Current Therapeutic Research 99 (2023) 100709

Contents lists available at ScienceDirect

Current Therapeutic Research

journal homepage: www.elsevier.com/locate/curtheres

Medical Cannabis Received by Patients According to Qualifying Condition in a US State Cannabis Program: Product Choice, Dosing, and Age-Related Trends

Xintian Lyu, BS[1], Sílvia M. Illamola, PharmD, PhD[1], Susan E. Marino, PhD[1,4], Ilo E. Leppik, MD[1,4,5], Stephen Dahmer, MD[2,3], Paloma Lehfeldt, MD[3], Jeannine M. Conway, PharmD[1], Rory P. Remmel, PhD[1], Kyle Kingsley, MD[3], Angela K. Birnbaum, PhD[1,4,*]

[1] *Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota*
[2] *Family Medicine and Community Health, Icahn School of Medicine at Mount Sinai, New York, New York*
[3] *Goodness Growth Holdings, Minneapolis, Minnesota.*
[4] *Center for Clinical and Cognitive Neuropharmacology, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota*
[5] *Department of Neurology, School of Medicine, University of Minnesota, Minneapolis, Minnesota*

ARTICLE INFO

Article history:
Received 23 February 2023
Accepted 2 June 2023

Key words:
CBD
Epilepsy
Medical cannabis
Pain
THC

ABSTRACT

Background: Little is known about the distribution of cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) to patients participating in state medical cannabis programs. The Minnesota cannabis program requires third-party testing of products with limited formulations of cannabis for distribution to patients.
Objective: To characterize the distribution of cannabis products, their CBD/THC content, and dosing among patients with qualifying conditions.
Methods: This is a retrospective analysis of ~50% of registered users receiving medical cannabis in Minnesota (June 16, 2016, to November 15, 2019). Data included formulation, CBD/THC prescribed doses, and qualifying conditions. The primary end points were calculated using daily dose and duration of use. Comparisons were made for CBD and THC total daily dose dispensed, patient age, and approved product. Nonparametric statistical tests were used (significance was set at $p < 0.05$).
Results: A total of 11,520 patients were listed with 1 qualifying condition. The most common condition was intractable pain (60.0%). Median dispensation duration varied from 53 days (cancer) to 322 days (muscle spasms). Most (≥62.8%) patients across all qualifying conditions received both CBD and THC. Median THC dose was lower in older (≥65 years) compared with younger adults with intractable pain ($p < 0.0001$) and cancer patients ($p = 0.0152$), and the same pattern was found CBD dose with seizure ($p = 0.0498$) patients. For commercial products with Food and Drug Administration indications, the median CBD total daily dose was 86.9% lower than the recommended doses for patients with seizures (Epidiolex: Jazz Pharmaceuticals, Palo Alto CA) and median THC total daily dose was 65.3% (Syndros: Benuvia Manufacturing, Round Rock, TX) or 79.3% lower (Marinol: Banner Pharmacaps, Inc., High Point, NC) for cancer patients.
Conclusions: A majority of patients received products containing both CBD and THC. Dosages varied by age group and were lower than recommended for conditions with Food and Drug Administration-approved products. Complex pharmacokinetics of THC and CBD, possible age-related changes in physiology, unknown efficacy, and potential for drug interactions all increase the need for monitoring of patients receiving cannabis products. (*Curr Ther Res Clin Exp*. 2023; 84:XXX–XXX)

* Address correspondence to: Angela K. Birnbaum, PhD, Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, 717 Delaware St SE, Minneapolis, MN 55414.
E-mail address: birnb002@umn.edu (A.K. Birnbaum).

https://doi.org/10.1016/j.curtheres.2023.100709

Introduction

Cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) are the most common constituents in currently available medical cannabis products.[1,2] Both CBD and THC have complicated pharmacokinetics causing significant variability in blood concentrations and possible changes in both symptom control and side effects. The amount of cannabinoid that reaches the systemic circulation after oral ingestion is low and highly dependent on fat content in food.[3,4] Metabolism by cytochrome P450 enzymes[5–9] increases the chance of potential drug–drug interactions. Indeed, the concentrations of several antiseizure medications are influenced when administered with CBD.[10–14] Variability in source plants and lot-to-lot variations in manufactured products heighten the potential for variability between patients and within a single patient.

Food and Drug Administration (FDA)-approved products of CBD or THC are available for limited conditions. Plant-extracted CBD is indicated for certain epilepsy syndromes (i.e., Lennox Gaustaut and Dravet) and seizures associated with tuberous sclerosis.[15] Synthetic THC is approved for chemotherapy-induced nausea and vomiting as well as anorexia-related weight loss in patients with AIDS.[16,17] Products with varying amounts of both CBD and THC prepared from extracts of the *Cannabis sativa* plant are available through many state cannabis programs.[18] As of April 24, 2023 38 states and 3 territories and the District of Columbia had state-sanctioned medical cannabis programs. State laws differ with respect to qualifying conditions and in the requirements that govern manufacturing and distribution of the products.[19] In many state programs, members of the public can petition the department of health to add qualifying medical conditions; thus, qualifying conditions represent a view of cannabis products based on anecdotal rather than medical evidence.

Currently there are no consistent guidelines for the use of CBD and THC products in patients among state programs. Cannabis products are available for certain qualifying conditions with some states allowing distribution of recreational cannabis,[19,20] thus increasing the potential for unanticipated and highly variable interactions with those medications being received by patients for other chronic conditions. Despite the increasing use of cannabis products, there is a knowledge gap on what formulations and doses of CBD or THC are being dispensed and consumed by patients in state programs, making it difficult to predict the extent of exposure in patients.

