MINNESOTA
OFFICE OF CANNABIS MANAGEMENT

Chronic Pain Patients in the Minnesota Medical Cannabis Program

01/31/2025

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Contents

Executive Summary 4
Participation 5
Medical Cannabis Use Patterns 5
Benefits 5
Adverse Side Effects 6
1. Introduction 7
Cannabis and Pain 7
2. Patients Registered Between March 2022 and March 2023 9
Description of Patients Enrolled 9
3. Medical Cannabis Use Patterns 15
Description of Purchased Products 15
4. Benefits 21
Benefit Received from Using Medical Cannabis 21
Standard Eight Symptom Data 21
Symptoms at Enrollment in the Minnesota Medical Cannabis Program 22
Changes in Symptoms 23
PEG Scale Data 29
PEG Scale Scores at Enrollment in the Minnesota Medical Cannabis Program 29
Changes in PEG Scale Scores 30
Change in PEG Composite Score by Cause of Pain 34
Change in Symptoms Among Patients Who Stayed in the Program at Least Eight Months 35
Changes in Prescribed Medication After Medical Cannabis Usage 43
5. Adverse Side Effects 44
Most Commonly Reported Side Effects 45
Adverse Event Reporting to Medical Cannabis Manufacturers 47
Appendix A. Additional Tables 48
References 62

Executive Summary

Pain is a complex experience made up of subjective factors and a common symptom of many conditions. It is known to affect many aspects of an individual's daily life, from emotions, stress, and relationships, to sleep quality, work, and physical abilities. Typically, pain patients are treated with nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids. However, the use of cannabis-based medicines to manage pain has become more popular (Guven Kose et al., 2022).

Pain is one of the most prominent symptoms treated in the Minnesota Medical Cannabis Program. The pain-related medical conditions of patients in the program include chronic pain, intractable pain, cancer with severe pain, terminal illness with severe pain, and sickle cell disease. Patients are asked to rate the severity of their pain when they enroll in the program and are then asked at various points of follow-up throughout their time receiving treatment.

This report draws on data from patient enrollment, medical cannabis purchases, symptom and side-effect ratings at the time of each purchase, and survey results to describe the experiences of patients who qualify for one of the chronic pain-related medical conditions.

There were differences in patient pain reduction between pain-related conditions. Meaningful pain relief within four months was found among 30.5% of intractable pain patients, 32.9% of chronic pain patients, and 28.3% of cancer pain patients. Amongst all pain-related conditions, almost one-third (31.7%) of patients experiencing moderate to severe pain at enrollment saw a meaningful reduction in pain symptoms within four months of treatment. Of those patients experiencing a meaningful reduction in symptoms, 49.7% of them were able to maintain the pain reduction for an additional four months after achieving it (Table 4.1).

These pain reduction numbers are similar to current research on treating pain with cannabis. Though these percentages may seem low, cannabis treatment offers other benefits to patients experiencing pain-related conditions that allows for their pain to be better managed and ultimately improve their quality of life. Many patients report that they have much higher quality sleep when treating their pain with cannabis. Getting better sleep often allows for patients to start the day in a better mental and emotional state.

A limitation to note in regard to sample size and final result percentages is that some patients are lost to follow-up. There are patients who tried medical cannabis but did not make another purchase or complete a follow-up survey rating their symptoms.

Participation

Between March 1, 2022, and Feb. 28, 2023, a total of 11,370 patients enrolled in the Minnesota Medical Cannabis Program for the first time with a pain-related condition (chronic pain, intractable pain, cancer with severe pain, terminal illness with severe pain, or sickle cell disease). Of those enrolled, 87.6% (n = 9,961) purchased medical cannabis through the program. This report focuses on patients that purchased medical cannabis through the program over the time period mentioned earlier. The top five primary causes of pain reported by patients was axial back pain (16.0%), radicular back pain (12.3%), osteoarthritis (11.2%), cancer (7.0%), and fibromyalgia or myofascial pain (6.7%).

Just over half of pain patients identified as male (52.4%) compared to female (46.6%). A majority of patients self-identified as White (82.1%), followed by Black, African or African American (5.9%). The average age of patients at enrollment was 50 years old, ranging from 3 to 101 years old. Over half of the patients live in the Twin Cities metro region (60.8%), followed by the Rochester region (8.1%).

Medical Cannabis Use Patterns

Each patient's purchasing transactions during their first enrollment year were analyzed. Pain patients purchased a total of 445,089 products. Products were classified by their route of administration and THC and CBD content. The most common route of administration for products was by inhalation (breathing in). Products in this category include raw cannabis flower and vape oil products. They accounted for 73.5% of products purchased. Enteral products, which pass through the gastrointestinal tract, including gummies, capsules, powders mixed with water and oral solutions, were the second most common products purchased, accounting for 22.6% of purchases. Oromucosal, which are absorbed through the lining of the mouth, and topical, applied to the skin, products accounted for less than 5% of purchased products. High THC products were the most popular products among all routes of administration.

Benefits

Prior to each medical cannabis purchase, patients are asked to fill out a patient self-evaluation (PSE). The PSE asks patients to rate the severity of eight standard symptoms in the past 24 hours from 0 to 10. The standard eight symptoms include anxiety, lack of appetite, depression, disturbed sleep, fatigue, nausea, pain, and vomiting. In this report, a ≥30% decrease in symptom score from enrollment score was considered to be a clinically significant change. A smaller proportion of pain patients experienced a ≥30% reduction in pain symptoms compared to other symptoms. This suggests that patients are less likely to reach clinically significant improvements in managing pain compared to the management of other symptoms. Only 31.7% of patients experiencing moderate to severe pain at enrollment saw a ≥30% reduction in pain symptoms within four months. Of those patients, 49.7% maintained ≥30% improvement in their pain for at least four months after initial improvement. Overall, of the 9,596 patients with moderate to severe pain, approximately 14.3% were able to both achieve ≥30% reduction and maintain it for at least four months.

Vomiting was the standard eight symptom most improved among pain patients, 40.7% of patients with moderate to severe vomiting at baseline were able to both achieve ≥30% reduction and maintain it for at least four months. Around one-third of patients with moderate to severe appetite lack (33.2%), depression (31.1%), and nausea (33.4%) at baseline were able to both achieve ≥30% reduction and maintain it for at least four months.

Along with the standard eight symptom questions, chronic and intractable pain patients are also given the pain, enjoyment, and general activity (PEG) scale. The PEG scale is a three-item scale that assesses pain intensity and interference with the patient's enjoyment of life and general activity in the past week. Proportion of patients achieving and maintaining reduction in PEG scores was similar to the pain standard eight symptoms.

Adverse Side Effects

In addition to symptom questions, the PSE also includes questions about adverse side effects. Only 15% (n = 1,495) of pain patients reported adverse side effects on their PSE. Over half of those patients reported one unique side effect (n = 922; 61.7%), with 89.3% reporting three or fewer unique side effects within one year of their first medical cannabis purchase. The majority (66.0%) of side effects reported were mild, and the most common side effect was dry mouth. Only 5.6% of patient-reported side effects were severe. The most commonly reported severe side effect was also dry mouth.

Adverse side effects can also be reported directly to the medical cannabis manufacturers, who then report them to SafetyCall International (a third-party adverse event reporting system). These reports have been deidentified and cannot be linked to specific patients, meaning it is unclear whether any of these reports are tied to a patient included for analysis. From March 2022 to April 2024, there were 22 adverse events reported to medical cannabis manufacturers, three of which were determined to be severe.

1. Introduction

In May 2014, Minnesota became the 22nd state to create a medical cannabis program. Distribution of cannabis products to qualified, enrolled patients began July 1, 2015. Minnesota's Medical Cannabis Program is distinct from those in nearly all other states due to the fact that the Minnesota Office of Cannabis Management's (OCM) Division of Medical Cannabis is required to study and learn from the experience of participants. Minnesota's online Registry, which integrates information from patients, certifying health care practitioners, and manufacturers, continuously captures program data. Data elements from the Registry have been selected to create a de-identified research dataset for reporting and research. This report draws on aspects of that research dataset to describe the experience of patients newly-enrolled in the program for pain-related conditions from March 1, 2022, through Feb. 28, 2023.

Cancer and terminal illness with severe or chronic pain are original qualifying conditions to the Minnesota Medical Cannabis Program. These conditions are defined as a patient with cancer or a terminal illness whose illness or treatment produces severe or chronic pain.

Intractable pain, a sub-condition of chronic pain, was introduced as a qualifying condition for the Minnesota Medical Cannabis Program in August 2016. Intractable pain is defined in the program as, "pain whose cause cannot be removed and, according to generally accepted medical practice, the full range of pain management modalities appropriate for this patient has been used without adequate result or with intolerable side effects."[1]

Chronic pain was introduced as a qualifying condition for the Minnesota Medical Cannabis Program in August 2020. Chronic pain does not have a single clear definition. The International Association for the Study of Pain defines pain as, "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"(Nicholas et al., 2019).

Sickle cell disease patients were included in this report as the disease can cause acute and chronic pain. Sickle cell disease was introduced as a qualifying condition to the Minnesota Medical Cannabis Program in August 2021.

This report provides an update on pain patient experience. The previous report titled "Intractable Pain Patients in the Minnesota Medical Cannabis Program: Experience of Enrollees During the First Five Months" was published on the Office of Medical Cannabis website in January, 2018 (*Intractable Pain Patients in the Minnesota Medical Cannabis Program*, 2018). This report will provide a description of patients who enrolled in the Minnesota Medical Cannabis Program for a pain-related condition and purchased cannabis for the first time between March 2022 and March 2023.

Cannabis and Pain

Pain is a complex experience made up of subjective factors and a common symptom of many conditions. It is known to affect many aspects of an individual's daily life, from emotions, stress, and relationships, to sleep quality, work, and physical abilities.

[1] Section 152.125, Subdivision 1.

There are three main pain systems: nociceptive, neuropathic, and central. Nociceptive pain is related to tissue damage, typically resulting in throbbing aching or sharp pain. This is due to an immune response to injury and is the body's way of warning the individual of danger. Neuropathic pain is related to inaccurate pain messages to the brain as a result of damage to nerves, and central pain is due to central nervous system dysfunction (Cohen et al., 2021; Guven Kose et al., 2022).

The expansive and subjective nature of pain as a symptom or condition makes it difficult to create a definitive pharmaceutical solution or treatment as the cause of pain is not always known. Typically, pain patients are treated with nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids; however, the use of cannabis-based medicines to manage pain has become more popular (Guven Kose et al., 2022).

The endocannabinoid system is a lipid signaling system that regulates things like mood, appetite, memory, the immune and cardiovascular systems, and pain. The endocannabinoid system functions throughout the body, however it is most commonly associated with neuronal tissue and the cannabinoid receptors CB_1 and CB_2. These receptors[2] play a role in downregulating pain during an inflammatory response due to injury or neuronal triggers (Pantoja-Ruiz et al., 2021; Steiner & Wotjak, 2008). The most common cannabinoids for these receptors are tetrahydrocannabinol (THC) and cannabidiol (CBD), which are both found in cannabis (Urits et al., 2019). Therefore, even though there is currently limited clinical research on the impact of medical cannabis on managing pain, there is considerable interest in exploring the potential.

A number of clinical trials and observational studies have been published investigating the effectiveness of cannabis or cannabinoids in reducing pain. There is variation between these studies with regard to type of pain treated, dose, and cannabinoid composition of treatment, which presents a challenge for synthesizing results. Several review articles have found conflicting evidence for the effectiveness of cannabis in treating pain (Fisher et al., 2021; McDonagh et al., 2022; Pantoja-Ruiz et al., 2021; Wang et al., 2021). Pantoja-Ruiz et al. found cannabinoids may be more effective for different types of pain. They found weak evidence for neuropathic pain, rheumatic pain, and headache, and modest evidence for multiple sclerosis and cancer related pain (Pantoja-Ruiz et al., 2021). In another systematic review, McDonagh et al. compared studies by THC and CBD content. They found that the strongest evidence of pain relief is for synthetic products with high THC:CBD ratios and extracted products with balanced THC:CBD ratios (McDonagh et al., 2022). However, it is important to note that the majority of studies found in this systematic review saw a preponderance of those two types of products. More research is needed to compare different types of products. Wang et al. conducted a systematic review and meta-analysis of clinical trials investigating cannabinoids and pain. They found a small increase in proportion of chronic pain patients experiencing pain relief and improvement in physical functioning among patients using non-inhaled medical cannabis compared to placebo (Wang et al., 2021).

