Intractable Pain Patients in the Minnesota Medical Cannabis Program: Experience of Enrollees During the First Five Months

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Contents

Executive Summary

In May 2014, Minnesota became the 22nd state to create a medical cannabis program. Distribution of extracted cannabis products in liquid or oil form to qualified, enrolled patients began July 1, 2015. Intractable pain was added to the list of qualifying conditions for the program effective August 1, 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." This report draws on data from enrollment, purchasing, symptom and side effect ratings at time of each purchase, and survey results to describe the experience of patients newly enrolled in the program for intractable pain during the first five months it was a qualifying condition.

Participation

Between August 1 - December 31, 2016 a total of 2290 patients were enrolled in the program under the qualifying condition of intractable pain; 45 of these patients were previously enrolled in the program under an additional qualifying condition. This report focuses on the 2245 patients who were certified for intractable pain and enrolled in the program for the first time during this interval Note that patients who took advantage of pre-enrollment during the month of July were given an effective enrollment date of August 1 for this report. Most of the patients were middle aged (64% between ages 36-64), <1% were <18, and 87% were ≤65. Distribution by race/ethnicity generally matched the state's demographics, with 87% of patients describing themselves as white. 52% were female. Fifteen percent (344 patients) were certified for one or more qualifying conditions in addition to intractable pain; severe and persistent muscle spasms was by far the most common additional qualifying condition.

Most patients (73%) live within the Twin Cities metro region, based on first three digits of zip code; 6% live in the St. Cloud region, 4% live in the Rochester region, and 4% live in the Mankato region. The program allows patients to have one or more parents or non-parent caregivers who register with the program, who then are allowed to transport and administer a patient's medical cannabis. Only 8% of patients had a registered caregiver, 2% had a registered parent or guardian, and 10% had either a registered parent/legal guardian or registered caregiver.

When certifying a patient for intractable pain, the health care practitioner indicates the primary cause of pain. The most common causes were axial (mechanical, localized) back pain – 23%, radicular (nerve, extends into legs) back pain – 14%, fibromyalgia/myofascial pain – 10%, neuropathy – 8%, and osteoarthritis – 7%.

A total of 268 health care practitioners registered with the program and certified for intractable pain the 2245 patients covered in this report; 85% were physicians, 9% were advanced practice registered nurses, and 6% were physician assistants.

Medical Cannabis Use Patterns

Each patient's medical cannabis purchasing transactions during their first enrollment year (or through November 2, 2017 if still within their first enrollment year) were analyzed. A total of 28,800 products were purchased through 17,189 transactions. For analytic purposes, products were classified according to the ratio of delta-9-tetrahydrocannabinol (THC) to cannabidiol (CBD) as follows:

- Very High THC:CBD (100:1 or higher)
- High THC:CBD (>4:1 up to 99:1)
- Balanced THC:CBD (1:1 up to 4:1)
- High CBD:THC (≥1:1 up to 99:1)
- Very High CBD:THC (100:1 or higher).

Products for inhalation (vaporized oil) accounted for 54% of products purchased, products for enteral administration (swallowed – includes capsules and oral solutions) accounted for 39%, oromucosal products accounted for 6%, and topical products <1%. When all routes of administration are combined, Very High THC:CBD products accounted for 57% of all product purchases, followed by Balanced products (33%), High THC:CBD products (6%), High CBD:THC products (4%), and Very High CBD:THC (<1%).

Examining purchasing history across all patients is very complex for reasons that include experimentation with different products over time. As a first approach to assessing routine use of products, most frequently purchased products were examined for each patient. For 28% of patients, two or more products were purchased the same number of times. The product types that emerged as most frequently purchased were Very High THC:CBD vaporization oil (30%), Balanced enteral preparations (14%), Very High THC:CBD enteral preparations (10%), and Balanced vaporization oil (6%).

Benefits

Information on patient benefits comes from the required Patient Self-Evaluation (PSE) completed by patients prior to each medical cannabis purchase, from patient and health care practitioner surveys (sent twice each enrollment year), and from pain scale information at certification by the health care practitioner. Results of analysis of these data indicate perceptions of a high degree of benefit for about half the patients.

Among respondents to the patient (54% response rate) and health care practitioner (40% response rate) surveys, a high level of benefit was reported by 61% and 43%, respectively (score of 6 or 7 on a seven-point scale). Little or no benefit (score of 1, 2, or 3) was reported by 10% of patients and 24% of health care practitioners.

The benefits extended beyond reduction in pain severity, though that was the benefit mentioned most often (64%). The benefit described second most often was improved sleep (27%), which likely has a synergistic relationship with reduction in pain severity. In some cases improved sleep, reduction of other pain medications and their side effects, decreased anxiety,

improved mobility and function, and other quality of life factors were cited as being the most important benefit. The pattern of described benefits was similar in the patient and the health care practitioner survey results.

An important part of this report is the verbatim comments written by patients, and the reader is encouraged to review these comments in *Appendix B: Patient-Reported Benefits from Medical Cannabis*. Examples of these comments include:

- "This program has opened up a world for me I thought I lost.
  I started on this just a few short months ago and am totally off my narco's and nicatin. I also have had less spasms and cramping through out my body. I even chanced getting on a motorcycle and going for a short ride with a friend before it snowed. Thought never do that again. It has also helped me gain weight. and silence some demons in my head from my PTSD. So, thank you. Now all I ask is make it affordable to stay on."
- "At first, when I began using the medical cannabis for pain, I Definitely noticed a Drastic Relief in my pain levels - that was So Wonderful - I was So Hopeful. Then, unfortunately, after the first week of using the cannabis regularly, the efficacy for the pain relief I had been receiving began to steadily wane..., to the point of no noticeable pain relief at all within a 6 to 8 week period - even though I carefully "upped" the dosage and the frequency of dosing, etc... I'm so disheartened..., but I know others with the same type of pain that I have that are experiencing and sustaining far better pain relief."
- "Medical cannabis has not made a difference for me. I have never used it before and was a little hesitant to try. When I did I found that I had no relief of pain and I didn't like the way I felt so I discontinued use."
- "The vaporizer has increased by ability to relax and fall asleep, something I struggled with a great deal due to pain. I have not found the other methods helpful. I do not feel it helps my pain, but simply makes me think about it less?"
- "Reduction in migraine occurrence and severity, improved sleep, less overall muscle aching and cramping, pain relief from arthritic joints, reduction in GI reflux which also aids sleep."
- "I have fibromyalgia. I lived my life in constant pain my daily pain on an average was an 8. I started taking medical cannabis in August. I now have a daily pain average between 2 and 3. After 2 weeks of cannabis I cooked my first meal in 15 years. My husband was doing all of the cooking and housework I am now able to help with it."

The symptom scores provided in the Patient Self-Evaluation data have the advantage of completeness, since they are required prior to each medical cannabis purchase. This data is used to calculate the composite PEG scale, a three-item scale that asks the patient to assess, over the past week, pain intensity and its interference with enjoyment of life and general activity. Using the PEG scale data, 42% achieved ≥30% reduction, and 22% both achieved and maintained ≥30% reduction over four months. The ≥30% reduction threshold is often used in pain studies to define clinically meaningful improvement.

Health care practitioners responding to the survey indicated a reduction in pain scale scores very similar to the change in PEG scores described above (41% achieved a ≥30% reduction).

A large proportion (58%) of patients on other pain medications when they started taking medical cannabis were able to reduce their use of these meds according to health care practitioner survey results. Opioid medications were reduced for 38% of patients (nearly 60% of these reduced at least one opioid by ≥50%), benzodiazepines were reduced for 3%, and other pain medications were reduced for 22%. If only the 353 patients (60.2%, based on medication list in first Patient Self-Evaluation) known to be taking opioid medications at baseline are included, 62.6% (221/353) were able to reduce or eliminate opioid usage after six months.

Adverse Side Effects

The safety profile of medical cannabis products available through the Minnesota program continues to appear quite favorable. By survey results, approximately 35-40% experience at least one physical or mental adverse effect, with the vast majority (approximately 90%) mild to moderate in severity in both the survey and Patient Self-Evaluation results. The most common adverse effects reported in the Patient Self-Evaluations are dry mouth, drowsiness, fatigue, and mental clouding/"foggy brain". An assessment of the 75 patients reporting severe adverse events, meaning "interrupts usual daily activities," found no apparent pattern in patient age, primary cause of pain, or type of medical cannabis product used. No serious adverse events (life threatening or requiring hospitalization) were reported for this group of patients during the observation period.

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 Department of Health's Office 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 data set for reporting and research. This report draws on aspects of that research data set to describe the experience of patients newly enrolled in the program for intractable pain from August 1 through December 31, 2016 – the first five months it was a qualifying condition.

Data in this report come from several aspects of the program's operations:

- Information from registration or enrollment of patients, health care practitioners, and caregivers;
- Information patients provide each time they visit a cannabis patient center (CPC) for purchase of cannabis products, including information on symptom severity and side effects;
- Details about each cannabis product purchased; and
- Information derived from responses to periodic surveys of patients and their certifying health care practitioners

Though there is certainly imprecision in some of the data collected by the program, this report provides important details that can be found in few other states. A notable part of the report is a set of statements regarding benefits and negative effects made by patients and health care practitioners. These are redacted to protect privacy, but otherwise presented as written on the surveys. The comments have been coded by type but the verbatim comments have a power of their own, reminding us that each enrollee is a unique individual, not just a number. A few comments are included elsewhere, but the reader is encouraged to spend time reviewing the full listing of responses in the appendices.

This is the second detailed report on patient experience produced by the Office of Medical Cannabis. The first, titled, "Minnesota Medical Cannabis Program: Patient Experiences from the First Program Year," was published on the Office of Medical Cannabis website in May, 2017. Many analyses from these two reports will be updated periodically and posted on the web site. In addition, studies of additional topics will be pursued over time.

2. Patients and Caregivers Registered in the First Program Year

Description of Patients Enrolled in the First Program Year

Qualifying Condition

On August 1, 2016, intractable pain became a qualifying medical condition for the Minnesota Medical Cannabis program. In the subsequent five months (August 2016-December 2016), a total of 2,290 patients were enrolled in the program under the qualifying condition of intractable pain; 45 of these patients were previously enrolled in the program under an additional qualifying condition and were excluded from descriptive analyses in this report. Of the 2,245 patients enrolled for the first time and certified for intractable pain, 1,177 (52.4%) were female, 1,054 (46.9%) were male and 14 (0.6%) did not respond. Patients can be certified by their healthcare practitioner for multiple qualifying conditions; among these intractable pain patients, 344 (15.3%) were certified for at least one additional qualifying condition. The most common additional qualifying condition was severe and persistent muscle spasms (n=264; 11.8%), followed by Crohn's disease (n=16; 0.7%), cancer (n=15; 0.7%) and seizures (n=15; 0.7%). Table 2.1 shows the frequency of additional qualifying medical conditions within the cohort.

Table 2.1. Count of intractable pain patients with additional qualifying medical conditions.

Conditions	Count (%)
Severe and Persistent Muscle Spasms	264 (11.8%)
Crohn's Disease	16 (0.7%)
Cancer	15 (0.7%)
Seizures	15 (0.7%)
Glaucoma	9 (0.4%)
HIV/AIDS	4 (0.2%)
Terminal Illness	6 (0.3%)
Tourette Syndrome	0 (0%)

ALS	0 (0%)
Total	2245

Age by Qualifying Condition

Average age of patients certified for intractable pain and enrolled from August-December 2016 was 52.3 years (SD: 15.6 years); breakdown of patients by age group is shown in Table 2.2.

Table 2.2. Intractable pain patient age.

Age	Count (%)
0-4 yrs	2 (0.1%)
5-17 yrs	8 (0.4%)
18-24 yrs	63 (2.8%)
25-35 yrs	309 (13.8%)
36-49 yrs	582 (25.9%)
50-64 yrs	847 (37.7%)
65+ yrs	434 (19.3%)

Race and Ethnicity

Intractable pain patients enrolled in the first five months were predominantly white (n=1945; 86.6%); 4% were black, 3% were American Indian, 2% identified as Hispanic and 5% did not respond (Table 2.3). Patients were given the option to select multiple race and ethnicity categories, so the counts reflect some patients more than once. Fifty-two patients (2.3%) selected more than one race/ethnicity and 106 patients (4.7%) declined the question. Compared to 2014 Census Bureau estimates of race/ethnicity in Minnesota, the distribution of responding members of the first program year cohort is generally similar, with a slightly higher proportion of American Indians (2.7% versus 1.9%) and lower proportion of Hispanics (2.4% versus 4.9%) and Asians (1.0% versus 5.0%).

Table 2.3. Self-reported race and ethnicity for intractable pain patients.

Race/Ethnicity	Count (%)
American Indian	61 (2.7%)
Asian	23 (1.0%)

Black	99 (4.4%)
Hawaiian	5 (0.2%)
White	1945 (86.6%)
Other	38 (1.7%)
No Answer	147 (6.5%)

**Patients could select more than one race/ethnicity and may be represented more than once each in this table.*

Registered Caregivers and Parents/Legal Guardians

If a patient is unable to pick up their medication from a cannabis patient center or is unable to administer the medication, their certifying health care practitioner may also certify the patient's need for a designated caregiver. This allows the enrolled patient to have a caregiver who then undergoes a background check and registers with the program. Registered caregivers can then legally obtain and possess the patient's medical cannabis on their behalf. Additionally, parents or legal guardians of patients can register with the program to act as caregiver and pick up or possess medication on behalf of the patient. Table 2.4 shows the proportion of patients who have registered caregivers or parents or legal guardians registered to pick up medication on behalf of the patient.

Table 2.4. Patients with caregiver(s) and/or parent(s)/legal guardian(s) registered in the program.

Patients with Caregiver or Parent/Legal Guardian	**Count (%)**
Patients with Registered Caregivers	178 (8%)
Patients with Registered Parent/Legal Guardian	37 (2%)
Patients with Caregivers and/or Parent/Legal Guardian	214 (10%)

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; the first three digits of ZIP codes compose a prefix which corresponds to an

approximate geographic region[1]. 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 2.5, along with the count of patients living in the corresponding ZIP codes.

Most patients live within the Twin Cities metro ZIP code region (73%); 6% of patients live in the Saint Cloud region, 4% live in the Rochester region and 4% live in the Mankato region.

Table 2.5. Intractable pain patients by ZIP code region (first three number prefixes).

ZIP Region	ZIP Prefixes	Count (%)
Saint Paul	550,551	769 (34%)
Minneapolis	553,554,555	874 (39%)
Duluth	556,557,558	78 (3%)
Rochester	559	101 (4%)
Mankato	560,561	94 (4%)
Willmar	562	63 (3%)
Saint Cloud	563	142 (6%)
Brainerd	564	38 (2%)
Detroit Lakes	565	41 (2%)
Bemidji	566	32 (1%)
Grand Forks	567	11 (0%)

Note: The Grand Forks region, corresponding to ZIP codes with a 567 prefix, refers to a region including Grand Forks, South Dakota, as well as several ZIP codes located in Minnesota near the western border. Patients living in this region reside in Minnesota.

Primary Cause of Intractable Pain

When a registered healthcare practitioner certifies that a patient has intractable pain and qualifies for the Minnesota Medical Cannabis program, the healthcare practitioner must report the patient's primary cause of intractable pain, choosing from several common causes or selecting "Other" and providing a narrative description of the pain cause. All pain cause entries other than the selection of common causes provided were reviewed and classified as one of the common causes or as another category (Table 2.6). The most common primary causes of intractable pain were axial and radicular back pain (n=521 (23%), and n=305 (14%), respectively), fibromyalgia or myofascial pain (n=233; 10%), neuropathies (including diabetic neuropathy, trigeminal neuralgia, post-herpetic neuropathy, HIV neuropathy and other

[1] http://pe.usps.com/Archive/HTML/DMMArchive20050106/print/L002.htm

neuropathies; n=172 (8%)) osteoarthritis (n=166; 7%). Of 2,245 patients included in this analysis, 147 (7%) were certified with an infrequently-reported primary cause of pain (less than 10 patients within the same category); a full tabulation of primary pain causes as reported by certifying HCPs is available in *Appendix A: Healthcare Practitioner-Reported Primary Cause of Intractable Pain.*

Table 2.6. Count of intractable pain patients by primary cause of pain.

