($p=0.001$) [81].

The strength of these studies is that almost all of the control group received some intervention

whose effects are already known, for instance, physiotherapy, pain education, or prescribed physical activity from physicians. It allowed us to compare the effectiveness of new interventions to standard care. Furthermore, studies evaluated not only pure pain reduction as an endpoint but also other factors associated with pain, such as quality of life, disability, general enjoyment, productivity, psychological burden, perceived impairment, catastrophizing, pain-induced anxiety, depression, and insomnia.

However, the effectiveness of these intervention programs over the long term is still unknown, as none of these studies have investigated the effects of digital treatments over an extended period. It is essential to develop interventions that can build intrinsic motivation to continue healthy behaviors beyond the active intervention.

Chapter 2: Medical cannabis use among Canadian Veterans and non-Veterans to manage chronic pain and comorbid mental health issues. A national survey

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2.1 Introduction

Cannabis has traditionally been used as a self-remedy for the management of symptoms related to physical illness and psychological health. For many conditions, however, the evidence to support optimal clinical use is of poor quality and/or inconsistent. Canadian Veterans are disproportionately impacted by conditions for which medical cannabis (MC) is frequently used. The Life after Service Study (LASS) demonstrated that Canadian Veterans, compared to Canadians who have not served, are more prone to suffer from a wide range of physical and mental health issues, including chronic pain, anxiety, post-traumatic stress disorder (PTSD), and insomnia [1,2]. Among Veterans, annual program expenditures for MC have been increasing rapidly. There are currently 617,800 Veterans in Canada and Veterans Affairs Canada has allocated $153,780,785 for MC to support 18,388 (3%) Veterans in the fiscal year 2021-2022. Program expenditures are expected to reach $195.2 million in the fiscal year 2022/2023 [6, 28].

Despite the uncertainty regarding the efficacy of MC, it is apparent that close to 20,000 Veterans, whose cannabis authorizations are paid for by Veterans Affairs Canada, continue to use this product to manage their medical conditions. MC is perceived a low-risk and safe product in comparison to many other drugs [7, 8]. There is however clear evidence for harms associated with

cannabis use, including potential adverse effects on mental health and associations with

respiratory, cardiovascular and gastrointestinal events. Cannabis use is a risk factor for motor vehicle accidents and partner and child violence [9]. A further concern for MC use is the risk of cannabis use disorder CUD [10]. CUD reports have grown significantly in the last decade, particularly among Veterans [11, 12]. The perceived net benefit of MC may be, in part, due to the fact that MC is often used to treat multiple conditions in the same individual [13]. Accordingly, if users believe that they are treating multiple conditions they may be more willing to accept the risk of an adverse secondary effect.

Little research has been conducted to investigate patterns and perceived effectiveness of MC usage among those who use it regularly. Given that Canadian Veterans use MC for a wide range of symptoms, they are an appropriate group to evaluate for further understanding and optimizing the use of MC. They might also help to identify the target conditions that are most likely to respond to MC based on current usage and perceived benefits. It is also essential to understand if the experience of Veterans is generalizable to other MC users. There has been relatively limited research on this issue, and only one study has explicitly evaluated the differences of the MC usage by Veterans vs non-Veterans, taking into account sex distinctions [14].

The current study assessed MC use among a convenience sample of Canadians, comparing Veterans and non- Veterans to identify differences in user characteristics (socio-demographic, health, lifestyle etc.) reasons for use, usage patterns, perceived effectiveness and sex-specific effects.

2.2 Methods

2.2.1 Recruitment

Between November and December 2021, Canadian MC users, both Veterans and non-Veterans, were recruited to complete an online questionnaire. Respondents were invited to participate in the "CannCorps Study" in a number of ways. Canadian Veterans, family members, and friends were recruited via an online platform dedicated to promoting health among Canadian Veterans and their families (www.MissionVav.com). The CannCorps Study was highlighted on the MissionVaV landing page and an active link provided to the online survey. Also, a posting on social media ('CannCorps' and 'MissionVav' Facebook pages) highlighted the survey which was also mentioned in a monthly newsletter to Veterans from Veteran Affairs Canada. Finally, the general public was invited to participate in a press release to Canadian news agencies.

2.2.2 Survey

The survey was available in English or French and took less than 10 minutes to complete on a computer, tablet, or smartphone. Participants were required to be at least 18 years of age and had used MC at least once in the past month or were considering use in the next month. Anonymity was maintained as no identifiers were collected and the email address of respondents was not recorded. The study was approved by the Institutional Review Board of the McGill University Health Center Research Institute.

The survey questions focused primarily on MC use patterns, reasons for use, and respondent's perception of efficacy of their specific MC therapy (See Survey Questionnaire in Appendix). Sociodemographic data including age, sex and ethnicity were collected. Additionally, data were

recorded on lifestyle habits that might impact physical and mental health symptoms such as physical activity, consumption of tobacco and alcohol.

Among the 115 questions, 45 (39%) focused on the respondent's perception of effectiveness of MC, and MC use patterns (mode of administration, usage frequency, current daily amount used, preferred dose, usage duration, preferred strain, concentrations of delta-9 tetrahydrocannabinol (THC), and cannabidiol (CBD) etc.). Participants were also questioned about their reasons for MC use, any concerns about MC use, whether they felt that cannabis use was out of control, and how difficult they found it to stop using. Questions were answered by yes/no, drop-down answer options, multiple choice responses, open-ended responses, and rating scales. Self-reported effectiveness was evaluated using a 0 to 10 visual analogue scale (0 = not at all effective, 10 = most effective).

2.2.3 Data Analysis

Descriptive statistics were used to summarize all responses. After stratifying the sample by Veteran status, chi-square tests (for categorical variables) and independent t-tests (for continuous variables) were used to compare the responses of Veterans vs non-Veterans. Non-parametric tests were used for highly skewed data. Linear and logistic regression models were performed to determine if cannabis usage among Veterans was significantly different from non-Veterans after adjustment for age and sex. Analyses were also completed for males and females separately. All analyses were conducted using Python version 3.10.

2.3 Results

The survey was completed by 158 respondents. After excluding 10 outliers who provided unrealistic responses, 148 participants were selected for further analyses. Among respondents,

90(63 %) self-identified as Veterans and 58 (37%) as non-Veterans. There were 99 males and 49 females. The mean age was 57years (range 19 to 84 years), 103(73%) were married, 128 (82%) identified as Caucasian/White background, and 85 (60%) were retired (Table 1). Compared to non-Veterans, Veterans were significantly ($p<0.05$) more likely to be male (83% vs 49%).

Subsequent analyses were sex specific. Both Veterans and non-Veterans were similar in terms of age, education levels, ethnic origin, and marital status. Both groups reported identical patterns of alcohol and cigarette usage, as well as physical activity habits (Table 2).

Male Veterans vs non-Veterans were significantly more likely to report problems with depression (50% vs 14%, $p <0.01$), anxiety (72% vs 18%, $p < 0.001$) and PTSD (36% vs 9%, $p< 0.001$). Female Veterans vs female non-Veterans were significantly more likely to use MC for conditions such as PTSD (60% vs 12%, $p<0.001$) and arthritis (60% vs 12%, $p<0.001$) (Table 3).

Perceived effectiveness of MC for both Veterans and non–Veterans were similar for the most common conditions and included: insomnia (8.3 vs 8), PTSD (8.3 vs 8.4), depression (8 vs 8.2), anxiety (8 vs 8.4), acute pain (7.8 vs 7.8), chronic pain (7.5 vs 7.8) and arthritis (7.4 vs 8) (Table 4). Perceived effectiveness scores were similar for male and female Veterans and non-Veterans. The mean score for effectiveness across all conditions was 7.4(SD=1.1).

The majority of respondents had used MC daily for at least 1 year, with oils identified as the most common mode of administration (58%; n=91), followed by edibles (38%; n = 59) and vaporized cannabis (34%; n=54) (Table 5). Both male and female Veterans were significantly more likely to use edible modes of administration compared to non-Veterans (65% vs 9%, $p < 0.001$ and 67% vs 25%, $p < 0.01$). Although not statistically significant, males tended to use MC in higher doses as compared to females (median amount for THC: 11.5 mg/day vs 4 mg/day; and median amount for

CBD 20 mg/day vs 8.5 mg/day). Male Veterans were more likely to use MC to treat a greater number of conditions including arthritis and several mental health problems ($p < 0.01$).

The dose of THC was positively associated with the number of conditions being treated ($p = 0.01$), whereas there was no statistically significant association between number of conditions and CBD doses ($p=0.8$). (Figure 1).

In multivariable analyses, adjusting for age and sex, Veterans compared to non-Veterans were more likely to use MC for depression, anxiety, PTSD, sleeping problems and arthritis and were more likely to use an edible mode of administration (all p-values <0.001).

Veterans were significantly less likely than non-Veterans to be concerned about the safety and adverse effects of MC use ($p = 0.017$). One hundred and eleven (75%) respondents from both groups reported that their MC use was never out of control, and 95(64%) respondents indicated that they never wished to stop the use of MC.

2.4 Discussion

The results of this study indicate many similarities between MC use by male and female Veterans and non-Veterans. Daily amounts of ingested THC, CBD, and the herbal product were similar for Veterans and non-Veterans. Both groups used MC to treat a variety of ailments and reported that MC provided substantial relief for both physical and mental health problems.

The main difference in MC choice was that edibles were more commonly used by Veterans. Reasons for greater use of edibles could be due to the longer duration of action of the ingested product compared to vaporized forms. Stigma associated with inhalation, with tendency to associate inhaled cannabis with recreational use may also have played a role in preferential use of

orally administered product. Oral administration can also be more discrete as there is avoidance of the smell associated with the inhaled product. Alternately, cost issues may have influenced the selection of preferred method of administration as MC products are fully reimbursed for Veterans compared to the out-of-pocket expenses for other Canadians. It is possible that the non-Veterans using MC may have accessed the product at times via the less expensive illegal market that focusses mostly on the dried product that is most conveniently inhaled.

Consistent with previous studies, these results indicate that MC is commonly used for a variety of physical and mental health complaints such as chronic pain, insomnia, anxiety, depression, PTSD, and arthritis [15, 18]. This prevalent use of and satisfaction with MC, often by self-administration, is in contrast to the limited evidence for substantial beneficial effects in the published literature [28, 29, 30]. Despite the lack of strong scientific evidence demonstrating the effectiveness of MC compared to placebo, there was a strong consistent belief among participants that MC was effective for treating a wide range of physical and mental health conditions. Perceived effectiveness scores were particularly high for the mental health problems, with average scores of 8 or greater. These results are consistent with previous observational studies [19-23]. Whether this represents a placebo effect, regression to the mean or true efficacy will require more scientific study. These data do provide guidance in targeting these studies to the management of chronic pain conditions and several mental health problems.