[2] Receptor (neuronal receptor): refers to a site within bodily cells (neurons) that cannabinoids can bind to – like a key fitting into a specific lock (key = cannabinoid, lock = cannabinoid receptor). Cannabinoids are either produced within the body (endocannabinoids or endogenous cannabinoids) or can be introduced into the body (cannabinoids like THC or CBD from the cannabis plant that a person may smoke, or man-made cannabinoids introduced into the body; exogenous cannabinoids). Receptor agonists cause or increase a biological response within the cell.

2. Patients Registered Between March 2022 and March 2023

Description of Patients Enrolled

Qualifying condition

A total of 11,370 patients were enrolled with a pain condition in the Minnesota Medical Cannabis Program for the first time between March 2022 and March 2023. Pain patients were determined by having a qualifying condition of chronic pain, intractable pain, cancer with severe or chronic pain, terminal illness with severe or chronic pain, or sickle cell disease. Of pain patients enrolled, 9,961 (87.6%) purchased cannabis from a Minnesota medical cannabis dispensary before June 2023. June was selected as the cut off for first cannabis purchase to allow for eight months of follow up. Details on pain-related patient qualifying conditions, as certified by a health care practitioner, are found in Table 2.1. Patients may be qualified for multiple conditions, for example chronic pain and intractable pain.

Table 2.1. Count of pain related qualifying conditions.

Qualifying condition	Number of patients
Chronic pain	9,174
Intractable pain	3,514
Cancer with severe or chronic pain*	698
Terminal illness with severe or chronic pain	39
Sickle Cell Disease	5

*Includes patients with cancer as primary cause of pain.

Many pain patients were also qualified for a non-pain related condition, most commonly PTSD (post-traumatic stress disorder) (n = 909, 9.1%), and muscle spasms (n = 336, 3.3%) (Table 2.2). Appendix A Table A1 contains the full list of additional qualifying conditions.

Table 2.2. Count of additional qualifying conditions in greater than 1% of pain patients.

Additional qualifying conditions	Number of patients (%)
Post-Traumatic Stress Disorder	909 (9.1)
Muscle spasms	336 (3.4)
Cancer with nausea or severe vomiting	233 (2.3)
Obstructive Sleep Apnea	171 (1.7)
Cancer with Cachexia or severe wasting	127 (1.3)
Crohn's Disease	104 (1.0)

*See full table of additional qualifying conditions in appendix.

Primary cause of pain

During the Minnesota Medical Cannabis Program certification process, a registered health care practitioner (physicians, advanced-practice registered nurses, and physician assistants) certifies that a patient has a pain-related condition and reports the patient's primary cause of pain. The health care practitioner can either select one from several common causes of pain or select the "other cause" option and provide a narrative description of the cause of pain. The most common causes of pain were axial back pain (n = 1,592, 16.0%) and radicular back pain (n = 1,222, 12.3%), followed by osteoarthritis (n = 1,120, 11.2%) (Table 2.3). A full tabulation of primary causes of pain as reported by certifying health care practitioners is available in Appendix A Table A2.

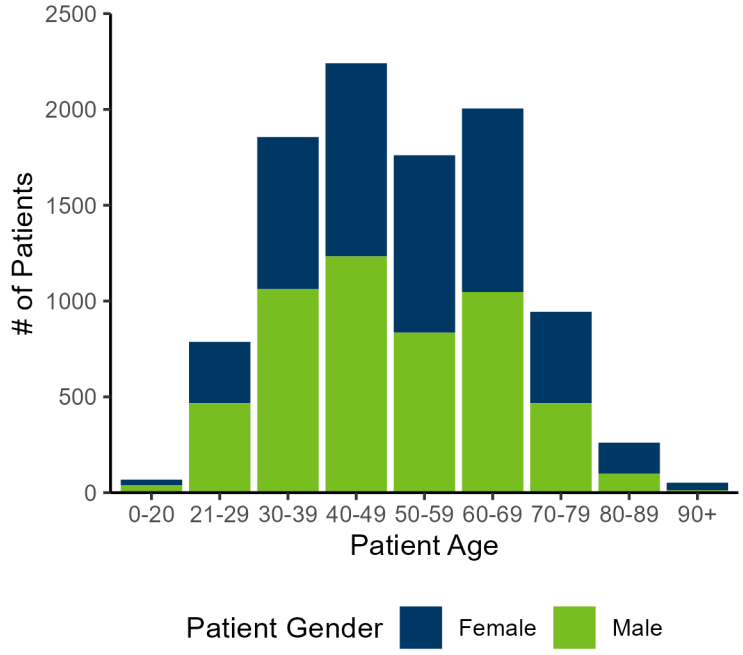
Table 2.3. Count of pain patients by primary cause of pain in greater than 1% of patients.

Primary cause of pain	Number of patients (%)
Other cause	1,662 (16.7)
Back Pain – axial	1,592 (16.0)
Back Pain – radicular	1,222 (12.3)
Arthritis – Osteoarthritis	1,120 (11.2)
Cancer	698 (7.0)
Fibromyalgia and Myofascial pain	671 (6.7)
Headache – migraine	573 (5.8)
Physical trauma (including vertebral compression fracture)	468 (4.7)
Neck pain	460 (4.6)
Arthritis – Rheumatoid	249 (2.5)
Neuropathy – other	250 (2.5)
Neuropathy – Diabetic	138 (1.4)
Headache – other	115 (1.2)
Postoperative pain	104 (1.0)
Complex Regional Pain Syndrome	99 (1.0)

Gender and age

A majority of pain patients identified as male (5,215, 52.4%) compared to female (4,643, 46.6%), while 103 (1.0%) preferred not to respond. The average age of pain patients at enrollment was 50 years old (standard deviation: 15.7 years). The youngest patient was 3 years old at certification, while the oldest was 101 years old (Figure 2.1).

Figure 2.1. Age of pain patients by gender.



Race and ethnicity

Pain patients enrolled for the first time between March 2022 and March 2023 self-identified predominantly as White (n = 8,175, 82.1%); 5.9% as Black, African, or African American, 2.0% as American Indian or Alaska Native, 0.9% as Asian, 0.1% as Hawaiian or other Pacific Islander, and 1.8% as another race (Table 2.4). Three hundred and five (3.1%) identified as two or more races, and 4.0% (n = 402) identified as having Hispanic ethnicity.

Table 2.4. Self-reported race for pain patients.

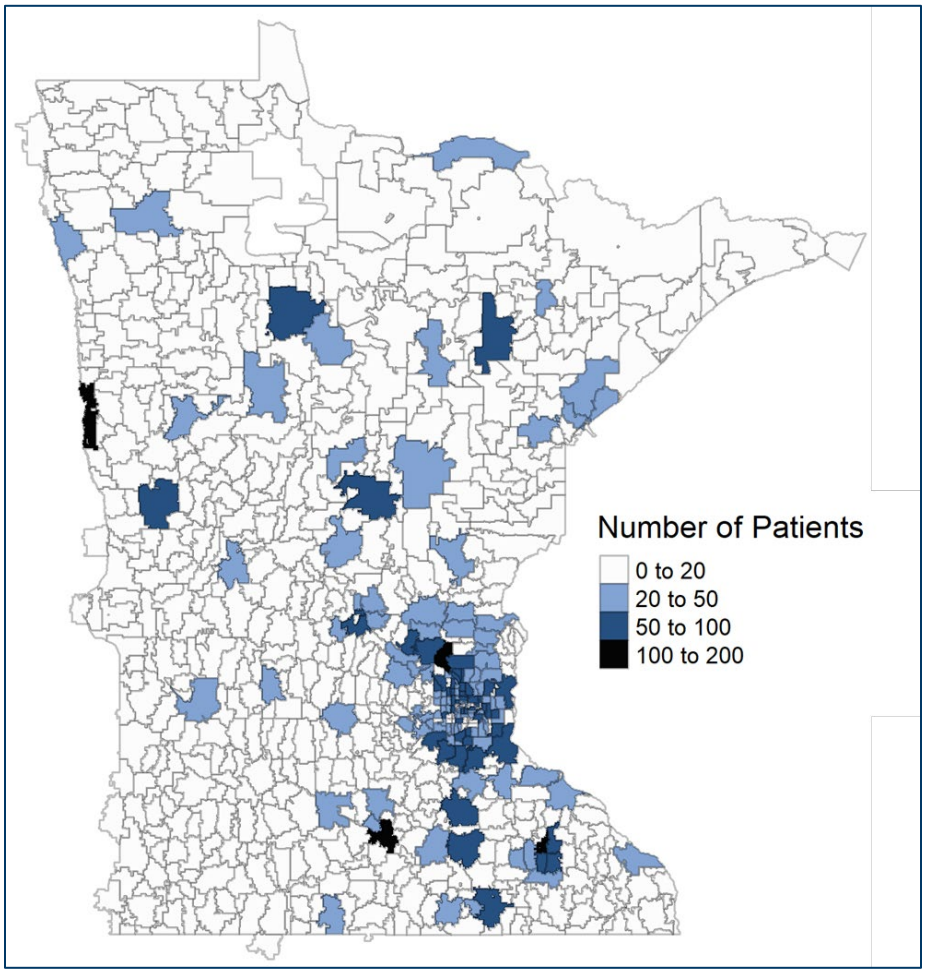
Race	Number of patients (%)
White	8,175 (82.1)
Black, African, or African American	583 (5.9)
American Indian or Alaska Native	201 (2.0)
Asian	88 (0.9)
Native Hawaiian or other Pacific Islander	10 (0.1)
Other race	183 (1.8)
Two or more races	305 (3.1)
No answer or unknown	416 (4.2)

Geographic distribution

At the time of registration, patients provide their home address for verification of Minnesota residency. Home addresses are retained in the patient's online Registry account but are not retained in the research database; in lieu of home address, patient ZIP codes are accessible for research purposes. The general geographic distribution of patients was examined using patient-reported ZIP codes in Figure 2.2.

The general geographic distribution of patients was examined using patient-reported ZIP codes; the first three digits of ZIP codes compose a prefix which corresponds to an approximate geographic region. The U.S. Postal Service assigns to each prefix labels that match the major city within the region and approximate surrounding cities; these region labels are shown in Table A3 along with the count of patients living in the corresponding ZIP codes. The majority of pain patients are located in the Twin Cities metro ZIP region, Minneapolis 34.7% and Saint Paul 26.1%; 8.1% live in the Rochester region, 6.2% in the Saint Cloud region, 6.1% in the Mankato region, and 6.0% in the Duluth region (Table A3).

Figure 2.2. Map of pain patients by ZIP code.



3. Medical Cannabis Use Patterns

Description of Purchased Products

Medical cannabis purchasing data is captured for patients enrolled in the Minnesota Medical Cannabis Program. For this report, purchasing data was extracted for all pain patients enrolled for the first time between March 1, 2022, and Feb. 28, 2023. This report describes all purchases that occurred within the first year. For patients whose first enrollment year had not yet ended at the time of data extraction (Feb. 28, 2024), all sales transactions (all products purchased at the same time in one sale) prior to that date were retained. The query provided a dataset containing:

- 130,206 sales transactions consisting of:
    - 445,089 product purchases, which
        - represented 9,960 patients

Products included in this dataset were categorized according to their route of administration and ratio of THC to CBD contained in the product. Routes of administration include enteral, inhalation, oromucosal, and topical routes of entry into the body (see Box 3.1). THC:CBD ratios ranged from products very high in THC to CBD to those very high in CBD to THC, as well as everything in between (see Box 3.1). As of this report, products that include raw cannabis flower (e.g. ground flower, flower, pre-roll products) do not include THC or CBD concentration in milligrams and cannot be classified by THC:CBD ratio in the same way as other products. They are instead classified by relative values of THC and CBD by percent of product weight.

Box 3.1. Categories to describe medical cannabis products purchased by patients.