The Minnesota State Cannabis program, considered more restrictive than other states,[19] mandates third-party testing and limited manufacturing (Minnesota Statutes §152.22-152.37). The original Minnesota cannabis law (MN Laws 2014, Ch 311- SF2470) made purified extracts from the marijuana plant available for certain medical conditions. Patients must be certified by a health care professional (physician, physician's assistant, or advanced practice registered nurse) as having at least 1 qualifying condition to gain access to CBD-dominant, CBD and THC-balanced, and THC-dominant products from a regulated cannabis patient center (dispensary). At the dispensary, a Minnesota-licensed pharmacist conducts an extensive interview and consults the health commissioner dosing recommendations (Minnesota Statute §152.29 subdiv.3 [2020]), both required by existing regulations. Patients are then dosed based on internal training of the dispensing pharmacists and patient preferences to determine the product(s) and dose for each patient. In Minnesota, all products must be tested for verification of THC and CBD quantity. At the time of this study, multiple formulations were available, including oral capsules, vaporizer, oil for vaporization, oral solution, and topical forms. The goal of this study was to characterize the distribution of cannabis products, their CBD and THC content, and dosing among patients with qualifying conditions, by age, and compared with available federally approved products.

Materials and Methods

Data source and patient population

This was a retrospective analysis based on data collected from individuals registered in the Minnesota State Cannabis Program who were dispensed products from 1 of the 2 registered manufacturers (Vireo Health of Minnesota) between June 16, 2016, and November 15, 2019. Participants in the state program must read and sign a Tennessen Notice and Acknowledgement form. State statute also specifies the use of patient data for scientific, peer-reviewed publication of research (Minnesota Statute 152.28). A data use agreement was signed between the University of Minnesota and Vireo for this study. Vireo distributes medical cannabis to approximately half of the registered patients in the state and is the only Minnesota manufacturer with a purified CBD product. In the program, patients are certified by a Minnesota-licensed practitioner to have a qualifying condition, register with the state, and then present to 1 of the dispensaries. The 14 qualifying conditions at the time of this study were: cancer associated with severe/chronic pain, nausea or vomiting, or cachexia or severe wasting; glaucoma; HIV/AIDS; Tourette syndrome; amyotrophic lateral sclerosis; seizures, including those characteristic of epilepsy; severe and persistent muscle spasms, including those characteristic of multiple sclerosis (MS); inflammatory bowel disease, including Crohn disease; terminal illness, with a probable life expectancy of <1 year; intractable pain; posttraumatic stress disorder (PTSD); autism; obstructive sleep apnea; Alzheimer disease (AD).[21] AD was added as a qualifying condition on August 1, 2019, <1 year from the end of the data collection period, therefore, AD patients were excluded from the data analysis. For patients who were certified with more than 1 qualifying condition, it was not possible to distinguish which indication would be the reason for treatment with medical cannabis, and they were excluded from the data analysis. Patient records determined to have data entry errors (e.g., calculated age younger than 0 years), no dosing information, or no qualifying condition were excluded. Patient inclusion information is presented in Fig. 1.

Data collection

Demographic information included date of birth, gender, weight, and qualifying condition(s) for which each individual was certified. Product name, administration instructions, amount of THC and CBD contained in the product (in milligrams), the number of products being dispensed to patients, days supplied (DaysSupply), and the dispensation visit date were recorded. Each product was categorized according to formulation (i.e., capsules, oral solution, vaporizer, oil for vaporization, tincture, and balm). Each dispensed product was also classified as daily use or use as needed based on instructions at time of dispensing. Sample products named as starter packs and available as both capsules and vaporizers allowed patients to try smaller quantities of 3 different compound combinations (green [1:1 THC:CBD], red [THC dominant], and yellow [4:1 THC:CBD]) and were routinely offered to patients on their first visit as a way to affordably try various formulations. These starter packs were distinguished from regular-sized products.

Data analysis

The database was reviewed for missing data and possible errors by visual and systematic inspection of variables. Out of 11,520 individuals 0.3% were missing date of birth, 78.9% gender, and 98.9%

