original contribution

Impact of Medical Cannabis on Patient-Reported Symptoms for Patients With Cancer Enrolled in Minnesota's Medical Cannabis Program

Susan P. Anderson, PhD[1]; Dylan M. Zylla, MD[2]; Deepa M. McGriff, MPH[1]; and Tom J. Arneson, MD, MPH[1]

QUESTION ASKED: What is the impact of participating in the Minnesota medical cannabis program on managing symptoms in patients with cancer, and is medical cannabis well tolerated among this patient population?

SUMMARY ANSWER: Within 4 months of starting medical cannabis, there was a significant reduction in the severity of symptoms across all eight measures included in the study (anxiety, lack of appetite, depression, disturbed sleep, fatigue, nausea, pain, and vomiting) compared with baseline. Clinically meaningful improvements were most evident for vomiting, with the least clinically meaningful improvements observed for fatigue.

WHAT WE DID: Patients with cancer enrolled in the Minnesota medical cannabis program reported the severity of their symptoms prior to each medical cannabis purchase (roughly monthly) on a 0 to 10 numerical rating scale (0 = symptom not present; 10 = symptom as bad as one can imagine), as well as any adverse effects they attributed to medical cannabis.

WHAT WE FOUND: Medical cannabis may help reduce the severity of symptoms in patients with cancer from severe to moderate/mild levels, and a substantial number of patients were able to achieve and maintain clinically meaningful improvements on symptoms. Medical cannabis seems to be well-tolerated among patients with cancer.

BIAS, CONFOUNDING FACTOR(S), DRAWBACKS, REAL-LIFE IMPLICATIONS: While a substantial proportion of patients with cancer reported improvements on symptoms, response bias may have been introduced in the study since those who experience benefit from medical cannabis may be more inclined to continue with the program. In addition, without reliable information on concomitant therapies, it is difficult to separate the effects of medical cannabis independently of other therapies on symptom control. This study is the first of its kind, to our knowledge, to report on US state medical cannabis program data in which symptom severity was assessed over a period of time. This provides valuable information to other states with a medical cannabis program where cancer is a qualifying condition. This study also allows health care practitioners a better understanding of potential benefits and risks that may be derived from medical cannabis treatment of their patients. Finally, these results may guide expectations for future researchers on the potential magnitude of symptom improvement that may be found in a more rigorous study design.

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CARE DELIVERY

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abstract

PURPOSE Minnesota's medical cannabis program is unique, in that it routinely collects patient-reported scores on symptoms. This article focuses on changes in symptom severity reported by patients with cancer during their first 4 months of program participation.

MATERIALS AND METHODS Patients with cancer in Minnesota's medical cannabis program reported symptoms (anxiety, lack of appetite, depression, disturbed sleep, fatigue, nausea, pain, and vomiting) at their worst over the last 24 hours before each medical cannabis purchase. Baseline scores on each of the eight symptoms were statistically compared with the average symptom scores reported in the first 4 months of program participation. Symptom scores were also calculated as percent change from baseline, with patients achieving and maintaining at least a 30% reduction in symptoms reported in this article. Patients also reported intensity of adverse effects.

RESULTS A significant reduction in scores was found across all symptoms when comparing baseline scores with the average score submitted within the first 4 months of program participation (all Ps $< .001$). The proportion of patients achieving 30% or greater symptom reduction within the first 4 months of program participation varied from 27% (fatigue) to 50% (vomiting), with a smaller proportion both achieving and maintaining those improvements. Adverse effects were reported in a small proportion of patients (10.5%).

CONCLUSION Patients with cancer enrolled in Minnesota's medical cannabis program showed significant reduction across all eight symptoms assessed within 4 months of program participation. Medical cannabis was well tolerated, and some patients attained clinically meaningful and lasting levels of improvement.