Medical cannabis products categorized by THC:CBD content ratio:

- **Very high THC to CBD:** 100:1 or higher
- **High THC to CBD:** greater than 4:1 up to 99:1
- **Balanced:** 1:1 up to 4:1
- **High CBD to THC:** less than 1:1 up to 1:99
- **Very high CBD to THC:** 1:100 or higher

Medical cannabis flower products categorized by relative values of THC and CBD: Values measured as % by product weight

- **High THC:** greater than 15%
- **Medium THC:** 5 to 15%
- **Low THC:** less than 5%
- **High CBD:** greater than 10%
- **Medium CBD:** 1 to 10%
- **Low CBD:** less than 1% or trace amount

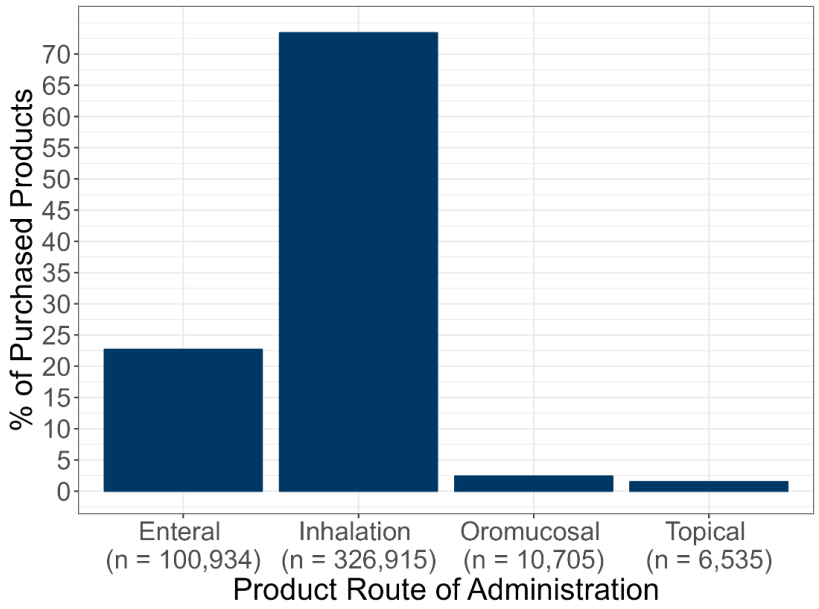
Product routes of administration (ROA):

- **Enteral:** entry through the gastrointestinal tract via swallowing (i.e., capsules, oral solutions)
- **Inhalation:** entry through lungs (i.e., vaporized oils, smoked flower)
- **Oromucosal:** sublingual sprays and tinctures absorbed through cheek/oral mucosa
- **Topical:** applied to body surface (i.e., balms)

Route of administration

Of all products included in this analysis, 73.4% were intended for inhalation. Commonly purchased inhalation products include raw flower, ground flower, pre-rolls, and vape cartridges. Enteral products, including gummies, capsules, and oral solutions, accounted for 22.7% of purchases. Oromucosal and topical products accounted for less than 5% of products purchased (respectively, 2.4% and 1.5% of all purchases) (Figure 3.1).

Figure 3.1. Product categorized by product's intended route of administration.

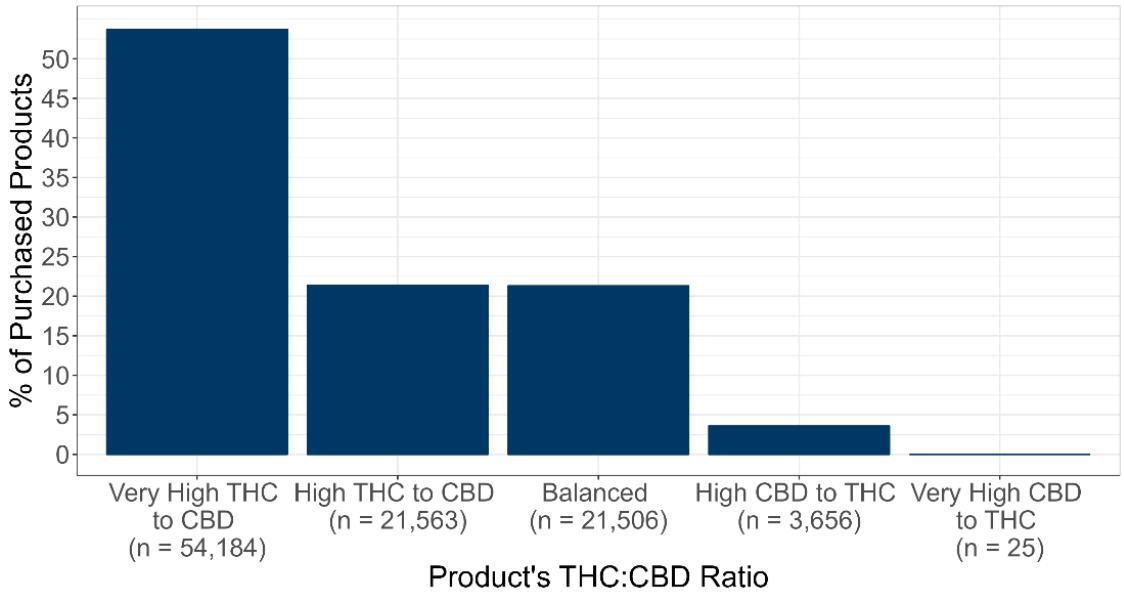


THC:CBD ratio

Enteral products

A majority of enteral products purchased by Minnesota Medical Cannabis Program patients had a very high THC:CBD ratio (53.7%), followed by high THC:CBD (21.4%), and balanced products (21.3%). Very high CBD:THC products were the least popular (0.0%) (Figure 3.2).

Figure 3.2. Enteral product transactions categorized by product's THC:CBD ratio.



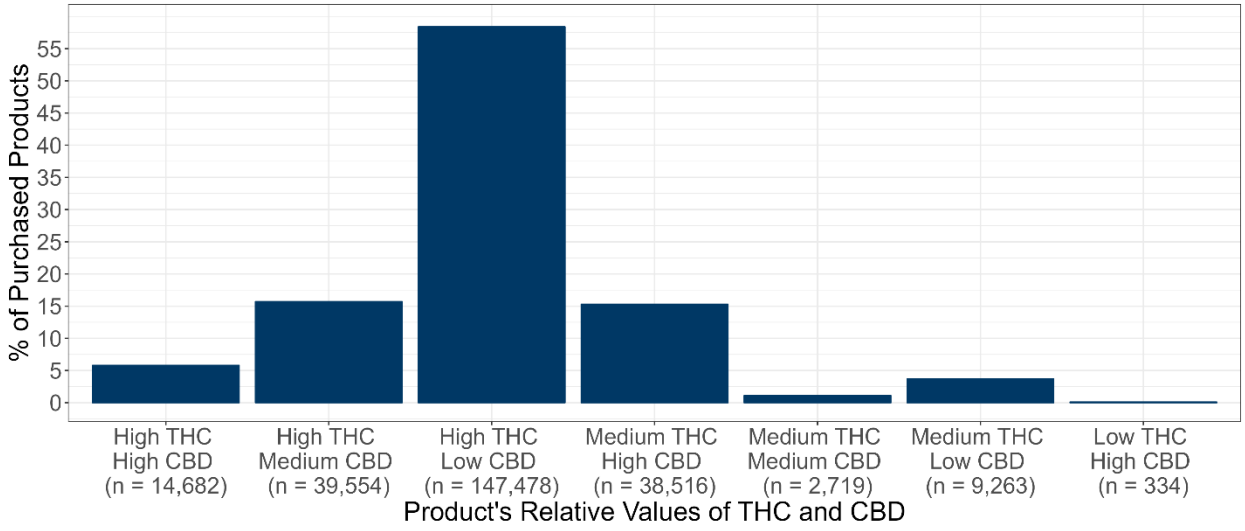
Inhalation products

Inhalation products sold in the Minnesota Medical Cannabis Program fall into two main categories: flower products and vaporization products. Flower was predominately chosen among inhalation products, accounting for 77.3% of products purchased. In addition, flower products were the most popular products among pain patients and accounted for 56.7% of all products purchased. Flower products include flower (70.7%) and pre-rolls (29.3%).

Medical manufacturers in Minnesota do not report milligrams of THC and CBD in their flower products, instead they report an approximate percentage of THC and CBD by product weight. Therefore, these products could not be categorized by THC:CBD ratio and are instead categorized by relative values of THC and CBD (Box 3.1).

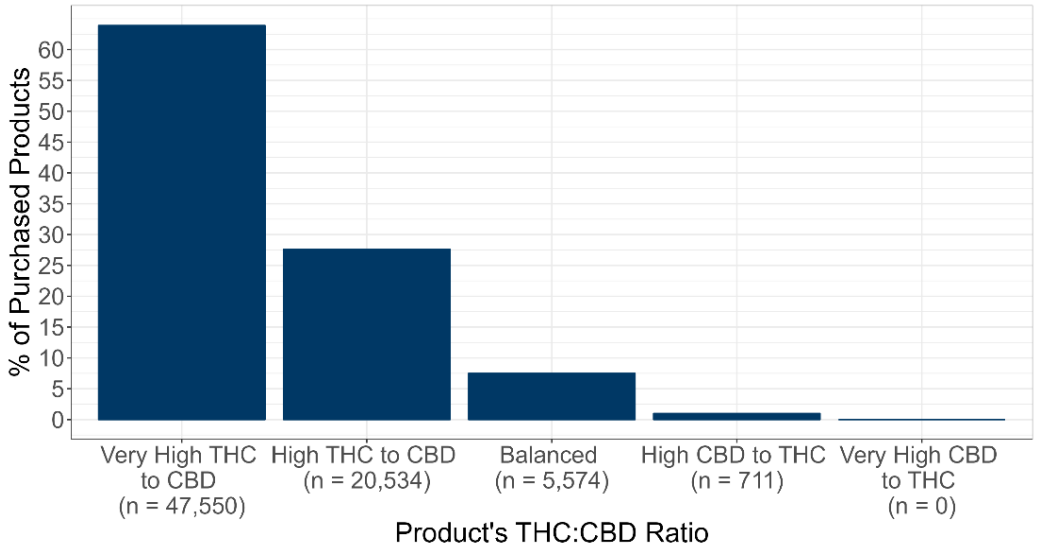
A majority of flower products purchased had high THC/low CBD (58.4%), followed by high THC/medium CBD (15.7%), and medium THC/high CBD (15.3%) products (Figure 3.3).

Figure 3.3. Inhalation flower product transactions organized by relative values of the THC and CBD.



Vaporization products are oils that are heated up and turned into a vapor, which the user inhales. Purchased vaporization products were overwhelmingly in the form of vape cartridges (98.3%), followed by vials of oil (1.6%), and syringes (0.1%). A majority of vaporization products had a very high THC:CBD ratio (63.9%), followed by high THC:CBD ratio (27.6%). Less than 10% of products purchased were balanced (7.5%) or high CBD:THC (1.0%) (Figure 3.4).

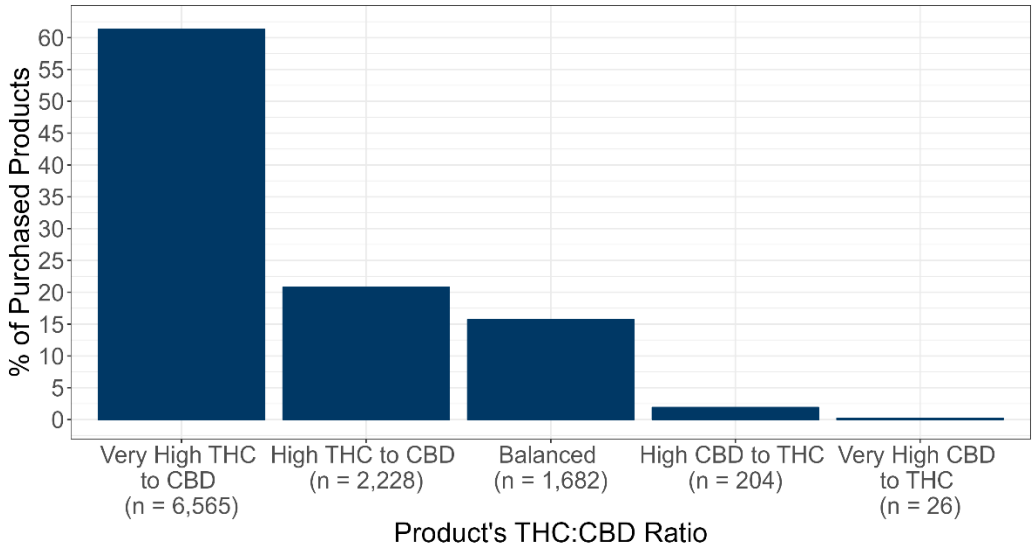
Figure 3.4. Inhalation vaporization product transactions organized by product's THC:CBD ratio.