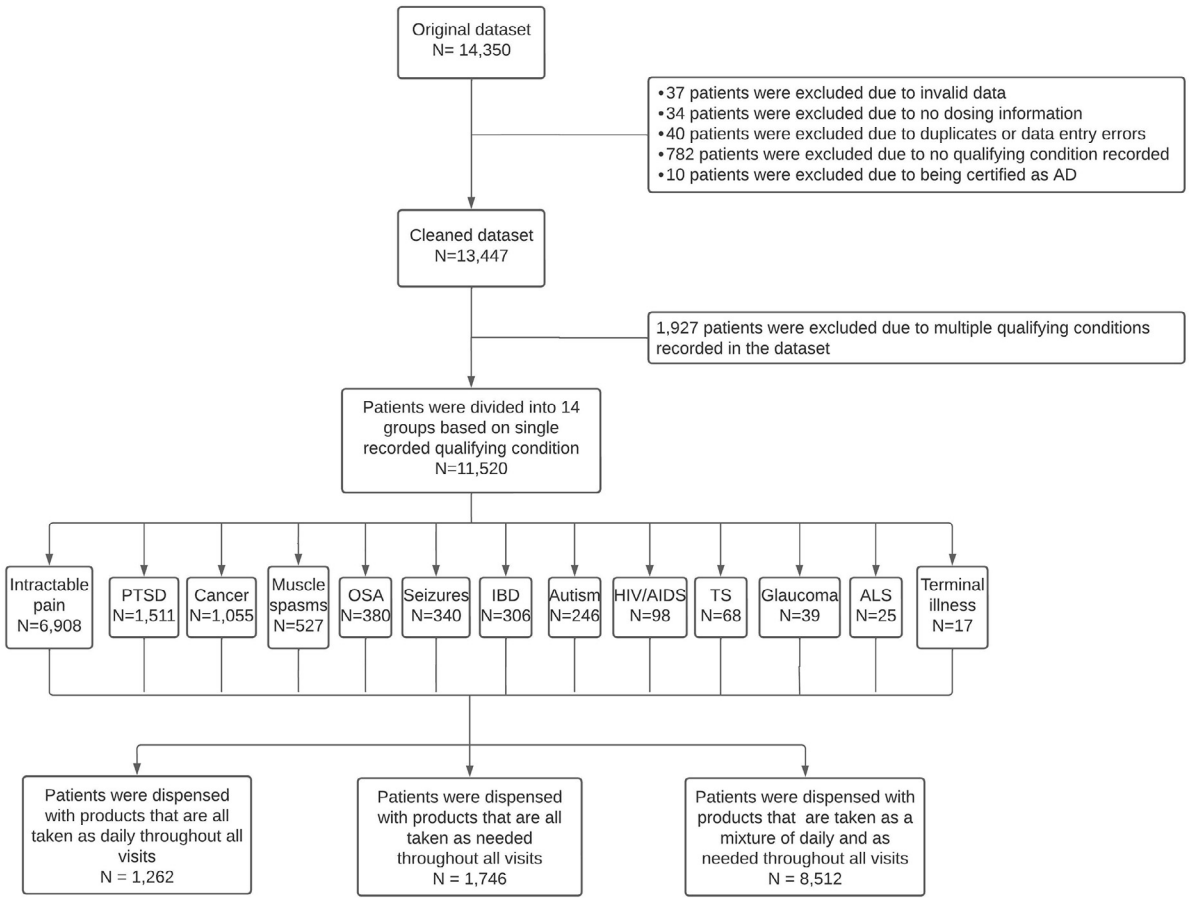

Figure 1. Flow chart of the study cohort assembly. Figure 1 shows the data cleaning (inclusion/exclusion criteria) and data analysis procedures. ALS = amyotrophic lateral sclerosis; IBD = inflammatory bowel disease; OSA = obstructive sleep apnea; PTSD = posttraumatic stress disorder; TS = Tourette syndrome.

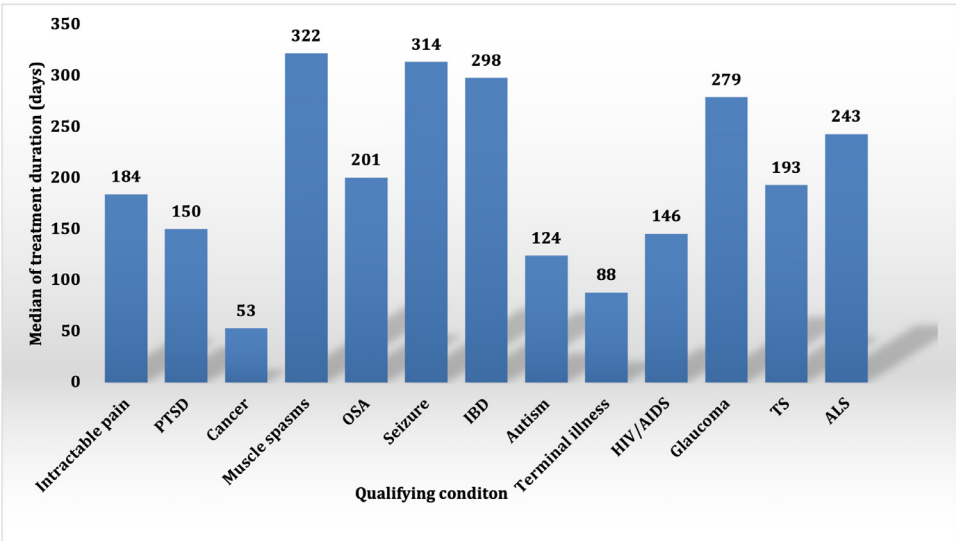

Figure 2. Dispensation duration across all qualifying conditions. Bars represent the median number of days in the study. Patients in the muscle spasms group had the longest dispensation duration, whereas patients in Alzheimer disease group had the shortest dispensation duration. The minimum dispensation durations were 0 for all qualifying condition groups because there were patients with only 1 dispensation visit in each group. The maximum dispensation durations were 1227, 1152, 1235, 1241, 468, 1236, 1244, 466, 461, 1236, 1149, 1235, and 1072 days across qualifying condition groups, respectively. ALS = amyotrophic lateral sclerosis; IBD = inflammatory bowel disease; OSA = obstructive sleep apnea; PTSD = posttraumatic stress disorder; TS = Tourette syndrome.

Table 1
Age distribution of patients who had only 1 qualifying condition.*

Qualifying condition	<18 y	≥18 and <65 y	≥65 y	Unknown
Intractable pain (n = 6,908)	22 (0.3)	5,272 (76.3)	1,595 (23.1)	19 (0.3)
PTSD (n = 1,511)	25 (1.7)	1,432 (94.8)	50 (3.3)	4 (0.3)
Cancer (n = 1,055)	26 (2.5)	656 (62.2)	364 (34.5)	9 (0.9)
Muscle spasms (n = 527)	3 (0.6)	432 (82.0)	91 (17.3)	1 (0.2)
OSA (n = 380)	0 (0.0)	333 (87.6)	46 (12.1)	1 (0.3)
Seizure (n = 340)	93 (27.4)	227 (66.8)	18 (5.3)	2 (0.6)
IBD (n = 306)	6 (2.0)	282 (92.2)	18 (5.9)	0 (0.0)
Autism (n = 246)	151 (61.4)	93 (37.8)	1 (0.4)	1 (0.4)
HIV/AIDS (n = 98)	0 (0.0)	94 (95.9)	4 (4.1)	0 (0.0)
TS (n = 68)	16 (23.5)	48 (70.6)	3 (4.4)	1 (1.5)
Glaucoma (n = 39)	0 (0.0)	24 (61.5)	15 (38.5)	0 (0.0)
ALS (n = 25)	0 (0.0)	20 (80.0)	5 (20.0)	0 (0.0)
Terminal illness (n = 17)	0 (0.0)	7 (41.2)	10 (58.8)	0 (0.0)