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INTRODUCTION

Cannabis use is becoming more common, especially in the cancer population. A New England survey indicates that many patients pay upwards of $3,000 a year to use cannabis, despite few scientific data proving a benefit.[1] Patients report that cannabis can decrease pain, mitigate nausea, improve sleep/mood, and stimulate appetite.[2] In Washington state, which has legalized both medical and recreational use of cannabis, 20% of patients surveyed reported using cannabis in the past month to help control cancer-related symptoms.[3] Minnesota enacted a law in May 2014 legalizing the medical use of cannabis for patients with cancer associated with severe/chronic pain, nausea or severe vomiting, or cachexia or severe wasting.[4] From July 1, 2015, when the program became operational, through December 31, 2017, 1,519 patients have been certified for a cancer-related condition and enrolled in the program.

Review articles have been written about potential benefits of cannabis in the cancer population, yet there have been few large, placebo-controlled randomized controlled trials.[5-7] The largest randomized controlled trial was a phase III trial of 397 patients with advanced cancer pain refractory to opioids comparing nabiximols to placebo.[8] The study did not meet its primary end point of significant improvements in pain.[8] In 1980 (before the current era of high-quality antiemetics), a randomized trial of 84 patients showed higher rates of nausea control and greater patient preference for delta-9-tetrahydrocannabinol (THC) than prochlorperazine.[9] Since 2000, 19 clinical studies (involving nearly 6,000 patients) have assessed how cannabis-containing products affect

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symptoms and global quality of life in patients with cancer (manuscript currently under peer review).

Both patients and clinicians have been surveyed about their attitudes regarding use of medical cannabis for cancer symptoms.[3,10-12] More than 50% of patients surveyed at a large cancer center in Washington state believed cannabis had a major benefit on cancer-related symptoms.[3] We surveyed the views of oncology providers in Minnesota and showed that, despite barriers to use, there is high level of support for cannabis use, research, and clinician education.[13]

Ultimately, patient-reported improvements in symptoms are the crucial end point. Do patients experience symptom improvement when using cannabis? If so, how much benefit do they obtain? As laws expand cannabis availability throughout the country, these questions must be addressed.[14] In this study, we report patients' self-evaluation of symptoms on starting medical cannabis and aim to answer some of these questions.

MATERIALS AND METHODS

Patients residing in Minnesota who wish to participate in Minnesota's medical cannabis program must meet at least one of the qualifying conditions of the program.[15] A health care practitioner must certify which qualifying condition(s) a patient has via Minnesota's online medical cannabis registry, and the certification subsequently triggers the online enrollment process for the patient. Health care practitioners can be Minnesota-licensed physicians, advanced practice registered nurses, and physician assistants. Health care practitioners must register with the Minnesota medical cannabis online registry to certify patients for the program. Health care practitioner participation in the program is voluntary.

Once a patient is enrolled in the program, they can legally purchase up to a 30-day supply of medical cannabis out of pocket from the two registered, in-state medical cannabis manufacturers. (As of the publication of this paper, two in-state medical cannabis manufacturers are required by Minnesota statute to be registered to cultivate, produce, and distribute all medical cannabis products for patients enrolled in Minnesota's medical cannabis program.) The certifying health care practitioner therefore does not have a prescribing role; rather, patients consult with a licensed pharmacist at one of the medical cannabis retail centers to determine appropriate formulation on the basis of symptoms and desired outcomes. Allowable forms of medical cannabis are liquids extracted from the cannabis plant formulated into oil for vaporization, capsules and oral solutions, tinctures, and topical agents. The primary cannabinoids found in retail products come in various ratios of THC to cannabidiol (CBD). Non–extraction-based, plant form cannabis products are not allowed in Minnesota's program.

Patients must complete a patient self-evaluation through the online Minnesota medical cannabis patient registry before each medical cannabis purchase. Data collected on these patient self-evaluations, specifically symptom data collected over time and the reporting of adverse effects, are the focus of this article.

This project was reviewed by the Minnesota Department of Health Institutional Review Board. The research in this paper was determined to fall under program evaluation, meaning institutional review board approval was unnecessary.

Patient Population

Patients who were certified for cancer and enrolled in the Minnesota medical cannabis program from July 1, 2015 to December 31, 2017 were identified through the program registry (specific cancer diagnoses are not collected in the registry). For analytic purposes, patients who had at least a 4-month observation window since starting medical cannabis were retained, resulting in a sample of 1,120 patients with cancer. No other exclusion criteria were applied to patients.