Oromucosal products

Oromucosal products include lozenges (55.3%), sublingual sprays (28.1%), and tinctures (16.5%). A majority of oromucosal products were very high THC:CBD ratio (61.3%), followed by high THC:CBD ratio (20.8%) and balanced (15.7%) products. Majority CBD products made up less than 3% of all oromucosal sales (Figure 3.5).

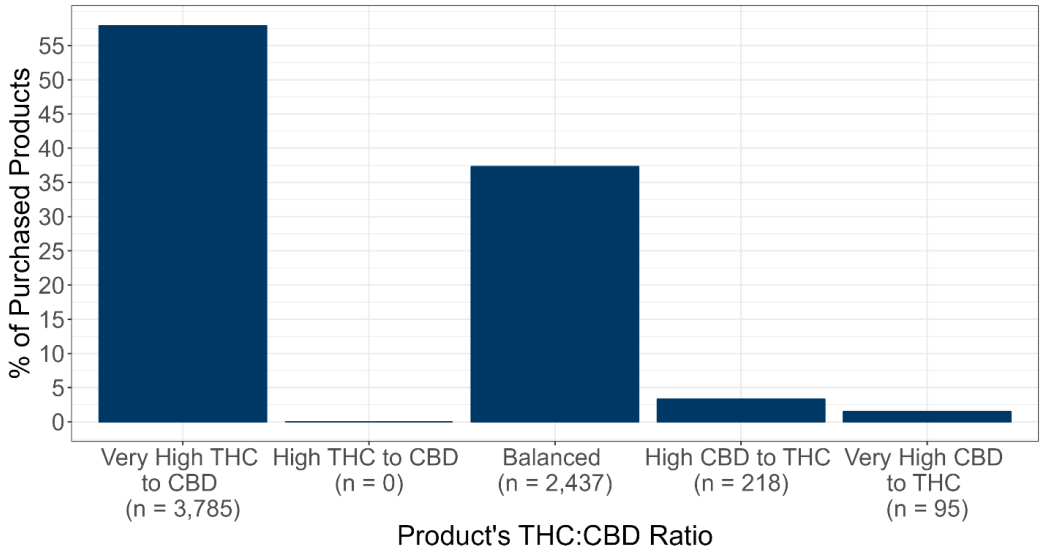
Figure 3.5. Oromucosal product transactions categorized by product's THC:CBD ratio.



Topical products

Topical medical cannabis products include balms (61.1%), bars (12.7%), and gel creams (26.3%). A majority of purchased topical products had a high THC:CBD ratio (57.9%), followed by balanced products (37.3%). A small percentage of topical products (4.8%) were formulated as majority CBD (Figure 3.6).

Figure 3.6. Topical product transactions categorized by product's THC:CBD ratio.



4. Benefits

Benefit Received from Using Medical Cannabis

Before each medical cannabis purchase, all patients in the Minnesota Medical Cannabis Program must fill out the patient self-evaluation (PSE). The PSE aims to help the patient discuss their symptoms and concerns with the medical cannabis pharmacist before making their next purchase. In the PSE, patients are asked about new medications, standard eight symptoms, condition-specific symptoms, side effects, and any perceived benefits from using medical cannabis.

An important part of this report is the comments on perceived benefits written by patients. While not all patients report benefits, below is a sample of quotes from pain patients in the Minnesota Medical Cannabis Program when asked about the benefits of medical cannabis.

- *"Ability to function and get things done. Less pain noticed."*
- *"1. Cannabis moderates my low back pain. 2. Cannabis usage helps me get longer and more restful sleep. 3. Cannabis helps control acute anxiety."*
- *“The benefits I experience from the use of cannabis revolve primarily around the pain I now feel pretty regularly from arthritis in the joints of my body and a long history of back problems. I know that movement helps but if I am too uncomfortable to even begin moving I know that my use of cannabis allows my mind/brain to separate itself a bit from my physical body. If I can mentally step back from the edge of that sword so to speak, then I don't have to rely on OTC painkillers to do the job. On that subject specifically, I cannot think of the last time I took any Advil, or Tylenol, my usual go to OTC pain medicines. I like that."*
- *“I am experiencing a Flare currently and It has been allowing me to be just functional. Otherwise, I would be in bed only right now.”*
- *"I am still receiving great benefit from taking the cannabis tablet before bed. I am able to sleep through the night in a position that doesn't cause me pain."*

Standard Eight Symptom Data

All patients, regardless of their certified condition(s), receive a set of eight symptom questions which are answered on a 0-10 numerical rating scale (NRS), with zero indicating absence of the symptom to 10 indicating that the symptom is as bad as the patient can imagine (see Box 4.1). Therefore, higher scores indicate greater symptom severity. Scores greater than or equal to four indicate moderate to severe symptoms. Patients are asked to rate symptom severity over the *past 24 hours*.

Box 4.1. Listing of the standard eight symptom measures that all patients answer, including the responses options available to patients.

Standard eight symptom measures:

- Anxiety
- Lack of appetite
- Depression
- Disturbed sleep
- Fatigue
- Nausea
- Pain
- Vomiting

Response options (0-10 NRS):

0 1 2 3 4 5 6 7 8 9 10

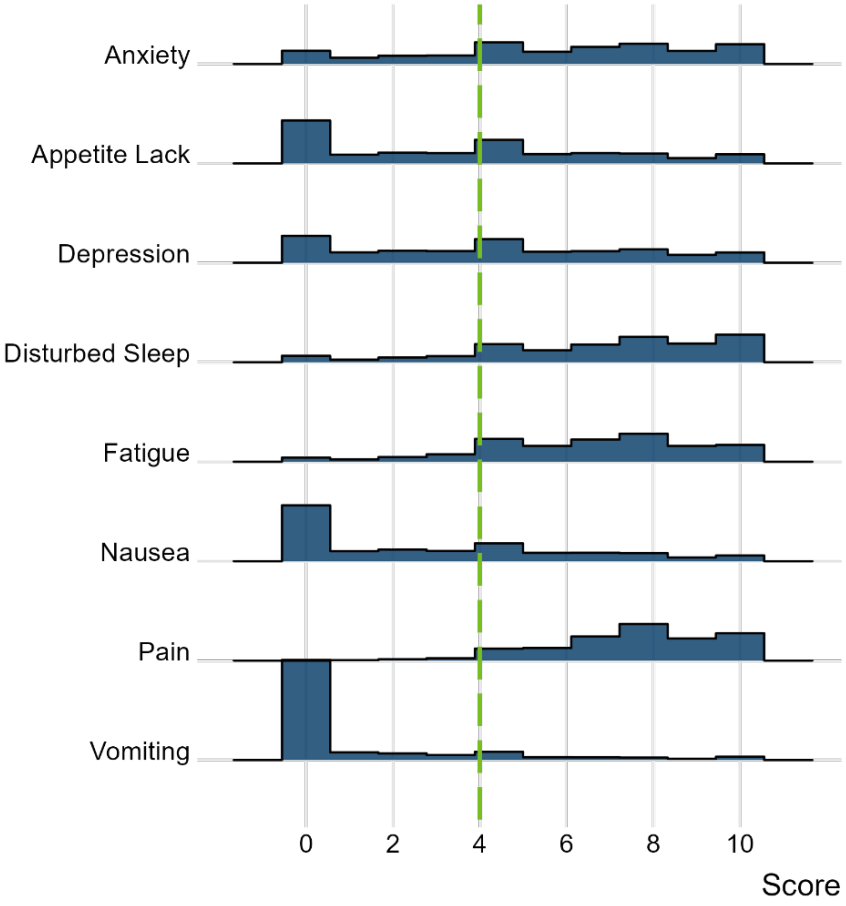
Symptom not present — Symptom as bad as one can imagine

The threshold of ≥30% reduction on a 0–10-point scale was chosen for the standard eight because this threshold has been documented in clinical trials to represent clinically meaningful change – especially for pain reduction and spasticity reduction. Examples of ≥30% change include moving from a score of 10 to a score of 7, from 9 to 6, from 8 to 5, from 7 to 4, etc. Similarly, a 30% threshold for symptom improvement on the PEG seems appropriate given that Krebs et al., 2009 (developers of the PEG scale) found that a three-point change generally reflects improvements on the Pain Global Rating of Change (Krebs et al., 2009).

Symptoms at Enrollment in the Minnesota Medical Cannabis Program

As expected, pain was the most commonly reported symptom with 96.5% of patients reporting moderate to severe pain before their first cannabis purchase. The average pain score at baseline was 7.7 (standard deviation: 1.91) (Table A4). A majority of patients also reported moderate to severe levels of fatigue (86.7%), disturbed sleep (85.7%), anxiety (74.2%), and depression (56.0%). High prevalence of disturbed sleep, fatigue, anxiety and depression among patients with chronic pain is not surprising. Sleep quality has been found to mediate the association between chronic pain and depression, meaning chronic pain leads to poor sleep which leads to depression in the patient (Karimi et al., 2023). Comparatively few patients reported moderate to severe levels of nausea (37.2%) and vomiting (15.1%) with most patients reporting a symptom score of 0 (Figure 4.1). Average and standard deviation of baseline standard eight symptom scores can be found in Table A4.

Figure 4.1. Distribution of standard eight symptom scores at enrollment. Horizontal line at a score of four indicates the cut-off for moderate to severe symptom score.



Changes in Symptoms

Almost one third (31.7%) of patients experiencing moderate to severe pain at enrollment saw a ≥30% reduction in pain symptoms within four months. Of those patients, 49.7% maintained ≥30% improvement in their pain for at least four months after initial improvement. Overall, of the 9,596 moderate to severe pain sufferers, approximately 14.3% were able to both achieve ≥30% reduction and maintain it for at least four months (Table 4.1A). There was a significant ($\chi^2(2, N = 9{,}596) = 9.44$, $p = 0.009$) difference in the proportion of patients achieving ≥30% pain symptom improvement within four months among the different types of pain (cancer pain, chronic pain, intractable pain) (Table A5). Greater than or equal to 30% pain symptom improvement was achieved by 30.5% of intractable pain patients, 32.9% of chronic pain patients, and 28.3% of cancer pain patients. There was no difference ($\chi^2(2, N = 2{,}751) = 0.16$, $p = 0.925$) in the proportion of patients who maintained ≥30% pain symptom improvement for at least four months (Table A6).

While moderate to severe vomiting was the least-reported symptom, it had proportionally the greatest symptom improvement. Overall, 15.1% (n=1,500) of pain patients reported moderate to severe vomiting before making their first purchase. Of those patients who reported moderate to severe vomiting, 62.8%

reported ≥30% improvement in their vomiting within four months of starting the program. Of those patients, 73.7% maintained ≥30% improvement in their vomiting for at least four months. Overall, of the 1,500 moderate to severe vomiting sufferers, approximately 40.7% were able to both achieve ≥30% reduction and maintain it for at least four months (Table 4.1A).

In addition to vomiting symptoms, a majority of patients with moderate to severe anxiety (50.8%), lack of appetite (57.3%), depression (56.3%), and nausea (56.7) had ≥30% improvement of symptoms within four months. Among patients with moderate to severe symptoms, close to one-third achieved and maintained ≥30% improvement of symptoms (anxiety, 27.5%; lack of appetite, 33.2%; depression, 31.3%; nausea, 33.4%) (Table 4.1A).

Table 4.1. Standard eight symptom benefits in pain patients. A) All pain patients (n = 9,944). B) Intractable pain (IP) patients (n = 3,683). C) Cancer pain patients (n = 697). D) Chronic pain patients, excluding intractable pain and cancer pain patients (n = 5,548).