On average MC was used by most respondents several times a day which was in line with other studies [13, 17, 19, 22, 24] suggesting that the MC provided symptom relief rather than modifying the disease pathophysiology.

A concerning observation of this study is that 60% of the respondents did not identify the strength or content (THC or CBD) of the cannabis product used. This lack of knowledge of product content by many users has been noted in previous studies [31, 32, 33]. Although MC is reported to be used as a medicinal product, the poor attention to amount or content of the product may be bolstered by a perception of safety of cannabis as a recreational and natural product. Alternately, lack of adequate knowledge by both patients and MC prescribers may also be a factor in poor knowledge of content. Furthermore, we have observed limited concerns about safety and side effects of MC, especially from Veterans.

Consistent with other studies one of the attractions of MC may be that, it is used to treat multiple physical and mental health complaints [19, 21-23, 25]. These multiple conditions are more prevalent among Canadian Veterans compared to the non-Veteran populations. This may help with mitigating polypharmacy burden as well as dealing with adherence to complicated pharmaceutical routines and their side effects. However, the complexity of effects of the large numbers of cannabinoid and non-cannabinoid molecules in the plant *Cannabis sativa* requires both study and understanding before any evidence-based recommendation can be made in this regard.

Sex-based analyses are an important strength of this study. Although sex-based analyses are generally recognised as important tools for detecting disparities and providing insights for research and policy, this strategy has not always been used in research of Veteran populations. We did not observe any significant differences between males and females regarding their MC use patterns. Although males tend to use MC in greater doses, these differences were not statistically significant ($p=0.09$).

Considering that females make up roughly 14% of the ~600, 000 Veterans now residing in Canada [16], female Veterans are grossly underrepresented in the literature with many studies reporting on male samples of Veterans (around 70% males) [27]. There is thus an urgent need to address the health-related needs of female Veterans in all future studies.

There are limitations to the current study that must be addressed. First, this was a convenience sample of respondents and the representativeness of these results to the population of users of MC remains to be confirmed. Second, the sample size was modest, with female responders particularly underrepresented, which may reduce the accuracy of the estimates provided. Third, it is possible that this sample of MC users was biased towards those who found it effective, while those who did not benefit did not reply to the survey. In addition, we do not have knowledge of the total numbers who might have been exposed to this survey, thus we cannot estimate the response rate.

There remain many uncertainties around MC use, particularly among Veterans. Further study should address the specific molecular effects of herbal cannabis products, including various concentrations of THC and CBD, the contribution of other molecules such as terpenes and flavonoids to a therapeutic effect (termed the entourage effect), the interaction of cannabinoids with other medications, and the development of tolerance and importantly, adverse effects especially for long-term use. Ideal dosing as well as methods of administration of MC will also require attention.

2.5 Conclusions

The responses from this sample of Canadians, both Veterans and non-Veterans indicate the belief that MC is an effective therapy for both physical and mental health symptoms. While we identified some important differences in user characteristics and MC use patterns between Canadian Veterans and non-Veterans, daily dosage and the perceived effectiveness were similar. These preliminary results should be considered when developing additional studies on MC use and effectiveness. Larger studies are required to validate these findings, but this study suggests that orally administered cannabis products for the primary conditions identified in this sample may be worth further study.

2.6 References:

1. Vélez JR, Thompson JM, Sweet J, et al. Identification of care need clusters in Veterans living with chronic pain – life after service studies 2016. Can J Pain. 2021 Apr 21; 5(1): 81-95. Available from: https://doi.org/10.1080/24740527.2021.18982 78. Medline:34189392
2. Teeters JB, Lancaster CL, Brown DG, et al. Substance use disorders in military Veterans: prevalence and treatment challenges. Subst Abuse Rehabil. 2017 Aug 30; 8: 69 77. Available from: https://doi.org/10.2147/SAR.S116720. Medline:28919834
3. Thompson JM, VanTil LD, Zamorski MA, Garber B, Dursun S, Fikretoglu D, et al. Mental health of Canadian Armed Forces Veterans: Review of population studies. Journal of Military, Veteran and Family Health. 2016 Mar 2; 2(1): 70-86. Available from: https://doi.org/ 10.3138/jmvfh.3258
4. Thompson JM, Pranger T, Sweet J, Vantil L, McColl MA, Besemann M, et al. Disability correlates in Canadian armed forces regular force Veterans. Disability and Rehabilitation.

2014 Sep 09; 37(10):884-91. Available from: https://doi.org/10.3109/09638288.2014.947441

5. Sterniczuk R, Whelan J. Cannabis use among Canadian Armed Forces Veterans. J Mil Veteran Fam Health. 2016 Dec 2; 2 (2): 43 - 52. Available from: https://doi.org/10.3138/jmvfh.3836
6. Available from: https://search.open.canada.ca/qpnotes/record/vac-acc,VAC-2022-QP-00005
7. Wilkinson ST, van Schalkwyk GI, Davidson L, D'Souza DC. The formation of marijuana risk perception in a population of substance abusing patients. The Psychiatric Quarterly. 2016; 87(1):177–187. Available from: https://doi.org/10.1007/s11126-015-9369-z
8. Earleywine M, Bolles JR. Marijuana, expectancies, and post-traumatic stress symptoms: A preliminary investigation. Journal of Psychoactive Drugs. 2014; 46(3):171–177. DOI: 10.1080/02791072.2014.920118
9. Campeny E, Lopez-Pelayo H, Nutt D, Blithikioti C, Oliveras C, Nuno L. et al. The blind men and the elephant: Systematic review of systematic reviews of cannabis use related health harms. Eur Neuropsychopharmacol. 2020 Apr;33:1-35. doi: 10.1016/j.euroneuro.2020.02.003
10. Karila L, Roux P, Rolland B, et al. Acute and long-term effects of cannabis use: a review. Curr Pharm Des. 2014;20(25):4112–18. doi:10.2174/13816128113199990620
11. Dillon HK, Van Voorhees EE, Elbogen BE, Beckham CJ, Calhoun SP. Cannabis Use Disorder, Anger, and Violence in Iraq/Afghanistan-era Veterans. J Psychiatr Res.2021 Jun; 138:375-379 doi: 10.1016/j.jpsychires.2021.04.018

12. Hill PK, Gold SM, Nemeroff BC, McDonald W, Grzenda A, Widge SA. et al. Risks and Benefits of Cannabis and Cannabinoids in Psychiatry. Am J Psychiatry. 2022 Feb;179(2):98-109. doi: 10.1176/appi.ajp.2021.21030320
13. Loflin MJ, Babson K, Sottile J, Normana SB, Grubere S, Bonn-Miller MO. A cross-sectional examination of choice and behavior of Veterans with access to free medicinal cannabis. Am J Drug Alcohol Abuse. 2019 May 28;45(5):506–513. doi:10.1080/00952990.2019.1604722
14. Hall AL, Sweet J, Tweel M, MacLean MB. Comparing negative health indicators in male and female Veterans with the Canadian general population. BMJ Mil Health 2022;168:82–87. doi:10.1136/bmjmilitary-2020-001526
15. Azcarate MP, Zhang JA, Keyhani S, Steigerwald S, Ishida HJ, Cohen EB. Medical Reasons for Marijuana Use, Forms of Use, and Patient Perception of Physician Attitudes Among the US Population. J Gen Intern Med. 2020 Jul;35(7):1979-1986. doi: 10.1007/s11606-020-05800-7
16. Metrik J, Bassett SS, Aston ER, Jackson KM, Borsari B. Medicinal versus Recreational Cannabis Use among Returning Veterans. Transl Issues Psychol Sci. 2018 March;4(1):6–20. doi:10.1037/tps0000133
17. Sterniczuk R, Whelan J. Cannabis use among Canadian Armed Forces Veterans. Journal of Military, Veteran and Family Health. 2016 Dec 2;2(2):43-52. doi:10.3138/jmvfh.3836
18. Leung J, Chan G, Stjepanović D, Chak Chung YJ, Hall W, Hammond D. Prevalence and self-reported reasons of cannabis use for medical purposes in USA and Canada. Psychopharmacology (Berl). 2022 May;239(5):1509-1519. doi: 10.1007/s00213-021-06047-8

19. Swift W, Gates P, Dillo P. Survey of Australians using cannabis for medical purposes. Harm Reduction Journal. 2005 Oct 04;2(18):1-10. doi:10.1186/1477-7517-2-18
20. Kvamme SL, Pedersen MM, Thomsen KR, Thylstrup B. Exploring the use of cannabis as a substitute for prescription drugs in a convenience sample. Harm Reduct J. 2021 Jul 10; 18(72). https://doi.org/10.1186/s12954-021-00520-5
21. Boehnke KF, Scott JR, Litinas E, Sisley S, Clauw DJ, Goesling J, Williams DA. Cannabis Use Preferences and Decision-making Among a Cross-sectional Cohort of MC Patients with Chronic Pain. The Journal of Pain. 2019 Nov;20(11):1362-1372. https://doi.org/10.1016/j.jpain.2019.05.009
22. Ware MA, Adams H, GUY GW. The medicinal use of cannabis in the UK: results of a nation-wide survey. Int J Clin Pract, 2005 March;59(3):291–295. doi:10.1111/j.1368-5031.2005.00271.x
23. Carter GT, Weydt P, Kyashna-Tocha M, Abrams DI. Medicinal cannabis: rational guidelines for dosing. IDrugs. 2004 May 1;7(5):464-70. PMID: 15154108.
24. Walsh Z, Callaway R, Belle-Isle L, Capler R, Kay R, Lucas P. et al. Cannabis for therapeutic purposes: Patient characteristics, access, and reasons for use. Int J Drug Policy. 2013 Nov;24(6):511-516. doi:10.1016/j.drugpo.2013.08.010
25. Manning L, Bouchard L. MC Use: Exploring the Perceptions and Experiences of Older Adults with Chronic Conditions. Clin Gerontol. 2021 Jan-Feb;44(1):32-41. doi:10.1080/07317115.2020.1853299
26. Turna J, MacKillop J. Cannabis use among military Veterans: A great deal to gain or lose? Clinical Psychology Review 2021 Jan 11;84:101958. https://doi.org/10.1016/j.cpr.2021.101958