Primary Pain Cause	**N (%)**
Back pain, axial	521 (23%)
Back pain, radicular	306 (14%)
Fibromyalgia/myofascial pain	233 (10%)
Neuropathy	172 (8%)
Diabetic Neuropathy	*23 (1%)*
Trigeminal neuralgia	*17 (1%)*
Post-Herpetic Neuropathy	*3 (0%)*
HIV Neuropathy	*1 (0%)*
Neuropathy, Other	*128 (6%)*
Osteoarthritis	166 (7%)
Neck pain	103 (5%)
Migraine Headache	86 (4%)
Trauma	81 (4%)
Rheumatoid Arthritis	72 (3%)
Headache Other Than Migraine	60 (3%)
Complex Regional Pain Syndrome	43 (2%)
Spinal Stenosis	36 (2%)
Postoperative Pain	29 (2%)
Myelopathies	28 (1%)
Pelvic Pain	22 (1%)
Spinal Cord Injury	22 (1%)
Disc (Vertebral) Herniation	21 (1%)
Abdominal Pain	17 (1%)
Cancer	16 (1%)

Ehler-Danlos Syndrome	16 (1%)
Connective Tissue Diseases (Excluding Rheumatoid Arthritis)	15 (1%)
Pancreatitis	12 (1%)
Arthritis, Other Inflammatory	11 (0%)
Sciatica	10 (0%)
Other	147 (7%)

3. Registered Healthcare Practitioners Certifying Early Intractable Pain Patients

The Minnesota Medical Cannabis program outlines a set of qualifying medical conditions which make a patient eligible for enrollment in the program. By Minnesota statute, a patient must be certified by a Minnesota-licensed physician, physician assistant (PA), or advanced practice registered nurse (APRN) as having one or more of the qualifying conditions. A Minnesota practitioner with appropriate credentials must first register with the Minnesota Medical Cannabis program before they can certify patients for the program: practitioners complete a short online form with their name and clinic information to register. Office of Medical Cannabis staff verify the provider's entered information and their Drug Enforcement Agency (DEA) license prior to approving the practitioner to certify patients. This chapter will describe registered healthcare practitioners who certified patients under the qualifying condition of intractable pain who were approved within the first five months of when intractable pain was added as a qualifying condition (August 2016- December 2016.)

Healthcare Practitioners By Type

A total of 268 healthcare practitioners (HCPs) who registered in the Minnesota Medical Cannabis program certified patients under intractable pain who enrolled in the program prior to December 31, 2016. Of these HCPs, 227 (85%) were physicians, 16 (6%) were PAs and 25 (9%) were APRNs (Table 3.1).

Table 3.1. Certifying healthcare practitioners for the first five months of intractable pain, by type.

Healthcare Practitioner Type	Count (%)
Physician	227 (85%)
Physician Assistant	16 (6%)
Advanced Practice Registered Nurse	25 (9%)

Certifying Physician Specialty

The Minnesota Board of Medical Practice lists information on Minnesota-licensed physicians and physician assistants. Included is self-reported "Area of Specialty" information indicating a

physician's certifications from the American Board of Medical Specialties or American Osteopathic Specialty Boards. While physician assistant specialty information is infrequently provided, physicians often list multiple certifications. For example, physicians practicing as infectious disease specialists may list certifications in the areas of Internal Medicine and Infectious Disease. A variety of specialties were represented among physicians certifying intractable pain patients, including Neurology and the Internal Medicine subspecialties of and Hospice and Palliative Medicine.

In cases where a physician listed an area of specialty and subspecialty, such as Internal Medicine and Infectious Disease, the subspecialty was chosen to represent the physician's practice (in this case, Infectious Disease). Table 3.2 shows the distribution of physician specialties; each physician is represented only once. One physician who is licensed in Minnesota and registered in the program does not have any listed specialties with the Board of Medical Practice; this physician is therefore excluded from Table 3.2. The most common specialty category for physicians is primary care (n=140; 52%), followed by Physical Medicine and Rehabilitation (n=16; 6%), Hospice and Palliative Medicine (n=12; 4%), and Neurology (n=12; 4%).

Table 3.2. Count of physicians by certification type.

Physician Certification Type	Count (%)
Primary Care	140 (52%)
Physical Medicine and Rehabilitation	16 (6%)
Hospice/Palliative Medicine	12 (4%)
Neurology	12 (4%)
Oncology	8 (3%)
Pain Medicine	6 (2%)
Geriatric Medicine	5 (2%)
Pediatric Specialty	5 (2%)
Anesthesiology	4 (1%)
Psychiatry	4 (1%)
Sports Medicine	3 (1%)
Surgery	3 (1%)
Infectious Disease	2 (1%)
Nephrology	2 (1%)
Rheumatology	2 (1%)
Radiology/Radiation Oncology	1 (0%)
Urology	1 (0%)

4. Medical Cannabis Use Patterns

Description of Purchased Products

Medical cannabis purchasing data is captured for enrolled MN patients through the online registry. For this report, purchasing data was extracted for Intractable Pain patients enrolled between August 1, 2016 through December 31, 2016. All purchases that occurred within each patient's first enrollment year were retained. For patients whose first enrollment year had not yet ended at the time of data extraction (November 2, 2017), all purchasing transactions prior to that date were retained. This query provided a dataset containing:

- 17,189 purchasing transactions consisting of:
- 28,800 product purchases, which
- Represented 2,181 patients (97.1% of the Intractable Pain cohort)

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 4.1). 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 4.1)

Box 4.1. Categories to describe medical cannabis products purchased by patients.

Medical Cannabis Products Categorized by THC:CBD Content Ratio:

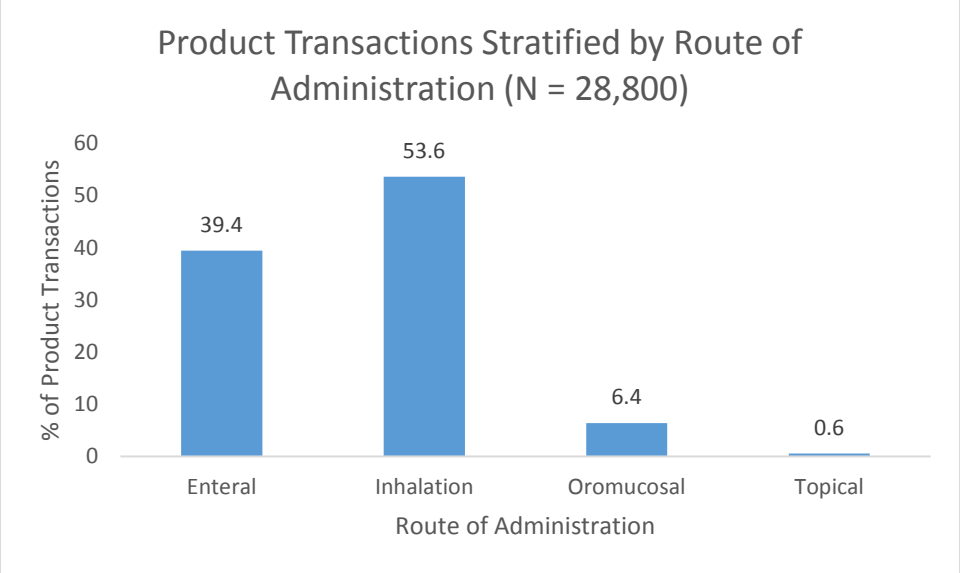
- **Very High THC to CBD** = 100:1 or higher
- **High THC to CBD** = >4:1 up to 99:1
- **Balanced** = 1:1 up to 4:1
- **High CBD to THC** = ≥1:1 up to 99:1
- **Very High CBD to THC** = 100:1 or higher

Product Routes of Administration (ROA):

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

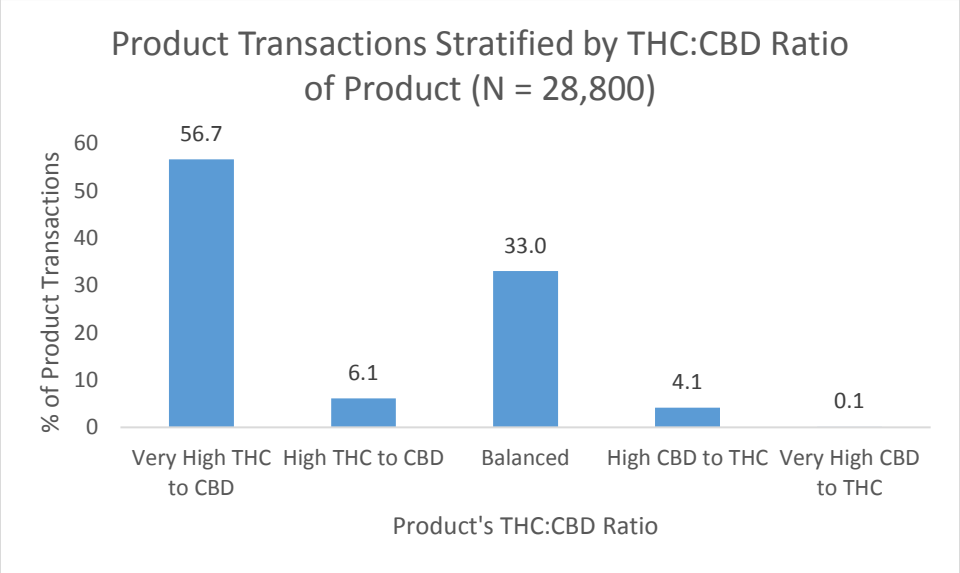
Analysis of purchased products indicates that just over half of all purchases (53.6%) were intended for inhalation and 39.4% for enteral administration. Together, these routes accounted for 93% of all products purchased. Oromucosal and topical products together accounted for less than 10% of all products purchased (respectively at 6.4% and 0.6% of all purchases). Note that topical products were not available for the full duration of the study period, becoming available over time starting in August 2017. See Figure 4.1.

Figure 4.1. Product transactions categorized by the product's intended route of administration (out of 28,800 products).



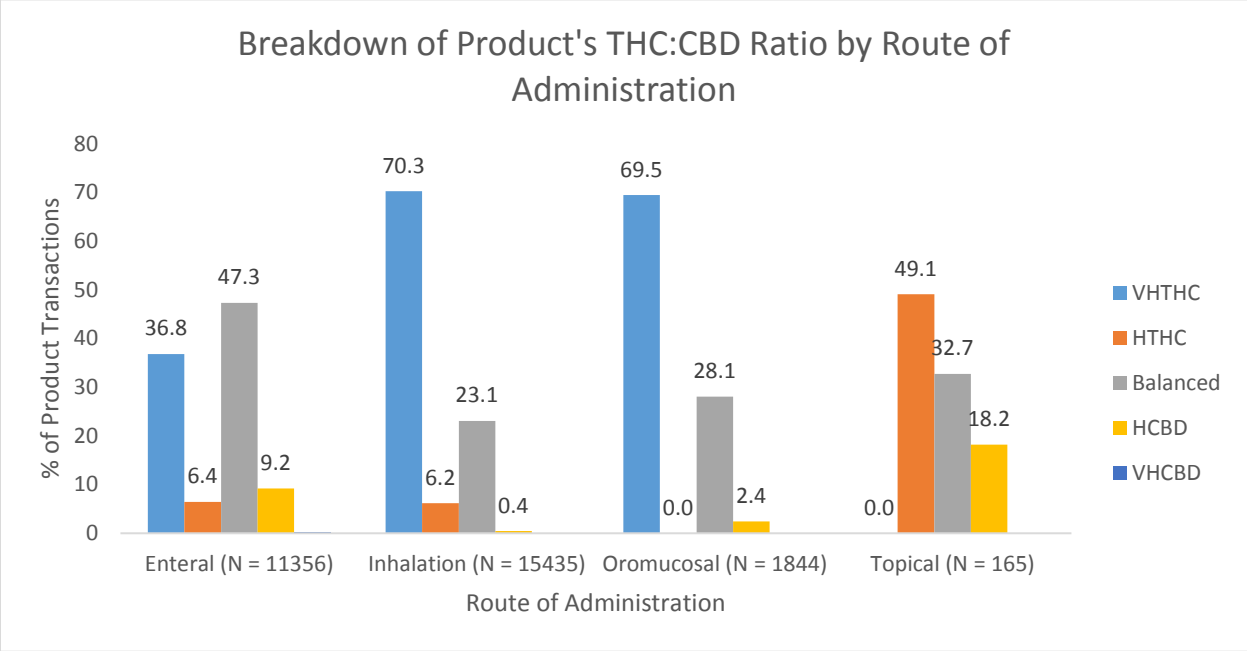
Analysis of products stratified by the THC:CBD ratio showed that products with Very High THC:CBD ratios were purchased most frequently (56.7% of all product purchases), followed by Balanced products (33.0%). High THC:CBD products and High CBD:THC products respectively accounted for 6.1% and 4.1% of all product transactions, with Very High CBD:THC products accounting for 0.1% of all products purchased. See Figure 4.2.

Figure 4.2. Product transactions categorized by THC:CBD ratio.



Product transactions were also examined by the products' THC:CBD ratio as a function of route of administration (see Figure 4.3 below). Balanced and Very High THC:CBD products were most frequently purchased among enterally administered products. Very High THC:CBD products accounted for roughly 70% of all purchased inhaled and oromucosal products. High THC:CBD products were purchased almost half the time for topical products, with Balanced and High CBD:THC products less frequently.

Figure 4.3. A percentage breakdown of product transactions by the THC:CBD product ratio types as a function of route of administration.



Most Frequently Purchased Product(s)

Analyzing purchasing patterns across patients is complicated in that there may be some experimentation involved when purchasing medical cannabis to find a dosage and formulation a patient believes is working for them. Another layer of complexity is the fact that products that patients have an affinity for may not necessarily be purchased in the same transaction. Therefore, understanding what is routinely used requires some careful thought and standardized operationalization of what would be considered 'routine' medication. As a first step, this report will present products most frequently purchased by patients. This particular approach is simplistic, but the idea is to continue to refine the operational definition of routine use over time in subsequent analyses.

All products purchased by any given patient were quantified by the number of times they were purchased. The most frequently purchased product(s) was then categorized according to their route of administration and THC:CBD ratio. For each product identified as most frequently purchased, the following calculations were performed within each patient across purchases of that product: summing of intended days supply of product usage, summing of THC dosages (mg), and summing of CBD dosages (mg). From these summed values, daily THC and CBD consumption of the product(s) purchased most frequently was calculated by dividing the summed THC dose and CBD dose by the summed days supply for each patient. Patients who

most frequently purchased the same product type(s) had their calculated daily THC and CBD dosages averaged together. This data is displayed in Table 4.1.

Table 4.1 identifies the most frequently purchased product types with an "X", along with the percentage of patients identified as having purchased that product most frequently (see 2nd column from right). The average daily THC and CBD dose for the patients who purchased the same product type most frequently are indicated in the right-most column. According to the data, 72.3% of all patients (n = 1577) purchased product(s) from one ROA-THC:CBD ratio category most frequently (see rows with one "X"). Just under a third of all patients making purchases most frequently purchased vaporized product(s) with Very High THC:CBD, followed by Balanced enteral (14.3%) and Very High THC:CBD enteral (10.2%) product types.

Table 4.1. Product type(s) most frequently purchased by each patient (out of 2,181 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					Topical						
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	% of Patients (n)	Avg Daily THC (mg) / Avg Daily CBD (mg)
					X															30.3 (660)	81.5 mg / 0.6 mg
		X																		14.3 (312)	22.9 mg / 20.4 mg
X																				10.2 (223)	24.4 mg / 0.1 mg
							X													6.4 (140)	75.4 mg / 62.1 mg
										X										3.3 (73)	30.8 mg / 0.1 mg
					X		X													3.3 (72)	512.7 mg / 23.6 mg
		X			X															3.2 (69)	69.6 mg / 22.3 mg
X		X																		2.8 (60)	84.2 mg / 68.8 mg
			X																	2.6 (57)	4.9 mg / 105.8 mg
X					X															2.5 (55)	166.4 mg / 0.7 mg
						X														1.9 (41)	134.8 mg / 5.9 mg
												X								1.8 (39)	23.5 mg / 22.7 mg
		X					X													1.6 (34)	48.5 mg / 31.5 mg
		X								X										1.5 (33)	55.8 mg / 29.3 mg
	X																			1.4 (30)	66.5 mg / 7.2 mg
X		X			X		X													0.8 (18)	116.1 mg / 39.9 mg
X		X			X															0.7 (16)	89.9 mg / 19.4 mg
		X	X																	0.7 (16)	24.7 mg / 110.5 mg
		X			X		X													0.7 (16)	143.2 mg / 50.2 mg
										X		X								0.6 (12)	52.2 mg / 22.1 mg
X										X										0.3 (7)	47.8 mg / 0.1 mg
		X			X					X										0.3 (7)	101.3 mg / 29.1 mg
					X	X														0.3 (7)	243.3 mg / 9.0 mg
X		X					X													0.3 (6)	99.3 mg / 34.6 mg
	X				X															0.3 (6)	168.3 mg / 5.6 mg
X		X	X																	0.2 (5)	56.7 mg / 181.5 mg
X			X																	0.2 (5)	14.6 mg / 88.6 mg
X					X		X													0.2 (5)	77.2 mg / 14.4 mg
X					X					X										0.2 (5)	116.7 mg / 0.7 mg
X							X													0.2 (5)	41.2 mg / 18.3 mg