ALS = amyotrophic lateral sclerosis; IBD = inflammatory bowel disease; OSA = obstructive sleep apnea; PTSD = posttraumatic stress disorder; TS = Tourette syndrome.
* Values are presented as n (%).

Table 2
Median of cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) total daily dose on the last visit across all products.

Condition*	n	Individuals dispensed CBD†	CBD total daily dose‡, mg	Individuals dispensed THC†	THC total daily dose,‡ mg
Intractable pain	4,628	3,138 (67.8)	3.3 (0.01–645.9)	4,612 (99.7)	13.4 (0.01–1,556.0)
PTSD†	993	658 (66.3)	4.0 (0.03–277.8)	991 (99.8)	19.2 (0.03–1,520.0)
Cancer	462	293 (63.4)	3.8 (0.04–312.5)	459 (99.4)	12.9 (0.3–1,166.7)
Muscle spasms	388	283 (72.9)	4.3 (0.1–137.8)	384 (99.0)	12.5 (0.04–198.6)
OSA‡	268	182 (67.9)	5.4 (0.1–175.0)	268 (100.0)	20.0 (0.5–472.9)
IBD§	229	176 (76.9)	2.9 (0.1–295.0)	229 (100.0)	13.4 (0.3–325.0)
Seizure	192	152 (79.2)	45.2 (0.02–428.6)	175 (91.1)	6.5 (0.3–231.3)

IBD = inflammatory bowel disease; OSA = obstructive sleep apnea; PTSD = posttraumatic stress disorder.
* Only the top-7 qualifying conditions were reported.
† Values are presented as n (%).
‡ Values are presented as median (range).

weight. Data cleaning and analyses were performed by the University of Minnesota research group (X.L., S.M.I., and A.K.B.). A data dictionary was supplied, and data queries answered by Vireo employees (S.D., P.L., and K.K.) during the data cleaning process. Age at each dispensation visit was calculated by subtracting the date of dispensation from the birthdate. Data were stratified by qualifying condition and age group (<18, ≥18 and <65, and ≥65 years). For each individual, the duration of dispensation (days supplied with medical cannabis products) and the median duration were calculated. The gap in days between the last visit and the end date of data collection was calculated for each patient. Patients were categorized into three groups based on their use of the products dispensed: all products daily throughout all visits, all products as needed, and a mixture of products as daily and as needed (Fig. 1).

To determine the daily dose (milligrams per day) for each product the last visit information for all patient adult groups (aged ≥18 years) was used. Each individual had to have information on at least 3 disposition visits to ensure doses did not include initial titration. Dose was calculated using information for the last visit by dividing the CBD or THC content (in milligrams) in a product by the DaysSupply or the time between visits (VisitGap). VisitGap was used as the denominator if it was larger than DaysSupply, indicating patients did not fill their prescription continuously. Doses from all products received on the same visit day were added together to represent the total daily dose (milligrams per day) of CBD or THC received. For patients dispensed with both CBD and THC on their last visit, the median and range of CBD to THC ratio were reported by qualifying condition. The number of formulations dispensed on the last visit was also calculated.

The comparison of the total daily doses from this study to recommended dosage of FDA-approved products included adult patients (aged 18 years or older) who were indicated to be taking cannabis daily. Children were not included in this subgroup analysis due to the lack of weight information in our dataset and the need to use a standardized body size approach. To achieve this, we employed a stable dose (i.e., maintenance dose) approach to be more comparable to doses referenced in the package insert. To be on a stable dose participants needed to be dispensed the same total daily dose for at least 2 consecutive visits. Because Epidiolex is a highly purified CBD extract, which is available in oral solution form to treat seizures,[15] only seizure patients who were dispensed an oral solution in the state program were used to calculate stable CBD total daily doses. Marinol and Syndros are synthetic THC in oral solution and capsule formulations to treat chemotherapy-induced nausea and vomiting and weight loss in patients with AIDS;[16,17] thus, only cancer and HIV/AIDS patients who were dispensed oral solution or capsules in the state program were used to calculate stable THC total daily doses. In cases where patients reached several stable doses, the last stable dose was selected. The stable CBD/THC doses were compared with the recommended maintenance or initial dose of FDA-approved products with the same formulation and qualifying condition, using standardized measures of body size (i.e., 70 kg for weight and 1.7 m^2 for body surface area).

As a measure of drug adherence, the DaysSupply of product was divided by the VisitGap and multiplied by 100%.[22] For patients who were dispensed more than 1 product, the longest DaysSupply of the products was used to calculate drug adherence. A median adherence for adult patients (age ≥18 years) in all 3 groups with at least 2 visits was calculated and reported by condition.

Statistical analysis

Descriptive analyses included calculation of median and range. Total daily dose and CBD to THC total daily dose ratio on the last visit was compared using a Kruskal-Wallis nonparametric test

Table 3
Patients dispensed cannabidiol (CBD) and/or Δ9-tetrahydrocannabinol (THC) on the last dispensation visit with CBD to THC total daily dose ratio.