27. Available from: https://www.veterans.gc.ca/eng/about-vac/news-media/facts-figures/summary
28. Black N, Stockings E, Campbell G, Tran TL, Zagic D, Hall DW et al. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. Lancet Psychiatry. 2019 Dec;6(12):995-1010. doi: 10.1016/S2215-0366(19)30401-8
29. Fitzcharles M-A, Baerwald C, Ablin J, Häuser W. Efficacy, tolerability and safety of cannabinoids in chronic pain associated with rheumatic diseases (fibromyalgia syndrome, back pain, osteoarthritis, rheumatoid arthritis): A systematic review of randomized controlled trials. Schmerz. 2016 Feb;30(1):47-61. doi: 10.1007/s00482-015-0084-3
30. Wang L, Hong JP, May C, Rehman Y, Oparin Y, Hong JC, et al. Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. BMJ. 2021 Sep 8;374:n1034. doi: 10.1136/bmj.n1034
31. Ste-Marie AP, Shir Y, Rampakakis E, Sampalis SJ, Karellis A, Cohen M. Survey of herbal cannabis (marijuana) use in rheumatology clinic attenders with a rheumatologist confirmed diagnosis. Pain 2016 Dec;157(12):2792-2797. doi: 10.1097/j.pain.0000000000000706
32. Fitzcharles M-A, Rampakakis E, Sampalis J, Shir Y, Cohen M, Starr M, et al. Medical Cannabis Use by Rheumatology Patients Following Recreational Legalization: A Prospective Observational Study of 1000 Patients in Canada. ACR Open Rheumatol 2020 May;2(5):286-293. doi: 10.1002/acr2.11138
33. Boehnke FK, Häuser W, Fitzcharles M-A. Cannabidiol (CBD) in Rheumatic Diseases (Musculoskeletal Pain). Curr Rheumatol Rep 2022 Jul;24(7):238-246. doi: 10.1007/s11926-022-01077-

Table 1: *Demographics and lifestyle habits of Veterans VS non-Veterans:*

	Veterans (N=90)	Non - Veterans(N=58)
Age(mean)	56	59
Female* **	15(17%)	34(51%)
BMI(mean)	29.3	26.9
Background:	80 Caucasian / White	48 Caucasian / White
	7 Aboriginal	2 Latin American
	1 Black	1 Korean
Marital status:		
Married	75(83%)	28(51%)
Divorced	11(12%)	5(9%)
Single	7(8%)	10(17%)
Education:		
Less than high school	3(3%)	0
High school graduate or equivalent	17(19%)	5(7%)
University, but no degree	18(20%)	4(7%)
Technical college, community college or CEGEP	40(44%)	14(24%)
University graduate	7(8%)	13(22%)
Graduate degree	4(4%)	6(10%)
Employment:		
Employed	17(19%)	11(19%)
Unemployed	12(13%)	9(15%)
Retired	60(67%)	25(43%)
Alcohol consumption:		
Never	22(24%)	14((24%)
2-4 times a month or less	37((41%)	19(33%)
2-3 times a week	21(23%)	10(17%)
Daily or almost daily:	10(11%)	10(17%)
Cigarette consumption:		
Not at all	78(87%)	53(91%)
At least once a week	11(12%)	3(5%)

Physical activity:		
Walking hours during the past 7 days	3.88(2.15)	3.37(2)
Moderate physical activity(hours)	4.1(2)	4.47(1.75)
Vigorous physical activity(hours)	1.78(0)	2.3(0)

*p<0.05, **p<0.01, ***p<0.001, data are presented as n (%) or mean (median)

Table 2: *Demographics and lifestyle habits of male and female Veterans VS non-Veterans:*

	Males(N= 103)		Females(N=39)	
	Veterans(N=75)	Non-Veterans(N=22)	Veterans(N=15)	Non-Veterans(N=24)
Age(mean)	57.2	55.5	52.6	60.7
BMI(mean)	29.9	28.2	26.5	25.8
Background:	66 Caucasian/White	20Caucasian/White	14 Caucasian/White	21 Caucasian/White
	6 Aboriginal	0	1 Aboriginal	2 Latin American
	1 Black	0		
Marital status:				
Married	61(60%)	18(81%)	12(80%)	13(54%)
Divorced	7(7%)	0	3(20%)	5(21%)
Single	7(7%)	4(18%)	0	5(21%)
Education:				
Less than high school	2(2%)	0	1(7%)	0
High school or equivalent	16(15%)	3(14%)	1(7%)	2(8%)
University but no degree	14(13%)	1(5%)	0	3(13%)
Technical/community college/CEGEP	33(32%)	7(32%)	7(47%)	7(29%)
University degree	5(5%)	6(27%)	2(13%)	7(29%)
Graduate degree	4(4%)	4(18%)	0	2(8%)
Employment:				
Employed	15(14%)	5(23%)	2(13%)	6(25%)
Unemployed	3(3%)	3(14%)	3(20%)	1(4%)
Retired	50(49%)	11(50%)	10(67%)	14(58%)
Alcohol consumption:				

Never	20(19%)	3(14%)	2(13%)	8(33%)
2-4 times a month or less	31(30%)	7(32%)	6(40%)	7(29%)
2-3 times a week	15(14%)	3(14%)	6(40%)	6(25%)
Daily or almost daily	9(9%)	9(41%)	1(7%)	3(13%)
Cigarette consumption:				
Not at all	66(64%)	21(95%)	12(80%)	24(100%)
At least once a week	8(8%)	1(5%)	0	0
Physical activity:				
Walking hours during the past 7 days	4.02(2)	4.9(3)	6.8(2.3)	4.29(2)
Moderate physical activity(hours)	4.03(2.2)	4.3(2)	2.89(1)	5.9(3)
Vigorous physical activity(hours)	1.64(0)	4.37(0)	1(0)	1(0)

*p<0.05, **p<0.01, ***p<0.001, data are presented as n (%) or mean (median)

***Table 3**: The number and percentages of Veterans and Non – Veterans using MC for the different conditions.*

	Males(N=103)		Females(N=39)	
	Veterans(N=75)	Non-Veterans(N=22)	Veterans(N=15)	Non-Veterans(N=24)
Chronic pain	44(58.6%)	12(55%)	12(80%)	17(71%)
Headaches/Migraines	14(18.7%)	3(14%)	6(40%)	5(21%)
Acute pain	29(38.7%)	6(27%)	6(40%)	6(25%)
Sleeping problems	60(80%)	10(45%)	12(80%)	12(50%)
Muscle spasm	14(19%)	6(27%)	6(40%)	6(25%)
PTSD	**37(49%)****	**1(5%)****	**9(60%)****	**3(13%)****
Depression	**38(50%) ****	**3(14%) ****	9(60%)	6(25%)
Anxiety	**54(72%) *****	**4(18%) *****	12(80%)	10(42%)
Arthritis	37(49%)	6(27%)	**9(60%) *****	**3(12%) *****

*p<0.05, **p<0.01, ***p<0.001, data are presented as n (%) or mean (median)

Table 4: *The mean scores of perceived effectiveness of different conditions:*

	Males(N=103)		Females(N=39)	
	Veterans(N=75)	Non-Veterans(N=22)	Female Veterans(N=15)	Female non-Veterans(N=24)
Headaches/Migraines	7.5	7	6.5	7.4
Arthritis	7.3	7.8	7.5	7.7
Chronic Pain	7.7	8.1	6.7	7.5
Acute pain	8	8.5	6.5	6.8
Depression	8.1	7.3	7.8	8
Anxiety	8.1	9	7.8	7.7
Sleeping problems	8.2	7.7	8.7	7.7
PTSD	8.3	8.5	8.4	8

*p<0.05, **p<0.01, ***p<0.001, data are presented as n (%) or mean (median)

Table 5: *Cannabis use patterns:*

	Males(N=103)		Females(N=39)	
	Veterans(N=75)	Non-Veterans(N=22)	Female Veterans(N=15)	Female non-Veterans(N=24)
Average mg/day THC	19.5(10)	20.4(11.5)	14.7(5)	10(3)
Average g/day Herbal	3.5(3)	1.7(2)	2.6(2.25)	1.2(1.5)
Average mg/day: CBD	49.2(10)	53.2(30)	48.2(10)	14.8(6.5)
Frequency: More than once daily	45(44%)	15(68%)	5(33%)	12(50%)
Frequency: Daily or almost daily	21(20%)	5(23%)	4(27%)	7(29%)
Duration:1-2 years or less	31(30%)	11(50%)	7(47%)	12(50%)
Duration: More than 2 years	37(36%)	9(41%)	7(47%)	10(42%)
Mode of administration: Oil	36(48%)	16(73%)	7(47%)	16(66%)

Mode of administration: Edible:	**49(65%) *****	**2(9%) *****	**10(67%) ****	**6(25%) ****
Mode of administration: Tincture	6(8%)	1(5%)	0	1(4%)
Mode of administration: Smoked	24(32%)	2(9%)	2(13%)	3(12%)
Mode of administration: Vaporized	35(47%)	7(32%)	4(27%)	4(17%)
Mode of administration: Topical	9(12%)	2(9%)	2(13%)	1(4%)
Preferred strain: Indica	28(37%)	4(18%)	6(40%)	3(12%)
Preferred strain: Sativa	22(29%)	1(5%)	4(27%)	2(8%)

N of different conditions:

1	2	4	1	3
2	6	2	0	7
3	10	5	2	3
4	11	3	2	3
5 and more	**39*****	**4*****	10	6

*p<0.05, **p<0.01, ***p<0.001, THC, tetrahydrocannabinol; CBD, cannabidiol, data are presented as n (%) or mean (median)