Table 4.1 cont. Product type(s) most frequently purchased by each patient (out of 2,181 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					Topical						
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	% of Patients (n)	Avg Daily THC (mg) / Avg Daily CBD (mg)
	X	X																		0.2 (5)	81.7 mg / 29.1 mg
		X			X							X								0.2 (5)	100.5 mg / 64.2 mg
		X				X														0.2 (5)	57.9 mg / 9.3 mg
		X										X								0.2 (5)	42.3 mg / 34.0 mg
			X		X		X													0.2 (4)	83.6 mg / 92.3 mg
			X		X															0.2 (4)	50.6 mg / 142.9 mg
X	X				X															0.1 (3)	175.9 mg / 7.6 mg
X		X	X		X		X													0.1 (3)	112.6 mg / 127.6 mg
X		X			X					X										0.1 (3)	94.6 mg / 21.2 mg
X		X								X										0.1 (3)	77.2 mg / 26.0 mg
		X	X		X		X													0.1 (3)	85.7 mg / 110.1 mg
		X			X	X	X													0.1 (3)	300.8 mg / 68.0 mg
		X			X		X			X										0.1 (3)	121.8 mg / 35.1 mg
					X		X			X		X								0.1 (3)	164.9 mg / 61.0 mg
					X					X										0.1 (3)	70.6 mg / 0.5 mg
					X							X								0.1 (3)	56.7 mg / 21.1 mg
						X	X													0.1 (3)	179.9 mg / 69.3 mg
X	X	X																		0.1 (2)	43.9 mg / 18.5 mg
X		X				X														0.1 (2)	69.9 mg / 6.8 mg
X			X		X		X					X								0.1 (2)	66.3 mg / 167.1 mg
X												X								0.1 (2)	31.4 mg / 17.8 mg
	X	X			X		X													0.1 (2)	226.0 mg / 73.0 mg
		X	X							X										0.1 (2)	41.4 mg / 71.3 mg
		X			X	X														0.1 (2)	133.8 mg / 10.2 mg
		X								X		X								0.1 (2)	85.4 mg / 46.5 mg
			X							X										0.1 (2)	30.7 mg / 50.1 mg
			X									X								0.1 (2)	17.4 mg / 93.4 mg
					X	X	X													0.1 (2)	282.9 mg / 33.5 mg
					X		X			X										0.1 (2)	61.5 mg / 16.8 mg
					X					X		X								0.1 (2)	78.3 mg / 15.1 mg
													X							0.1 (2)	5.3 mg / 100.2 mg

Table 4.1 cont. Product type(s) most frequently purchased by each patient (out of 2,181 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					Topical					% of Patients (n)	Avg Daily THC (mg) / Avg Daily CBD (mg)
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC		
X	X	X	X		X		X													0.0 (1)	242.7 mg / 111.2 mg
X	X	X			X		X									X				0.0 (1)	105.3 mg / 22.5 mg
X	X	X			X		X													0.0 (1)	293.4 mg / 57.3 mg
X	X		X		X		X													0.0 (1)	205.5 mg / 248.9 mg
X	X				X		X					X								0.0 (1)	115.8 mg / 22.8 mg
X	X					X														0.0 (1)	171.3 mg / 19.2 mg
X	X																X			0.0 (1)	61.6 mg / 19.9 mg
X		X	X		X															0.0 (1)	71.1 mg / 135.3 mg
X		X	X				X													0.0 (1)	177.5 mg / 147.9 mg
X		X	X							X										0.0 (1)	103.5 mg / 345.1 mg
X		X			X	X	X													0.0 (1)	220.1 mg / 13.1 mg
X		X			X			X		X							X			0.0 (1)	177.6 mg / 145.5 mg
X		X			X					X		X								0.0 (1)	199.7 mg / 57.0 mg
X		X					X			X										0.0 (1)	122.2 mg / 48.4 mg
X		X								X		X								0.0 (1)	123.3 mg / 61.6 mg
X		X										X								0.0 (1)	40.9 mg / 31.0 mg
X			X		X		X													0.0 (1)	433.9 mg / 1439.2 mg
X			X				X													0.0 (1)	53.3 mg / 116.4 mg
X			X									X								0.0 (1)	38.2 mg / 98.2 mg
X					X	X	X													0.0 (1)	220.0 mg / 38.8 mg
X					X	X														0.0 (1)	282.5 mg / 10.8 mg
X						X	X													0.0 (1)	100.4 mg / 34.6 mg
X						X														0.0 (1)	147.7 mg / 7.3 mg
X							X			X		X								0.0 (1)	71.9 mg / 27.1 mg
X							X					X								0.0 (1)	72.2 mg / 56.2 mg
X										X		X								0.0 (1)	102.3 mg / 36.6 mg
X												X				X				0.0 (1)	37.4 mg / 21.7 mg
	X	X	X		X					X										0.0 (1)	160.4 mg / 114.2 mg
	X	X			X		X			X										0.0 (1)	553.8 mg / 154.8 mg
	X	X			X															0.0 (1)	86.1 mg / 9.6 mg

Table 4.1 cont. Product type(s) most frequently purchased by each patient (out of 2,181 patients), along with average daily THC/CBD dose (mg).

Enteral					Inhalation					Oromucosal					Topical						
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	% of Patients (n)	Avg Daily THC (mg) / Avg Daily CBD (mg)
	X	X					X													0.0 (1)	236.4 mg / 176.0 mg
	X		X																	0.0 (1)	77.9 mg / 558.7 mg
	X				X	X	X													0.0 (1)	334.6 mg / 44.3 mg
	X				X	X														0.0 (1)	366.1 mg / 11.7 mg
	X				X		X													0.0 (1)	133.8 mg / 41.6 mg
	X						X													0.0 (1)	257.2 mg / 49.1 mg
	X									X										0.0 (1)	36.2 mg / 4.8 mg
		X	X	X								X								0.0 (1)	66.1 mg / 309.8 mg
		X	X		X	X	X													0.0 (1)	161.5 mg / 140.5 mg
		X	X		X					X										0.0 (1)	70.3 mg / 67.0 mg
		X	X		X															0.0 (1)	32.2 mg / 55.1 mg
		X	X			X				X										0.0 (1)	71.3 mg / 144.9 mg
		X	X														X			0.0 (1)	17.5 mg / 107.5 mg
		X			X		X			X		X								0.0 (1)	166.9 mg / 65.8 mg
		X			X		X					X								0.0 (1)	223.8 mg / 97.5 mg
		X			X		X									X	X			0.0 (1)	212.3 mg / 61.7 mg
		X			X		X											X		0.0 (1)	165.3 mg / 66.5 mg
		X			X			X												0.0 (1)	101.2 mg / 123.8 mg
		X				X	X													0.0 (1)	135.3 mg / 37.7 mg
			X			X														0.0 (1)	123.9 mg / 54.6 mg
			X				X													0.0 (1)	15.1 mg / 53.1 mg
			X							X		X								0.0 (1)	32.2 mg / 58.2 mg
					X	X				X										0.0 (1)	297.2 mg / 11.2 mg
					X		X										X			0.0 (1)	58.5 mg / 28.4 mg
					X											X	X	X		0.0 (1)	226.8 mg / 28.0 mg
							X					X								0.0 (1)	17.4 mg / 17.4 mg
								X		X		X								0.0 (1)	55.9 mg / 100.7 mg
								X												0.0 (1)	4.4 mg / 88.0 mg

5. Benefits

Summary

Information on patient benefits comes from the Patient Self-Evaluation (PSE) completed by patients prior to each medical cannabis purchase, from patient and health care practitioner surveys, and from pain scale information at certification by the health care practitioner. Results of analysis of these data indicate perceptions of a high degree of benefit for about half the patients.

Survey Data

Patients responded to a survey question asking them how much benefit they believe they received from using medical cannabis on a scale from 1 (no benefit) to 7 (great deal of benefit). There was a 54% response rate to the survey. Across all responding patients, 61% indicated a benefit rating of 6 or 7. A small but important proportion of patients indicated little or no benefit: 10% gave a rating of 1, 2, or 3. When patients were asked what the most important benefit was for them, 56% indicated pain reduction, 20% improved sleep, 7% reduction of other pain medications, and 4% reduction in anxiety. A total of 64% mentioned pain reduction as a benefit, regardless of whether or not it was the most important benefit.

An important part of this report is the verbatim comments written by patients, and the reader is encouraged to review these comments in *Appendix B: Patient-Reported Benefits from Medical Cannabis*. Examples of these comments include:

- “This program has opened up a world for me I thought I lost.
  I started on this just a few short months ago and am totally off my narco's and nicatin. I also have had less spasms and cramping through out my body. I even chanced getting on a motorcycle and going for a short ride with a friend before it snowed. Thought never do that again. It has also helped me gain weight. and silence some demons in my head from my PTSD. So, thank you. Now all I ask is make it affordable to stay on.”
- “At first, when I began using the medical cannabis for pain, I Definitely noticed a Drastic Relief in my pain levels - that was So Wonderful - I was So Hopeful. Then, unfortunately, after the first week of using the cannabis regularly, the efficacy for the pain relief I had been receiving began to steadily wane..., to the point of no noticeable pain relief at all within a 6 to 8 week period - even though I carefully "upped" the dosage and the frequency of dosing, etc... I'm so disheartened..., but I know others with the same type of pain that I have that are experiencing and sustaining far better pain relief.”

- "Medical cannabis has not made a difference for me. I have never used it before and was a little hesitant to try. When I did I found that I had no relief of pain and I didn't like the way I felt so I discontinued use."
- "The vaporizer has increased by ability to relax and fall asleep, something I struggled with a great deal due to pain. I have not found the other methods helpful. I do not feel it helps my pain, but simply makes me think about it less?"
- "Reduction in migraine occurrence and severity, improved sleep, less overall muscle aching and cramping, pain relief from arthritic joints, reduction in GI reflux which also aids sleep."
- "I have fibromyalgia. I lived my life in constant pain my daily pain on an average was an 8. I started taking medical cannabis in August. I now have a daily pain average between 2 and 3. After 2 weeks of cannabis I cooked my first meal in 15 years. My husband was doing all of the cooking and housework I am now able to help with it."

Health care practitioners were somewhat more conservative in assessment of benefit to their patients: 43% indicated a benefit rating of 6 or 7 and 24% gave a rating of 1,2, or 3. Distribution of type of benefit was similar to patient survey responses. There was a 40% response rate to the health care practitioner survey.

Analysis of patient and health care practitioner benefit ratings by primary cause of pain suggests some differences by pain type. However, for all but a handful of pain types, the number of patients in each group is too small to be sure of differences. Among the more common pain causes, benefit scores are somewhat higher in both patient and health care practitioner results for fibromyalgia/myofascial pain, rheumatoid arthritis, migraine headache, and neck pain.

In addition to the 1-7 benefit rating health care practitioners provide on surveys, they also give updated scores on pain assessment tools. Pain assessment scores provided when they certified the patient for intractable pain were compared with the score given on the 6-month survey. A reduction of ≥30% was used to define clinically meaningful improvement, and 41% met this threshold (50% when the PEG tool was used; 39% when the 0-10 numerical rating scale was used – these were by far the two most commonly used tools).

A large proportion (58%) of patients on other pain medications when they started taking medical cannabis were able to reduce their use of these meds according to health care practitioner survey results. Opioid medications were reduced for 38% of patients (nearly 60% of these reduced at least one opioid by ≥50%), benzodiazepines were reduced for 3%, and other pain medications were reduced for 22%. If only the 353 patients (60.2%, based on medication list in first Patient Self-Evaluation) known to be taking opioid medications at baseline are included, 62.6% (221/353) were able to reduce or eliminate opioid usage after six months.

Patient Self-Evaluation Data

The intractable pain patients included in this report had a high burden of symptoms. A majority had at least moderate levels of fatigue (94%), disturbed sleep (91%), anxiety (77%), depression

(67%), and lack of appetite (53%) – as well as pain. For each of these symptoms except for pain intensity and fatigue, 30-40% of patients achieved and maintained ≥30% symptom reduction. Pain intensity (over the last 24 hours) showed lower levels of improvement, with 28% achieving ≥30% improvement and only 10% both achieving and maintaining ≥30% improvement over four months.

Data from responses to the composite PEG scale suggests higher levels of improvement. The PEG is a three-item scale that asks the patient to assess, over the past week, pain intensity and its interference with enjoyment of life and general activity. Using PEG scale data, 42% achieved ≥30% reduction and 22% both achieved and maintained ≥30% reduction over four months. The higher level of improvement seen with the PEG scale is likely a result of its capture of pain's impact on quality of life as well as pain intensity and, perhaps, its use of the past week's experience (rather than the past 24 hours). It is interesting to see differences in the three PEG component scores. A larger proportion of patients showed improvement in pain interfering with enjoyment of life (48.8%) and general activity (48.8%) than average pain intensity (35.1%). This finding is consistent with survey comments indicating a wider range of benefits than only reduction in pain intensity – including some patients who clearly expressed big improvement in their quality of life even though the pain intensity had not changed.

Analysis of change in PEG score by primary cause of pain showed few clear differences, though there is a suggestion that patients with migraine headache had relatively higher rates of improvement and patients with pain due to trauma were less likely to show improvement.

Medical cannabis products used when a patient achieved ≥30% reduction in pain scores tended to include Very High THC:CBD vaporization oil, often in combination with a Balanced THC:CBD enteral or vaporization oil product. Some patients used Balanced THC:CBD products only; use of high CBD:THC products was relatively uncommon.

Benefits Reported on Patient Experience Survey and Health Care Practitioner Survey

Utilizing expertise within the Minnesota Department of Health, the Office of Medical Cannabis developed a Patient Experience survey, which captures information on benefits and harms of program participation. A parallel survey for each patient was developed for their certifying health care practitioner, which captures similar information from the clinician's perspective. In addition to this, health care practitioners were also asked to provide any clinical observations they noted about the patient's experience with medical cannabis. When intractable pain became a qualifying condition in the Minnesota Medical Cannabis program, a few additional questions were added to surveys sent for patients certified for intractable pain. Healthcare practitioners are asked to report whether the patient was able to reduce or eliminate the use of any pain medications as a result of medical cannabis. They are also asked in the survey, as they are asked during the initial certification process for patient enrollment, to report the patient's pain level as a score on a validated pain assessment. They can select from a number of common pain assessment tools or enter a score for a different assessment tool.

Survey Methodology

The surveys are provided through an online platform; in the patient's first program year they are sent to patients three months, then six months after the patient's first medical cannabis purchase and are sent to healthcare practitioners six months after the patient's first medical cannabis purchase. Patients and healthcare practitioners access the surveys through the subject's registry page and through introductory emails containing unique links. To maximize survey submission rates, the survey can be submitted with incomplete responses to any of the questions. Each of the surveys is available online to the recipient for 45 days. Patient recipients receive reminder emails after one week; after two weeks with no response, paper copies of surveys are mailed to the recipient. For patients without online access the full process is accomplished by phone or mail.

Survey Data Preparation

Patients and their certifying HCPs were asked to report the benefits and negative effects, if any, they have experienced as a result of medical cannabis treatment (in order of importance to the patient.) Survey responses from patients and health care practitioners on perceived benefits and perceived negative effects were reported in free-text format; each response was individually reviewed and classified into a category of benefit or negative effects. Reported benefits typically included either direct improvement of symptoms related to the patient's qualifying condition or more general improvements in health or quality of life, referred to in this report as global health benefits. Many responses included more than one type of benefit; in these cases, the first reported benefit was presumed to be the most important benefit. In this report, we examine both overall perceptions of benefit, as well as type of reported benefit. For

patients certified for intractable pain, reports of pain reduction, spasm reduction or improvement in neuropathy-related symptoms were considered to be direct symptom improvements; other benefits were generally considered to be global health benefits and were further classified into categories (Table 5.3.)

Patient-Reported Benefits

Of 2,245 patients certified for intractable pain between August 2016-December 2016, 2,175 (96.9%) made a first purchase of medical cannabis before July 15, 2017 and were sent a survey three months after their first purchase. Among these patients, 1,173 (53.9%) responded to the survey. Response rates by age category varied somewhat, with a slight underrepresentation of younger patients (Table 5.1). Response rates by race/ethnicity also varied and tended to underrepresent minority groups, particularly black or Hispanic patients (Table 5.2).

Table 5.1. Patient response rates by age group.

Age Group	Total	Patient Responses
0-4 yrs	2	1 (50%)
5-17 yrs	8	3 (38%)
18-24 yrs	58	28 (48%)
25-35 yrs	299	140 (47%)
36-49 yrs	570	325 (57%)
50-64 yrs	823	465 (57%)
65+ yrs	415	211 (51%)

Table 5.2. Patient survey response rate by race and ethnicity.