Measures

Symptom data. Eight symptom measures were included in the online patient self-evaluation, which assessed the following: anxiety, lack of appetite, depression, disturbed sleep, fatigue, nausea, pain, and vomiting. Patients were required to report on each symptom at its worst over the previous 24 hours using a 0 to 10 numerical rating scale (0 = symptom not present; 10 = symptom as bad as one can imagine). The frequency of reporting on the patient self-evaluation was variable, because it was a function of when medical cannabis purchases were made; however, patients completed a patient self-evaluation close to every month, on average. Symptom scores provided before the first medical cannabis purchase were defined as baseline.

Adverse effects. Patients were also asked to report adverse effects on the patient self-evaluation. For each adverse effect reported, patients were also required to indicate the severity of that adverse effect as mild (symptoms do not interfere with daily activities), moderate (symptoms may interfere with daily activities), or severe (symptoms interrupt usual daily activities).

Data Analysis

Demographic data on patients and physician specialties are reported as percentages and frequencies. Medical cannabis use was analyzed by extracting medical cannabis purchasing data and tallied according to product route of administration (enteral, inhalation, oromucosal), and THC:CBD ratio. Topical products were introduced during the study period, with only 5% of this patient cohort having used one. For this reason, topical products were dropped from analysis. To simplify description by THC:CBD ratio, we

grouped products as follows: high THC:CBD (> 4:1), balanced (1:1 to 4:1), and high CBD:THC (> 1:1).

Paired comparisons. A statistical comparison was conducted, with the Wilcoxon signed-rank test (two sided) between baseline symptom scores and symptom scores averaged over 4 months (4-month period after first purchase). Patients who had data at both time periods were included in the analysis.

Percent change in symptom severity. A decrease in symptom severity of 30% or more from baseline was used to represent clinically meaningful improvement. This threshold is often used in published studies—especially for improvement in pain and spasms.[16,17] Percent change was calculated by comparing each symptom score submission to those submitted at baseline, as follows: [(new score − baseline score)/baseline score]. Therefore, negative percent change values reflect a decrease in symptom scores (improvement) relative to baseline. All patients reporting symptoms at baseline (baseline score ≥ 1) were included in this analysis, regardless of whether they made additional medical cannabis purchases beyond their first one. This allows for a conservative estimate of symptom improvement.

If a patient achieved 30% or greater symptom reduction anytime during the 4 months after their first purchase, the patient was counted as achieving clinically meaningful improvement. If the patient achieved symptom improvement within 4 months of their first purchase, the first instance of this achievement was identified, and the subsequent 4-month period was examined for overall maintenance of this effect (4-month follow-up period). More precisely, all symptom score submissions in this 4-month follow-up period were averaged and compared with the baseline score; patients who still maintained an average 30% or greater symptom reduction were defined as demonstrating overall maintenance of clinically meaningful symptom improvement.

Adverse effect reporting. All reports of adverse effects that occurred within 4 months of a patient's first purchase were extracted, categorized, and adjudicated where necessary. These responses were further processed so that each unique adverse effect was captured once in the data set for each patient and at the highest severity level reported. For example, if an adverse effect was reported multiple times by a patient, it was captured only once in the final data set and at the highest severity level reported. All analyses were performed in R 3.4.2.

RESULTS

Patient Demographics

Median age for the 1,120 patients with cancer was 59 years (interquartile range, 48-66 years), with 73.0% of patients age 50 years or older. Only 2.8% (n = 31) were pediatric patients with cancer. Just over half of the patients reported they were male (51.7%; n = 579). Racial makeup of patients generally mirrored Minnesota census data,[18] with some underrepresentation from a few minority groups (black and Asian). Other than cancer, 117 patients (15.3%) were certified for other conditions that qualified them for Minnesota's medical cannabis program (Table 1).