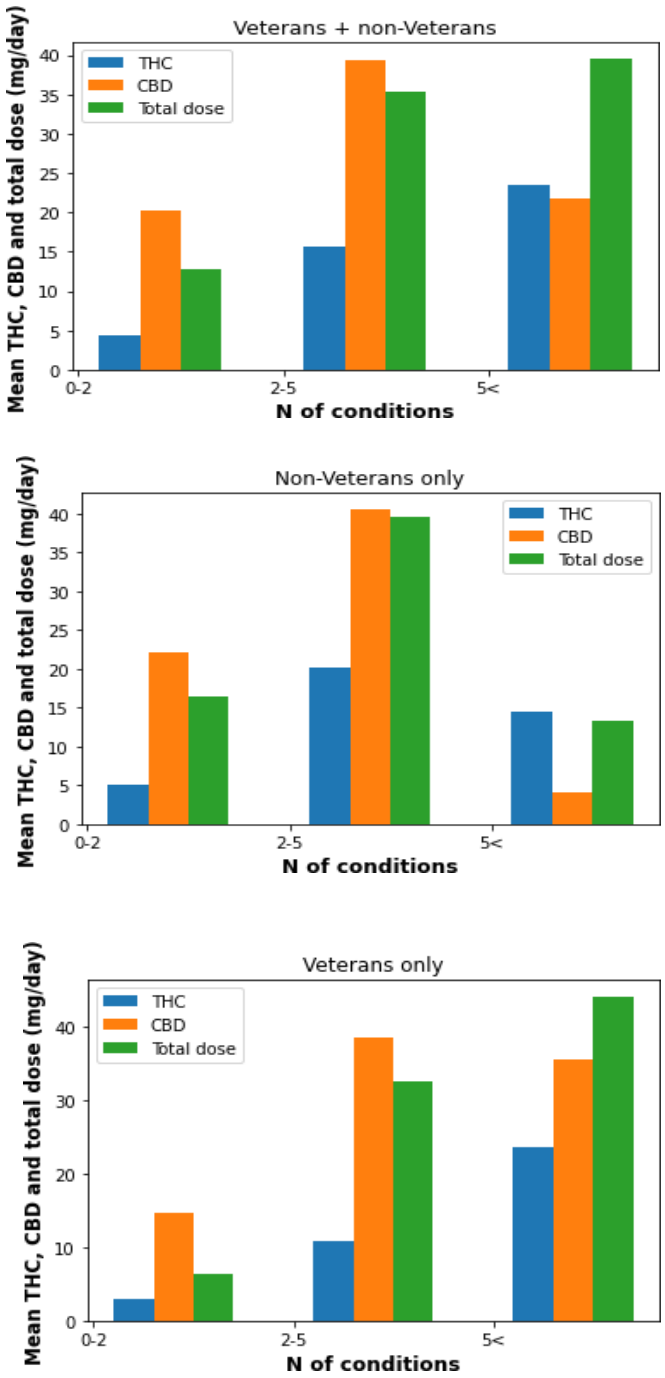

Figure 1: The association between number of conditions that MC is used for, and CBD, THC and total doses.

Appendix 1 *(The survey questions):*

1. During the past month have you used cannabis for medical reasons (to treat disease or improve symptoms)?

- Yes
- No, but I am thinking about using Cannabis for medical reasons in the next month
- No
- No answer

2. I currently use MC for the following conditions:

- Epilepsy
- Multiple sclerosis, amyotrophic lateral sclerosis, spinal cord injury
- Arthritis
- Dystonia
- Huntington's disease
- Parkinson's disease
- Tourette's syndrome
- Glaucoma
- Anxiety or stress
- Depression
- PTSD
- Schizophrenia/psychosis
- Alzheimer's disease/dementia
- Skin diseases
- Irritable bowel syndrome
- Inflammatory bowel diseases (e.g., Crohn's, colitis)
- Liver disease
- Obesity/diabetes
- Cancer
- Prefer not to say
- Other

3. For which of the following symptoms do you use cannabis for medical purposes?

- Acute pain (severe or sudden pain that resolves within a certain amount of time)
- Chronic non-cancer pain (persistent pain, lasting for months or even longer)

- Cancer pain
- Nausea/vomiting
- Wasting/weight loss and/or lack of appetite (e.g., from AIDS or cancer)

- Headaches/migraines
- Muscle spasms
- Seizures
- Problems sleeping
- Alcohol withdrawal symptoms
- Opioid withdrawal symptoms
- Palliative care
- Prefer not to say
- Other

4. How much does cannabis help you with your disease/symptoms?['Condition']

- From 1(not at all) to 10(Very much)

5. Daily amount used currently (choose what applies):[Herbal cannabis, THC g/day, CBD g/day]

Open answer:

6. Frequency of use:

- More than once daily
- Daily or almost daily
- 3-4 days per week
- 1-2 days / week
- 2-3 days / month
- 1 day per month
- Less than 1 day per month
- No answer

7. Mode of administration:

- Edible
- Oil
- Tincture
- Smoked
- Vaporized
- Topical
- Other

8. What is the THC /CBD product name?

Open answer

9. How long have you used MC?

- < 1 year (91)
- 1 - 2 years (92)
- 3 - 4 years (93)
- 5 - 10 years (94)
- 10 years (95)
- No answer

10. What is your preferred strength of THC / CBD?

Open answer

11. What is your preferred strain?

- Indica (111)
- Sativa (112)
- Hybrid (113)
- No preference (114)
- No answer

12. How concerned are you about the safety and side effects of MC use?

- Very much concerned (141)
- Slightly concerned (142)
- Neither concerned nor unconcerned (143)
- Slightly not concerned (144)
- Very much unconcerned (145)
- No answer

13. Did you think your use of cannabis was out of control?

- Never / Almost never (000)
- Sometimes (001)
- Often (002)
- Always / Nearly always (003)
- No answer

14. Did the prospect of missing a dose of cannabis makes you anxious or worried?

- Never / Almost never (000)
- Sometimes (001)
- Often (002)
- Always / Nearly always (003)
- No answer

15. Did you worry about your use of cannabis?

- Never / Almost never (000)
- Sometimes (001)
- Often (002)
- Always / Nearly always (003)
- No answer

16. Did you wish you could stop the use of cannabis?

- Never / Almost never (000)
- Sometimes (001)
- Often (002)
- Always / Nearly always (003)
- No answer

17. How difficult did you find it to stop, or go without cannabis?

- Not difficult
- Quite difficult
- Very difficult
- Impossible
- No answer

18. During the past 30 days, how often did you smoke cigarettes?

- Daily
- Less than daily, but at least once a week
- Less than once a week, but at least once in the past month
- Not at all
- No answer

19. If you smoke daily, on average how many cigarettes do you smoke each day?

Open answer

20. During the past 30 days, how often did you smoke tobacco in other forms (pipe, cigar, etc.)?

- Daily
- Less than daily, but at least once a week
- Less than once a week, but at least once in the past month
- Not at all

21. If you smoke tobacco in other forms daily, on average how many times per day do you smoke?

Open answer

22. How often do you have a drink containing alcohol?

- Never
- Monthly or less
- 2 to 4 times a month
- 2 - 3 times a week
- 4 - 6 times a week
- Everyday
- No answer

23. How many drinks containing alcohol do you have on a typical day when you are drinking?

- 1-2 (261)
- 3-4 (262)
- 5-6 (263)
- 7-9 (264)
- 10 or more (265)
- No answer

24. How would you currently rate your general health?

- Excellent (271)
- Very good (272)
- Good (273)
- Fair (274)
- Poor (275)
- No answer

25. Have you ever been treated for a substance abuse problem?

- Answer
- Yes (1)
- No (0)
- Unknown / Prefer not to answer (3)
- No answer

26. If you have been treated for a substance abuse problem, please describe.

Open answer

27. Over the past 2 weeks, how often have you been bothered by any of the following problems?

- Answer
- Not at all (301)
- Several days (302)
- More than half the days (303)
- Nearly every day (304)
- No answer

28. Over the past 2 weeks, how often have you been bothered by any of the following problems? (feeling down, feeling nervous, depressed, hopeless, anxious or on a edge)

- Answer
- Not at all (301)
- Several days (302)
- More than half the days (303)
- Nearly every day (304)
- No answer

29. Do you have pain that is always present?

- Yes
- No
- No answer

30. Do you have periods of pain that reoccur from time to time?

- Yes
- No
- No answer

31. How often does this pain limit your daily activities?

- Answer
- Never (11)
- Rarely (12)
- Sometimes (13)
- Often (14)
- Always (15)
- No answer

32. When you are experiencing this pain, how much difficulty do you have with your daily activities?

- Answer
- No difficulty (21)
- Some difficulty (22)
- A lot of difficulty (23)
- You cannot do most activities (24)
- No answer

33. How often do you use massage therapy (self-massage or provided by partner) to reduce your symptoms?

- Answer
- More than once a day (421)
- Every day (422)
- 5-7 days per week (423)
- 3-4 days per week (424)

- 1-2 days per week (425)
- Less than once per week (426)
- Occasionally (427)
- Rarely (428)
- Never (429)
- No answer

34. How often does the massage therapy improve your symptoms?

- Answer
- All the time (431)
- Some of the time (432)
- Rarely (433)
- Never (434)
- No answer

35. During the past 7 days, how much total time did you spend walking (at least 10 minutes at a time)?

Open answer

36. During the past 7 days, how much total time did you spend walking (at least 10 minutes at a time)?

Open answer

37. Not counting any time you answered for walking in the previous question, how much total time did you spend doing moderate physical activity (at least 10 minutes at a time)? Examples of moderate physical activity include carrying light loads, bicycling or swimming at a regular pace, doubles tennis, raking or picking up leaves, or sweeping floors.

Open answer

38. During the past 7 days, how much total time did you spend doing vigorous physical activity (at least 10 minutes at a time)? Examples of vigorous physical activity include aerobics, fast bicycling or swimming, jogging, playing soccer, heavy lifting, or digging. If you do no vigorous activity enter '0'.

Open answer

39. Rate how confident you are that you could perform the following activities. [I can walk briskly for 20 minutes without stopping.] [I can run or jog for 10 minutes without stopping.] [I can climb 3 flights of stairs without stopping.] [I can exercise for 20 minutes ata level hard enough to cause a large increase in heart rate and breathing.]

- Answer
- Not at all Confident (391)
- Slightly Confident (392)
- Moderately Confident (393)
- Very Confident (394)
- Extremely Confident (395)
- No answer

40. If we offered you a free web-based program to help you, your family, and friends improve their healthy lifestyle habits would you sign up?