Qualifying condition*	n	Individuals dispensed CBD only or CBD-predominant (THC <1%) only†	Individuals dispensed THC-predominant (CBD 1%) only†	Dispensed with both CBD and THC	
				Individuals†	Median of CBD to THC total daily dose ratio (range)‡
Intractable pain	4,628	16 (0.3)	1,490 (32.2)	3,122 (67.5)	0.3 (0.003–81.0)
PTSD	993	2 (0.2)	335 (33.7)	656 (66.1)	0.1 (0.005–67.7)
Cancer	462	3 (0.6)	169 (36.6)	290 (62.8)	0.3 (0.010–20.0)
Muscle spasms	388	4 (1.0)	105 (27.1)	279 (71.9)	0.3 (0.003–59.0)
OSA	268	0 (0.0)	92 (34.3)	176 (65.7)	0.1 (0.015–9.0)
IBD	229	0 (0.0)	47 (20.5)	182 (79.5)	0.3 (0.008–19.0)
Seizure	192	17 (8.9)	40 (20.8)	135 (70.3)	16.1 (0.005–60.5)

IBD = inflammatory bowel disease; OSA = obstructive sleep apnea; PTSD = posttraumatic stress disorder.
* Only the top-7 qualifying conditions were reported.
† Values are presented as n (%).
‡ The minimum CBD to THC total daily dose ratio was reported to 3 decimal places due to small values.

($p < 0.05$) regardless of age group across all qualifying condition groups. Total daily dose on the last visit was compared with a Mann Whitney *U* test ($p < 0.05$) between younger and older adults (aged ≥18 to <65 and ≥65 years) within each qualifying condition. All analyses were performed with R Software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Of 13,447 patients, 11,520 (85.7%) patients were listed as having only 1 qualifying condition (Fig. 1). The most common single condition was intractable pain (6,908 [60.0%] and the least frequent was terminal illness (17 [0.1%]). For patients with only one qualifying condition recorded, the majority (8,920 [77.4%]) were between ages 18 and 65 years except for those patients with autism (61.4% of patients aged 18 years or younger) and terminal illness (58.8% of patients aged 65 years or older) (Table 1). For individuals with only 1 qualifying condition recorded, 7,771 (67.5%) received a starter pack with 7,195 (92.6%) receiving the starter pack at the initial visit (data not shown). For the 7,195 individuals with a starter pack at their first dispensation visit, 6,100 (84.8%) continued and received additional medical cannabis products (data not shown). Median dispensation duration in days by condition varied from 53 days for patients with cancer to 322 days for patients with muscle spasms (Fig. 2). Besides muscle spasms, longer dispensation durations were seen with seizure (median, 314 days) and inflammatory bowel disease (median, 298 days). Of patients with 1 qualifying condition, 1,921 (16.7%) patients had only 1 dispensation visit (data not shown). Thirty-seven percent of patients had data within the last 60 days of the study signifying that the end of therapy (i.e., end of duration calculation) could be due to the end of the data collection period.

The median (range) dose of CBD and THC in adult patients on the last visit is presented in Table 2. The median age of adults receiving THC or CBD formulations was 49.2 years (range, 18.1–98.6) (data not shown). A majority (≥62.8%) of patients across qualifying conditions received doses containing both CBD and THC-dominant formulations. The median CBD to THC total daily dose ratio was >1 only in seizure patients (Table 3). On the last visit most patients (66.5%), regardless of qualifying conditions, were dispensed with 1 formulation; however, some patients received up to 5 formulations. For the 4,906 patients being dispensed 1 formulation: 2,143 (43.7%) received vaporizer, 1,337 (27.3%) capsules, 706 (14.4%) oil for vaporization, and 720 (14.7%) other formulations (oral solution, tincture, or balm) (data not shown). Across the last 3 visits of 7,378 patients, 2,487 (33.7%) patients did not change their formulation, 1,592 (21.6%) did not change their CBD total daily dose, and 117 (1.6%) did not change their THC total daily dose (data not shown). For patients who changed their CBD total daily dose, 726 (12.5%) patients always increased and 697 (12.0%) always decreased their dose from visit to visit. Among patients who changed their THC total daily dose, 1,165 (16.0%) patients always increased and 1,129 (15.5%) always decreased their dose. There were 3,837 patients who were always dispensed with both CBD and THC across their last 3 visits with 601 (15.7%) patients who did not change their CBD to THC total daily dose ratio. For patients who changed their CBD to THC total daily dose ratio (n = 3,236 [84.3%]), 312 (9.6%) always increased their ratio and 528 (16.3%) always decreased their ratio. There are significant differences in both THC (p <0 .0001) and CBD ($p < 0.0001$) total daily dose and CBD to THC total daily dose ratio ($p < 0.0001$) in at least 2 qualifying condition groups (data not shown). Older adults aged 65 years or older received significantly less THC compared with younger patients in intractable pain and cancer patients and the same pattern was found in CBD total daily dose in for seizure patients (Table 4).

For those indications with FDA commercial products (i.e., seizure and cancer), the median CBD total daily dose was 86.9% lower than the recommended doses for patients with seizures (n = 16, Epidiolex [oral solution]) and the median THC total daily dose was 65.3% lower (n = 10, Syndros [oral solution]) or 79.3% lower (n = 16, Marinol [capsules]) for cancer patients (Table 5).[15–17] The comparison was not made for HIV/AIDS patients because no patient reached a THC stable dose.

The range of adherence was as low as 0.1% (seizure) and as high as 765.4% (HIV/AIDS) (Table 6). The median of drug adherence across qualifying conditions ranged from 28.6% (Tourette syndrome) to 71.4% (autism).