Patient Medical Cannabis Use

Among all patients, 40% used products in only one of the following THC:CBD ratio categories: 29% used only high THC:CBD products, 10% used only balanced THC:CBD products, and 1% used only high CBD:THC products. A total of 42% used both high THC:CBD and balanced THC:CBD products, 2% used both balanced THC:CBD and high CBD:THC products, and 11% used all three (high THC:CBD, balanced, and high CBD:THC products).

Across patients, 31% used products in only one of the following routes of administration: 15% used only enteral products, 11% used only inhaled/vaporized products, and

TABLE 1. Demographics of Patients With Cancer (n = 1,120)

				Additional Qualifying Conditions		Race and Ethnicity	
Age (years)	Female	Male	Age	Condition	Patients	Race	Patients
0-4	0.2 (1)	1.0 (6)	0.6 (7)	Terminal illness	8.8 (99)	White	87.4 (979)
5-17	1.5 (8)	2.8 (16)	2.2 (24)	Intractable pain	3.7 (41)	Black	3.4 (38)
18-24	0.9 (5)	2.1 (12)	1.5 (17)	Muscle spasms	3.0 (34)	Native American	1.9 (21)
25-35	6.0 (32)	8.3 (48)	7.2 (80)	Seizures	0.5 (6)	Asian	1.8 (20)
36-49	17.8 (95)	13.1 (76)	15.4 (171)	IBD, including Crohn's disease	0.5 (6)	Unknown	1.3 (14)
50-64	45.3 (242)	40.9 (237)	43.0 (479)			Other	0.9 (10)
≥ 65	28.3 (151)	31.8 (184)	30.1 (335)	HIV/AIDS	0.2 (2)	Pacific Islander	0.0 (0)
						Prefer not to answer	4.7 (53)
Sex, %	48.0 (534)	52.0 (579)	100 (1113)				
						Hispanic ethnicity	1.3 (15)

NOTE. Data given as % (No.) unless otherwise noted. Seven patients (< 1%) chose to not indicate sex and are excluded from the age × sex table. IBD, inflammatory bowel disease.

5% used only oromucosal products. A total of 36% used both enteral and inhaled products, 14% used both enteral and oromucosal products, 5% used both inhaled and oromucosal products, and 11% used enteral, inhaled, and oromucosal products.

Health Care Practitioners and Physician Specialties

A total of 269 health care practitioners had certified the 1,120 patients with cancer included in this article, with most registered as physicians (n = 206), followed by advanced practice registered nurses (n = 42) and physician assistants (n = 21). Specialty information was derived for physicians via the Minnesota Board of Medical Practice and adjudicated for analytic purposes. Oncologists made up the largest physician group (n = 94), followed by primary care physicians (n = 62) and hospice and palliative medicine physicians (n = 21). These three specialties accounted for 86% of all certifying physicians in this patient cohort.

Paired Comparisons

Out of 1,120 patients, 743 (66%) had data at both baseline and within the 4-month period after their first medical cannabis purchase and were included in this analysis. A Mann-Whitney *U* Test indicated that baseline symptom scores between patients who only submitted one patient self-evaluation (those who made one purchase) and those making multiple submissions (those making more than one purchase) were not different across all symptoms, except for anxiety and lack of appetite. Patients making one purchase scored lower at baseline on anxiety (median = 6) than those with multiple purchases (median = 7; U = 127,780; P = .025), whereas patients with one purchase scored higher at baseline on lack of appetite (median = 8) than those with multiple purchases (median = 7; U = 154,010, P = .003).

Wilcoxon signed-rank tests were performed within patients to compare baseline responses on each symptom measure, with the average of symptom scores reported in the following 4-month period (n = 743). Analyses showed significant improvement in symptom scores between the two measurement periods (baseline *v* 4-month average score) for all standard eight measures (Fig 1). Figure 1 shows a shift in the distribution of symptom scores at baseline compared with the following 4-month score average. Many symptoms transitioned out of the highest severity levels (7 to 10) over this 4-month period.