- Answer
- Yes (1)
- No (0)
- Don't know (3)
- No answer

41. In your own words, what features would you like to see on the website?

Open answer

42. How important do you think each of the following factors are in determining whether you would take part in an on-line program specifically designed to help women and men improve their healthy lifestyle habits? [Knowing the on-line program was developed by experts in the field], [The on-line program was recommended by another veteran] [The program sends out e-mail reminders to re-visit the website] [The program sends out weekly tips to keep me motivated by e-mail] [The on-line program provides interactive

features (e.g., taking quizzes and playing games)] [Being able to see my progress in reaching goals] [A family member or friends can sign up too] [The on-line program includes a feature to set personal goals] [The on-line program includes an on-line community for feedback and support] [The on-line program gives rewards (e.g., medallions or stars) when goals are achieved]

- Answer
- Not at all important (411)
- Slightly Important (412)
- Moderately Important (413)
- Very Important (414)
- Extremely Important (415)
- No answer

43. How old are you?

Open answer

44. What sex were you assigned at birth, meaning on your original birth certificate?

- Male
- Female
- No answer

45. What gender do you currently identify with?

- Man
- Woman
- Other gender identity
- No answer

46. What is your current weight? [kg] [lbs]

Open answer

47. How tall are you? [feets][inches][cm]

Open answer

48. I am a

- Veteran
- Family member of Veteran
- Caregiver for a veteran
- Other
- No answer

49. Were you born in Canada?

- Yes (1)
- No (0)
- No answer

50. In what region were you born?

Open answer

51. How many years have you lived in Canada?

Open answer

52. Which group best represents your ethnic origin?

- Aboriginal (e.g., First Nations, Inuit, Métis) (531)
- Arab (532)
- Black (533)
- Chinese (534)
- Filipino (535)
- Japanese (536)
- Korean (537)
- Latin American (538)

- South Asian (e.g. Indian, Pakistani, Bangladeshi, Sri Lankan) (539)
- Southeast Asian (e.g. Cambodian, Indonesian, Laotian, Vietnamese) (540)
- West Asian (e.g. Afghan, Iranian) (541)
- Caucaisian / White (542)
- Other
- No answer

53. I am

- Employed (541)
- Retired (542)
- Unemployed (543)
- Student (544)
- Other
- No answer

54. Which of the following best describes the area where you live?

- Urban (551)
- Suburban (552)
- Rural (553)
- No answer

55. Marital Status – Which of the following best describes you now?

- Single (561)
- Divorced / Separated (562)
- Married / Co-habitating (563)
- Widowed (564)
- No answer

57. Do you have dependents living at home (children or older relatives that you care for)?

- Yes (1)
- No (0)

- No answer

58. What is the highest level of education that you completed?

- Less than high school (581)
- Completed some high school (582)
- High school graduate or equivalent (583)
- Technical college, community college or CEGEP (584)
- Completed some university, but no degree (585)
- University graduate (586)
- Completed some post-graduate but no degree (587)
- Completed post-graduate school (e.g., MSc., M.D., PhD) (588)
- No answer

Chapter 3:

3.1 Discussion of all findings:

According to chapter 2, MC is used to treat various medical disorders, including chronic pain and mental health issues. However, the effectiveness of MC for these conditions remains questionable. Rapidly increasing cannabis use for medical purposes suggests there is a significant unmet need among Canadian Veterans. Numerous individuals continue to experience severe symptoms despite treatment, highlighting the need for further options.

In recent years, interest in lifestyle medicine has increased. It has been determined that lifestyle factors, particularly physical activity and diet, have a good effect on the mental and physical health of older adults [13]. Increased physical activity has been linked to decreased mortality and hospitalisation among individuals aged 70 and older [16]. Healthy behaviours are advised for the management and prevention of a wide range of diseases, including hypertension [82], chronic musculoskeletal pain [83], and depression [84]. Life expectancy is closely correlated with the development of many diseases, and a substantial amount of analyses and studies have led to a consensus that lifestyle interventions can prevent many illnesses.

Lifestyle strategies are more supported by evidence than MC for the management of chronic diseases associated with mental health issues and can effectively replace the use of MC. There is a current push for pain treatment to move away from reliance on medications, unsuccessful procedures, and surgeries, toward comprehensive pain management that involves nonpharmacological solutions.

Specific lifestyle strategies that might reduce MC use or provide an alternative to MC include regular exercise, relaxation techniques, strategies for improving sleep quality, healthy eating.

However, the critical obstacle is engaging individuals to change their lifestyle patterns through education, tracking, and feedback. Reaching individuals who live in small towns or rural areas is an additional challenge. Online digital health promotion is one possible solution in this case. In the previous chapters of this thesis, a literature review revealed that RCTs have demonstrated that digital health interventions promoting healthy lifestyle behaviours, such as regular exercise, mindfulness, CBT, can effectively alleviate chronic pain symptoms.

Median global internet and smartphone use in 2015 was 67% and 43%, respectively, indicating that digital health interventions are becoming increasingly accessible [85]. Smartphone usage is slightly greater among people with mental health issues than the general population, suggesting that having a mental health disorder does not prevent people from getting involved in technology [86]. Earlier versions of the OHPP (online health promotion programs) have been shown in the literature to be effective at encouraging participants to enhance their healthy lifestyle habits (exercise, stress management, healthy eating, etc.) and resulting in measurable health benefits for up to 2 years (decreased stress, fatigue, insomnia, etc.) [87]. These programs could modify lifestyle behaviours if it can be demonstrated that they are engaging and successful at long-term behaviour change [88]. However, there are lots of challenges around digital health interventions. One of them is the significantly prevalent dropout rates [88, 93]. It is particularly true for open-access users that are less likely to adhere to the whole treatment regimen than trial participants [94]. Following the release of the COVID Coach app (which provides 30 different health interventions), the Department of Veterans Affairs of the United States issued research highlighting the difficulties associated with digital solutions [89]. While 49,297 people downloaded the app in the first four months, 49% used it only once, and less than 2% used it for 15 days or longer.

Studies on the usefulness of the DHI (Digital Health Intervention) are not always favorable, with numerous research indicating little benefits [90]. Participants' inconsistent use of DHIs, contributes to the insufficient effectiveness [91]. A systematic review of DHI use among health care professionals reported a number of common themes, such as a high degree of acceptance and a low degree of usage [92].

Parish et al. (2014) built a social media website for Veterans and discovered that Veterans with PTSD engaged with the DHI significantly less (assessed by the frequency of logins) than Veterans without PTSD [95]. Throughout this qualitative study, some Veterans claimed that the online interactions provoked their PTSD symptoms, prompting them to stop using the platform [95]. The authors hypothesised that trauma avoidance, as well as the related cognitive difficulties (concentration, memory), and concomitant disorders (substance misuse, depression), may have decreased the likelihood of participation [95]. Therefore, analyzing and comprehending engagement has been recognized as a crucial factor for enhancing the impact of DHIs [91]. However, it is challenging to identify dose-response associations (i.e., effective engagement) and to compare these interactions across DHIs due to the lack of continuity [96]. The lack of a unified definition and comprehension of user engagement and its assessment remains a significant obstacle [96]. It may be due to the complexity of DHI design, which entails input from multiple disciplines, particularly clinical mental health knowledge and experience, computer user interface, and software engineering [96].

Why is engagement so crucial? The engagement has a significant influence on the efficacy of digital health intervention programs, according to many studies. For example, Funk et al. (2010) found that consistently active users had a lower rate of weight regain (P=0.003) than less active users [102]. Numerous factors, such as demographics, emotional status, social aspects, and

technology friendliness, have been demonstrated to influence engagement [97]. According to several studies, the use of a DHI is correlated with older age [97] and with more severe initial symptoms [98]. There is also some indication that being a woman with a higher level of education is associated with effective engagement [99]. In contrast, several researches have linked higher levels of education with lower engagement rates [100]. Furthermore, a subsequent study revealed no correlations between demographic variables and engagement [101]. These diverse findings one more time prove the complexity of the solution to the engagement problem.

Since the lack of user engagement is one of the leading causes of attrition, if a program can be shown to be engaging, it will be effective at long-term behaviour management. There is an urgent need to design an online intervention program for Veterans with chronic pain that can handle the limitations of digital health interventions, such as early dropouts and engagement problems.

When designing online interventions or mobile applications, it is very important to include healthcare professionals in the process and to base all information on scientific evidence [104]. Pain applications are usually created in industry rather than academia [105]. This might be due to the fact that the pace in academia is slow [105]. In contrast, digital solutions created outside academia typically feature user-friendliness, flexibility, and quick implementation (end user) routes [106]. Those mobile apps that appear to be able to integrate user friendliness and adaptability with robust evidence, promise to have great potential for increasing the effectiveness of interventions [106].

Overall, it is crucial that new approaches reflect current best practice recommendations for interdisciplinary, patient-centered pain management [107]. Process assessments of interventions

should be designed beforehand in order to determine which intervention components are beneficial for which users and in which situation [108].

The survey outlined in chapter 2 included questions about the perspectives of participants regarding their participation in web-based programs that promote healthy lifestyle habits. Sixty one (42%) respondents stated that they would sign up if they were offered a free web-based program to help them and their family to improve their healthy lifestyle habits. The survey contained the questions such as "In your own words, what features would you like to see on the website?". According to the comments, both Veterans and non-Veterans are interested in participating in such programs given that it is easy to navigate to different parts of the program and if the online program includes a feature to set personal goals. Respondents also indicated that it was important for them to know that the online program was developed by experts in the field, highlighting once again the significance of designing such programs with the assistance of healthcare professionals.

3.2 Future steps:

There is a dire need to develop innovative, engaging, and effective strategy to improve lifestyle habits for Veterans with chronic pain. Particular emphasis should be placed on the recruitment of female Veterans. In every racial/ethnic group, women are tended to report more variety of chronic pain issues in comparison with men. [109,110]. Misdiagnoses, delays in correct diagnoses, incorrect and unequal treatment, gender discrimination, neglect and stigma, discrimination, and exclusion from the healthcare system contribute to inequities in pain care for women. [111]. Women experience pain with greater intensity, duration, and frequency than men [112]. More opioids and benzodiazepines are prescribed to women than men. [112,113] Although men are more

likely to die from prescribed opioid analgesics than women, women have had a fivefold larger rise in mortality since 1999 [114].

3.3 Conclusion:

Chronic pain is a prevalent global issue that is especially challenging for the Veteran community. It is a frequent problem among Canadians that cannot be adequately treated with the medications and health services currently available. The efficacy of MC in the treatment of chronic pain and comorbid mental health problems is still uncertain and inconsistent. In this instance, nonpharmacological techniques, such as behavioural therapy for chronic pain treatment, acquires importance and popularity. However, face-to-face delivery of such interventions has its barriers, such as reaching individuals living in small towns or rural areas. There is a need to develop evidence-based online pain management programs for individuals with chronic pain. If such programs can be shown to be effective, it will be a significant step forward in addressing unmet medical needs. Any scalable and effective intervention to reduce chronic pain among Canadian Veterans will have a substantial impact on productivity and health care cost. More research should be conducted on the needs assessment of Veterans to determine the features of such web-based programs in order to make them more engaging and effective.