Race/Ethnicity	Total	Patient Responses
American Indian	56	28 (50%)

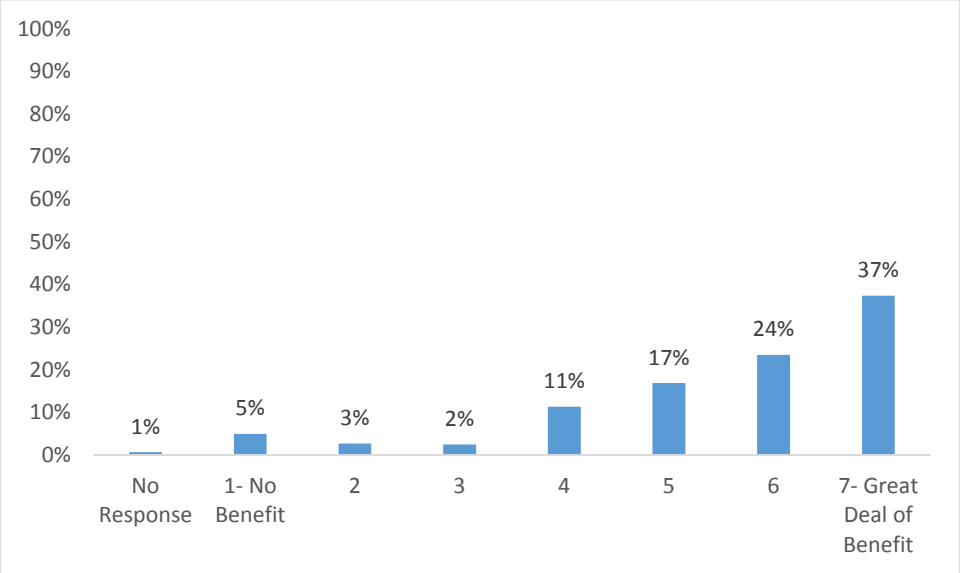
Asian	20	11 (55%)
Black	89	39 (44%)
Hawaiian	4	4 (100%)
White	1899	1058 (56%)
Hispanic	54	25 (46%)
Other	37	20 (54%)

Patient Perceptions of Benefit from Medical Cannabis

The Patient Experience survey asks patients to report how much benefit they have experienced as a result of medical cannabis, on a scale from 1 (representing no benefit) to 7 (representing a great deal of benefit). Patients are also asked to report the types of benefits they have experienced as a result of medical cannabis. Figure 5.1 shows the distribution of scores on the benefit scale from respondents- the percentages use the total number of survey respondents as the denominator, though in a small number of cases (n=8) surveys were returned incomplete and did not report a benefit score.

Of 1,173 patients who responded to the survey, 715 patients (61%) reported a benefit score of 6 or 7, indicating a high degree of benefit from medical cannabis.

Figure 5.1. Patient-Perceived Benefit in Survey Respondents (N=1,173).



Patient responses regarding types of benefits experienced as a result of medical cannabis treatment are shown in Table 5.3 and Figure 5.2. Table 5.3 shows the most important benefits reported by patients, as determined from the order of benefits listed. Figure 5.2 shows overall frequency of each benefit category, regardless of whether or not it was the most important benefit reported by a patient.

Of 1,173 patient respondents, 656 (56%) reported pain reduction as the most important benefit from medical cannabis (Table 5.3). Global health benefits not directly related to symptom reduction were also reported as the most important benefit: improvement in sleep quality/quantity (n=118; 10%), reduction of other medications or side effects related to other medications (n=78; 7%), reduction of anxiety (n=48; 4%), increase in mobility or ability to function (n=38; 3%), improvement in overall quality of life (n=21; 2%), increase in appetite or reduction of nausea or vomiting (n=17; 1%), reduced depression (n=3) and increase in alertness or improvement of cognitive function (n=3). Among respondents, 163 (14%) did not report any benefits (though in a few cases they reported benefit scores of ≥2). In a few other cases, patients reported a benefit without an accompanying benefit score; these responses are reflected in the total number of responses in each category but not in the breakdown of responses by scores. This included five patients reporting pain reduction and three patients reporting increased alertness or improvement of cognitive function.

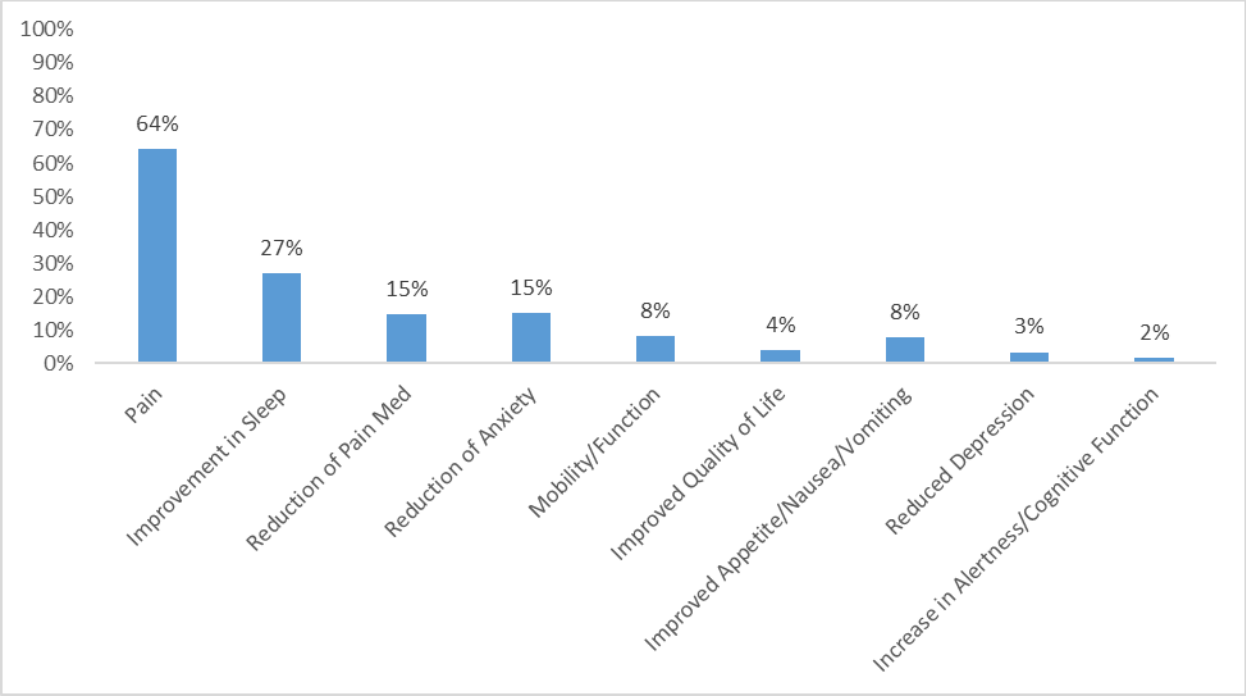
A total of 753 (64%) reported pain reduction as one of the benefits experienced from medical cannabis (not necessarily the most important benefit) (Figure 5.2). Most commonly reported global health benefits which were not necessarily reported as the most important benefit were: improvement in sleep quality/quantity (n=315; 27%), reduction of anxiety (n=178; 15%) and reduction of other medications or side effects related to other medications (n=173; 15%). A full tabulation of patient-reported benefits can be found in *Appendix B: Patient-Reported Benefits from Medical Cannabis.*

Table 5.3. Most important benefits reported by patients, by type and benefit score.

Most Important Benefit	Total	1	2	3	4	5	6	7
Pain Reduction	656 (56%)	0	9	11	80	113	174	264
Improvement in Sleep	118 (10%)	2	5	5	24	29	26	27
Reduction of Pain Medications/Side Effects	78 (7%)	0	0	1	1	11	19	46

Reduction of Anxiety	48 (4%)	1	3	2	5	10	8	19
Mobility/Function	38 (3%)	0	0	0	5	4	8	21
Improved Quality of Life	21 (2%)	0	0	0	0	4	3	14
Improved Appetite/Nausea/Vomiting	17 (1%)	0	0	1	2	5	1	8
Reduced Depression	3 (0%)	0	0	1	0	0	0	2
Increase in Alertness/Cognitive Function	3 (0%)	0	0	0	0	0	0	0

Figure 5.2. Frequency of all patient-reported benefits, by type.



Patient Suggestions

Patients were asked to provide feedback on the program; all responses submitted from the first year cohort are tabulated in *Appendix C: Patient Suggestions for Improving the Program*. Many patients used this space to elaborate on the program's impact on their lives; others suggested

changes to the program's administration or reported concerns related to product cost or access to cannabis patient centers.

Healthcare Practitioner-Reported Benefits

Of 2,245 patients certified for intractable pain between August 2016-December 2016, 2,163 (96.3%) made a first purchase of medical cannabis by March 15, 2017 and their certifying healthcare practitioners were sent a survey six months after their first purchase. Of these surveys, 897 (40.0%) were filled out by healthcare practitioners. Healthcare practitioner response rates by patient age category varied slightly and tended to underrepresent younger patients (Table 5.4). Response rates by patient race/ethnicity also varied and tended to underrepresent minority groups (Table 5.5).

Table 5.4. Healthcare practitioner survey response rates by age group.

Age Group	Total	HCP Responses
0-4 yrs	2	0 (0%)
5-17 yrs	8	2 (25%)
18-24 yrs	58	15 (26%)
25-35 yrs	296	88 (30%)
36-49 yrs	569	177 (31%)
50-64 yrs	818	275 (34%)
65+ yrs	412	135 (33%)

Table 5.5. Healthcare practitioner survey response rates by race and ethnicity.

Race/Ethnicity	Total	HCP Responses
American Indian	56	15 (27%)
Asian	20	6 (30%)
Black	88	19 (22%)
Hawaiian	4	2 (50%)

White	1891	617 (33%)
Hispanic	53	17 (32%)
Other	37	15 (41%)

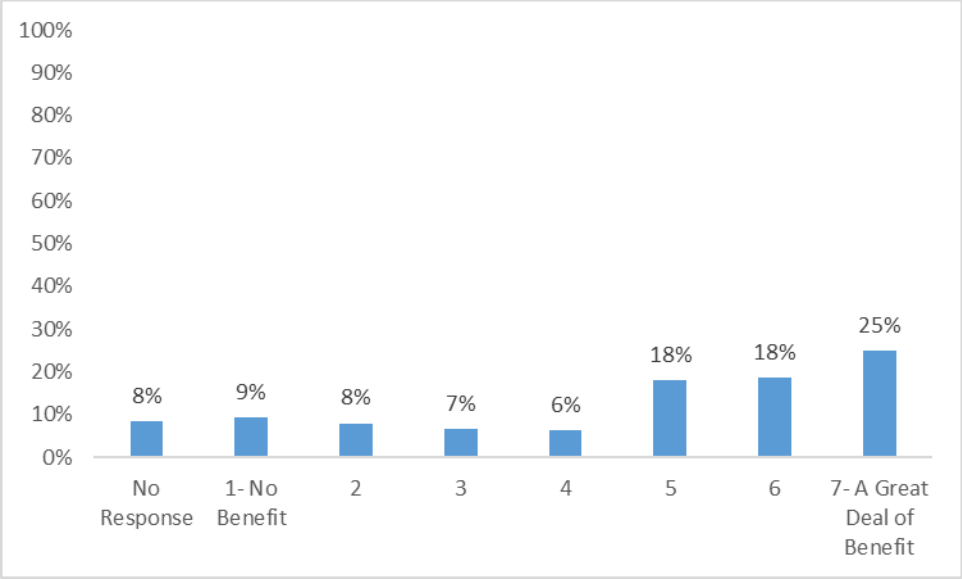
Review of submitted HCP responses revealed that in some cases, healthcare practitioners indicated they had not seen the patient since certification and therefore they had no clinical updates to provide; these surveys were eliminated (n=205), and the remaining 692 (30.8% of surveys) were included in analyses described below.

Healthcare Practitioner Perceptions of Benefit from Medical Cannabis

The Healthcare Practitioner survey asks HCPs to report how much benefit they believe the patient has experienced as a result of medical cannabis, on a scale from 1 (representing no benefit) to 7 (representing a great deal of benefit). They are also asked to report the types of benefits the patient experienced as a result of medical cannabis. Figure 5.3 shows the distribution of scores on the benefit scale from respondents- the percentages use the total number of survey respondents as the denominator, though in some cases (n=58) surveys were returned incomplete and did not report a benefit score.

Of 692 completed surveys, 301 (43%) reported a patient benefit score of 6 or 7, indicating a high degree of benefit from medical cannabis.

Figure 5.3. Healthcare Practitioner-Perceived Benefit in Survey Respondents (N=692).



Healthcare practitioner survey responses regarding types of benefits experienced as a result of medical cannabis treatment are shown in Table 5.6 and Figure 5.4. Table 5.6 shows the most important benefits reported by patients, as determined from the order of benefits listed. Figure 5.4 shows overall frequency of each benefit category, regardless of whether or not it was the most important benefit reported by a patient.

Of 692 healthcare practitioner survey responses, 311 (45%) reported pain reduction as the most important benefit from medical cannabis (Table 5.6). As with patient responses, among HCP responses global health benefits not directly related to symptom reduction were also frequently reported as the most important benefit: improvement in sleep quality/quantity (n=73; 11%), reduction of other medications or side effects related to other medications (n=62; 9%) , increase in mobility or ability to function (n=26; 4%), reduction of anxiety (n=14; 2%), improvement in overall quality of life (n=11; 2%), increase in appetite or reduction of nausea or vomiting (n=11; 2%), and increase in alertness or improvement of cognitive function (n=2).

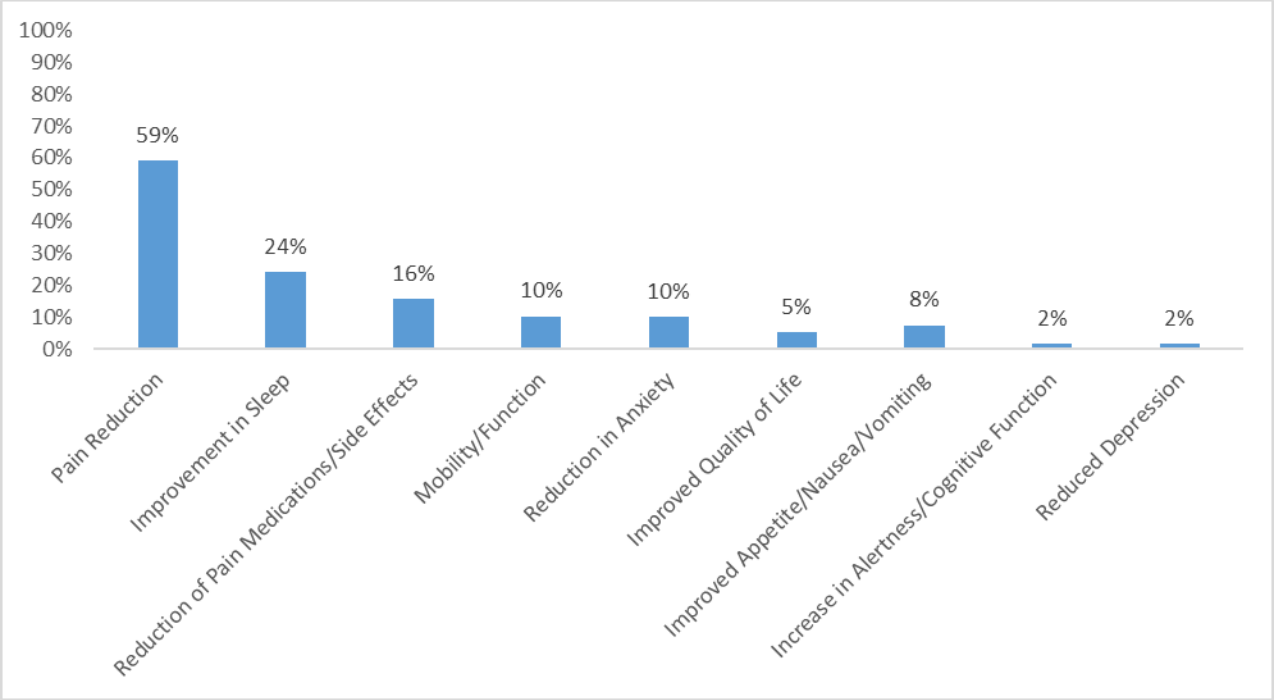
A total of 409 (59%) HCP survey responses reported pain reduction as one of the benefits experienced from medical cannabis (not necessarily the most important benefit) (Figure 5.4). Most commonly reported global health benefits which were not necessarily reported as the most important benefit were: improvement in sleep quality/quantity (n=167; 24%), reduction of other medications or side effects related to other medications (n=110; 16%), increase in mobility or ability to function (n=72; 10%), and reduction of anxiety (n=71; 10%). In some cases, healthcare practitioners reported a benefit without an accompanying benefit score; these responses are reflected in the total number of responses in each category but not in the

breakdown of responses by scores (three reports of pain reduction, two reports of improvement in sleep, one report of improved quality of life and one report of improved appetite). A full compilation of healthcare practitioner-reported benefits is available in *Appendix D: Healthcare Practitioner-Reported Benefits from Medical Cannabis.*

Table 5.6. Most important benefits reported by healthcare practitioners, by type and benefit score.

	Total	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Pain Reduction	311 (45%)	2	16	26	25	65	80	94
Improvement in Sleep	73 (11%)	1	7	5	7	16	16	19
Reduction of Pain Medications/Side Effects	62 (9%)	0	2	3	2	15	14	26
Mobility/Function	26 (4%)	0	0	1	1	10	5	9
Reduction of Anxiety	14 (2%)	0	4	0	1	1	1	7
Improved Quality of Life	11 (2%)	0	1	0	1	1	3	4
Improved Appetite/Nausea/Vomiting	11 (2%)	0	4	1	0	2	1	2
Increase in Alertness/Cognitive Function	2 (0%)	0	0	1	1	0	0	0
Reduced Depression	0 (0%)	0	0	0	0	0	0	0

Figure 5.4. Frequency of all healthcare practitioner-reported benefits, by type.