Achieving 30% Symptom Improvement

All patients reporting a symptom at baseline were included in the analysis (ie, baseline score ≥ 1). The third column of Table 2 shows that, except for vomiting, more than 80% of all patients with cancer experienced each symptom to some degree. Not all symptoms showed similar degrees of improvement across patients. For example, close to half of all patients experiencing vomiting at baseline showed 30% or greater improvement within 4 months of their first medical cannabis purchase (Table 2, third column). Furthermore, of those achieving clinically meaningful improvements in vomiting within 4 months of first purchase (n = 297), 56.2% maintained, on average, that improvement in the following 4 months after first achieving 30% or greater improvement (Table 2, fifth column). Of those experiencing vomiting at baseline (n = 596), 28.0% of them both achieved and maintained 30% or greater improvement (Table 2, sixth column).

In contrast, the proportion of patients experiencing symptom improvements in fatigue or pain was relatively low compared with other symptoms measured on the patient self-evaluation. Just over a quarter of patients with fatigue or pain at baseline achieved 30% or greater improvement within 4 months of first purchase; of those patients, fewer than 40% maintained that improvement in the following 4 months after their initial improvement. Finally, for patients experiencing fatigue (n = 1,113) or pain (n = 1,086) at baseline (10.5% and 11.5%, respectively), both groups achieved and maintained 30% or greater improvement.

Adverse Effects

Minnesota medical cannabis products seemed to be relatively safe, with 118 patients (10.5% of the 1,120 patients in the cohort) reporting any adverse effects within 4 months of their first medical cannabis purchase. These 118 patients submitted 212 adverse effect responses, with 90.1% of adverse effects being of mild (44.3%) or moderate (45.8%) severity. The most commonly reported adverse effects are listed in Table 3, which generally aligns with the clinical literature on adverse effects of cannabis and cannabinoids.

DISCUSSION

Across eight symptoms, there was a significant reduction in symptom severity within 4 months of purchasing medical cannabis among the two-thirds of patients with cancer who enrolled in the Minnesota medical cannabis program and purchased products on at least two occasions (Fig 1). A substantial proportion of all patients were able to attain 30% or greater symptom reduction in scores for each symptom. In addition, cannabis use seems safe. Only 1.3% of patients reported adverse effects that affected usual activities of daily living.

The proportion who attained 30% or greater symptom reduction within 4 months of program participation varied considerably across symptoms, ranging from 49.8% (vomiting) to 27.0% (fatigue). Not all the patients who achieved 30% or greater reduction of a particular symptom maintained that level of improvement over the next 4 months. The proportion who maintained 30% or greater improvement was lowest for pain (38.3%) and fatigue (39.0%); for the other symptoms, it was closer to half, ranging from lack of appetite (48.2%) to vomiting (56.2%).