Discussion

Our study provides data from a state-specific program regarding medical cannabis products dispensed to patients with specific qualifying chronic conditions. There is a wide range of CBD and THC doses being dispensed to patients within and across formulations and qualifying conditions. The age of patients varied by condition (e.g., only 3.3% of the PTSD patients were elderly vs 34.5% of the cancer patients). Most patients were receiving medical cannabis for intractable pain, with 67.5% receiving both CBD and THC on the last dispensation visit recorded. Although extracted CBD is approved for treating seizures and there are FDA-approved indications for THC-only products, a majority of patients across all indications in the state program received formulations that contained both CBD and THC.

The pharmacokinetics of CBD and THC are known to be highly variable across patients. There is a strong association between absorption of CBD and fat content in food[3] that can contribute to the variability seen within and across patients; this may result in varying doses if doses are self-titrated to effect. Pharmacists

Table 4
Cannabidiol (CBD)/Δ9- tetrahydrocannabinol (THC) total daily dose comparison between age groups (≥18 years and <65 or ≥65 years).

Condition	Age	Number of patient dispensed with CBD	Median CBD total daily dose (mg/day) (range)	p-value for CBD	Number of patient dispensed with THC	Median THC total daily dose (mg/day) (range)	p-value for THC
Intractable pain	18-65	2,470	3.2 (0.01 – 645.9)	<0.0001*	3,679	14.7 (0.01 - 1,556.0)	<0.0001*
	≥65	668	4.4 (0.1 – 365.3)		933	10.1 (0.03 - 471.0)	
Cancer	18-65	205	3.4 (0.04 – 312.5)	0.0371*	319	14.2 (0.4 - 259.1)	0.0152*
	≥65	88	4.2 (0.1 – 200.0)		140	11.3 (0.3 - 1,166.7)	
Seizure	18-65	137	49.1 (0.02 – 428.6)	0.0498*	-	-	-
	≥65	15	22.3 (0.4 – 178.1)		-	-	

* Only conditions with significant differences of total daily dose between age groups were reported.

Table 5
Comparison of doses received by patients in state program to Food and Drug Administration (FDA) -approved product recommendations.

Cannabinoid	Condition	Formulation	n	Median dosage (mg/day)	FDA recommended dosage* (mg/day)	Compared with the FDA products
CBD	Seizure	Oral solution (Epidiolex‡)	16	91.5	700	Lower
THC	Cancer	Capsules (Marinol§)	16	8.8	34.0-51.0†	Lower
THC	Cancer	Oral solution (Syndros‖)	10	12.4	28.6-42.8†	Lower

CBD = cannabidiol; THC = Δ9- tetrahydrocannabinol.
* Calculated based on average body size of 70 kg or 1.7 m^2.
† The mean of the FDA recommended doses were used for calculation.
‡ Epidiolex: Jazz Pharmaceuticals, Palo Alto CA.
§ Marinol: Banner Pharmacaps, Inc., High Point, NC.
‖ Syndros: Benuvia Manufacturing, Round Rock, TX.

Table 6
Median of drug adherence for patients throughout all visits.

Condition	n	Drug adherence,* %
Intractable pain	5,803	35.7 (0.2–750.0)
PTSD	1,224	36.4 (0.2–540.0)
Cancer	719	32.5 (0.4–502.7)
MS	461	32.5 (0.3–266.7)
OSA	326	44.5 (0.6–230.8)
IBD	265	35.2 (0.6–502.3)
Seizure	216	52.9 (0.1–144.3)
Autism	79	71.4 (3.3–329.4)
HIV/AIDS	70	29.1 (1.6–765.4)
TS	44	28.6 (1.1–175.0)
Glaucoma	32	34.0 (1.2–133.3)
ALS	23	44.1 (9.5–230.8)
Terminal illness	11	37.0 (9.1–108.0)

ALS = amyotrophic lateral sclerosis; IBD = inflammatory bowel disease; MS = multiple sclerosis; OSA = obstructive sleep apnea; PTSD = posttraumatic stress disorder; TS = Tourette syndrome.
* Values are presented as median (range).

were trained to encourage consistent administration of product with food, however no information was available to indicate if doses were indeed taken according to these instructions. Patients in the state program received up to 5 different formulations during their treatment, but 66.5% of patients had only 1 formulation prescribed on their last visit. The effect on the pharmacokinetics of each compound when coadministered in multiple formulations is not known. The bioavailability of cannabis is low and variable and differs by route of administration with the bioavailability of vaporized formulations being reported to be higher than the bioavailability of oral formulations.[23,24] Therefore, switching of formulations among individual patients could increase variability in drug concentrations and potentially influence response and drug interactions.

Both CBD and THC are highly metabolized by cytochrome P450 enzymes, increasing the likelihood of drug interactions.[25] Older adults also experience multiple comorbidities and receive more medications than younger adults further increasing the possibility of drug interactions. In this study, the age of patients varied by condition with few older patients in some conditions such as PTSD and more in conditions that are prevalent in elderly populations. The doses received were different between younger and older adults for THC, but not CBD regardless of condition. Doses in this study reflect those received or adjusted through the dispensary and information on efficacy, comedications, and the presence of side effects was not available. A more detailed study containing drug exposure and efficacy data by indication is needed to distinguish between effective treatment, placebo effect, age effects, and perceived desired cannabinoid effects. It is also unclear if clinically relevant drug interactions occur at the doses reported in this dataset and more investigation is needed.