3.4 References:

1. Lipman, A., Webster, L. (2015). The economic impact of opioid use in the management of chronic nonmalignant pain. Journal of Managed Care & Specialty Pharmacy, 21(10), 891–899.

2. Baldridge, S., Wallace, L., Kadakia, A. (2018). The epidemiology of outpatient pain treatment in pediatrics. Journal of Pain Research, 11, 913–921.

3. Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. J Pain. 2015 Aug;16(8):769-80. doi: 10.1016/j.jpain.2015.05.002.

4. van Hecke, O., Torrance, N., Smith, B. H. (2013). Chronic pain epidemiology and its clinical relevance. BJA: British Journal of Anaesthesia, 111(1), 13–18.

5. Gaskin DJ, Richard P. The Economic Costs of Pain in the United States. In: Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington (DC): National Academies Press (US); 2011. Appendix C. Available from: https://www.ncbi.nlm.nih.gov/books/NBK92521/

6. de Siqueira, S. (2018). Existential meaning of patients with chronic facial pain. Journal of Religion and Health.

7. Dezutter, J., Offenbaecher, M., Vallejo, M. A., Vanhooren, S., Thauvoye, E., Toussaint, L. (2016). Chronic pain care. International Journal of Psychiatry in Medicine, 51(6), 563–575.

8. VanDenKerkhof EG, VanTil L, Thompson JM, Sweet J, Hopman WM, Carley ME, Sudom K. Pain in Canadian Veterans: analysis of data from the Survey on Transition to Civilian Life. Pain Res Manag. 2015 Mar-Apr;20(2):89-95. doi: 10.1155/2015/763768

9. Cheung CW, Choi SW, Wong SSC, Lee Y, Irwin MG. Changes in Prevalence, Outcomes, and Help-seeking Behavior of Chronic Pain in an Aging Population Over the Last Decade. Pain Pract. 2017 Jun;17(5):643-654. doi: 10.1111/papr.12496

10. Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, DeBar L, Kerns R, Von Korff M, Porter L, Helmick C. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016. MMWR Morb Mortal Wkly Rep. 2018 Sep 14;67(36):1001-1006. doi: 10.15585/mmwr.mm6736a2.

11. Knutson KL, Phelan J, Paskow MJ, Roach A, Whiton K, Langer G, Hillygus DS, Mokrzycki M, Broughton WA, Chokroverty S, Lichstein KL, Weaver TE, Hirshkowitz M. The National Sleep Foundation's Sleep Health Index. Sleep Health. 2017 Aug;3(4):234-240. doi: 10.1016/j.sleh.2017.05.011.

12. Sheng J, Liu S, Wang Y, Cui R, Zhang X. The Link between Depression and Chronic Pain: Neural Mechanisms in the Brain. Neural Plast. 2017;2017:9724371. doi: 10.1155/2017/9724371

13. Woo J, Ho SC, Yu AL. Lifestyle factors and health outcomes in elderly Hong Kong chinese aged 70 years and over. Gerontology. 2002 Jul-Aug;48(4):234-40. doi: 10.1159/000058356.

14. de Heer EW, Gerrits MM, Beekman AT, Dekker J, van Marwijk HW, de Waal MW, Spinhoven P, Penninx BW, van der Feltz-Cornelis CM. The association of depression and anxiety

with pain: a study from NESDA. PLoS One. 2014 Oct 15;9(10):e106907. doi: 10.1371/journal.pone.0106907.

15. Hooten WM. Chronic Pain and Mental Health Disorders: Shared Neural Mechanisms, Epidemiology, and Treatment. Mayo Clin Proc. 2016 Jul;91(7):955-70. doi: 10.1016/j.mayocp.2016.04.029. Epub 2016 Jun 22. PMID: 27344405.

16. Taylor DPhysical activity is medicine for older adults. Postgraduate Medical Journal 2014;90:26-32.

17. Center for Disease Control and Prevention(2020, January 8). America's drug Overdose Epidemic: Data to Action. Available from: https://www.cdc.gov/injury/features/prescription-drug-overdose/index.html

18. Kolodny A. How FDA Failures Contributed to the Opioid Crisis. AMA J Ethics. 2020 Aug 1;22(1):E743-750. doi: 10.1001/amajethics.2020.743.

19. Shah A, Craner J, Cunningham JL. Medical cannabis use among patients with chronic pain in an interdisciplinary pain rehabilitation program: Characterization and treatment outcomes. J Subst Abuse Treat. 2017 Jun;77:95-100. doi: 10.1016/j.jsat.2017.03.012. Epub 2017 Apr 6. PMID: 28476279.

20. National Institute on Drug Abuse. (2018, May 31). Available from: https://nida.nih.gov/research-topics/marijuana/nih-research-cannabis-cannabinoids

21. Boehnke KF, Litinas E, Clauw DJ. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. J Pain. 2016 Jun;17(6):739-44. doi: 10.1016/j.jpain.2016.03.002.

22. Cabral GA, Rogers TJ, Lichtman AH. Turning Over a New Leaf: Cannabinoid and Endocannabinoid Modulation of Immune Function. J Neuroimmune Pharmacol. 2015 Jun;10(2):193-203. doi: 10.1007/s11481-015-9615-z.

23. Guindon J, Hohmann AG. The endocannabinoid system and pain. CNS Neurol Disord Drug Targets. 2009 Dec;8(6):403-21. doi: 10.2174/187152709789824660.

24. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017 Sep 16;390(10100):1211-1259. doi: 10.1016/S0140-6736(17)32154-2.

25. Hadi MA, McHugh GA, Closs SJ. Impact of chronic pain on patients' quality of life: A comparative mixed-methods study. J Patient Exp. 2018;4:1, 149-161. doi:10.1177/ 2374373518786013.

26. Van Til L, Sweet J, Thompson JM, Poireier A, McKinnon K, Sudom K, Dursun S, Pedlar D. Wellbeing of Canadian regular force veterans. Findings from the LASS 2016 survey. https://cimvhr.ca/vacreports/data/reports/VanTil%202017_Well-Being% 20of%20CAF%20Veterans%20LASS%202016.pdf

27. Schopflocher D, Taenzer P, Jovey R. The prevalence of chronic pain in Canada. Pain Res Manag. 2011;16 (6):445–50. doi:10.1155/2011/876306.

28. U.S. Department of Veteran Affairs 2018. Available from: https://www.research.va.gov/topics/pain.cfm

29. Vandenkerkhof EG, Vantil L, Thompson JM, Sweet J, Hopman WM, Carley ME, Sudom K. Pain in Canadian veterans: analysis of data from the survey on transition to civilian life. Pain Res Manag. 2015;20(2):89–95. doi:10.1155/2015/763768.

30. Nahin RL. Severe pain in veterans: the effect of age and sex, and comparisons with the general population. J Pain. 2017;18(3):247–54. doi:10.1016/j.jpain.2016.10.021.

31. Veteran Affairs Canada. Available from: https://www.veterans.gc.ca/eng/about-vac/research/research-directorate/info-briefs/chronic-pain

32. Desai G, T S J, G SK, L M, G R G, Bajaj A, K T, Chaturvedi SK. Disentangling comorbidity in chronic pain: A study in primary health care settings from India. PLoS One. 2020 Nov 30;15(11):e0242865. doi: 10.1371/journal.pone.0242865.

33. Simons LE, Elman I, Borsook D. Psychological processing in chronic pain: a neural systems approach. Neurosci Biobehav Rev. 2014 Feb;39:61-78. doi: 10.1016/j.neubiorev.2013.12.006.

34. Currie SR, Wang J. More data on major depression as an antecedent risk factor for first onset of chronic back pain. Psychol Med. 2005 Sep;35(9):1275-82. doi: 10.1017/S0033291705004952.

35. Pavlova M, Kopala-Sibley DC, Nania C, Mychasiuk R, Christensen J, McPeak A, Tomfohr-Madsen L, Katz J, Palermo TM, Noel M. Sleep disturbance underlies the co-occurrence of trauma and pediatric chronic pain: a longitudinal examination. Pain. 2020 Apr;161(4):821-830. doi: 10.1097/j.pain.0000000000001769.

36. Li JX. Pain and depression comorbidity: a preclinical perspective. Behav Brain Res. 2015 Jan 1;276:92-8. doi: 10.1016/j.bbr.2014.04.042.

37. Barke A, Preis MA, Schmidt-Samoa C, Baudewig J, Kröner-Herwig B, Dechent P. Neural Correlates Differ in High and Low Fear-Avoidant Chronic Low Back Pain Patients When Imagining Back-Straining Movements. J Pain. 2016 Aug;17(8):930-43. doi: 10.1016/j.jpain.2016.05.005.

38. Knutson KL, Phelan J, Paskow MJ, Roach A, Whiton K, Langer G, Hillygus DS, Mokrzycki M, Broughton WA, Chokroverty S, Lichstein KL, Weaver TE, Hirshkowitz M. The National Sleep Foundation's Sleep Health Index. Sleep Health. 2017 Aug;3(4):234-240. doi: 10.1016/j.sleh.2017.05.011.

39. Olson K. Pain and Sleep: Understanding the Interrelationship. Pract Pain Manag. 2014;14(9). https://www.practicalpainmanagement.com/treatments/pharmacological/treating-pain-patients-chronic-kidney-disease-review-literature

40. Gasperi M, Afari N, Goldberg J, Suri P, Panizzon MS. Pain and Trauma: The Role of Criterion A Trauma and Stressful Life Events in the Pain and PTSD Relationship. J Pain. 2021 Nov;22(11):1506-1517. doi: 10.1016/j.jpain.2021.04.015.

41. Williamson JB, Porges EC, Lamb DG, Porges SW. Maladaptive autonomic regulation in PTSD accelerates physiological aging. Front Psychol. 2015 Jan 21;5:1571. doi: 10.3389/fpsyg.2014.01571.