A)

Standard eight symptom measure	n (%) of patients reporting at moderate to severe levels at baseline	n (%) of patients with ≥30% symptom improvement within four months, among those who had moderate to severe levels at baseline	# of patients with data in four-month period following initial ≥30% symptom improvement	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Anxiety	7379 (74.2)	3751 (50.8)	3345	2032 (60.7)	27.5%
Appetite lack	4780 (48.1)	2741 (57.3)	2440	1585 (65.0)	33.2%
Depression	5571 (56.0)	3136 (56.3)	2751	1731 (62.9)	31.1%
Disturbed sleep	8518 (85.7)	4170 (49.0)	3745	2217 (59.2)	26.0%
Fatigue	8624 (86.7)	3601 (41.8)	3222	1707 (53.0)	19.8%
Nausea	3699 (37.2)	2079 (56.2)	1863	1236 (66.3)	33.4%
Pain	9596 (96.5)	3040 (31.7)	2752	1368 (49.7)	14.3%
Vomiting	1500 (15.1)	942 (62.8)	829	611 (73.7)	40.7%

B)

Standard eight symptom measure	n (%) of patients reporting at moderate to severe levels at baseline	n (%) of patients with ≥30% symptom improvement within four months, among those who had moderate to severe levels at baseline	# of patients with data in four-month period following initial ≥30% symptom improvement	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Anxiety	2677 (72.7)	1355 (50.6)	1199	720 (60.1)	26.9%
Appetite lack	1708 (46.4)	993 (58.1)	882	573 (65.0)	33.5%
Depression	2059 (55.9)	1139 (55.3)	999	631 (63.2)	30.6%
Disturbed sleep	3173 (86.2)	1565 (49.3)	1394	803 (57.6)	25.3%
Fatigue	3210 (87.2)	1339 (41.7)	1205	634 (52.6)	19.8%
Nausea	1336 (36.3)	770 (57.6)	689	470 (68.2)	35.2%
Pain	3591 (97.5)	1094 (30.5)	975	489 (50.2)	13.6%
Vomiting	540 (14.7)	342 (63.3)	348	241 (69.3)	44.6%

C)

Standard eight symptom measure	n (%) of patients reporting at moderate to severe levels at baseline	n (%) of patients with ≥30% symptom improvement within four months, among those who had moderate to severe levels at baseline	# of patients with data in four-month period following initial ≥30% symptom improvement	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Anxiety	488 (70.0)	185 (37.9)	157	103 (65.6)	21.1%
Appetite lack	427 (61.3)	182 (42.6)	155	93 (60.0)	21.8%
Depression	374 (53.7)	169 (45.2)	129	83 (64.3)	22.2%
Disturbed sleep	585 (83.9)	221 (37.8)	188	107 (56.9)	18.3%
Fatigue	636 (91.2)	196 (30.8)	168	77 (45.8)	12.1%
Nausea	331 (47.5)	137 (41.4)	107	67 (62.6)	20.2%
Pain	621 (89.1)	176 (28.3)	144	72 (50.0)	11.6%
Vomiting	139 (19.9)	66 (47.5)	54	38 (70.4)	27.3%

D)

Standard eight symptom measure	n (%) of patients reporting at moderate to severe levels at baseline	n (%) of patients with ≥30% symptom improvement within four months, among those who had moderate to severe levels at baseline	# of patients with data in four-month period following initial ≥30% symptom improvement	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Anxiety	4204 (75.8)	2210 (52.6)	1988	1209 (60.8)	28.8%
Appetite lack	2636 (47.5)	1562 (59.3)	1401	917 (65.5)	34.8%
Depression	3128 (56.4)	1826 (58.4)	1621	1015 (62.6)	32.4%
Disturbed sleep	4747 (85.6)	2381 (50.2)	2161	1306 (60.4)	27.5%
Fatigue	4762 (85.8)	2061 (43.3)	1844	993 (53.9)	20.9%
Nausea	2025 (36.5)	1169 (57.7)	1066	698 (65.5)	34.5%
Pain	5371 (96.8)	1769 (32.9)	1633	807 (49.4)	15.0%
Vomiting	817 (14.7)	531 (65.0)	536	382 (71.3)	46.6%

PEG Scale Data

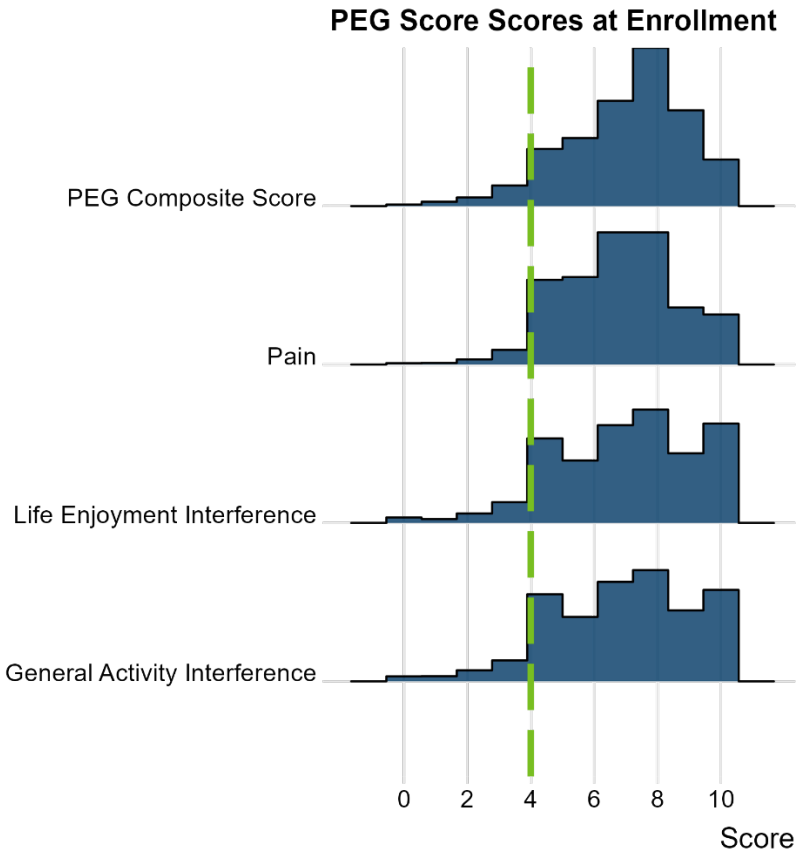
The PEG scale is a three-item scale that assesses pain intensity and its interference with the patient's enjoyment of life and general activity (P = **p**ain; E = **e**njoyment of life; G = **g**eneral activity) (Krebs et al., 2009). As a validated tool, it has been proposed as an alternative to longer pain assessments that are administered in clinical settings. The scale asks patients to think back on their *last week* and rate the following on a 0-10 numerical rating scale (NRS): their average level of pain, pain interfering with their enjoyment of life, and pain interfering with general activity. A composite PEG score is derived by adding the scores on the three items and dividing by three. The three individual items on the PEG can also be analyzed on their own. For this report, the composite PEG and individual items will be analyzed in a similar fashion to the standard eight questions.

PEG scale questions were asked in the PSE if a patient was certified for chronic pain or intractable pain. Patients who were certified for cancer pain were not prompted to answer PEG scale questions if they were not also certified for chronic or intractable pain.

PEG Scale Scores at Enrollment in the Minnesota Medical Cannabis Program

Over 90% of patients indicated moderate to severe levels of all PEG items, pain (96.0%), life enjoyment interference (93.0%), and general activity interference (92.6%) (Table 4.2, Figure 4.2). PEG score mean and standard deviation can be found in Table A7.

Figure 4.2. Distribution of PEG scores at enrollment. Horizontal line at a score of four indicates the cut-off for moderate to severe symptom score.



Changes in PEG Scale Scores

Overall, 93.8% (n=8,746) of pain patients reported moderate to severe PEG composite scores before making their first purchase. Of those patients who reported moderate to severe composite scores, 39.2% reported ≥30% improvement in their composite score within four months of starting the program. Of those patients, 54.2% maintained ≥30% improvement in their composite score for at least four months. Overall, of the 8,746 patients with moderate to severe composite scores, approximately 19.1% were able to both achieve ≥30% reduction and maintain it for at least four months (Table 4.2).

Of the PEG scale components, interference in life enjoyment and interference with general activities had the greatest improvement. Among those with moderate to severe interference, 44.6% saw ≥30% reduction in scores for life enjoyment interference and 44.4% saw ≥30% reduction in scores for general activity interference (Table 4.2).

Table 4.2. PEG score benefits in pain patients A) All pain patients (n = 9,944). B) Intractable pain (IP) patients (n = 3,683). C) Cancer pain patients (n = 697). D) Chronic pain patients, excluding intractable pain and cancer pain patients (n = 5,548).

A)

PEG Scale and components	n (%) of patients reporting at moderate to severe levels at baseline	n (%) of patients with ≥30% symptom improvement within four months, among those who had moderate to severe levels at baseline	# of patients with data in four-month period following initial ≥30% symptom improvement	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Composite	8746 (93.8)	3425 (39.2)	3079	1668 (54.2)	19.1%
Pain	8951 (96.0)	2928 (32.7)	2669	1343 (50.3)	15.6%
Life enjoyment interference	8674 (93.0)	3868 (44.6)	3470	1932 (55.7)	22.3%
General activity interference	8633 (92.6)	3832 (44.4)	3431	1905 (55.5)	22.1%

B)

PEG Scale and components	n (%) of patients reporting at moderate to severe levels at baseline	n (%) of patients with ≥30% symptom improvement within four months, among those who had moderate to severe levels at baseline	# of patients with data in four-month period following initial ≥30% symptom improvement	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Composite	3455 (93.8)	1321 (38.2)	1170	633 (54.1)	18.3%
Pain	3537 (96.0)	1127 (31.9)	1023	528 (51.6)	14.9%
Life enjoyment interference	3428 (93.1)	1487 (43.4)	1329	745 (56.1)	21.7%
General activity interference	3418 (92.8)	1499 (43.9)	1333	724 (54.3)	21.2%

C)

PEG Scale and components	n (%) of patients reporting at moderate to severe levels at baseline	n (%) of patients with ≥30% symptom improvement within four months, among those who had moderate to severe levels at baseline	# of patients with data in four-month period following initial ≥30% symptom improvement	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Composite	86 (90.5)	29 (33.7)	26	16 (61.5)	18.6%
Pain	87 (91.6)	28 (32.2)	24	15 (62.5)	17.2%
Life enjoyment interference	86 (90.5)	33 (38.4)	30	14 (46.7)	16.3%
General activity interference	85 (89.5)	31 (36.5)	27	18 (66.7)	21.2%

D)

PEG Scale and components	n (%) of patients reporting at moderate to severe levels at baseline	n (%) of patients with ≥30% symptom improvement within four months, among those who had moderate to severe levels at baseline	# of patients with data in four-month period following initial ≥30% symptom improvement	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Composite	5204 (93.8)	2075 (39.9)	1883	1019 (54.1)	19.6%
Pain	5326 (96.8)	1773 (33.3)	1622	800 (49.3)	15.0%
Life enjoyment interference	5150 (93.0)	2348 (45.5)	2111	1173 (55.6)	22.8%
General activity interference	5129 (92.4)	2302 (44.9)	2071	1163 (56.2)	22.7%

Change in PEG Composite Score by Cause of Pain

To investigate whether patients with different primary causes of pain showed variable levels of pain improvement, OCM researchers compared PEG composite scores among patients belonging to the top five primary causes of pain. Cancer pain was excluded from the top five list due to reduced number of patients with PEG scores. The “other cause” category was also excluded from the top five list because OCM researchers are aiming to estimate if cannabis effectiveness in reducing pain is dependent on etiology of pain cause. The top five pain causes are back pain (axial), back pain (radicular), osteoarthritis, fibromyalgia/myofascial pain, and headache (migraine). Initial and maintained improvement of PEG composite score for all pain causes can be found in Table A10.

There was a significant difference ($\chi^2(4, N = 5{,}170) = 27.24$, $p < 0.001$) in proportion of patients with ≥30% PEG composite score improvement within four months among those with moderate to severe scores between top five pain causes (Table 4.3). Migraine headache had the highest proportion of patients achieving ≥30% PEG composite score improvement (47.5%), while fibromyalgia/myofascial pain had the lowest (35.6%) (Table 4.3). This pattern was also observed with proportion of patients who achieved and maintained ≥30% PEG composite score improvement ($\chi^2(4, N = 1{,}681) = 12.93$, $p = 0.012$) (Table 4.3). Migraine headache patients had the highest proportion of patients maintaining PEG

composite score improvement for at least four months (61.0%). Of the 509 migraine headache patients who reported moderate to severe headache at baseline, 26.7% achieved ≥30% PEG composite score improvement and maintained it for at least four months (Table 4.3).

Change in Symptoms Among Patients Who Stayed in the Program at Least Eight Months

As discussed above, proportions of patients who were able to achieve ≥30% symptom relief and maintain it for at least four months is a conservative estimate that does not account for patients leaving the program. The above proportions are calculated assuming no loss to follow-up, using the number of patients with moderate to severe scores at baseline as the denominator.

Medical cannabis patients may leave the program at any time by either formally removing themselves from the Registry or not renewing their medical cannabis certification. In addition, patients may simply stop purchasing medical cannabis at any time. Patients cite the cost of medical cannabis, inaccessibility of medical cannabis dispensaries, and ineffectiveness of symptom management as major reasons for leaving the program.