Our results offer insight on product choice, major cannabinoid quantities, and doses received based on pharmacist selection and patient preference rather than doses prescribed by physicians. Because medical providers are limited in their ability to engage in the cannabis space, the state programs represent a departure from the usual role of physicians as prescribers. Because patients need to pay for their cannabis out of pocket, duration of dispensation may be a proxy for affordability, efficiency in finding a therapeutic product and dose, or continued perceived efficacy to justify ongoing cost. By this measure, muscle spasms of MS have the longest median duration of use. Current evidence supports that in adults with MS-related spasticity, short-term use of oral cannabinoids improves patient-reported spasticity symptoms.[26] Starter packs are an attempt to allow patients early access to varying dose ratios of THC to CBD. A majority (67.5%) of patients received a starter pack. Among patients who received a starter pack at their first visit, 84.8% of patients remained in the program. Continued voluntary participation in the self-pay program suggests these patients found at least 1 formulation of value, consistent with data from the Minnesota program showing that of patients experiencing moderate to severe symptoms at baseline, anywhere between 33% and 66% achieved at least a 30% reduction in symptom severity (symptom improvement) within 4 months of their first medical cannabis purchase.[27] Future studies with appropriate placebo

groups are needed to address the extent of efficacy in different conditions.

Interpreting adherence estimates for medical cannabis presents an interesting challenge. Prescription-only medication dispensing has significant oversight by pharmacy practice laws and restrictions due to insurance. The dispensing of medical cannabis in Minnesota is a patient-driven process and determination of the dose taken by a patient can be a balance between effectiveness and cost they can afford. This results in a patient having the autonomy to change doses and formulations at their own pace, which may explain the adherence estimates well above 100%.

Limitations

Our data reflect product(s) dispensed to patients without confirmation of actual doses ingested by patients. Although data included in our analyses do not include other sources of cannabis from both legal and illicit sources, dispensed doses are reflective of the amount of cannabis available to patients and provide a measure of the extent of exposure to compounds that could influence treatment and clinical end points. Key information was not available on patient comorbidities, other treatment modalities utilized by patients, and thorough medical history. Weight was not available for the majority of patients; thus, doses adjusted for weight could not be calculated, necessitating use of standard body size measurements to calculate total daily doses based on dose per body size recommendations. Sex and gender information was not available and the potential implications of sex differences in dosing could not be further explored.[28] Approximately one-third of patients were still receiving cannabis within 60 days of the end of the study; therefore, the duration of cannabis use could be underestimated in our study. Attempting to evaluate adherence is difficult, especially when more than 1 product is available, products are available from multiple unregulated sources, and there are no regulations dictating how often purchases can be made.

Conclusions

In medical cannabis programs there is an overlap of qualifying conditions with existing FDA-approved drug products. In specific conditions like seizure disorder, where purified CBD has proven efficacy and an FDA-approved drug, patients in a state program used combinations of both THC and CBD. Patients with chronic conditions have a high prevalence of medication treatment; thus, comedications would be expected to be more prevalent in patients who qualify for state product increasing the potential for drug–drug interactions. In addition, older patients have increased comorbidities and medication use when compared with younger adults, making them more susceptible to drug interactions. Given that the majority of products received by patients include THC-containing formulations, more research is needed to understand the long-range influence of use, especially in conditions where CBD products have been indicated. The complicated pharmacokinetics of THC and CBD along with possible age-related changes in physiology, unknown effect on efficacy, and the potential for drug interactions increases the need for monitoring of patients receiving these products.

Declaration of Competing Interest

S. Dahmer, P. Lehfeldt, and K. Kingsley are employed by and have stock ownership in Goodness Growth Holdings (formerly Vireo Health). J. Conway is a consultant for Cannabinoid Education Working Group-Jazz Pharmaceuticals and A. Birnbaum holds a patent for parental carbamazepine. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

Acknowledgments

Supported in part by the MacMillan Innovative Epilepsy Research and Education Fund and Medical Discovery Team on Addiction Pilot Grant Award, University of Minnesota.

The authors thank the Minnesota Department of Health for answering questions on the Minnesota program.

All authors had access to the data and a role in writing the manuscript; however, S. Dahmer, P. Lehfeldt, and K. Kingsley were not involved in data analyses or interpretation of data except for verification of data collection queries and accuracy of the original and revised manuscript.