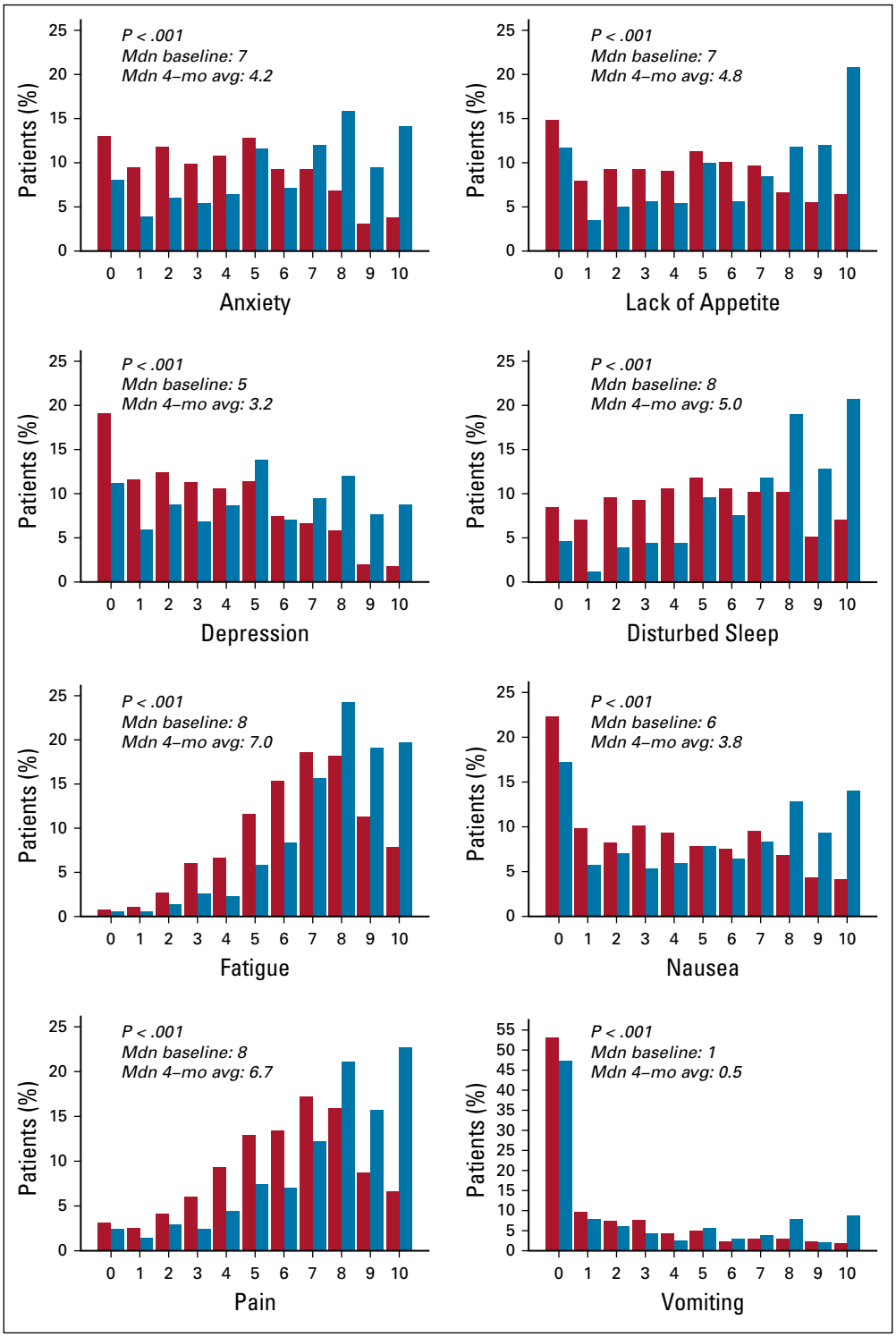

FIG 1. Baseline and subsequent 4-month average symptom score distributions (n = 743). Blue bars indicate baseline score, and red bars indicate subsequent 4-month average (avg) score. Mdn, median.

Our findings can be compared with two studies of patients with cancer newly enrolled in Israel's medical cannabis program. Both studies enrolled a wide variety of patients with cancer, who used a variety of cannabis flower and oil products. The more recent study found a change in distribution of Numeric Rating Scale (0 to 10 scale) pain scores between baseline and 6 months that seems to represent a larger degree of pain reduction than we found.[2] In the second study, reduction in pain severity between baseline and 6 weeks, using a 5-point scale, seems similar to the reduction seen in our findings, although in this study a larger share reported elimination of pain.[19] Reductions in nausea and vomiting and improvements in appetite and sleep seemed generally similar to ours, although symptoms

TABLE 2. Percentage and Frequency of Patients Achieving and Maintaining 30% or Greater Symptom Improvement

Symptom Measure	Patients Reporting Symptoms at Baseline (ie, score ≥ 1), % (No.)	Patients Reporting Symptoms at Baseline Who Achieved ≥ 30% Symptom Improvement Within 4 Months of First Purchase, % (No.)	Follow-Up Period		% of Patients Who Both Achieved ≥ 30% Symptom Improvement and Retained That Degree of Improvement for at Least 4 Months
			No. of Patients With Data in 4-Month Period After Initial ≥ 30% Symptom Improvement	Patients Who Achieved ≥ 30% Symptom Improvement Who Maintained it for ≥ 4 Months, % (No.)	
Anxiety	91.9 (1,029)	41.6 (428)	329	54.9 (235)	22.8
Appetite lack	89.3 (1,000)	38.8 (388)	293	48.2 (187)	18.7
Depression	88.4 (990)	44.5 (441)	331	50.3 (222)	22.4
Disturbed sleep	95.8 (1,073)	41.8 (449)	343	48.1 (216)	20.1
Fatigue	99.4 (1,113)	27.0 (300)	240	39.0 (117)	10.5
Nausea	82.4 (923)	40.5 (374)	283	49.7 (186)	20.2
Pain	97.0 (1,086)	30.0 (326)	237	38.3 (125)	11.5
Vomiting	53.2 (596)	49.8 (297)	222	56.2 (167)	28.0