Healthcare Practitioner Reports of Reduction in Pain Medications

Healthcare practitioners who certify patients for intractable pain are posed the following question in the survey they receive: "Over the past 6 months has this 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)." Of 692 survey responses, 68 reports indicated that the patient did not use pain medication six months prior and 38 responses were left blank. Of the remaining 586 reports, 340 (58.0%) reports indicated a reduction of pain medications and 246 (42.0%) reports indicated no reduction in pain medication use. Among reports of reduced pain medication use, 13 (3.8%) did not specify types or quantities of reduced medications. A total of 221 reports indicated that the patients reduced their use of opioids, representing 37.7% of all patients for whom we have information on reduction of pain medications since starting medical cannabis. If only the 353 patients (60.2%, based on medication list in first Patient Self-Evaluation) known to be taking opioid medications at baseline are included, 62.6% (221/353) were able to reduce or eliminate opioid usage after six months. Of these 221 patients, 127 (57.5%) were reported as reducing at least one opioid by 50% or more.

Sixteen reports indicated reduction of at least one benzodiazepine medication, with 10 surveys indicating a reduction of 50% or more of at least one benzodiazepine. Additionally, 128 reports

indicated that the patient reduced at least one pain medication other than an opioid or benzodiazepine, with 71 (55.5%) reporting a reduction of 50% or more of at least one other pain medication. Pain medications other than opioids or benzodiazepines reported in this section included a variety of pain medications, as well as generic references to "pain medications" without specifying a medication name or type. As a result, the proportion of reports describing reduction of opioids or benzodiazepines is likely an underestimate. A full compilation of HCP responses to the question of pain medication reduction from medical cannabis treatment can be found in *Appendix E: Healthcare Practitioner-Reported Reduction of Pain Medication*.

Patient and Health Care Practitioner-Reported Benefit Scores by Pain Cause

Benefit scores from the Patient Experience Survey and Healthcare Practitioner Survey of ≥6 were classified as "high degree of benefit"; benefit scores of ≤3 were classified as "low degree of benefit." The proportion of patient and HCP survey respondents reporting high or low degrees of benefit was stratified by primary pain cause, as reported at initial certification for Intractable Pain (Table 5.7) Among the most common pain causes (n≥100), patients with migraine headache, neck pain, neuropathy and fibromyalgia/myofascial pain reported a high degree of benefit most frequently (74%, 66%, 60%, and 59% of patient respondents, respectively); patients with axial back pain reported a high degree of benefit less frequently than patients with other types of pain (35%). Healthcare practitioner survey responses for patients with fibromyalgia/myofascial pain, neck pain and osteoarthritis reported a high degree of benefit most frequently (54%, 49%, and 45% of HCP respondents, respectively.)

Table 5.7. Patient and healthcare practitioner benefit scores, by primary cause of pain.

Primary Pain Cause	Patient Survey Responses	PES Benefit Score ≤3	PES Benefit Score ≥6	HCP Survey Responses	HCP Benefit Score ≤3	HCP Benefit Score ≥6
Back pain, axial	260 (50%)	21 (8%)	90 (35%)	157 (30%)	60 (38%)	61 (39%)
Back pain, radicular	149 (49%)	22 (15%)	84 (56%)	77 (25%)	25 (32%)	31 (40%)
Fibromyalgia/myofascial pain	135 (58%)	15 (11%)	80 (59%)	65 (28%)	14 (22%)	35 (54%)
Neuropathy	102 (59%)	10 (10%)	61 (60%)	53 (31%)	21 (40%)	20 (38%)
Osteoarthritis	78 (47%)	12 (15%)	40 (51%)	53 (32%)	18 (34%)	24 (45%)

Neck pain	56 (54%)	6 (11%)	37 (66%)	35 (34%)	9 (26%)	17 (49%)
Migraine Headache	43 (50%)	0 (0%)	32 (74%)	31 (36%)	6 (19%)	15 (48%)
Trauma	41 (51%)	3 (7%)	26 (63%)	39 (48%)	8 (21%)	20 (51%)
Rheumatoid Arthritis	42 (58%)	3 (7%)	25 (60%)	26 (36%)	4 (15%)	14 (54%)
Headache Other Than Migraine	31 (52%)	2 (6%)	19 (61%)	20 (33%)	6 (30%)	8 (40%)
Complex Regional Pain Syndrome	27 (63%)	0 (0%)	14 (52%)	15 (35%)	7 (47%)	5 (33%)
Spinal Stenosis	22 (61%)	4 (18%)	12 (55%)	11 (31%)	4 (36%)	3 (27%)
Postoperative Pain	21 (72%)	3 (14%)	15 (71%)	16 (55%)	5 (31%)	5 (31%)
Myelopathies	15 (54%)	0 (0%)	12 (80%)	2 (7%)	1 (50%)	0 (0%)
Pelvic Pain	11 (50%)	2 (18%)	6 (55%)	6 (27%)	2 (33%)	3 (30%)
Spinal Cord Injury	10 (45%)	2 (20%)	4 (40%)	9 (41%)	3 (33%)	2 (22%)
Disc (Vertebral) Herniation	8 (38%)	0 (0%)	3 (38%)	4 (19%)	1 (25%)	2 (50%)
Abdominal Pain	11 (65%)	1 (9%)	7 (64%)	6 (35%)	2 (33%)	1 (17%)
Cancer	6 (38%)	0 (0%)	3 (50%)	2 (13%)	1 (50%)	0 (0%)
Ehler-Danlos Syndrome	8 (50%)	0 (0%)	3 (38%)	5 (31%)	2 (40%)	2 (40%)
Connective Tissue Diseases (Excluding Rheumatoid Arthritis)	3 (20%)	0 (0%)	2 (67%)	3 (20%)	3 (100%)	0 (0%)
Pancreatitis	7 (58%)	0 (0%)	6 (86%)	2 (17%)	0 (0%)	1 (50%)
Arthritis, Other Inflammatory	4 (36%)	1 (25%)	3 (75%)	5 (45%)	0 (0%)	5 (100%)
Sciatica	4 (40%)	0 (0%)	3 (75%)	5 (50%)	1 (20%)	4 (80%)

Health Care Practitioner-Reported Pain Assessment Score

At each certification and re-certification of a patient with intractable pain, the certifying healthcare practitioner is required to report the pain assessment tool used to evaluate the patient's pain symptoms, date of most recent assessment and assessment score. Options for

pain assessment tool are the PEG (Pain, Enjoyment, General Activity) 3-Item Scale (a three-question assessment on a 0-10 scale)[2], the Pain Intensity Numerical Scale (pain intensity in the past 24 hours on a 0-10 scale), the Brief Pain Inventory- Short Form Pain Interference Composite Score or Pain Severity Composite Score (each is a calculated average of different 0-10 scaled components), the Oswestry Low Back Disability Index (questionnaire scored from 0%-100% disability)[3], or the Neuropathic Pain Scale: Pain Intensity Score (pain intensity on a 0-10 scale)[4]. Healthcare practitioners also could opt to describe another pain assessment tool and provide a score using that assessment. In several cases HCPs reported a pain score using the Health Assessment Questionnaire- Disability Index (scored on a scale from 0-3). Table 5.8 shows the distribution of pain assessment tools used and proportion of patients in each group with a score considered to reflect moderate or severe pain. On 0-10 scales, a score of ≥4 was considered moderate or severe. Scores on the Oswestry Low Back Disability Index were considered to be moderate or severe if ≤21% per the tool's scoring instructions; scores on the Health Assessment Questionnaire-Disability Index pain scale of ≤1.0 were considered to be moderate or severe. Overall, 96% of patients in the Intractable Pain 5-month cohort had moderate or severe pain scores. Patients whose pain was assessed using the Oswestry Low Back Disability Index had an overall 75% incidence of moderate or severe disability.

Table 5.8. Distribution of pain assessment types and moderate/severe pain scores at initial certification.

	Patients With Baseline Pain Scores	Patients with Moderate or Severe Pain
PEG 3-Question Scale	909	902 (99%)
Pain Intensity Numerical Rating Scale	825	776 (94%)
Brief Pain Inventory- Short Form/Pain Severity Composite Score	238	235 (99%)
Brief Pain Inventory- Short Form/Pain Interference Composite Score	42	41 (98%)

[2] Krebs, E. E., Lorenz, K. A., Bair, M. J., Damush, T. M., Wu, J., Sutherland, J. M., Asch S, 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.

[3] Fairbank JC, Pynsent PB. The Oswestry Disability Index. Spine (Phila Pa 1976). 200 Nov 15;25(22):2940-52; discussion 2952.

[4] Galer B, Jensen M. Development and preliminary validation of a pain measure specific to neuropathic pain. The neuropathic pain scale. Neurology 1997;48:332-338.

Oswestry Low Back Disability Index	128	96 (75%)
Neuropathic Pain Scale: Pain Intensity Score	50	50 (100%)
Health Assessment Questionnaire- Disability Index	50	50 (100%)
Total	2242	2150 (96%)

**Four pain score entries were not reported in usable formats and are not included above.*

The Healthcare Practitioner Survey sent six months after the patient's first purchase of medical cannabis also asks HCPs to report an updated pain assessment score. Of 692 completed HCP 6-month surveys for the Intractable Pain 5-month cohort, 489 (70.7%) used the same pain assessment tool in reporting a pain score and therefore provided scores that could be compared to the initial pain assessment score at certification: 111 (22.7% of paired scores) used the PEG 3-Item Scale, 368 (75.3% of paired scores) used the Pain Intensity Numerical Rating Scale, 7 (1.4% of paired scores) used the Brief Pain Inventory- Short Form Pain Severity Composite Score and 2 (0.4% of paired scores) used the Brief Pain Inventory- Short Form Pain Interference Composite Score. One report used the Health Assessment Questionnaire Disability Index pain scale. Within the group of paired scores with matching pain assessment tools, 202 HCP survey responses (41.3%) reported a recent pain score 30% or more lower than the pain score reported at certification (Table 5.9).

Table 5.9. Patients With Pain Score Reduction After 6 Months of Program Participation.

	Patients with Baseline and 6-Month Pain Scores	**Patients with 30% Reduction in Pain Score or Greater**
PEG 3-Question Scale	111	56 (50%)
Pain Intensity Numerical Rating Scale	368	142 (39%)
Brief Pain Inventory- Short Form/Pain Severity Composite Score	7	2 (27%)
Brief Pain Inventory- Short Form/Pain Interference Composite Score	2	1 (50%)

Rheumatology Modified Health Assessment Questionnaire and Pain Scale	1	1 (100%)
Total	489	202 (41%)

Healthcare Practitioner Suggestions and Clinical Observations

As with patients, healthcare practitioners were asked to provide feedback on the program; all responses submitted from the first year cohort are tabulated in *Appendix F: Healthcare Practitioner Suggestions for Improving the Program*. In addition, HCPs were asked to share any clinical observations they had on the patient, with provided examples including drug interactions. All responses were tabulated in *Appendix G: Healthcare Practitioner-Reported Clinical Observations*.

Benefits Reported on the Patient Self-Evaluation

A separate source of information on benefits apart from the Patient Experience Survey (discussed in the previous section) is the symptom data provided by patients on the Patient Self-Evaluation. Completion of the Patient Self-Evaluation (PSE) is required prior to every medical cannabis purchase including prior to each patient's first purchase. This allows the opportunity to understand the symptom status of the patient at the outset of program participation (symptom baseline) and how it is changing over time with their medical cannabis usage.

Two sets of measures are collected on the PSE, which includes a standard set of questions that all patients receive (the "standard 8"), as well as condition-specific questions which a subset of patients receive depending on their certified conditions. In the case of Intractable Pain (IP) patients, they receive three additional questions beyond the Standard 8 to assess pain intensity and interference developed by Krebs et al.: the PEG Scale[5]. These two sets of symptom measures and results will be discussed in this section for IP patients enrolled in the program from August 1, 2016 through December 31, 2016.

Standard 8 Symptom Data

All patients, regardless of their certified condition(s), receive a set of 8 symptom questions which are answered on a 0-10 numerical rating scale (NRS), with 0 indicating absence of the symptom to 10 indicating that the symptom is as bad as the patient can imagine (see Box 5.1). Therefore, higher scores indicate greater symptom severity. Patients are asked to rate symptom severity over the *past 24 hours*.

[5] Krebs EE, Lorenz KA, Bair MJ, et al. Development and initial validation of the PEG, a three-item scale assessing pain intensity and interference. *Journal of General Internal Medicine*. 2009; 24(6): 733-738. doi:10.1007/s11606-009-0981-1

Box 5.1. Listing of the Standard 8 symptom measures that all patients answer, including the responses options available to patients.

Standard 8 Symptom Measures:

Anxiety	Fatigue
Lack of Appetite	Nausea
Depression	Pain
Disturbed Sleep	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 image

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 = pain; E = enjoyment of life; G = general activity). 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 8 questions.

Research Objectives

To understand the degree of benefits each patient obtained during their participation in the program, the following three questions were explored for each Standard 8 symptom measure and PEG scale:

QUESTION 1

Of those patients who experienced moderate to severe symptoms at baseline (score of 4 or higher at baseline), what percentage of them experienced at least a 30% improvement in symptoms within four months of their first medical cannabis purchase? The threshold of ≥30% reduction on a 0-10 point scale was chosen for the Standard 8 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 3-point change generally reflects improvements on the Pain Global Rating of Change.

QUESTION 2

If a patient achieved at least a 30% improvement on symptoms within 4 months of their first medical cannabis purchase (determined in Question 1), what percentage of them will, on average, still maintain that level of improvement in the four months following that initial 30% symptom improvement? [Four-month follow-up period]

QUESTION 3

What medical cannabis products were purchased just *prior* to the patient's first report of ≥30% improvement on the PSE? What was the average daily intake of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) for these product types?

To address Question 1 the following procedure was adopted for each standard 8 measure and for the PEG: all patients who scored 4 or higher at baseline were identified as those experiencing moderate to severe symptoms, and all symptom responses that were submitted within 4 months of their first medical cannabis purchase were retained. From this dataset, each patient's standard 8 and PEG responses were compared to their baseline responses over time. The first instance a patient achieved at least a 30% symptom improvement was recorded, effectively demonstrating when – during the first 4 months following their first medical cannabis purchase – the patient achieved clinically meaningful symptom improvement, if at all.

Calculating the percentage of patients who achieved ≥30% symptom improvement within 4 months of their first medical cannabis purchase (Question 1) was done in the following way: the number of patients achieving ≥30% symptom improvement within 4 months was divided by the number of patients who made a first purchase (all patients with a baseline PSE submission). This allows for a conservative estimation of symptom benefit since a patient may have discontinued purchasing medical cannabis because of lack of effectiveness.

Since Question 1 examines symptom improvement within 4 months of their first medical cannabis purchase, patients who had not been enrolled in the program for at least 4 months since their first medical cannabis purchase were not included in the analysis. When PSE data were extracted in early November 2017, 2174 patients from this report's Intractable Pain cohort (96.8% of the IP patients enrolled between August 1, 2016 through December 31, 2016) had been enrolled for at least 4 months since their first medical cannabis purchase—results on the standard 8 symptom measures and PEG are reported on this cohort subset.

Question 2 was addressed by observing all symptom responses in the four months *following* the time point when the patient first achieved ≥30% symptom improvement. For each patient, all symptom responses identified during those follow-up four months were averaged together.

Patients who, on average, still maintained at least a 30% symptom improvement from baseline were defined as showing persistence in their symptom benefits.

For Question 3, products that were purchased just *prior* to each patient's initial ≥30% symptom improvement were identified and categorized by their THC/CBD ratio and intended route of administration (ROA). See Box 5.2 for definitions of these categories.

Box 5.2. 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** = >4:1 up to 99:1
- **Balanced** = 1:1 up to 4:1
- **High CBD to THC** = ≥1:1 up to 99:1
- **Very High CBD to THC** = 100:1 or higher

Product Routes of Administration (ROA):

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

Results: Standard 8 Measures

To view the distribution of patient responses at baseline on the Standard 8 symptoms, please see *Appendix H: Baseline Responses on Symptom Measures in the Patient Self-Evaluation*. Table 5.10 below lists the Standard 8 symptom measures along with results on symptom improvement and persistence in patients who experienced at least moderate to severe symptoms at baseline (n = 2174). This table addresses Questions 1 and 2 of the research objective for this section of the report. The third column from the left shows the percentage of patients experiencing moderate to severe symptoms for any given Standard 8 measure—these are the patients that were followed through the course of the analysis. Results suggest that, apart from vomiting and nausea, the majority of patients experience high symptom burden. For example, as anticipated by the focus of this report (Intractable Pain), 99.6% of patients experienced at least moderate pain at baseline.