References

1. ElSohly MA, Radwan MM, Gul W, Chandra S, Galal A. Phytochemistry of Cannabis sativa L. *Prog Chem Org Nat Prod*. 2017;103:1–36. doi:10.1007/978-3-319-45541-9_1.
2. Adams R, Hunt M, Clark JH. Structure of cannabidiol, a product isolated from the marihuana extract of Minnesota wild hemp. I. *J Am Chem Soc*. 1940;62(1):196–200. doi:10.1021/ja01858a058.
3. Birnbaum AK, Karanam A, Marino SE, et al. Food effect on pharmacokinetics of cannabidiol oral capsules in adult patients with refractory epilepsy. *Epilepsia*. Aug 2019;60(8):1586–1592. doi:10.1111/epi.16093.
4. Stott CG, White L, Wright S, Wilbraham D, Guy GW. A phase I study to assess the effect of food on the single dose bioavailability of the THC/CBD oromucosal spray. *Eur J Clin Pharmacol*. Apr 2013;69(4):825–834. doi:10.1007/s00228-012-1393-4.
5. Harvey DJ, Samara E, Mechoulam R. Comparative metabolism of cannabidiol in dog, rat and man. *Pharmacol Biochem Behav*. Nov 1991;40(3):523–532. doi:10.1016/0091-3057(91)90358-9.
6. Jiang R, Yamaori S, Takeda S, Yamamoto I, Watanabe K. Identification of cytochrome P450 enzymes responsible for metabolism of cannabidiol by human liver microsomes. *Life Sci*. Aug 1 2011;89(5-6):165–170. doi:10.1016/j.lfs.2011.05.018.
7. Mazur A, Lichti CF, Prather PL, et al. Characterization of human hepatic and extrahepatic UDP-glucuronosyltransferase enzymes involved in the metabolism of classic cannabinoids. *Drug Metab Dispos*. Jul 2009;37(7):1496–1504. doi:10.1124/dmd.109.026898.
8. Anderson GD, Chan LN. Pharmacokinetic Drug Interactions with Tobacco, Cannabinoids and Smoking Cessation Products. *Clin Pharmacokinet*. Nov 2016;55(11):1353–1368. doi:10.1007/s40262-016-0400-9.
9. Stott C, White L, Wright S, Wilbraham D, Guy G. A Phase I, open-label, randomized, crossover study in three parallel groups to evaluate the effect of Rifampicin, Ketoconazole, and Omeprazole on the pharmacokinetics of THC/CBD oromucosal spray in healthy volunteers. *Springerplus*. Dec 2013;2(1):236. doi:10.1186/2193-1801-2-236.
10. Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia*. Aug 2015;56(8):1246–1251. doi:10.1111/epi.13060.
11. Anderson LL, Absalom NL, Abelev SV, et al. Coadministered cannabidiol and clobazam: Preclinical evidence for both pharmacodynamic and pharmacokinetic interactions. *Epilepsia*. Nov 2019;60(11):2224–2234. doi:10.1111/epi.16355.
12. Ben-Menachem E, Gunning B, Arenas Cabrera CM, et al. A Phase II Randomized Trial to Explore the Potential for Pharmacokinetic Drug-Drug Interactions with Stiripentol or Valproate when Combined with Cannabidiol in Patients with Epilepsy. *CNS Drugs*. Jun 2020;34(6):661–672. doi:10.1007/s40263-020-00726-4.
13. Patsalos PN, Szaflarski JP, Gidal B, VanLandingham K, Critchley D, Morrison G. Clinical implications of trials investigating drug-drug interactions between cannabidiol and enzyme inducers or inhibitors or common antiseizure drugs. *Epilepsia*. Sep 2020;61(9):1854–1868. doi:10.1111/epi.16674.
14. Morrison G, Crockett J, Blakey G, Sommerville K. A Phase 1, Open-Label, Pharmacokinetic Trial to Investigate Possible Drug-Drug Interactions Between Clobazam, Stiripentol, or Valproate and Cannabidiol in Healthy Subjects. *Clin Pharmacol Drug Dev*. Nov 2019;8(8):1009–1031. doi:10.1002/cpdd.665.
15. Greenwich Biosciences, Inc. *Epidiolex (cannabidiol) [package insert]*. U.S. Food and Drug Administration website; 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/210365s005s006s007lbl.pdf. Revised July 2020. Accessed February 14.
16. Insys Therapeutics. *Syndros (dronabinol) [package insert]*. U.S. Food and Drug Administration website; 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205525s003lbl.pdf. Revised May 2017. Accessed February 14.
17. AbbVie, Inc. Marinol (dronabinol) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018651s029lbl.pdf. Revised August 2017. Accessed February 14, 2022.
18. Cash MC, Cunnane K, Fan C, Romero-Sandoval EA. Mapping cannabis potency in medical and recreational programs in the United States. *PLoS One*. 2020;15(3):e0230167. doi:10.1371/journal.pone.0230167.

19. National Conference of State Legislatures. State Medical Cannabis Laws. https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx.
20. Pruyn SA, Wang Q, Wu CG, Taylor CL. Quality Standards in State Programs Permitting Cannabis for Medical Uses. *Cannabis Cannabinoid Res*. Mar 28 2022. doi:10.1089/can.2021.0164.
21. Minnesota Department of Health. Medical cannabis program to add chronic pain, macular degeneration as qualifying conditions. https://www.health.state.mn.us/news/pressrel/2019/cannabis120219.html.
22. Saberi P, Caswell N, Amodio-Groton M, Alpert P. Pharmacy-refill measure of adherence to efavirenz can predict maintenance of HIV viral suppression. *AIDS Care*. Jul 2008;20(6):741–745. doi:10.1080/09540120701694006.
23. Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clin Pharmacol Ther*. Sep 1980;28(3):409–416. doi:10.1038/clpt.1980.181.
24. Spindle TR, Cone EJ, Goffi E, et al. Pharmacodynamic effects of vaporized and oral cannabidiol (CBD) and vaporized CBD-dominant cannabis in infrequent cannabis users. *Drug Alcohol Depend*. Jun 1 2020;211:107937. doi:10.1016/j.drugalcdep.2020.107937.
25. Lopera V, Rodriguez A, Amariles P. Clinical Relevance of Drug Interactions with Cannabis: A Systematic Review. *J Clin Med*. Feb 22 2022;11(5). doi:10.3390/jcm11051154.
26. Markova J, Essner U, Akmaz B, et al. Sativex((R)) as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial. *Int J Neurosci*. Feb 2019;129(2):119–128. doi:10.1080/00207454.2018.1481066.
27. Minnesota Department of Health Office of Medical Cannabis. Benefits Reported on the Patient Self-Evaluation: Patients with First Enrollment July 2015-June 2017. https://www.health.state.mn.us/people/cannabis/docs/about/cohort/c2015_2017_benefitspse.pdf.
28. Cuttler C, Mischley LK, Sexton M. Sex Differences in Cannabis Use and Effects: A Cross-Sectional Survey of Cannabis Users. *Cannabis Cannabinoid Res*. 2016;1(1):166–175. doi:10.1089/can.2016.0010.