42. Labianca R, Sarzi-Puttini P, Zuccaro SM, Cherubino P, Vellucci R, Fornasari D. Adverse effects associated with non-opioid and opioid treatment in patients with chronic pain. Clin Drug Investig. 2012 Feb 22;32 Suppl 1:53-63. doi: 10.2165/11630080-000000000-00000

43. Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: controversies, current status, and future directions. Exp Clin Psychopharmacol. 2008 Oct;16(5):405-16. doi: 10.1037/a0013628.

44. Ali A, Arif AW, Bhan C, Kumar D, Malik MB, Sayyed Z, Akhtar KH, Ahmad MQ. Managing Chronic Pain in the Elderly: An Overview of the Recent Therapeutic Advancements. Cureus. 2018 Sep 13;10(9):e3293. doi: 10.7759/cureus.3293.

45. Macintyre PE, Roberts LJ, Huxtable CA. Management of Opioid-Tolerant Patients with Acute Pain: Approaching the Challenges. Drugs. 2020 Jan;80(1):9-21. doi: 10.1007/s40265-019-01236-4.

46. Morcillo-Muñoz Y, Castellano MHJ, Exposito FJD, Sanchez-Guarnido AJ, Alcantara MG, Baena-Parejo MI. Multimodal Interventions to Improve the Management of Chronic Non-Malignant Pain in Primary Care Using Participatory Research. Clin Pract. 2021 Aug 26;11(3):561-581. doi: 10.3390/clinpract11030072.

47. Hurley M, Dickson K, Hallett R, Grant R, Hauari H, Walsh N, Stansfield C, Oliver S. Exercise interventions and patient beliefs for people with hip, knee or hip and knee osteoarthritis: a mixed methods review. Cochrane Database Syst Rev. 2018 Apr 17;4(4):CD010842. doi: 10.1002/14651858.CD010842.pub2.

48. Gaudiano BA. Cognitive-behavioural therapies: achievements and challenges. Evid Based Ment Health. 2008 Feb;11(1):5-7. doi: 10.1136/ebmh.11.1.5.

49. Majeed MH, Ali AA, Sudak DM. Mindfulness-based interventions for chronic pain: Evidence and applications. Asian J Psychiatr. 2018 Feb;32:79-83. doi: 10.1016/j.ajp.2017.11.025.

50. Department of Veterans Affairs, Department of Defense. Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain. Washington, DC: Department of Veterans Affairs and Department of Defense; 2003. Available at: https://www.va.gov/painmanagement/docs/chronicpainguidelinesva2003.pdf

51. Joint Commission (TJC). (2012). Safe use of opioids in hospitals. The Joint Commission Sentinel Event Alert. 49.

52. Hogg MN, Gibson S, Helou A, DeGabriele J, Farrell MJ. Waiting in pain: a systematic investigation into the provision of persistent pain services in Australia. Medical Journal of Australia. 2012;196(6):386-90.

53. Keogh E, Rosser BA, Eccleston C. e-Health and chronic pain management: current status and developments. Pain. 2010;151(1):18-21.

54. Dang A, Arora D, Rane P. Role of digital therapeutics and the changing future of healthcare. J Family Med Prim Care. 2020 May 31;9(5):2207-2213. doi: 10.4103/jfmpc.jfmpc_105_20.

55. Andersson G, Bergström J, Buhrman M, Carlbring P, Holländare F, Kaldo V, et al. Development of a New Approach to Guided Self-Help via the Internet: The Swedish

Experience. Journal of technology in human services. 2008;26(2-4):161-81. doi: https://doi.org/10.1080/15228830802094627

56. Hedman E, Ljótsson B, Lindefors N. Cognitive behavior therapy via the Internet: a systematic review of applications, clinical efficacy and cost–effectiveness. Expert Review of Pharmacoeconomics & Outcomes Research. 2012;12(6):745-64. doi: 10.1586/erp.12.67.

57. Hedman E, El Alaoui S, Lindefors N, Andersson E, Rück C, Ghaderi A, et al. Clinical effectiveness and cost-effectiveness of Internet- vs. group-based cognitive behavior therapy for social anxiety disorder: 4-Year follow-up of a randomized trial. Behaviour Research and Therapy. 2014;59:20-9. doi: 10.1016/j.brat.2014.05.010.

58. Ljótsson B, Andersson G, Andersson E, Hedman E, Lindfors P, Andréewitch S, et al. Acceptability, effectiveness, and cost-effectiveness of internet-based exposure treatment for irritable bowel syndrome in a clinical sample: a randomized controlled trial. BMC gastroenterology. 2011;11(1):110. doi: 10.1186/1471-230X-11-110.

59. Hedman E, Carlbring P, Ljótsson B, Andersson G. Internetbaserad psykologisk behandling : evidens, indikation och praktiskt genomförande. Stockholm: Natur & Kultur; 2014.

60. Andersson G, Titov N, Dear BF, Rozental A, Carlbring P. Internet-delivered

psychological treatments: from innovation to implementation. World Psychiatry. 2019;18(1):20-8. doi: 10.1002/wps.20610

61. Buhrman M, Gordh T, Andersson G. Internet interventions for chronic pain

including headache: A systematic review. Internet Interventions. 2016;4(P1):17-34 doi: 10.1016/j.invent.2015.12.001

62. Statcounter. Mobile and tablet internet usage exceeds desktop for first time worldwide 2016. Available from: https://gs.statcounter.com/press/mobile-and-tablet-internet-usage-exceeds-desktop-for-first-time-worldwide

63. Rosser BA, Eccleston C. Smartphone applications for pain management. Journal of Telemedicine and Telecare. 2011;17(6):308-12. doi: 10.1258/jtt.2011.101102.

64. Huber S, Priebe JA, Baumann KM, Plidschun A, Schiessl C, Tölle TR. Treatment of Low Back Pain with a Digital Multidisciplinary Pain Treatment App: Short-Term Results. JMIR Rehabil Assist Technol. 2017 Dec 4;4(2):e11. doi: 10.2196/rehab.9032.

65. Shebib, R., Bailey, J.F., Smittenaar, P. et al. Randomized controlled trial of a 12-week digital care program in improving low back pain. npj Digital Med 2019;2,1. doi:https://doi.org/10.1038/s41746-018-0076-7

66. Chhabra HS, Sharma S, Verma S. Smartphone app in self-management of chronic low back pain: a randomized controlled trial. Eur Spine J. 2018 Nov;27(11):2862-2874. doi: 10.1007/s00586-018-5788-5

67. Browne JD, Vaninetti M, Giard D, Kostas K, Dave A. An Evaluation of a Mobile App for Chronic Low Back Pain Management: Prospective Pilot Study. JMIR Form Res. 2022 Oct 13;6(10):e40869. doi: 10.2196/40869

68. Ruehlman LS, Karoly P, Enders C. A randomized controlled evaluation of an online chronic pain self management program. Pain. 2012 Feb;153(2):319-330. doi: 10.1016/j.pain.2011.10.025.

69. Nelligan RK, Hinman RS, Kasza J, Crofts SJC, Bennell KL. Effects of a Self-directed Web-Based Strengthening Exercise and Physical Activity Program Supported by Automated Text Messages for People With Knee Osteoarthritis: A Randomized Clinical Trial. JAMA Intern Med. 2021 Jun 1;181(6):776-785. doi: 10.1001/jamainternmed.2021.0991

70. Rickardsson J, Gentili C, Holmström L, Zetterqvist V, Andersson E, Persson J, Lekander M, Ljótsson B, Wicksell RK. Internet-delivered acceptance and commitment therapy as microlearning for chronic pain: A randomized controlled trial with 1-year follow-up. Eur J Pain. 2021 May;25(5):1012-1030. doi: 10.1002/ejp.1723.

71. Weise H, Zenner B, Schmiedchen B, Benning L, Bulitta M, Schmitz D, Weise K. The Effect of an App-Based Home Exercise Program on Self-reported Pain Intensity in Unspecific and Degenerative Back Pain: Pragmatic Open-label Randomized Controlled Trial. J Med Internet Res. 2022 Oct 28;24(10):e41899. doi: 10.2196/41899.

72. Pach D, Blödt S, Wang J, Keller T, Bergmann B, Rogge AA, Barth J, Icke K, Roll S, Witt CM. App-Based Relaxation Exercises for Patients With Chronic Neck Pain: Pragmatic Randomized Trial. JMIR Mhealth Uhealth. 2022 Jan 7;10(1):e31482. doi: 10.2196/31482.

73. Rodríguez Sánchez-Laulhé P, Luque-Romero LG, Barrero-García FJ, Biscarri-Carbonero Á, Blanquero J, Suero-Pineda A, Heredia-Rizo AM. An Exercise and Educational and Self-management Program Delivered With a Smartphone App (CareHand) in Adults With Rheumatoid Arthritis of the Hands: Randomized Controlled Trial. JMIR Mhealth Uhealth. 2022 Apr 7;10(4):e35462. doi: 10.2196/35462.

74. Anan T, Kajiki S, Oka H, Fujii T, Kawamata K, Mori K, Matsudaira K. Effects of an Artificial Intelligence-Assisted Health Program on Workers With Neck/Shoulder Pain/Stiffness

and Low Back Pain: Randomized Controlled Trial. JMIR Mhealth Uhealth. 2021 Sep 24;9(9):e27535. doi: 10.2196/27535.

75. Kristjánsdóttir ÓB, Fors EA, Eide E, Finset A, Stensrud TL, van Dulmen S, Wigers SH, Eide H. A smartphone-based intervention with diaries and therapist feedback to reduce catastrophizing and increase functioning in women with chronic widespread pain. part 2: 11-month follow-up results of a randomized trial. J Med Internet Res. 2013 Mar 28;15(3):e72. doi: 10.2196/jmir.2442.

76. Amorim AB, Pappas E, Simic M, Ferreira ML, Jennings M, Tiedemann A, Carvalho-E-Silva AP, Caputo E, Kongsted A, Ferreira PH. Integrating Mobile-health, health coaching, and physical activity to reduce the burden of chronic low back pain trial (IMPACT): a pilot randomised controlled trial. BMC Musculoskelet Disord. 2019 Feb 11;20(1):71. doi: 10.1186/s12891-019-2454-y.

77. Irvine AB, Russell H, Manocchia M, Mino DE, Cox Glassen T, Morgan R, Gau JM, Birney AJ, Ary DV. Mobile-Web app to self-manage low back pain: randomized controlled trial. J Med Internet Res. 2015 Jan 2;17(1):e1. doi: 10.2196/jmir.3130.