The fourth column in Table 5.10 displays the percentage of patients (among those who experienced moderate to severe symptoms at baseline) who achieved at least a 30% improvement in symptoms within 4-months of their first purchase compared to their baseline measure. Interestingly, patients were less likely to experience at least a 30% improvement in pain compared to other symptoms. Just over a quarter of moderate to severe sufferers of pain achieved at least a 30% reduction in pain. Of those who achieved ≥30% pain reduction, roughly 40% were able to maintain it in the follow-up four months since their initial improvement (Column 6). Overall, of the 2165 moderate to severe pain sufferers, approximately 11% were able to both achieve ≥30% pain reduction and maintain it for at least 4 months (Column 7). Patients appeared to be more responsive to other symptoms, whereby roughly 50-60% of patients achieved ≥30% symptom improvement, with a greater proportion of patients who achieved the ≥30% improvement maintaining it in the 4-month follow-up as well. Out of all symptoms, patients appeared to show greatest response to vomiting symptoms, although the proportion of patients initially reporting this symptom was smaller overall.

Table 5.10. Standard 8 symptom benefits in Intractable Pain patients.

			INITIAL 4-MONTH PERIOD	FOLLOW-UP PERIOD		
	Standard 8 Symptom Measure	**% of Patients Reporting at Moderate to Severe Levels at Baseline (n)**	**% of Patients Achieving ≥30% Symptom Improvement within 4 months of First Purchase out of all Moderate to Severe Baseline Scorers (n)**	**# of Patients with Data in 4-mo Period Following initial ≥30% Symptom Improvement**	**% of Patients Who Achieved ≥30% Symptom Improvement that Maintained it for at least 4 months (n)**	**% of Patients that Both Achieved ≥30% Symptom Improvement and Retained that Degree of Improvement for at least 4 months.**
IP Patients (n = 2174)	Anxiety	77.2 (1679)	57.6 (967)	832	58.9 (570)	33.9
	Appetite Lack	53.1 (1154)	61.4 (709)	614	60.9 (432)	37.4
	Depression	66.8 (1453)	59.7 (867)	741	59.9 (519)	35.7
	Disturbed Sleep	90.9 (1977)	55.7 (1102)	961	56.5 (623)	31.5
	Fatigue	93.7 (2036)	45.2 (920)	813	50.9 (468)	23.0
	Nausea	47.3 (1028)	64.4 (662)	571	62.4 (413)	40.2
	Pain	99.6 (2165)	27.9 (603)	540	39.3 (237)	10.9
	Vomiting	20.1 (437)	72.5 (317)	268	71.3 (226)	51.7

As discussed previously, it is important to keep the following in mind when examining results in Table 5.10. Calculations on the percentage of patients achieving/maintaining ≥30% improvement was performed to give a conservative estimate of benefit. Patients who did not make any additional purchases (and therefore did not submit any additional symptom data) were included in the denominator for the analyses in Table 5.10. It is reasonable to assume that some patients may have discontinued purchasing medical cannabis because of a lack of effectiveness, although they may have discontinued use for other reasons as well (i.e., affordability of medical cannabis, side effects, etc.). Therefore, calculations of symptom benefit are attenuated by including these patients into the denominator.

Medical Cannabis Use Preceding Initial Symptom Improvement

To describe what medical cannabis products patients used just prior to their initial symptom improvement, all patients who achieved ≥30% symptom improvement were identified (patients in Column 4 of Table 5.10). The purchasing transaction immediately preceding each patient's initial improvement was extracted, with all products purchased in that transaction categorized according to the products' intended route of administration (ROA) and THC:CBD content ratio. Due to the sheer size of displaying this information and the complexity in interpreting it, full tables are displayed in *Appendix I: Medical Cannabis Products Purchased Prior to Initial ≥30% Symptom Improvement* rather than in this section of the report. This report will instead focus on the general patterns in medical cannabis consumption that typically preceded initial symptom reduction. [As a space-saving measure, please note that the Topical route of administration does not appear in the tables in *Appendix I: Medical Cannabis Products Purchased Prior to Initial ≥30% Symptom Improvement*; no topical products appeared in any transactions preceding initial symptom improvement].

Regardless of the Standard 8 symptom in question, the same product types generally appeared as the most frequently consumed ones in roughly 53-55% of all patients when initially achieving ≥30% symptom improvement. Inhaled products with a Very High THC:CBD ratio were most commonly consumed by patients, usually followed by a combination of a Very High THC:CBD inhaled product and Balanced enteral product. Other most commonly found products preceding symptom improvement typically paired a Very High THC:CBD inhaled product with something else—usually a Very High THC:CBD enteral product or paired with another inhaled product (a Balanced inhaled product).

Table 5.11 shows the most commonly consumed medical cannabis products that preceded initial improvements in pain, as reported on the PSE. The second column from the right displays the percentage of patients who consumed the same product types just before the initial report of symptom improvement (consumed product(s) are denoted with an "X"), with the average daily THC/CBD dose (mg) among those patients shown in the right-most column. [Note: Oromucosal route of administration is not shown in the table below as a space-saving measure; none of the top 5 most frequently consumed products were for oromucosal administration]

Table 5.11. Top 5 medical cannabis product type(s) purchased by Intractable Pain patients just prior to achieving the initial 30% reduction in the Standard 8 pain measure.

Enteral					Inhalation						
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	% of Patients out of 602 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
					X					20.4 (123)	72.3 mg / 0.5 mg
		X			X					10.6 (64)	72.9 mg / 22.2 mg
X					X					8.6 (52)	120.2 mg / 0.6 mg
		X								8.6 (52)	35.0 mg / 30.6 mg
					X		X			7.8 (47)	214.8 mg / 22.4 mg

Results: PEG Scale

PEG scale data were extracted during the same time period as the Standard 8 measures (early November 2017) which resulted in the same subset of the IP cohort being represented in the dataset (n = 2174). This subset reflected patients who enrolled under IP as one of their certifying conditions from August 1, 2016 through December 31, 2016. In addition, at the time of data extraction, these patients had at least a 4-month observation period since their first medical cannabis purchase.

Table 5.12 below shows the results on the PEG scale. The table shows the composite PEG score as well as results on the individual PEG items. Due to the IP focus of this report, it is not surprising to see that close to all IP patients scored moderate to high on the PEG composite (Column 3). Of those patients, 42.3% experienced ≥30% improvement (reduction) on the PEG composite score within 4 months of their first purchase (Column 4). In addition, roughly half of the patients who experienced ≥30% reduction on the PEG composite maintained it in the four-month follow-up period (Column 6). Overall, just under a quarter (21.8%) of all moderate to high scorers on the PEG composite experienced both improvements in pain management and maintained it in the following four months.

Some differences emerge when analyzing the PEG by the individual components (see Table 5.12). For example, a greater proportion of patients showed improvements in pain interfering with enjoyment of life (48.8%) and general activity (48.6%) than Average Pain (35.1%). This is generally in line with patient survey comments that, while some patients may not experience clinically meaningful reduction in pain intensity, medical cannabis may contribute to improvements in quality of life type factors.

A comparison of the Standard 8 pain responses and the individual PEG-Pain component also draws an interesting contrast. While speculative, the greater responsiveness of patients on the PEG-Pain component suggests that the differences may lie in the question itself. While the Standard 8 pain measure asks patients to rate pain severity at its worst in the last 24 hours, the

PEG-Pain component asks patients to rate their average pain in the last week. A smaller reference point on the Standard 8 pain measure ("last 24 hours"), as well as the emphasis on pain extremes may lead to responses that are susceptible to daily fluctuations; PEG-Pain may be a more robust measure of pain.

Table 5.12. Improvements on the PEG scale in Intractable Pain patients.

	PEG Scale and Components	% of Patients Reporting Moderate to High PEG Scores at Baseline (n)	% of Patients Achieving ≥30% Improvement on the PEG within 4 months of First Purchase out of all Moderate to Severe Baseline Scorers (n)	# of Patients with Data in 4-mo Period Following initial ≥30% PEG Improvement	% of Patients Who Achieved ≥30% PEG Improvement that Maintained it for at least 4 months (n)	% of Patients that Both Achieved ≥30% Improvements on the PEG and Retained that Degree of Improvement for at least 4 months.
IP Patients (n = 2174)	Composite	97.9 (2129)	42.3 (900)	802	51.6 (464)	21.8
	Pain	98.1 (2132)	35.2 (751)	667	46.9 (352)	16.5
	Life Enjoyment Interference	97.5 (2120)	48.8 (1034)	915	51.1 (528)	24.9
	General Activity Interference	97.1 (2112)	48.6 (1027)	904	52.9 (543)	25.7

Table 5.13 shows the most commonly consumed medical cannabis products that preceded initial ≥30% reductions (improvements) on the PEG composite score. The second column from the right displays the percentage of patients who consumed the same product types just before the initial report of improvements on the PEG composite score (consumed product(s) are denoted with an "X"), with the average daily THC/CBD dose (mg) among those patients shown in the right-most column. [Note: Oromucosal route of administration is not shown in the table below as a safe saving-measure; none of the top 5 most frequently consumed products were for oromucosal administration]

Similar to findings on the Standard 8 measure, roughly half of all patients consumed the same product types when they initially reached ≥30% reduction on the PEG composite score. Inhaled products with a Very High THC:CBD ratio was most commonly consumed by patients, followed by a combination of a Very High THC:CBD inhaled product and Balanced enteral product.

Table 5.13. Top 5 medical cannabis product type(s) purchased by Intractable Pain patients just prior to achieving the initial 30% improvement on the PEG composite score.

Enteral					Inhalation						
Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	Very High THC to CBD	High THC to CBD	Balanced	High CBD to THC	Very High CBD to THC	% of Patients out of 899 (n)	Avg Daily THC Use (mg) / Avg Daily CBD Use (mg)
					X					18.6 (167)	69.4 mg / 0.5 mg
		X			X					11.8 (106)	76.6 mg / 26.6 mg
		X								7.6 (68)	34.7 mg / 27.4 mg
					X		X			7.5 (67)	99.7 mg / 23.8 mg
X					X					6.2 (56)	88.5 mg / 0.5 mg

Results: PEG Composite Stratified by Primary Cause of Pain

To examine for any differences in the PEG due to pain cause, the PEG composite score was stratified by the patient's primary cause of pain. Primary cause of pain was reported by the patient's health care practitioner (HCP) at the time of certification and adjudicated where appropriate for analysis.

Table 5.14 shows PEG composite scores as a function of pain cause. Overall results generally show similar PEG composite scores across individuals with different primary causes of pain (note that Table 5.14 omits thirty-seven primary pain causes from the list because they each consisted of one patient). However, with the exception of the first several rows of data, the small sample sizes in the table do not allow for reliable interpretation of the data. For patient groups with greater sample sizes, the most noticeable differences were observed between patients whose primary cause of pain was migraines (Row 7) and those whose primary cause of pain was trauma (including vertebral compression fracture (Row 8)). The migraine group had

relatively higher rates of improvement on the PEG composite score compared to other groups with larger sample sizes. In contrast, those whose primary cause of pain was trauma were less likely to show improvements on their PEG composite scores.

Table 5.14. Improvements on the PEG composite score in Intractable Pain patients, stratified by primary cause of pain.

PEG Composite Results Stratified by Patient's Primary Cause of Pain	% of Patients Reporting Moderate to High PEG Scores at Baseline (n)	% of Patients Achieving ≥30% Improvement on the PEG within 4 months of First Purchase out of all Moderate to Severe Baseline Scorers (n)	# of Patients with Data in 4-mo Period Following initial ≥30% PEG Improvement	% of Patients Who Achieved ≥30% PEG Improvement that Maintained it for at least 4 months (n)	% of Patients that Both Achieved ≥30% Improvements on the PEG and Retained that Degree of Improvement for at least 4 months.
Back pain, axial (n = 503)	97.4 (490)	41.0 (201)	183	54.7 (110)	22.4
Back pain, radicular (n = 295)	98.3 (290)	45.5 (132)	116	56.8 (75)	25.9
Fibromyalgia/myofascial pain (n = 222)	99.1 (220)	42.3 (93)	79	46.2 (43)	19.5
Arthritis: osteoarthritis (n = 161)	100.0 (161)	42.9 (69)	61	49.3 (34)	21.1
Neuropathy: other (n = 128)	97.7 (125)	41.6 (52)	45	51.9 (27)	21.6
Neck pain (n = 103)	98.1 (101)	41.6 (42)	35	45.2 (19)	18.8
Headache: migraine (n = 83)	96.4 (80)	53.8 (43)	42	55.8 (24)	30.0
Trauma (including vertebral compression fracture) (n = 77)	94.8 (73)	27.4 (20)	16	45.0 (9)	12.3
Arthritis: rheumatoid (n = 72)	98.6 (71)	43.7 (31)	26	35.5 (11)	15.5
Headache: other (n = 60)	98.3 (59)	47.5 (28)	28	35.7 (10)	16.9
Complex regional pain syndrome (n = 42)	95.2 (40)	30.0 (12)	12	41.7 (5)	12.5
Spinal stenosis (n = 33)	100.0 (33)	30.3 (10)	7	50.0 (5)	15.2
Postoperative pain (n = 29)	96.6 (28)	53.6 (15)	14	53.3 (8)	28.6
Myelopathies (n = 27)	96.3 (26)	50.0 (13)	12	76.9 (10)	38.5
Neuropathy: diabetic (n = 22)	100.0 (22)	54.5 (12)	12	66.7 (8)	36.4
Spinal cord injury (n = 22)	95.5 (21)	4.8 (1)	1	0.0 (0)	0.0
Pelvic pain (n = 21)	100.0 (21)	47.6 (10)	8	50.0 (5)	23.8
Disc (vertebral) herniation (n = 18)	100.0 (18)	44.4 (8)	8	75.0 (6)	33.3
Trigeminal neuralgia (n = 17)	100.0 (17)	52.9 (9)	9	66.7 (6)	35.3
Abdominal Pain (n = 16)	100.0 (16)	43.8 (7)	6	28.6 (2)	12.5
Ehler-Danlos Syndrome (n = 16)	100.0 (16)	56.3 (9)	8	77.8 (7)	43.8

Table 5.14 cont. Improvements on the PEG composite score in Intractable Pain patients, stratified by primary cause of pain.

PEG Composite Results Stratified by Patient's Primary Cause of Pain	% of Patients Reporting Moderate to High PEG Scores at Baseline (n)	% of Patients Achieving ≥30% Improvement on the PEG within 4 months of First Purchase out of all Moderate to Severe Baseline Scorers (n)	# of Patients with Data in 4-mo Period Following initial ≥30% PEG Improvement	% of Patients Who Achieved ≥30% PEG Improvement that Maintained it for at least 4 months (n)	% of Patients that Both Achieved ≥30% Improvements on the PEG and Retained that Degree of Improvement for at least 4 months.
Cancer (n = 15)	86.7 (13)	30.8 (4)	4	75.0 (3)	23.1
Connective Tissue Diseases (excluding Rheumatoid Arthritis) (n = 15)	100.0 (15)	46.7 (7)	5	42.9 (3)	20.0
Pancreatitis (n = 11)	100.0 (11)	36.4 (4)	4	25.0 (1)	9.1
Arthritis, other inflammatory (n = 10)	100.0 (10)	60.0 (6)	6	50.0 (3)	30.0
Foot Pain (n = 9)	100.0 (9)	55.6 (5)	5	60.0 (3)	33.3
Lupus (n = 9)	100.0 (9)	55.6 (5)	5	60.0 (3)	33.3
Sciatica (n = 9)	100.0 (9)	44.4 (4)	3	25.0 (1)	11.1
Hip Pain, non-arthritis (n = 8)	100.0 (8)	25.0 (2)	2	50.0 (1)	12.5
Inflammatory bowel disease (n = 7)	85.7 (6)	50.0 (3)	2	33.3 (1)	16.7
Multiple sclerosis (n = 7)	100.0 (7)	28.6 (2)	2	0.0 (0)	0.0
Shoulder Pain (n = 7)	100.0 (7)	0.0 (0)	--	--	--
Lyme Disease (n = 6)	100.0 (6)	33.3 (2)	2	50.0 (1)	16.7
Dystonia (n = 5)	100.0 (5)	40.0 (2)	2	50.0 (1)	20.0
Hand/Wrist Pain (n = 5)	100.0 (5)	60.0 (3)	3	66.7 (2)	40.0
Knee Pain (n = 4)	100.0 (4)	25.0 (1)	1	0.0 (0)	0.0
Post-stroke pain (n = 4)	100.0 (4)	50.0 (2)	2	50.0 (1)	25.0
Endometriosis (n = 3)	100.0 (3)	33.3 (1)	0	--	--
Neuropathy: post-herpetic (n = 3)	100.0 (3)	33.3 (1)	1	100.0 (1)	33.3
Reflex Sympathetic Dystrophy (n = 3)	100.0 (3)	66.7 (2)	2	100.0 (2)	66.7
Traumatic Brain Injury (n = 3)	100.0 (3)	66.7 (2)	1	0.0 (0)	0.0
Vascular disease (n = 3)	66.7 (2)	50.0 (1)	1	0.0 (0)	0.0

Table 5.14 cont. Improvements on the PEG composite score in Intractable Pain patients, stratified by primary cause of pain.