Length of time in the Minnesota Medical Cannabis Program was calculated as time from a patients' first medical cannabis purchase to their most recent patient self-evaluation. All patients included in this report had the opportunity to participate in the program for at least eight months. Among pain patients described in this report (n = 9,961), 10.4% (n = 1,040) only purchased medical cannabis one time before leaving the program, 13.1% (n = 1,302) purchased multiple times and participated in the program between one-four months, 10.1% (n = 1,005) were in the program between five-eight months, and 66.4% (n = 6,614) were in the program for more than eight months.

To investigate benefits received from medical cannabis among pain patients who remained in the Minnesota Medical Cannabis Program for at least eight months, OCM researchers preformed the same analysis described in the above section. Among patients who were in the program for at least eight months who had moderate to severe pain at baseline, 18.4% (n = 1,178) were able to achieve ≥30% symptom improvement and maintain it for at least four months, compared to 14.3% among all patients. This increase in proportion of patients achieving and maintaining symptom relief was seen in all standard eight symptoms (Table 4.4). Proportion of patients able to achieve ≥30% PEG composite score improvement and retain it for at least four months also increased among patients who remained in the program for at least eight months (24.0%), compared to 19.1% among all patients (Table 4.5).

It is important to note that patients who choose to stop participating in the Minnesota Medical Cannabis Program do not give a reason for leaving the program. Therefore, it is possible that patients may leave because they are not experiencing symptom relief, which may artificially inflate the proportion of patients experiencing symptom relief compared to the "true" proportion if all patients remained in the program for at least eight months. This report provides both the "conservative" estimate using all patients who enrolled in the program as the denominator, as well as the "liberal" estimates using only patients who remained in the program from eight months knowing that the true value may lie somewhere in the middle.

Table 4.3. PEG composite score benefit in pain patients by top five primary cause of pain.

Primary cause of pain	n (%) of patients reporting at moderate to severe levels at baseline	n (%) of patients with ≥30% symptom improvement within four months, among those who had moderate to severe levels at baseline	# of patients with data in four-month period following initial ≥ 30% symptom improvement	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients who both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Back pain, axial	1,474 (92.8)	542 (36.8)	485	248 (51.1)	16.8%
Back pain, radicular	1,176 (96.4)	426 (36.2)	383	194 (50.7)	16.5%
Arthritis: Osteoarthritis	1,057 (94.5)	443 (41.0)	382	211 (55.2)	20.0%
Fibromyalgia/ Myofascial pain	655 (97.6)	233 (35.6)	208	94 (45.2)	14.4%
Headache: migraine	509 (89.0)	242 (47.5)	223	136 (61.0)	26.7%

Table 4.4. Benefits in the standard eight symptoms among patients who remained in the Minnesota Medical Cannabis Program for at least eight months. A) All pain patients. B) Intractable pain (IP) patients. C) Cancer pain patients. D) Chronic pain patients, excluding intractable pain and cancer pain patients.

A)

Standard eight symptom measure	# of patients who stayed in the program at least eight months reporting moderate to severe levels at baseline	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Anxiety	4922	1719	34.9%
Appetite lack	3098	1332	43.0%
Depression	3651	1431	39.2%
Disturbed sleep	5672	1875	33.1%
Fatigue	5674	1460	25.7%
Nausea	3098	1037	33.5%
Pain	6385	1178	18.4%
Vomiting	981	518	52.8%

B)

Standard eight symptom measure	# of patients who stayed in the program at least eight months reporting moderate to severe levels at baseline	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Anxiety	1821	618	33.9%
Appetite lack	1129	484	42.9%
Depression	1382	525	38.0%
Disturbed sleep	2170	686	31.6%
Fatigue	2161	553	25.6%
Nausea	1129	397	35.2%
Pain	2444	431	17.6%
Vomiting	361	187	51.8%

C)

Standard eight symptom measure	# of patients who stayed in the program at least eight months reporting moderate to severe levels at baseline	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Anxiety	230	73	31.7%
Appetite lack	174	67	38.5%
Depression	168	59	35.1%
Disturbed sleep	262	82	31.3%
Fatigue	274	61	22.3%
Nausea	174	47	27.0%
Pain	274	56	20.4%
Vomiting	60	27	45.0%

D)

Standard eight symptom measure	# of patients who stayed in the program at least eight months reporting moderate to severe levels at baseline	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Anxiety	2869	1028	35.8%
Appetite lack	1791	780	43.6%
Depression	2098	846	40.3%
Disturbed sleep	3235	1106	34.2%
Fatigue	3234	844	26.1%
Nausea	1791	592	33.1%
Pain	3663	691	18.9%
Vomiting	559	303	54.2%

Table 4.5. Benefits in PEG scores among patients who remained in the Minnesota Medical Cannabis Program for at least eight months. A) All pain patients. B) Intractable pain (IP) patients. C) Cancer pain patients. D) Chronic pain patients, excluding intractable pain and cancer pain patients.

A)

PEG Scale and components	# of patients who stayed in the program at least eight months reporting moderate to severe levels at baseline	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Composite	5940	1428	24.0%
Pain	6094	1141	18.7%
Life enjoyment interference	5895	1663	28.2%
General activity interference	5858	1635	27.9%

B)

PEG Scale and components	# of patients who stayed in the program at least eight months reporting moderate to severe levels at baseline	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Composite	2339	553	23.6%
Pain	2408	453	18.8%
Life enjoyment interference	2327	650	27.9%
General activity interference	2317	620	26.8%

C)

PEG Scale and components	# of patients who stayed in the program at least eight months reporting moderate to severe levels at baseline	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Composite	48	15	31.3%
Pain	48	14	29.2%
Life enjoyment interference	48	14	29.2%
General activity interference	47	17	36.2%

D)

PEG Scale and components	# of patients who stayed in the program at least eight months reporting moderate to severe levels at baseline	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Composite	3553	860	24.2%
Pain	3638	674	18.5%
Life enjoyment interference	3520	999	28.4%
General activity interference	3494	998	28.6%

Changes in Prescribed Medication After Medical Cannabis Usage

Health care practitioners (HCPs) who certify patients for intractable or chronic pain are asked about changes in pain medication following patient enrollment in the Minnesota Medical Cannabis Program. This survey to HCPs is triggered six months following the patient's first purchase. HCPs are asked: "Over the past six months, has the patient's use of medical cannabis assisted in reducing dosage or eliminating other medications used for pain?" The three response options are: "Yes (specify change(s) in medication(s)" and the HCP is prompted to enter information in an open text field, "No," or "Not applicable (patient not taking any medications for pain 6 months ago)." Among HCPs who reported their patient was taking medications for pain (n = 590), 145 (24.6%) reported a reduction in pain medications in the six months after starting to use medical cannabis.

5. Adverse Side Effects

In addition to reporting benefits of medical cannabis and rating condition symptoms, the patient self-evaluation (PSE) is also used to report adverse side effects of medical cannabis use. Prior to each medical cannabis purchase, patients must fill out their PSE and include any adverse side effects experiences. At the medical cannabis dispensary, patients can discuss these side effects and any other concerns with the medical cannabis pharmacist. Patients can choose from 31 side effect options (e.g., anxiety, dry mouth, headache), or an "other" option where they may write their own side effect not listed as an option. Each adverse side effect is rated by the patient as mild, moderate, or severe (see Box 5.1 for definitions).

Box 5.1. Definitions on severity provided to patients for adverse side effect reporting.

Adverse side effect severity definitions:

- **Mild:** Symptoms do not interfere with daily activities.
- **Moderate:** Symptoms may interfere with daily activities.
- **Severe:** Symptoms interrupt usual daily activities.

For this report, side effect data from the PSE was extracted for all pain patients enrolled for the first time between March 1, 2022, and Feb. 28, 2023. This report describes all purchases that occurred within the first year. For patients whose first enrollment year had not yet ended at the time of data extraction (March 13, 2024), all purchasing transactions prior to that date were retained. This query produced:

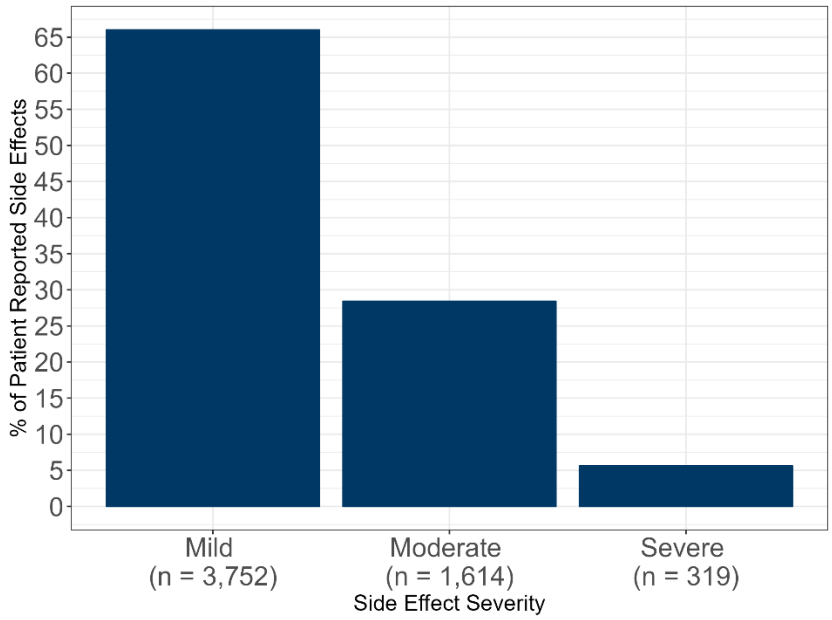
- 5,685 patient-reported side effect responses from
- 1,495 (15.0%) patients

A major limitation of these data is loss to follow-up. If a patient had a side effect after taking medical cannabis and decided not to purchase again, there is no record of the last side effect. Therefore, there is likely under-reporting of moderate to severe side effects thorough the PSE. However, patients, caregivers, and health care practitioners can report side effects directly to the medical cannabis manufacturer. These reports are reported to the Division of Medical Cannabis and will be discussed later in this report.

Of patients reporting side effects in a PSE (n = 1,495), over half reported one unique side effect (n = 922; 61.7%), with 89.3% reporting three or fewer unique side effects within one year of their first medical cannabis purchase.

A vast majority of the reported side effects reported were mild (n = 3,752; 66.0%), 28.4% were moderate (n = 1,614), and only 5.6% were reported to be severe (n = 319) (Figure 5.1).

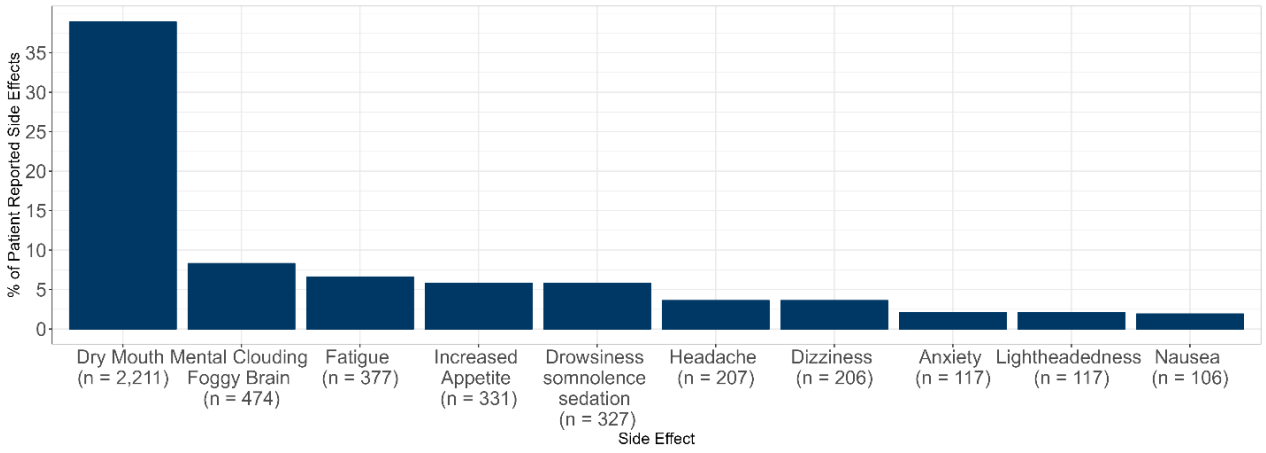
Figure 5.1. Severity of patient reported side effects.