78. Toelle TR, Utpadel-Fischler DA, Haas KK, Priebe JA. App-based multidisciplinary back pain treatment versus combined physiotherapy plus online education: a randomized controlled trial. NPJ Digit Med. 2019 May 3;2:34. doi: 10.1038/s41746-019-0109-x.

79. Rini C, Porter LS, Somers TJ, McKee DC, DeVellis RF, Smith M, Winkel G, Ahern DK, Goldman R, Stiller JL, Mariani C, Patterson C, Jordan JM, Caldwell DS, Keefe FJ. Automated Internet-based pain coping skills training to manage osteoarthritis pain: a randomized controlled trial. Pain. 2015 May;156(5):837-848. doi: 10.1097/j.pain.0000000000000121.

80. Abadiyan F, Hadadnezhad M, Khosrokiani Z, Letafatkar A, Akhshik H. Adding a smartphone app to global postural re-education to improve neck pain, posture, quality of life, and endurance in people with nonspecific neck pain: a randomized controlled trial. Trials. 2021 Apr 12;22(1):274. doi: 10.1186/s13063-021-05214-8.

81. Mecklenburg G, Smittenaar P, Erhart-Hledik JC, Perez DA, Hunter S. Effects of a 12-Week Digital Care Program for Chronic Knee Pain on Pain, Mobility, and Surgery Risk: Randomized Controlled Trial. J Med Internet Res. 2018 Apr 25;20(4):e156. doi: 10.2196/jmir.9667.

82. Gee ME, Pickett W, Janssen I, Johnson JA, Campbell NR. Health behaviors for hypertension management in people with and without coexisting diabetes. J Clin Hypertens (Greenwich). 2013 Jun;15(6):389-96. doi: 10.1111/jch.12093.

83. Meade LB, Bearne LM, Sweeney LH, Alageel SH, Godfrey EL. Behaviour change techniques associated with adherence to prescribed exercise in patients with persistent musculoskeletal pain: Systematic review. Br J Health Psychol. 2019 Feb;24(1):10-30. doi: 10.1111/bjhp.12324.

84. Hetrick SE, Cox GR, Witt KG, Bir JJ, Merry SN. Cognitive behavioural therapy (CBT), third-wave CBT and interpersonal therapy (IPT) based interventions for preventing depression in children and adolescents. Cochrane Database Syst Rev. 2016 Aug 9;2016(8):CD003380. doi: 10.1002/14651858.CD003380.pub4.

85. Poushter J. Smartphone ownership and internet usage continues to climb in emerging economies 2016, Available online: http://www.pewglobal.org/2016/02/22/smartphone-ownership-and-internet-usage-continues-to-climb-in-emerging-economies/

86. Torous J, Friedman R, Keshavan M. Smartphone ownership and interest in mobile applications to monitor symptoms of mental health conditions. JMIR Mhealth Uhealth. 2014 Jan 21;2(1):e2. doi: 10.2196/mhealth.2994.

87. Lowensteyn I, et al. The Sustainability of a Workplace Am J Health Promot. 2019;33(6):850-858. doi: 10.1177/0890117118823165

88. Yang X, Ma L, Zhao X, Kankanhalli A. Factors influencing user's adherence to physical activity applications: A scoping literature review and future directions. Int J Med Inform. 2020 Feb;134:104039. doi: 10.1016/j.ijmedinf.2019.104039.

89. Jaworski BK, Taylor K, Ramsey KM, Heinz A, Steinmetz S, Pagano I, Moraja G, Owen JE. Exploring Usage of COVID Coach, a Public Mental Health App Designed for the COVID-19 Pandemic: Evaluation of Analytics Data. J Med Internet Res. 2021 Mar 1;23(3):e26559. doi: 10.2196/26559

90. Marcolino MS, Oliveira JAQ, D'Agostino M, Ribeiro AL, Alkmim MBM, Novillo-Ortiz D. The Impact of mHealth Interventions: Systematic Review of Systematic Reviews. JMIR Mhealth Uhealth. 2018 Jan 17;6(1):e23. doi: 10.2196/mhealth.8873.

91. Grady A, Yoong S, Sutherland R, Lee H, Nathan N, Wolfenden L. Improving the public health impact of eHealth and mHealth interventions. Aust N Z J Public Health. 2018 Apr;42(2):118-119. doi: 10.1111/1753-6405.12771.

92. White A, Thomas DS, Ezeanochie N, Bull S. Health Worker mHealth Utilization: A Systematic Review. Comput Inform Nurs. 2016 May;34(5):206-13. doi: 10.1097/CIN.0000000000000231.

93. Schubart JR, Stuckey HL, Ganeshamoorthy A, Sciamanna CN. Chronic health conditions and internet behavioral interventions: a review of factors to enhance user engagement. Comput Inform Nurs. 2011 Feb;29(2):81-92. doi: 10.1097/NCN.0b013e3182065eed.

94. Kelders SM, Kok RN, Ossebaard HC, Van Gemert-Pijnen JE. Persuasive system design does matter: a systematic review of adherence to web-based interventions. J Med Internet Res. 2012 Nov 14;14(6):e152. doi: 10.2196/jmir.2104.

95. Parish MB, Apperson M, Yellowlees PM. Engaging U.S. veterans with PTSD in online therapy. Psychiatr Serv. 2014 May 1;65(5):697. doi: 10.1176/appi.ps.650501.

96. Ryan C, Bergin M, Wells JS. Theoretical Perspectives of Adherence to Web-Based Interventions: a Scoping Review. Int J Behav Med. 2018 Feb;25(1):17-29. doi: 10.1007/s12529-017-9678-8.

97. Beatty L, Binnion C. A Systematic Review of Predictors of, and Reasons for, Adherence to Online Psychological Interventions. Int J Behav Med. 2016 Dec;23(6):776-794. doi: 10.1007/s12529-016-9556-9.

98. Fuhr K, Schröder J, Berger T, Moritz S, Meyer B, Lutz W, Hohagen F, Hautzinger M, Klein JP. The association between adherence and outcome in an Internet intervention for depression. J Affect Disord. 2018 Mar 15;229:443-449. doi: 10.1016/j.jad.2017.12.028.

99. Geraghty AW, Torres LD, Leykin Y, Pérez-Stable EJ, Muñoz RF. Understanding attrition from international Internet health interventions: a step towards global eHealth. Health Promot Int. 2013 Sep;28(3):442-52. doi: 10.1093/heapro/das029.

100. Couper MP, Alexander GL, Zhang N, Little RJ, Maddy N, Nowak MA, McClure JB, Calvi JJ, Rolnick SJ, Stopponi MA, Cole Johnson C. Engagement and retention: measuring breadth and depth of participant use of an online intervention. J Med Internet Res. 2010 Nov 18;12(4):e52. doi: 10.2196/jmir.1430.

101. Glasgow RE, Christiansen SM, Kurz D, King DK, Woolley T, Faber AJ, Estabrooks PA, Strycker L, Toobert D, Dickman J. Engagement in a diabetes self-management website: usage patterns and generalizability of program use. J Med Internet Res. 2011 Jan 25;13(1):e9. doi: 10.2196/jmir.1391.

102. Funk KL, Stevens VJ, Appel LJ, Bauck A, Brantley PJ, Champagne CM, Coughlin J, Dalcin AT, Harvey-Berino J, Hollis JF, Jerome GJ, Kennedy BM, Lien LF, Myers VH, Samuel-Hodge C, Svetkey LP, Vollmer WM. Associations of internet website use with weight change in a long-term weight loss maintenance program. J Med Internet Res. 2010 Jul 27;12(3):e29. doi: 10.2196/jmir.1504.

103. Obro LF, Heiselberg K, Krogh PG, Handberg C, Ammentorp J, Pihl GT, Osther PJS. Combining mHealth and health-coaching for improving self-management in chronic care. A scoping review. Patient Educ Couns. 2021 Apr;104(4):680-688. doi: 10.1016/j.pec.2020.10.026.

104. Lalloo AC, Jibb NL, Rivera NJ, Agarwal NA, Stinson NJ. "There's a Pain App for That": Review of Patient-targeted Smartphone Applications for Pain Management. The Clinical Journal of Pain. 2015;31(6):557-63.

105. Wilson K, Bell C, Wilson L, Witteman H. Agile research to complement agile development: a proposal for an mHealth research lifecycle. npj Digital Medicine. 2018;1(1).

106. Donker T, Petrie K, Proudfoot J, Clarke J, Birch M-R, Christensen H. Smartphones for Smarter Delivery of Mental Health Programs: A Systematic Review. Journal of medical Internet research. 2013;15(11):e247.

107. World Health Organization, 2020.

108. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, Moore L, O'Cathain A, Tinati T, Wight D, Baird J. Process evaluation of complex interventions: Medical Research Council guidance. BMJ. 2015 Mar 19;350:h1258. doi: 10.1136/bmj.h1258.

109. Hardt J, Jacobsen C, Goldberg J, Nickel R, Buchwald D. Prevalence of chronic pain in a representative sample in the United States. Pain Med. 2008 Oct;9(7):803-12. doi: 10.1111/j.1526-4637.2008.00425.x.

110. Unruh AM. Gender variations in clinical pain experience. Pain. 1996 May-Jun;65(2-3):123-67. doi: 10.1016/0304-3959(95)00214-6.

111. Campaign to End Chronic Pain in Women. Chronic pain in women: neglect, dismissal and discrimination. 2010. http://www.endwomenspain.org/

112. Campbell CI, Weisner C, Leresche L, Ray GT, Saunders K, Sullivan MD, Banta-Green CJ, Merrill JO, Silverberg MJ, Boudreau D, Satre DD, Von Korff M. Age and gender trends in long-term opioid analgesic use for noncancer pain. Am J Public Health. 2010 Dec;100(12):2541-7. doi: 10.2105/AJPH.2009.180646.

113. Paulozzi LJ, Strickler GK, Kreiner PW, Koris CM; Centers for Disease Control and Prevention (CDC). Controlled Substance Prescribing Patterns--Prescription Behavior Surveillance

System, Eight States, 2013. MMWR Surveill Summ. 2015 Oct 16;64(9):1-14. doi: 10.15585/mmwr.ss6409a1.

114. Centers for Disease Control and Prevention (CDC). Vital signs: overdoses of prescription opioid pain relievers and other drugs among women--United States, 1999-2010. MMWR Morb Mortal Wkly Rep. 2013 Jul 5;62(26):537-42.