PEG Composite Results Stratified by Patient's Primary Cause of Pain	% of Patients Reporting Moderate to High PEG Scores at Baseline (n)	% of Patients Achieving ≥30% Improvement on the PEG within 4 months of First Purchase out of all Moderate to Severe Baseline Scorers (n)	# of Patients with Data in 4-mo Period Following initial ≥30% PEG Improvement	% of Patients Who Achieved ≥30% PEG Improvement that Maintained it for at least 4 months (n)	% of Patients that Both Achieved ≥30% Improvements on the PEG and Retained that Degree of Improvement for at least 4 months.
Central Pain Syndrome (n = 2)	100.0 (2)	0.0 (0)	--	--	--
Cervical Radiculopathy (n = 2)	100.0 (2)	50.0 (1)	0	--	--
Elbow Pain (n = 2)	100.0 (2)	50.0 (1)	1	100.0 (1)	50.0
Hidradenitis suppurativa (n = 2)	100.0 (2)	0.0 (0)	--	--	--
Mast Cell Disease (n = 2)	100.0 (2)	50.0 (1)	1	0.0 (0)	0.0
Muscular dystrophy (n = 2)	50.0 (1)	100.0 (1)	1	100.0 (1)	100.0
Osteochondritis (n = 2)	100.0 (2)	50.0 (1)	1	100.0 (1)	50.0
Phantom Limb Pain (n = 2)	100.0 (2)	50.0 (1)	1	100.0 (1)	50.0
Scoliosis (n = 2)	100.0 (2)	50.0 (1)	1	0.0 (0)	0.0
Sickle Cell Disease (n = 2)	50.0 (1)	0.0 (0)	--	--	--
Sjogren's Syndrome (n = 2)	100.0 (2)	0.0 (0)	--	--	--
Thoracic Outlet Syndrome (n = 2)	100.0 (2)	100.0 (2)	2	50.0 (1)	50.0

Benefits Reported on the Patient Self Evaluation: Conclusions

Results on the Standard 8 measures suggest high symptom burden on Intractable Pain patients. For symptoms other than pain and fatigue, roughly 30-40% of patients initially experiencing moderate to severe symptoms both achieved and maintained at least a 30% reduction in symptoms. Pain intensity (over the past 24 hours) showed less improvement; 28% achieved ≥30% improvement, and only 11% both achieved and maintained ≥30% improvement. Data from the PEG scale showed greater rates of improvement in patients on pain-related items compared to the Standard 8 pain measure suggesting that the two measures may be assessing pain impact differently. Using the PEG composite measure, 42% achieved ≥30% reduction, and 22% both achieved and maintained ≥30% reduction. When examining individual PEG scale items, rates of improvement appeared to be higher for pain-related quality of life type factors than compared to a measure of pain intensity. Analysis of overall PEG scores stratified by patients' primary cause of pain did not show strong differences between groups, although small sample sizes limited reliable interpretation of results.

6. Adverse Side Effects

Summary

This chapter provides insight into the frequency and severity of adverse (negative) side effects through three sources of information: the Patient Self-Evaluation (PSE) completed by the patient prior to each medical cannabis purchase, patient and health care practitioner (HCP) surveys, and adverse event reports to the two medical cannabis manufacturers.

The three information resources tell a similar story – one quite similar to what was reported for patients who enrolled in the MN medical cannabis program during its first year of operation (July 1, 2015-June 30, 2016): a substantial minority of patients experience adverse physical or mental effects of some kind, and in the vast majority of cases they are of mild to moderate intensity. The proportion of patients with at least one adverse effect varied from 16% in the PSE data to 35% in HCP surveys to 40% in patient surveys. Most patients with at least one adverse effect experience only one. Approximately 90% of all reported adverse effects are mild or moderate in severity as reported on the PSE or a score of 1 through 5 on the 7-point severity scale used in patient and HCP surveys. The most common adverse effects are dry mouth, drowsiness, and fatigue. An assessment of the 75 patients reporting severe adverse events, meaning "interrupts usual daily activities," found no apparent pattern in patient age, primary cause of pain, or type of medical cannabis product used. No serious adverse events (life threatening or requiring hospitalization) were reported for this group of patients during the observation period.

Some limitations of the data should be mentioned. For example, when the patient completes a Patient Self-Evaluation and has it reviewed in consultation with pharmacist staff, the completeness and accuracy of reported side effects ultimately depend on the attention and good communication of the patient. Perhaps a more significant risk for under-reporting through PSE data is the situation when a patient has an intolerable side effect and decides to make no more purchases of medical cannabis. If the patient doesn't go to a cannabis patient center for another purchase, the patient doesn't fill out another PSE, so the side effect is not documented through this mechanism. From anecdotal report and survey responses, we know this does occur. However, inquiries made of patients who have discontinued medical cannabis purchasing suggests this does not happen often. Finally, a weakness of the survey data is that many responders did not complete the question on the most significant negative effect and a substantial proportion who did indicated cost or access issues, rather than physical or mental side effects. Though physical or mental side effects were probably minor or not present if the respondent indicated cost or access issues as the most significant negative effect, we don't know that for sure. And we are unable to characterize most significant negative effect for those who did not submit a response.

Though the limitations mentioned in the paragraph above no doubt undercount the frequent of physical and mental side effects to some degree, their impact does not seem likely to significantly change the main conclusions of the analyses reported in this section: the safety profile of the medical cannabis products available through the Minnesota program continues to appear quite favorable.

Adverse Side Effects Reported on the Patient Self-Evaluation

In addition to reporting on symptom benefits on the Patient Self-Evaluation (as discussed in the preceding section), patients also have the opportunity to report adverse side effects on this evaluation which is administered prior to every medical cannabis purchasing transaction. Information collected at this time include what the side effect is (patients can choose from a dropdown menu or write one in), the severity of the side effect (see Box 6.1 for definitions), and any additional comments they'd like to provide regarding the side effect (additional comments are optional). During a patient's visit to a Cannabis Patient Center (CPC) to purchase medical cannabis, the pharmacist can review the patient's completed Patient Self-Evaluation (PSE) and also discuss side effects that were reported by the patient to factor it into any recommendations on medical cannabis dosing and formulation.

Box 6.1. 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

Adverse side effects were examined among the 2,245 patients certified and enrolled in the medical cannabis program under Intractable Pain from August 1, 2016 through December 31, 2016. For this report, all side effect data submitted within 4 months of each patient's first medical cannabis purchase was analyzed. In the cases where patients had written in their side effects (as opposed to choosing a dropdown menu option), each entry was evaluated carefully and adjudicated as best as possible for analytical purposes.

Of the 2,245 patients in this cohort report, 2,181 patients (97% of cohort) had submitted any PSE data within 4 months of their first medical cannabis purchase. Of this patient subset, 341 (15.6%) patients reported adverse side effects. These responses from the 341 patients were further processed so that each unique side effect was captured once in the dataset for each patient and at the highest severity level reported. In other words, if a patient reported the same side effect multiple times, only one of those responses was kept in the analysis at the highest severity level reported. This resulted in 730 side effect responses in that dataset from the 341 patients.

Of patients reporting side effects (n = 341), most (55.7%) reported one unique side effect, with 86.6% of all patients reporting three or fewer unique side effects within four months of their first medical cannabis purchase. This pattern is similar to data on patients who enrolled during

the first year of MN Medical Cannabis' program operation (patients enrolled August 1, 2015 through June 30, 2016).

The most commonly reported side effects amongst patients were Dry Mouth, Drowsiness/Somnolence/Sedation, Fatigue, and Mental Clouding/"Foggy Brain". Figure 6.1 shows a rank ordering of the top 15 most frequently reported side effects among patients. Overall distribution for commonly reported side effects is similar to patients enrolled during the first year of MN Medical Cannabis' program operation. Side effects reported by fewer than 3% of patients are listed in Table 6.1.

Figure 6.1. Top 15 most commonly reported adverse side effects represented by the percentage of patients reporting them (out of 341 patients).

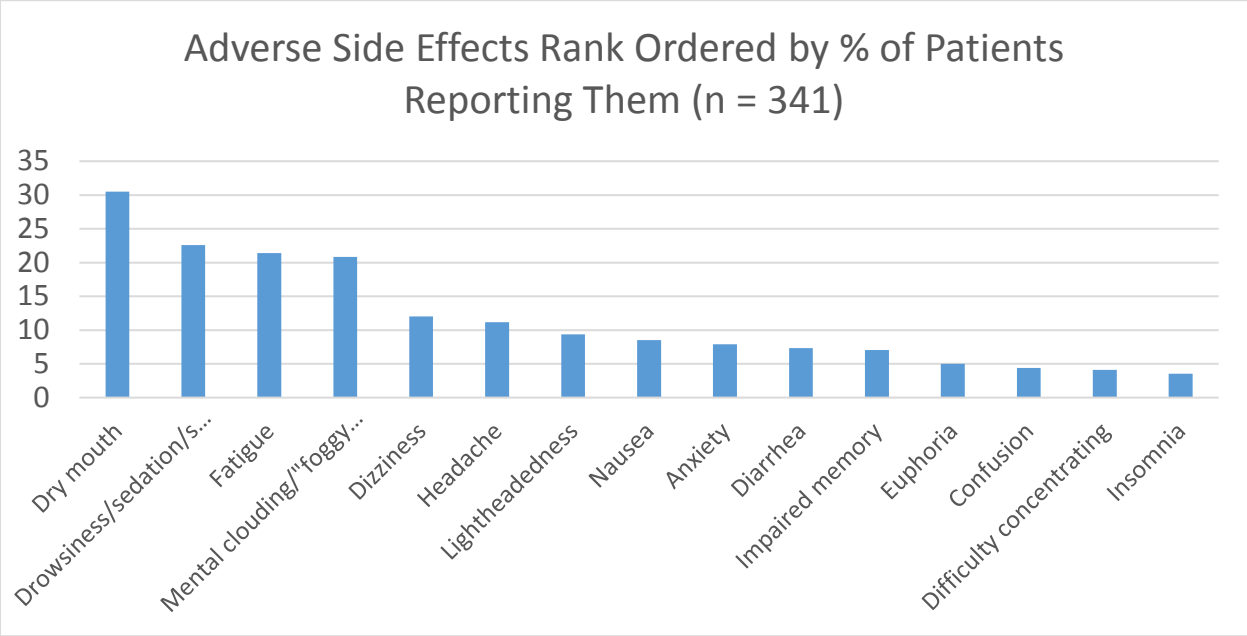


Table 6.1. Adverse side effects that were reported by less than 3% of patients (out of 341 patients reporting side effects).

Adverse Side Effect	% of Patients out of all Reporting Side Effects (n)
Disorientation	2.9 (10)
Asthenia (muscle weakness)	2.6 (9)
Constipation	2.6 (9)
Dysphoria (intense feeling of unease or unpleasantness)	2.6 (9)
Increased appetite (undesired)	2.6 (9)
Abdominal/epigastric pain	2.3 (8)
Coughing/lung irritation	2.3 (8)
Blurred Vision	2.1 (7)
Tinnitus (ringing in the ears)	1.8 (6)
Paranoia	1.5 (5)
Tremor	1.5 (5)
Panic attack	1.2 (4)
Numbness	0.9 (3)
Tachycardia (rapid heart rate)	0.9 (3)
Bizarre dreams or nightmares	0.6 (2)
Chest pain	0.6 (2)
Dry eyes	0.6 (2)
Eye redness	0.6 (2)
Heartburn	0.6 (2)
Increased sweating	0.6 (2)
Mouth irritation/burning	0.6 (2)

Adverse Side Effect	% of Patients out of all reporting side effects (n)
Sore throat	0.6 (2)
Weight gain	0.6 (2)
"Stoned" feeling	0.3 (1)
Acne	0.3 (1)
Body ache	0.3 (1)
Congestion	0.3 (1)
Decreased appetite	0.3 (1)
Eye pressure sensation	0.3 (1)
Fatty stool	0.3 (1)
Increased pain	0.3 (1)
Itching	0.3 (1)
Lethargy	0.3 (1)
Muscle spasms	0.3 (1)
Muscle tension	0.3 (1)
Nerve tingling	0.3 (1)
Personality/mood change	0.3 (1)
Post nasal drip	0.3 (1)
Rash on face	0.3 (1)
Skin rash	0.3 (1)
Slurred speech	0.3 (1)

Severe Adverse Side Effects

The 75 side effect responses that were reported as severe were reported by 55 patients. See Table 6.2.

The most frequently reported side effect reported as severe was fatigue (n = 11), followed by headache (n = 8), dizziness (n = 7), drowsiness/sedation/somnolence (n = 7), mental clouding/"foggy brain" (n = 5), dry mouth (n = 5), abdominal/epigastric pain (n = 5), nausea (n = 5), insomnia (n = 5), anxiety (n = 3), and 10 additional symptoms reported once or twice each. This distribution is similar to the distribution of reported side effects overall, except for insomnia and abdominal/epigastric pain appearing relatively more frequently among severe side effects. For example, 62.5% of all patients reporting abdominal/epigastric pain as a side effect rated it as severe. Among patients reporting insomnia as a side effect, 41.7% of them found this side effect to be severe. The interpretation of these severity differences across unique side effects, however, is unclear as the number of patients reporting side effects are relatively low overall.

Table 6.2. Number of patients reporting specific types of side effects along with the percentage of those respondents who indicated that the side effect was severe.

Adverse Side Effect	# of Patients Reporting as a Side Effect	% of Patients Reporting Side Effect as Severe
Dry mouth	104	4.8 (5)
Drowsiness/sedation/somnolence	77	9.1 (7)
Fatigue	73	15.1 (11)
Mental clouding/"foggy brain"	71	7.0 (5)
Dizziness	41	17.1 (7)
Headache	38	21.1 (8)
Lightheadedness	32	6.3 (2)
Nausea	29	17.2 (5)
Anxiety	27	11.1 (3)
Diarrhea	25	8.0 (2)
Impaired memory	24	0.0 (0)
Euphoria	17	0.0 (0)
Confusion	15	6.7 (1)
Difficulty concentrating	14	7.1 (1)
Insomnia	12	41.7 (5)
Disorientation	10	10.0 (1)
Asthenia (muscle weakness)	9	22.2 (2)
Constipation	9	22.2 (2)
Dysphoria (intense feeling of unease or unpleasantness)	9	11.1 (1)

Adverse Side Effect	# of Patients Reporting as a Side Effect	% of Patients Reporting Side Effect as Severe
Increased appetite (undesired)	9	0.0 (0)
Abdominal/epigastric pain	8	62.5 (5)
Coughing/lung irritation	8	12.5 (1)
Blurred Vision	7	0.0 (0)
Tinnitus (ringing in the ears)	6	0.0 (0)
Paranoia	5	0.0 (0)
Tremor	5	0.0 (0)
Panic attack	4	25.0 (1)
Numbness	3	0.0 (0)
Tachycardia (rapid heart rate)	3	0.0 (0)
Bizarre dreams or nightmares	2	0.0 (0)
Chest pain	2	0.0 (0)
Dry eyes	2	0.0 (0)
Eye redness	2	0.0 (0)
Heartburn	2	0.0 (0)
Increased sweating	2	0.0 (0)
Mouth irritation/burning	2	0.0 (0)
Sore throat	2	0.0 (0)
Weight gain	2	0.0 (0)

Table 6.2 cont. Number of patients reporting specific types of side effects along with the percentage of those respondents who indicated that the side effect was severe.

Adverse Side Effect	# of Patients Reporting as a Side Effect	% of Patients Reporting Side Effect as Severe
"Stoned" feeling	1	0.0 (0)
Acne	1	0.0 (0)
Body ache	1	0.0 (0)
Congestion	1	0.0 (0)
Decreased appetite	1	0.0 (0)
Eye pressure sensation	1	0.0 (0)
Fatty stool	1	0.0 (0)
Increased pain	1	0.0 (0)
Itching	1	0.0 (0)

Adverse Side Effect	# of Patients Reporting as a Side Effect	% of Patients Reporting Side Effect as Severe
Lethargy	1	0.0 (0)
Muscle spasms	1	0.0 (0)
Muscle tension	1	0.0 (0)
Nerve tingling	1	0.0 (0)
Personality/mood change	1	0.0 (0)
Post nasal drip	1	0.0 (0)
Rash on face	1	0.0 (0)
Skin rash	1	0.0 (0)
Slurred speech	1	0.0 (0)

Compared to the whole IP cohort in this report, respondents reporting at least one severe side effect were more likely to be female (76.4% vs. 52.4%), but the average age of severe side effect responders (53.9 ± 16.4 years old) was similar to the whole cohort average (52.3 ± 15.6 years old). Roughly three-quarters of patients reporting at least one severe side effect had previously purchased a Balanced enteral product.

Each record (row) in Table 6.3 represents side effect responses from a specific Patient Self-Evaluation for a given patient. The right-most column indicates the severe side effect(s) that were reported. The product type(s) that were purchased just prior to their reporting are found in columns 5-8 in the table.