Most Commonly Reported Side Effects

The most commonly reported side effects among patients were dry mouth, mental clouding or "foggy brain," fatigue, and increased appetite (Figure 5.2). Figure 5.2 illustrates the top 10 reported side effects; a full list of reported side effects can be found in the appendix (Table A11). "Other" side effect was the third most commonly reported side effect (n = 474); "other" was removed from the below table because the responses were free text and not coded into separate categories of side effects.

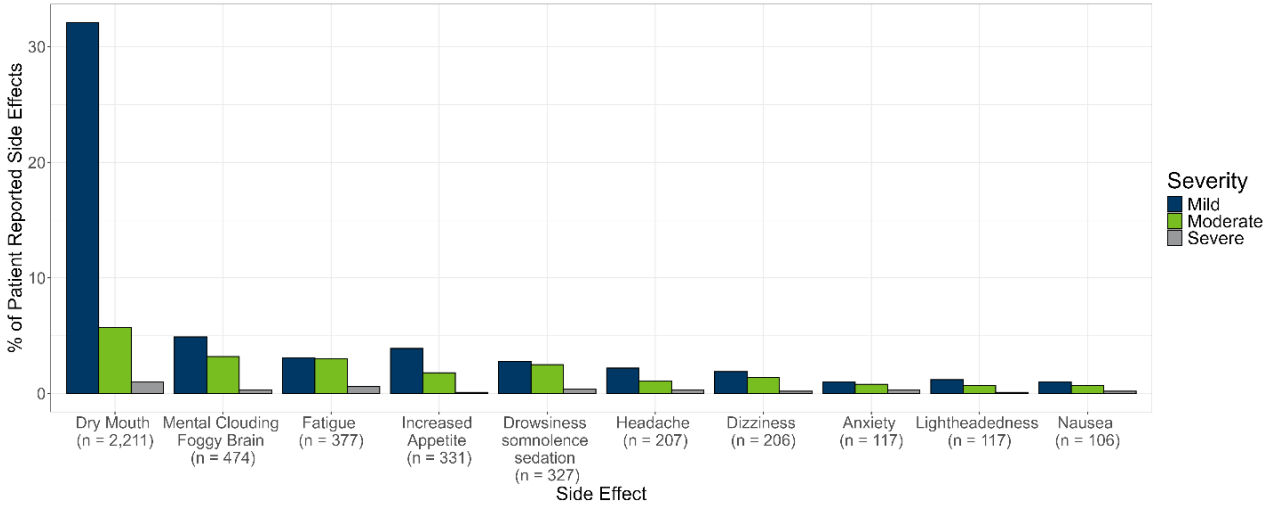
Figure 5.2. Top 10 most commonly reported adverse side effects by pain patients.



Common side effects by severity

Among the top 10 most commonly reported side effects, most were mild, followed by moderate and few were severe (Figure 5.3).

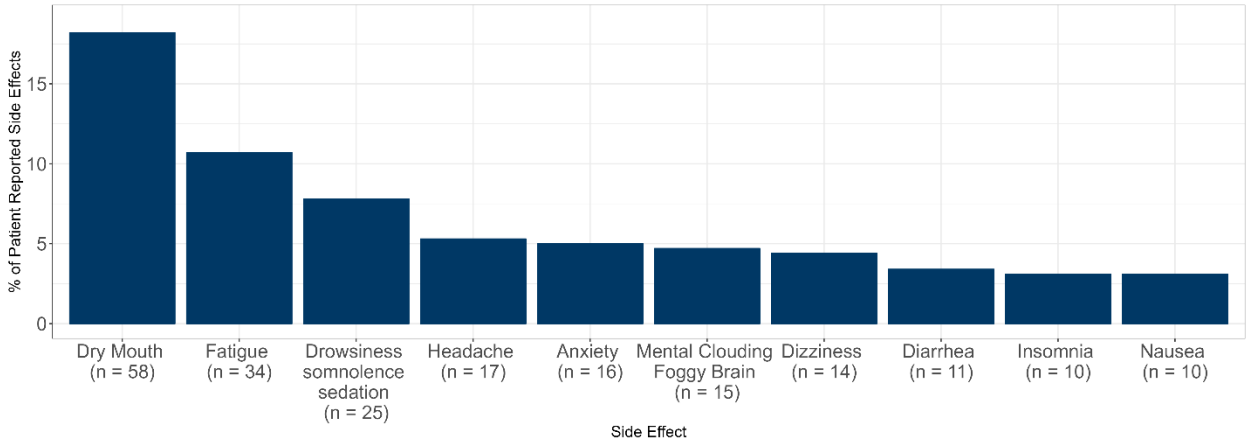
Figure 5.3. Top 10 most reported side effects by severity.



Severe adverse side effects

Through the PSE, 319 side effects were reported as severe by 171 patients. Compared to the whole pain patient cohort, patients reporting a severe side effect were more likely to be female (74.3% vs. 52.4% in all patients). The mean age of patients reporting severe side effects (55.6 ± 15.7 years) was slightly older than the full cohort (50.6 ± 15.7 years). Dry mouth was the most common severe side effect (n = 58, 18.2%), followed by other side effect (n = 45, 14.1%), fatigue (n = 34, 10.7%), and drowsiness/sedation/somnolence (n = 25, 7.8%) (Figure 5.4).

Figure 5.4. Top 10 side effects reported as severe.



Adverse Event Reporting to Medical Cannabis Manufacturers

Both Minnesota medical cannabis manufacturers have procedures for documenting potential adverse events via telephone and email communication received from enrolled patients, the patients' family and registered caregivers, as well as health care practitioners. These adverse events are reported to the Division of Medical Cannabis without patient identifiers. Since identifying information (i.e. patient name or patient ID number) is not reported back to the Division of Medical Cannabis, OCM cannot determine which if these patients had a pain-related condition or not. Therefore, this report will describe all adverse events reported to medical cannabis manufacturers during the study period, regardless of their qualifying condition(s).

From March 2022 to April 2024, there were 22 adverse events reported to medical cannabis manufacturers. The most significant symptom of reported adverse events were mostly neurological (i.e. hallucination, memory impairment, panic attack, dizziness, and sleep disturbance). Other adverse side effects reported include hypertension, peripheral swelling, frequent urination, itching, vomiting, and coughing blood. Of the reported adverse events, three were determined to be a serious event by staff reviewing the event report. These events included symptoms of hallucinations, hives, and loss of consciousness.

Appendix A. Additional Tables

Table A1. Full list of additional qualifying conditions.

Additional qualifying conditions	Number of patients (%)
Post Traumatic Stress	909 (9.1)
Muscle Spasms	336 (3.4)
Cancer with nausea or severe vomiting	233 (2.3)
Obstructive Sleep Apnea	171 (1.7)
Cancer with Cachexia or severe wasting	127 (1.3)
Crohn's Disease	104 (1.0)
Seizures	58 (0.6)
Glaucoma	42 (0.4)
Terminal illness with nausea or severe vomiting	18 (0.2)
Terminal illness with Cachexia or severe wasting	18 (0.2)
Autism Spectrum Disorder	17 (0.2)
Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome	9 (0.1)
Motor or Vocal Tic Disorder	6 (0.1)
Obsessive-Compulsive Disorder	6 (0.1)
Tourette Syndrome	6 (0.1)
Amyotrophic Lateral Sclerosis	3 (0.0)
Alzheimer's Disease	2 (0.0)

Table A2. Full list of additional pain causes.

Primary cause of pain	Number of patients (%)
Other Cause	1,662 (16.7)
Back Pain – axial	1,592 (16.0)
Back Pain – radicular	1,222 (12.3)
Arthritis – Osteoarthritis	1,120 (11.2)
Cancer	698 (7.0)
Fibromyalgia and Myofascial pain	671 (6.7)
Headache – migraine	573 (5.8)
Physical trauma (including vertebral compression fracture)	468 (4.7)
Neck pain	460 (4.6)
Arthritis – Rheumatoid	249 (2.5)
Neuropathy – other	250 (2.5)
Neuropathy – Diabetic	138 (1.4)
Headache – other	115 (1.2)
Postoperative pain	104 (1.0)
Complex Regional Pain Syndrome	99 (1.0)
Disc (vertebral) herniation	93 (0.9)
Spinal Stenosis	67 (0.7)
Pelvic Pain	47 (0.5)

Primary cause of pain	Number of patients (%)
Multiple Sclerosis	43 (0.4)
Endometriosis	40 (0.4)
Sciatica	37 (0.4)
Lupus	34 (0.3)
Inflammatory Bowel Disease	27 (0.3)
Spinal cord injury	27 (0.3)
Trigeminal Neuralgia	23 (0.2)
Myelopathies	19 (0.2)
Vascular Disease	19 (0.2)
Post-stroke pain	17 (0.2)
Neuropathy – Post-Herpetic	15 (0.2)
Parkinson's	9 (0.1)
Muscular Dystrophy	5 (0.1)
Neuropathy – HIV	2 (0.0)

Table A3. Pain patients by ZIP code region (first three number prefixes).

ZIP region	ZIP prefixes	Count (%)
Saint Paul	550,551	2,604 (26.1)
Minneapolis	553,554,555	3,458 (34.7)
Duluth	556,557,558	595 (6.0)
Rochester	559	805 (8.1)
Mankato	560,561	612 (6.1)
Willmar	562	227 (2.3)
Saint Cloud	563	614 (6.2)
Brainerd	564	340 (3.4)
Detroit Lakes	565	400 (4.0)
Bemidji	566	181 (1.9)
Grand Forks	567	109 (1.1)

Table A4. Mean and standard deviation of standard eight symptom scores at baseline by pain group.

Standard eight symptom measure	Cancer pain	Chronic pain	Intractable pain	Total
n	697	5,548	3,683	9,944
Anxiety (mean (SD))	5.39 (3.07)	5.96 (3.15)	5.74 (3.23)	5.83 (3.18)
Appetite lack (mean (SD))	4.85 (3.41)	3.62 (3.32)	3.53 (3.31)	3.67 (3.34)
Depression (mean (SD))	4.18 (3.04)	4.39 (3.30)	4.38 (3.34)	4.37 (3.30)
Disturbed sleep (mean (SD))	6.69 (2.81)	6.86 (2.81)	6.91 (2.78)	6.87 (2.80)
Fatigue (mean (SD))	6.95 (2.28)	6.52 (2.57)	6.65 (2.49)	6.60 (2.52)
Nausea (mean (SD))	3.70 (3.28)	2.87 (3.18)	2.86 (3.18)	2.93 (3.19)
Pain (mean (SD))	6.74 (2.43)	7.73 (1.83)	7.84 (1.86)	7.70 (1.91)
Vomiting (mean (SD))	1.64 (2.80)	1.23 (2.48)	1.22 (2.46)	1.26 (2.50)

Table A5. N (%) of patients with ≥30% standard eight symptom improvement within four months, among those who had moderate to severe levels at baseline by pain group.

Standard eight symptom measure	Intractable pain	Cancer pain	Chronic pain	Chi-square p-value
Anxiety	1,355 (50.6)	185 (37.9)	2,210 (52.6)	<0.001
Appetite lack	993 (58.1)	182 (42.6)	1,562 (59.3)	<0.001
Depression	1,139 (55.3)	169 (45.2)	1,826 (58.4)	<0.001
Disturbed sleep	1,565 (49.3)	221 (37.8)	2,381 (50.2)	<0.001
Fatigue	1,339 (41.7)	196 (30.8)	2,061 (43.3)	<0.001
Nausea	770 (57.6)	137 (41.4)	1,169 (57.7)	<0.001
Pain	1,094 (30.5)	176 (28.3)	1,769 (32.9)	0.008
Vomiting	342 (63.3)	66 (47.5)	531 (65.0)	<0.001

Table A6. N (%) of patients who achieved ≥30% standard eight symptom improvement that maintained it for at least four months by pain group.

Standard eight symptom measure	Intractable pain	Cancer pain	Chronic pain	Chi-square p-value
Anxiety	720 (60.1)	103 (65.6)	1,209 (60.8)	0.4062
Appetite lack	573 (65.0)	93 (60.0)	917 (65.5)	0.4018
Depression	631 (63.2)	83 (64.3)	1,015 (62.6)	0.9046
Disturbed sleep	803 (57.6)	107 (56.9)	1,306 (60.4)	0.1979
Fatigue	634 (52.6)	77 (45.8)	993 (53.9)	0.1307
Nausea	470 (68.2)	67 (62.6)	698 (65.5)	0.3495
Pain	489 (50.2)	72 (50.0)	807 (49.4)	0.9337
Vomiting	241 (69.3)	38 (70.4)	382 (71.3)	0.8137

Table A7. Mean and standard deviation of PEG scores at baseline by pain group.