NOTE. N = 1,120 patients with cancer.

tended to be more severe at baseline in our cohort. Reduction in fatigue seemed to be larger in this second study than in our results.[19]

Reports of adverse effects were uncommon (10.5% of patients), with most adverse effects rated as mild or moderate in severity. Although the proportion of patients reporting adverse effects is lower than what is reported in clinical trials, the most commonly reported adverse effects seem to align well with those reported in clinical trials using THC- and CBD-extracted products.[20-22] A nonresponse bias may account for this lower rate (eg, patients experiencing immediate, serious adverse effects might have stopped using cannabis and therefore not completed subsequent safety surveys).

There are some limitations to address in this study. First, there may be potential for response bias within this patient sample, because those who continue paying for medical cannabis are most likely experiencing some level of benefit. One-third of all patients with cancer in this study only made one purchase (only baseline symptom severity submitted).

TABLE 3. Top 10 Reported Adverse Effects (N = 1,120)

Top 10 Adverse Effects	Patients, % (No.)
Drowsiness/somnolence/sedation	2.5 (28)
Dry mouth	2.2 (25)
Fatigue	1.9 (21)
Increased appetite	1.5 (17)
Dizziness	1.3 (15)
Mental clouding/foggy brain	1.3 (15)
Nausea	1.1 (12)
Headache	0.9 (10)
Euphoria	0.6 (7)
Lightheadedness	0.6 (7)

To mitigate response bias, we retained all patients who experienced symptoms at baseline when calculating the proportion of those who achieved/maintained 30% or greater symptom improvement—regardless of whether they continued with the program (made additional medical cannabis purchases beyond their first one). This calculation gives a conservative estimate of the proportion of patients achieving and maintaining improvements in symptoms. However, our rate of adverse events may continue to be under-reported.

Second, this study does not provide conclusive evidence on the efficacy of medical cannabis in treating symptoms, something that can be produced via a randomized, controlled trial in which the researchers have careful control over multiple factors. Rather, this study estimates the magnitude of potential improvement that may be found in patients with cancer using cannabis extraction products. This estimated magnitude of patient-perceived improvement may be particularly useful in guiding expectations in a randomized clinical trial setting. In addition, clinical trials are in a better position to adopt the use of validated tools in measuring symptom improvement—something challenging to implement at a state program level. Zylla et al[23] have launched a prospective, randomized, observational study of patients with cancer requiring opioids and are tracking results longitudinally for all patients using validated symptom surveys to better define the benefits/risks of medical cannabis.

Last, concomitant therapies are not reliably collected within the program, which means that the ability to parse the efficacy of medical cannabis on symptom improvement from other concomitant therapies (eg, timing of chemotherapy) cannot be addressed within this study. In addition, the symptom improvements observed in this study may be more sensitive to particular therapies than others, which may lead to a potential bias in outcomes reported here.

In conclusion, cannabis use seems safe in this population, with few serious adverse effects reported. Although cannabis may not completely alleviate symptoms, reducing the symptoms of patients with cancer from severe to moderate/mild levels may drastically improve quality of life. Our findings can help in planning future clinical trials, which are needed to elucidate the appropriate use of cannabinoid products for managing symptoms in patients with cancer.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHOR CONTRIBUTIONS

Conception and design: Susan P. Anderson, Dylan M. Zylla, Tom J. Arneson
Collection and assembly of data: All authors
Data analysis and interpretation: Susan P. Anderson, Dylan M. Zylla, Tom J. Arneson
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Tom J. Arneson
Stock and Other Ownership Interests: Johnson & Johnson

No other potential conflicts of interest were reported.