PSE-Reported Adverse Side Effects: Conclusions

Less than a quarter of IP patients (~16%) in this cohort reported adverse side effects on the Patient Self-Evaluation within 4 months of their first purchase. The distribution of commonly reported side effects generally matched side effects commonly found in the clinical literature. Severe adverse side effects were relatively uncommon (~10% of all side effect responses) but were more likely to be reported by female than male patients.

Table 6.3. Patients self-reporting "severe" side effects: patient age, gender, and condition, product types purchased at most recent visit, and type of side effect reported.

Patient	Age	Gender	Conditions(s)	Very High THC Product(s)	High THC Product(s)	Balanced THC:CBD Product(s)	High CBD Product(s)	Severe Side Effect Reported
P1	57	F	IP	Enteral, Inhalation	--	Inhalation	--	Dry mouth, Insomnia, Mental clouding/"foggy brain"
P2	68	F	IP	--	--	Enteral, Inhalation	--	Fatigue
P3	38	M	IP	Inhalation	--	Inhalation	--	Headache
P4	46	F	IP, Muscle Spasms	Enteral	--	Inhalation	--	Insomnia
P5	51	M	IP	--	--	Enteral	--	Anxiety
P6	40	F	IP	Oromucosal	--	Enteral	--	Dizziness
P7	58	M	IP, Muscle Spasms	Inhalation	--	Enteral	--	Fatigue
P8	40	F	IP	Inhalation	--	Enteral	--	Dizziness
P9	73	F	IP	--	Enteral	--	--	Diarrhea
P10	53	F	IP	Inhalation	--	Enteral	--	Coughing/lung irritation
P11	26	F	IP	Enteral, Inhalation	--	Enteral	--	Headache
P12	51	F	IP	--	--	Enteral, Inhalation	--	Fatigue
P13	37	F	IP	Enteral, Inhalation	--	--	--	Abdominal/epigastric pain
P14	59	F	IP	Oromucosal	--	--	Enteral	Mental clouding/"foggy brain"
P15	50	F	IP, Muscle Spasms	Enteral, Inhalation	--	Enteral	--	Nausea
P16	33	F	IP	--	Enteral	--	--	Asthenia (muscle weakness), Drowsiness/somnolence/sedation

Table 6.3 cont. Patients self-reporting "severe" side effects: patient age, gender, and condition, product types purchased at most recent visit, and type of side effect reported.

Patient	Age	Gender	Conditions(s)	Very High THC Product(s)	High THC Product(s)	Balanced THC:CBD Product(s)	High CBD Product(s)	Severe Side Effect Reported
P17	77	F	IP, Muscle Spasms	Enteral	--	Enteral, Inhalation	--	Drowsiness/somnolence/sedation
P18	88	F	IP	--	--	Enteral, Inhalation	--	Drowsiness/somnolence/sedation
P19	30	F	IP	Inhalation, Oromucosal	--	--	--	Headache
P20	48	F	IP	Inhalation	--	--	--	Headache
P21	39	F	IP, Muscle Spasms	--	Inhalation	--	--	Dry mouth
P22	45	F	IP	Inhalation	--	Inhalation	--	Drowsiness/somnolence/sedation
P23	44	M	IP, Muscle Spasms	Oromucosal	--	Enteral, Oromucosal	--	Insomnia
P24	52	F	IP	Inhalation	--	Inhalation	--	Drowsiness/somnolence/sedation
P25	32	M	IP	Oromucosal	--	Oromucosal	--	Fatigue
P26	43	M	IP	Enteral	--	Enteral	--	Abdominal/epigastric pain
P27	74	F	IP	--	--	Enteral	--	Dizziness
P28	40	F	IP	Inhalation	--	Enteral	--	Nausea
P29	60	F	IP	--	--	--	Enteral	Mental clouding/"foggy brain"
P30	72	F	IP, Muscle Spasms	--	--	Enteral	--	Difficulty Concentrating, Mental clouding/"foggy brain"
P30	72	F	IP, Muscle Spasms	Enteral	--	--	--	Drowsiness/somnolence/sedation, Fatigue
P31	57	F	IP, Muscle Spasms	Enteral	Inhalation	--	Enteral	Insomnia
P32	52	F	IP	Oromucosal	--	Oromucosal	--	Headache
P33	84	F	IP	--	--	Enteral	--	Dizziness

Table 6.3 cont. Patients self-reporting "severe" side effects: patient age, gender, and condition, product types purchased at most recent visit, and type of side effect reported.

Patient	Age	Gender	Conditions(s)	Very High THC Product(s)	High THC Product(s)	Balanced THC:CBD Product(s)	High CBD Product(s)	Severe Side Effect Reported
P34	64	F	IP	Oromucosal	--	Enteral	--	Abdominal/epigastric pain, Diarrhea
P35	45	F	IP	Enteral	--	Inhalation	--	Headache
P36	76	F	IP	--	--	Enteral	--	Dry mouth, Insomnia, Nausea
P37	87	F	IP	--	--	Enteral	--	Constipation
P38	41	F	IP	--	--	Enteral, Inhalation	--	Anxiety, Fatigue
P39	61	M	IP, Muscle Spasms	Inhalation	--	--	--	Nausea
P40	82	M	IP	Inhalation	--	--	--	Lightheadedness
P41	52	F	IP	Enteral	--	Enteral	--	Abdominal/epigastric pain
P42	27	F	IP	--	--	Enteral	--	Dizziness
P43	54	F	IP, Muscle Spasms	--	--	Enteral	--	Dizziness
P43	54	F	IP, Muscle Spasms	--	--	Enteral	--	Anxiety, Panic attack
P44	44	F	IP, Seizures	--	--	Inhalation	Enteral	Fatigue
P45	74	M	IP, Seizures	--	--	Enteral	--	Asthenia (muscle weakness)
P46	53	M	IP	Inhalation	--	Enteral, Inhalation	--	Mental clouding/"foggy brain"
P47	46	F	IP	Inhalation	--	--	--	Dry mouth
P48	67	M	IP	--	--	Inhalation	--	Dysphoria (intense feeling of unease or unpleasantness)
P49	33	F	IP, Seizures	--	--	Enteral, Inhalation	--	Headache
P50	50	F	IP, Inflammatory Bowel Disease	--	--	Oromucosal	--	Fatigue, Headache, Nausea

Table 6.3 cont. Patients self-reporting "severe" side effects: patient age, gender, and condition, product types purchased at most recent visit, and type of side effect reported.

Patient	Age	Gender	Conditions(s)	Very High THC Product(s)	High THC Product(s)	Balanced THC:CBD Product(s)	High CBD Product(s)	Severe Side Effect Reported
P51	82	M	IP	--	Enteral	Enteral	--	Confusion, Dizziness, Fatigue, Lightheadedness
P52	70	F	IP	--	--	Enteral	--	Drowsiness/somnolence/sedation
P53	35	M	IP, Muscle Spasms	Enteral	--	Enteral, Inhalation	--	Fatigue
P54	38	F	IP	--	--	Inhalation	--	Disorientation
P55	66	F	IP	Oromucosal	--	--	--	Abdominal/epigastric pain, Constipation, Dry mouth, Fatigue

Adverse Side Effects Reported on Surveys

Patient-Reported Negative Effects of Medical Cannabis

For overall patient survey response rate and comparison of responders and non-responders, please refer to the Benefits chapter.

The Patient Experience survey asks respondents to report the degree, or severity, of any negative effects experienced from using medical cannabis, on a scale from 1 (no negative effects) to 7 (a great deal of negative effects). The survey then asked the respondent to describe, in their own words, any negative effects they experienced as a result of medical cannabis treatment, ordering the negative effects by importance to them. When patients reported more than one negative effect, the first negative effect was considered to be the most important. Table 6.4 shows the distribution of most important negative effects by severity score within three broad categories: physical side effects (including dry mouth, fatigue, headache, dizziness, blurred vision); mental side effects (including mental clouding, paranoia, sedation or symptoms related to "high"); and issues related to accessing the medications (distance to distribution center, inconvenient operating hours for distribution centers, etc. Though patients were asked to assess cost in a separate question, some nonetheless included cost as a negative effect). Figure 6.2 shows the overall frequency of all reports of negative effects by category, as described above. Among all reported negative effects, 18% were physical side effects, 17% were mental side effects, and 3% were access-related issues.

Among patient respondents, 513 (43.7%) reported at least one negative effect related to medical cannabis use that could be classified as either a physical side effect, mental side effect, or access issue. Most reported negative effects (64.7%) were associated with a negative effect score of 1-3; in many cases patients reporting a score of 1 (indicating no negative effects) described negative effects in response to the open-ended negative effects question and were therefore included in proportion of patients experiencing negative effects and in Table 6.4 below.

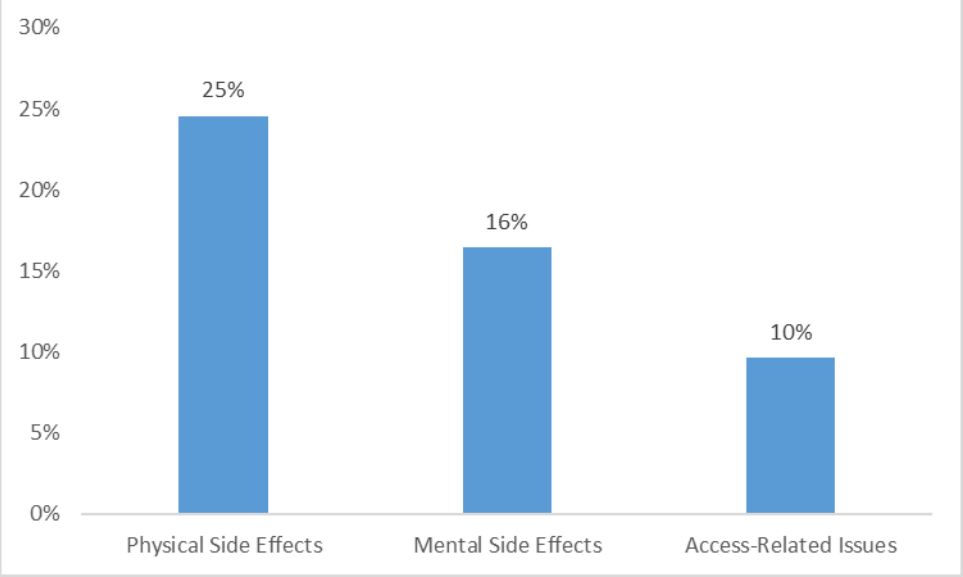
Overall, physical side effects were more commonly reported as the most important negative effect (n=257; 22%) compared to either mental side effects (n=154; 13%) or access-related issues (n=102; 9%). Total frequency of physical and mental side effects, regardless of whether they were considered to be the most important negative effect, were also generally low (24% and 16%, respectively). Overall, negative effects tended to be reported as mild or moderate: scores of 1-3 were more common than scores of 4-7.

A full tabulation of patient-reported negative effects can be found in *Appendix J: Patient-Reported Negative Effects from Medical Cannabis*.

Table 6.4. Patient-reported most important negative effects by type.

Most Important Negative Effect	Total	1	2	3	4	5	6	7
Physical Side Effects	257 (22%)	24 (2%)	99 (8%)	40 (3%)	56 (5%)	8 (1%)	12 (1%)	15 (1%)
Mental Side Effects	154 (13%)	7 (1%)	46 (4%)	28 (2%)	40 (3%)	15 (1%)	9 (1%)	5 (0%)
Access-Related Issues	102 (9%)	57 (5%)	20 (2%)	11 (1%)	9 (1%)	1 (0%)	1 (0%)	3 (0%)

Figure 6.2. Frequency of all patient-reported negative effects, by type.



Healthcare Practitioner-Reported Negative Effects of Medical Cannabis

For overall healthcare practitioner survey response rate and comparison of responders and non-responders, please refer to the Benefits chapter.

In parallel with the Patient Experience survey, the Healthcare Practitioner Survey asks respondents to report the degree, or severity, of any negative effects they believe the patient received from using medical cannabis, on a scale from 1 (no negative effects) to 7 (a great deal of negative effects). The survey then asked the respondent to describe any negative effects the patient experienced as a result of medical cannabis treatment, ordering the negative effects by importance to them. When more than one negative effect was reported, the first negative effect was considered to be the most important. Table 6.5 shows the distribution of most important negative effects by severity score within three broad categories: physical side effects (including dry mouth,

fatigue, headache, dizziness, blurred vision); mental side effects (including mental clouding, paranoia, sedation or symptoms related to "high"); and issues related to accessing the medications (distance to distribution center, inconvenient operating hours for distribution centers, etc. Though patients were asked to assess cost in a separate question, some nonetheless included cost as a negative effect). Figure 6.3 shows the overall frequency of reports of negative effects by category, as described above.

Among healthcare practitioner respondents, 212 (30.6%) reported at least one negative effect related to medical cannabis use that could be classified as either a physical side effect, mental side effect, or access issue. Most reported negative effects (70.3%) were associated with a negative effect score of 1-3; in some cases healthcare practitioners reporting a score of 1 (indicating no negative effects) described negative effects in response to the open-ended negative effects question and were therefore included in proportion of patients experiencing negative effects and in Table 6.5 below.

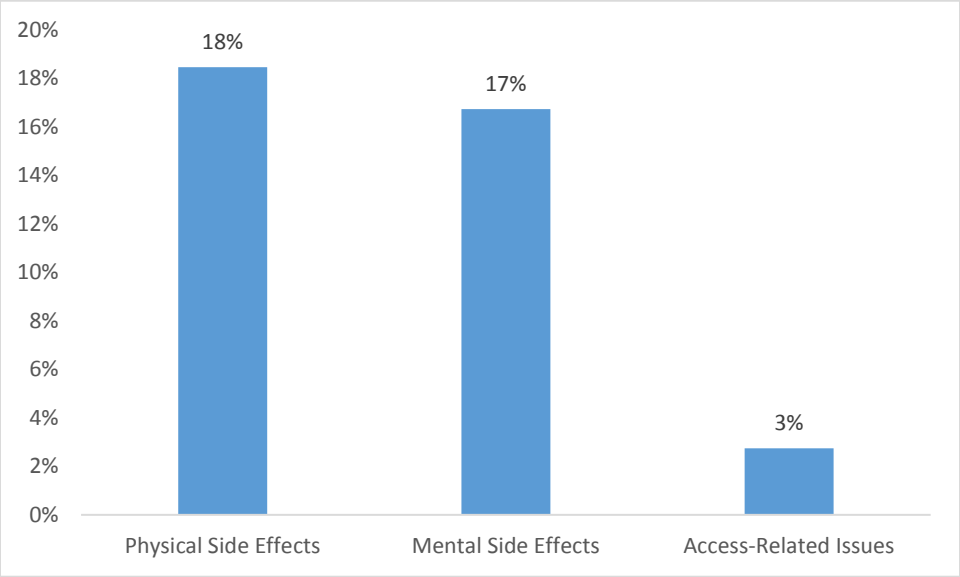
Overall, Healthcare Practitioner Survey results mirrored Patient Experience Survey results, though overall the frequency of reporting negative effects was lower in HCP surveys compared to patient surveys. Physical side effects were most often reported as the most important negative effect (n=121; 17%), followed by mental side effects (n=72; 10%) and access-related issues (n=19; 3%). Total frequency of physical and mental side effects were comparable (18% and 17%, respectively) and healthcare practitioners rarely reported access-related issues as a negative effect. This could be due to a more clinical interpretation of "negative effect. As in patient reports, negative effects tended to be reported as mild or moderate, with scores of 1-3 making up the majority of reported negative effects.

A full tabulation of healthcare practitioner-reported negative effects can be found in *Appendix K: Healthcare Practitioner-Reported Negative Effects from Medical Cannabis*.

Table 6.5. Healthcare practitioner-reported most important negative effects by type.

Most Important Negative Effect	Total	1	2	3	4	5	6	7
Physical Side Effects	121 (17%)	10 (1%)	61 (9%)	22 (3%)	7 (1%)	7 (1%)	3 (0%)	7 (1%)
Mental Side Effects	72 (10%)	1 (0%)	24 (3%)	17 (2%)	7 (1%)	5 (1%)	6 (1%)	9 (1%)
Access-Related Issues	19 (3%)	7 (1%)	5 (1%)	2 (0%)	0 (0%)	1 (0%)	1 (0%)	0 (0%)

Figure 6.3. Frequency of healthcare practitioner-reported negative effects, by type.



Adverse Event Reporting to Medical Cannabis Manufacturers

Both Minnesota medical cannabis manufacturers have procedures for documenting potential adverse events via telephone and e-mail communication received from enrolled patients, the patients' family and registered caregivers, as well as health care practitioners. These adverse events are reported to the Office of Medical cannabis.

In the case of a "serious adverse incident" that may be attributed to medical cannabis consumption, it is the duty of patients, their registered caregivers, and health care practitioners to report them. These incidences are events that lead to hospitalization, death, sustained disability/incapacitation, or are generally life-threatening (see program rules under 4770.4002). No serious adverse incidents were reported for the intractable pain patients enrolled between August 1, 2016 through December 31, 2016.