PEG Scale and components	Cancer pain	Chronic pain	Intractable pain	Total
n	95	5,548	3,683	9,326
PEG composite score (mean (SD))	6.78 (2.20)	7.05 (1.89)	7.18 (1.91)	7.09 (1.90)
Pain (mean (SD))	6.60 (2.09)	6.98 (1.80)	7.07 (1.83)	7.01 (1.81)
Life enjoyment interference (mean (SD))	6.86 (2.43)	7.12 (2.21)	7.25 (2.21)	7.17 (2.22)
General activity interference (mean (SD))	6.88 (2.47)	7.04 (2.21)	7.20 (2.23)	7.10 (2.22)

Table A8. N (%) of patients with ≥30% PEG score improvement within four months, among those who had moderate to severe levels at baseline by pain group.

PEG Scale and components	Intractable pain	Cancer pain	Chronic pain	Chi-square p-value
Composite	1,321 (38.2)	29 (33.7)	2,075 (39.9)	0.179
Pain	1,127 (31.9)	28 (32.2)	1,773 (33.3)	0.369
Life enjoyment interference	1,487 (43.4)	33 (38.4)	2,348 (45.5)	0.074
General activity interference	1,499 (43.9)	31 (36.5)	2,302 (44.9)	0.215

Table A9. N (%) of patients who achieved ≥30% PEG score improvement that maintained it for at least four months by pain group.

PEG Scale and components	Intractable pain	Cancer pain	Chronic pain	Chi-square p-value
Composite	633 (54.1)	16 (61.5)	1,019 (54.1)	0.751
Pain	528 (51.6)	15 (62.5)	800 (49.3)	0.252
Life enjoyment interference	745 (56.1)	14 (46.7)	1,173 (55.6)	0.584
General activity interference	724 (54.3)	18 (66.7)	1,163 (56.2)	0.289

Table A10. PEG composite score benefit in pain patients by primary cause of pain.

Primary cause of pain	n (%) of patients reporting at moderate to severe levels at baseline	n (%) of patients with ≥30% symptom improvement within four months, among those who had moderate to severe levels at baseline	# of patients with data in four-month period following initial ≥ 30% symptom improvement	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Arthritis: Osteoarthritis	1057 (94.5)	443 (41.0)	382	211 (55.2)	20.0%
Arthritis: Rheumatoid	236 (94.8)	79 (33.5)	64	36 (56.3)	15.3%
Back pain, axial	1474 (92.8)	542 (36.8)	485	248 (51.1)	16.8%
Back pain, radicular	1176 (96.4)	426 (36.2)	383	194 (50.7)	16.5%
Cancer	86 (90.5)	29 (33.7)	26	16 (61.5)	18.6%
Complex Regional Pain Syndrome	98 (99.0)	34 (34.7)	29	12 (41.4)	12.2%
Disc (vertebral) herniation	84 (91.3)	30 (35.7)	30	17 (56.7)	20.2%
Endometriosis	34 (85.0)	19 (55.9)	18	6 (33.3)	17.6%
Fibromyalgia/ Myofascial pain	655 (97.6)	233 (35.6)	208	94 (45.2)	14.4%

Primary cause of pain	n (%) of patients reporting at moderate to severe levels at baseline	n (%) of patients with ≥30% symptom improvement within four months, among those who had moderate to severe levels at baseline	# of patients with data in four-month period following initial ≥ 30% symptom improvement	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Headache: migraine	509 (89.0)	242 (47.5)	223	136 (61.0)	26.7%
Headache: other	106 (92.2)	51 (48.1)	48	33 (68.8)	31.1%
Inflammatory Bowel Disease	15 (92.6)	13 (52.0)	12	9 (75.0)	60.0%
Lupus	33 (97.1)	10 (30.3)	10	4 (40.0)	12.1%
Multiple Sclerosis	37 (86.0)	12 (32.4)	10	5 (50.0)	13.5%
Muscular Dystrophy	4 (80.0)	2 (50.0)	2	2 (100.0)	50.0%
Myelopathies	19 (100.0)	7 (36.8)	7	3 (42.9)	15.8%
Neck pain	430 (93.7)	165 (38.4)	145	78 (53.8)	18.1%
Neuropathy: Diabetic	131 (94.9)	55 (42.0)	49	22 (44.9)	16.8%
Neuropathy: HIV	2 (100.0)	0 (0.0)	-	-	-
Neuropathy: other	235 (94.4)	75 (31.9)	69	43 (62.3)	18.3%

Primary cause of pain	n (%) of patients reporting at moderate to severe levels at baseline	n (%) of patients with ≥30% symptom improvement within four months, among those who had moderate to severe levels at baseline	# of patients with data in four-month period following initial ≥ 30% symptom improvement	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Neuropathy: post-herpetic	15 (100.0)	7 (46.7)	6	4 (66.7)	26.7%
Other Cause	1525 (91.9)	636 (41.7)	582	339 (58.2)	22.2%
Parkinson's	9 (100.0)	3 (33.3)	3	1 (33.3)	11.1%
Pelvic pain	44 (93.6)	20 (45.5)	18	11 (61.1)	25.0%
Post-stroke pain	16 (94.1)	4 (25.0)	3	1 (33.3)	6.3%
Postoperative pain	99 (95.2)	41 (41.4)	37	21 (56.8)	21.2%
Sciatica	36 (97.3)	13 (36.1)	12	5 (41.7)	13.9%
Spinal cord injury	26 (96.3)	9 (34.6)	7	4 (57.1)	15.4%
Spinal Stenosis	65 (97.0)	29 (44.6)	21	12 (57.1)	18.5%
Trauma (including vertebral compression fracture)	438 (94.0)	188 (42.9)	174	96 (55.2)	21.9%

Primary cause of pain	n (%) of patients reporting at moderate to severe levels at baseline	n (%) of patients with ≥30% symptom improvement within four months, among those who had moderate to severe levels at baseline	# of patients with data in four-month period following initial ≥ 30% symptom improvement	n (%) of patients who achieved ≥30% symptom improvement that maintained it for at least four months	% of patients that both achieved ≥30% symptom improvement and retained that degree of improvement for at least four months
Trigeminal Neuralgia	23 (100.0)	11 (47.8)	10	4 (40.0)	17.4%
Vascular Disease	18 (94.7)	6 (33.3)	5	1 (20.0)	5.6%

Table A11. Count and percentage of all reported side effects by patients in their first year.

Side effect	N (%)
Dry mouth	2,535 (37.3)
Other	704 (10.3)
Mental clouding/"foggy brain"	532 (7.8)
Increased appetite	448 (6.6)
Fatigue	420 (6.2)
Drowsiness/somnolence/sedation	377 (5.5)
Dizziness	231 (3.4)
Headache	219 (3.2)
Anxiety	158 (2.3)
Lightheadedness	127 (1.9)
Nausea	114 (1.7)
Difficulty concentrating	102 (1.5)
Impaired memory	79 (1.2)
Paranoia	85 (1.2)
Confusion	70 (1)
Constipation	69 (1)
Diarrhea	66 (1)
Blurred vision	60 (0.9)

Side effect	N (%)
Tachycardia (rapid heart rate)	52 (0.8)
Dysphoria (intense feeling of unease or unpleasantness)	41 (0.6)
Insomnia	44 (0.6)
Tinnitus (ringing in the ears)	44 (0.6)
Disorientation	35 (0.5)
Euphoria (intense feeling of well-being or pleasure)	34 (0.5)
Panic attack	32 (0.5)
Tremor	28 (0.4)
Abdominal/epigastric pain	18 (0.3)
Asthenia (muscle weakness)	23 (0.3)
Numbness	21 (0.3)
Vomiting	17 (0.2)
Chest pain	8 (0.1)
Slurred speech	10 (0.1)

References

Cohen, S. P., Vase, L., & Hooten, W. M. (2021). Chronic pain: An update on burden, best practices, and new advances. *Lancet (London, England)*, *397*(10289), 2082–2097. https://doi.org/10.1016/S0140-6736(21)00393-7

Fisher, E., Moore, R. A., Fogarty, A. E., Finn, D. P., Finnerup, N. B., Gilron, I., Haroutounian, S., Krane, E., Rice, A. S. C., Rowbotham, M., Wallace, M., & Eccleston, C. (2021). Cannabinoids, cannabis, and cannabis-based medicine for pain management: A systematic review of randomised controlled trials. *PAIN*, *162*, S45. https://doi.org/10.1097/j.pain.0000000000001929

Guven Kose, S., Kose, H. C., Celikel, F., Tulgar, S., De Cassai, A., Akkaya, O. T., & Hernandez, N. (2022). Chronic Pain: An Update of Clinical Practices and Advances in Chronic Pain Management. *The Eurasian Journal of Medicine*, *54*(1), S57–S61. https://doi.org/10.5152/eurasianjmed.2022.22307

Intractable Pain Patients in the Minnesota Medical Cannabis Program. (2018, January 1). Division of Medical Cannabis. https://mn.gov/ocm/dmc/data-reports/special-reports/intractable-pain.jsp

Karimi, R., Mallah, N., Scherer, R., Rodríguez-Cano, R., & Takkouche, B. (2023). Sleep quality as a mediator of the relation between depression and chronic pain: A systematic review and meta-analysis. *British Journal of Anaesthesia*, *130*(6), 747–762. https://doi.org/10.1016/j.bja.2023.02.036

Krebs, E. E., Lorenz, K. A., Bair, M. J., Damush, T. M., Wu, J., Sutherland, J. M., Asch, S. M., & Kroenke, K. (2009). Development and Initial Validation of the PEG, a Three-item Scale Assessing Pain Intensity and Interference. *Journal of General Internal Medicine*, *24*(6), 733–738. https://doi.org/10.1007/s11606-009-0981-1

McDonagh, M. S., Morasco, B. J., Wagner, J., Ahmed, A. Y., Fu, R., Kansagara, D., & Chou, R. (2022). Cannabis-Based Products for Chronic Pain: A Systematic Review. *Annals of Internal Medicine*, *175*(8), 1143–1153. https://doi.org/10.7326/M21-4520

Nicholas, M., Vlaeyen, J. W. S., Rief, W., Barke, A., Aziz, Q., Benoliel, R., Cohen, M., Evers, S., Giamberardino, M. A., Goebel, A., Korwisi, B., Perrot, S., Svensson, P., Wang, S.-J., Treede, R.-D., & IASP Taskforce for the Classification of Chronic Pain. (2019). The IASP classification of chronic pain for ICD-11: Chronic primary pain. *Pain*, *160*(1), 28–37. https://doi.org/10.1097/j.pain.0000000000001390

Pantoja-Ruiz, C., Restrepo-Jimenez, P., Castañeda-Cardona, C., Ferreirós, A., & Rosselli, D. (2021). Cannabis and pain: A scoping review. *Brazilian Journal of Anesthesiology*, *72*(1), 142–151. https://doi.org/10.1016/j.bjane.2021.06.018

Steiner, M. A., & Wotjak, C. T. (2008). Role of the endocannabinoid system in regulation of the hypothalamic-pituitary-adrenocortical axis. *Progress in Brain Research*, *170*, 397–432. https://doi.org/10.1016/S0079-6123(08)00433-0

Urits, I., Borchart, M., Hasegawa, M., Kochanski, J., Orhurhu, V., & Viswanath, O. (2019). An Update of Current Cannabis-Based Pharmaceuticals in Pain Medicine. *Pain and Therapy*, *8*(1), 41–51. https://doi.org/10.1007/s40122-019-0114-4

Wang, L., Hong, P. J., May, C., Rehman, Y., Oparin, Y., Hong, C. J., Hong, B. Y., AminiLari, M., Gallo, L., Kaushal, A., Craigie, S., Couban, R. J., Kum, E., Shanthanna, H., Price, I., Upadhye, S., Ware, M. A., Campbell, F., Buchbinder, R., … Busse, J. W. (2021). Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: A systematic review and meta-analysis of randomised clinical trials. *BMJ (Clinical Research Ed.)*, *374*, n1034. https://doi.org/10.1136/bmj.n1034