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ORIGINAL ARTICLE

A randomized trial of medical cannabis in patients with stage IV cancers to assess feasibility, dose requirements, impact on pain and opioid use, safety, and overall patient satisfaction

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Abstract

Purpose The prevalence of medical cannabis (MC) use in patients with cancer is growing, but questions about safety, efficacy, and dosing remain. Conducting randomized, controlled trials (RCTs) using state-sponsored MC programs is novel and could provide data needed to guide patients and providers.

Methods A pilot RCT of patients with stage IV cancer requiring opioids was conducted. Thirty patients were randomized 1:1 to early cannabis (EC, n = 15) versus delayed start cannabis (DC, n = 15). The EC group obtained 3 months (3 M) of MC through a state program at no charge, while the DC group received standard oncology care without MC for the first 3 M. Patients met with licensed pharmacists at one of two MC dispensaries to determine a suggested MC dosing, formulation, and route. Patients completed surveys on pain levels, opioid/MC use, side effects, and overall satisfaction with the study.

Results Interest in the study was high as 36% of patients who met eligibility criteria ultimately enrolled. The estimated mean daily THC and CBD allotments at 3 M were 34 mg and 17 mg, respectively. A higher proportion of EC patients achieved a reduction in opioid use and improved pain control. No serious safety issues were reported, and patients reported high satisfaction.

Conclusion Conducting RCTs using a state cannabis program is feasible. The addition of MC to standard oncology care was well-tolerated and may lead to improved pain control and lower opioid requirements. Conducting larger RCTs with MC in state-sponsored programs may guide oncology providers on how to safely and effectively incorporate MC for interested patients.

Keywords Medical cannabis · Pain · Opioids · Cancer · Patient-reported outcomes

Introduction

Patients with advanced cancer often experience debilitating symptoms including pain, nausea, and anxiety. Cannabis (marijuana) use is becoming more prevalent among patients with cancer [1], perhaps due to its perceived ability to help manage multiple symptoms with minimal side effects [2, 3]. Since 2000, at least 20 studies have assessed the impact of cannabis across a variety of symptoms in patients with cancer [4, 5]. Recently, two large registry studies involving more than 4000 patients show that patients with cancer who use medical cannabis report clinically meaningful improvements in symptoms while also reducing the use of opioids, benzodiazepines, and other supportive medications [6, 7].

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Despite the increase in medical cannabis use, guidance from medical professionals is markedly lacking. For clinicians involved in the recommendation of medical cannabis and those personnel involved in product dispensation to patients, the majority of US states currently do not require any formal training [8]. One study shows that 3 in 4 patients want information about cannabis from their cancer care team, yet only 15% receive it [1]. Only 30% of oncologists feel they have sufficient training to make informed recommendations about cannabis [9], and 85% want more education [10]. Questions regarding cannabis availability, dosing, costs, and efficacy and safety must be addressed in order for both patients and oncology providers to feel comfortable incorporating cannabis into clinical oncology practice [4]. Patients and physicians need answers to questions such as (a) which patients may benefit most from cannabis; (b) what is the best dose, route, and formulation/ratio of tetrahydrocannabinol (THC) and cannabidiol (CBD); and (c) is cannabis safe to use with current anti-neoplastics including chemotherapy, targeted therapy, and immunotherapy.

Conducting well-designed randomized trials with currently available cannabis products is difficult. Current challenges to interventional studies with cannabis include the need for a schedule 1 DEA license; safeguards and protections for the proper handling and storage of cannabis; collaborating with the Food and Drug Administration to submit an investigational new drug application; coordinating with the National Institute on Drug Abuse (NIDA) to obtain research-grade cannabis; and securing research funding [11, 12]. While over 30 states have established comprehensive medical cannabis programs, many programs use whole plant products instead of purified extraction products with defined amounts of THC and CBD. In symptomatic patients with advanced cancer, ensuring cannabis is not only effective, but safe and well-tolerated is important. No guidelines exist to assist patients or clinicians on the types and doses of cannabis to utilize for treating cancer-related symptoms, and pragmatic trials are needed.

We conducted a pilot randomized, controlled trial of early vs delayed start medical cannabis in cannabis-naïve patients with a variety of advanced cancers to assess: (a) feasibility of doing interventional trials with a state-sponsored cannabis program, (b) suggested dose escalation strategy for cannabis products, (c) impact of cannabis on cancer-related pain and opioid utilization, (d) safety, and (e) overall patient satisfaction. Results from this study will inform patients and clinicians on dosing and safety at a time when data is absent and help guide future researchers on the many challenges facing adequately powered prospective interventional trials in the care of patients with cancer.

Methods

Patient selection

Eligible patients were at least 18 years of age, had evidence of incurable or stage IV cancer, used any opioids within 1 month of the start of the study, had an ECOG performance status of ≤ 2 and a life expectancy of at least 3 months, and were eligible to register with the Minnesota medical cannabis program (MMCP). Patients were excluded if they used any cannabis-derived product within 3 months of enrollment or had untreated brain metastases, a diagnosis of dementia, epilepsy, traumatic brain injury, schizophrenia, or a schizoaffective disorder. Patients were enrolled from a large community oncology practice (all HealthPartners and Park Nicollet cancer clinics including 28 oncologists) throughout Minneapolis and St. Paul, MN. Informed consent was obtained.

Study design

The study was approved by the HealthPartners Institutional Review Board, Minnesota Department of Health Office of Medical Cannabis, Vireo Health of Minnesota (VHM), and LeafLine Labs (LLL). Thirty eligible patients were randomized 1:1 to early cannabis (EC, $n = 15$) versus delayed cannabis (DC, $n = 15$). The EC group obtained up to 3 months of medical cannabis through the MMCP at no charge, while the DC group received standard oncology care without cannabis for the first 3 months and then offered a 3 month trial of cannabis at no charge.

Measures

On a monthly basis, patients completed validated symptom surveys with patient-reported symptom monitoring (PRSM) questionnaires [13], a pain log (documenting average daily pain scores over a 7-day period via a 0–10 visual analog scale rating), and a medication diary where participants listed all analgesic/opioid medications (from which a total monthly oral morphine equivalent (OME) was calculated) and cannabis products ingested. In addition to patient logs, cannabis dispensaries provided comprehensive lists of all cannabis products dispensed including dosing instructions provided for each patient.

Cannabis-related safety information was collected in multiple ways. First, dispensaries at VHM and LLL contacted the study team with any cannabis-related adverse event (AE). Second, reports were obtained from SafetyCall International (the organization mandated by the MMCP for dispensaries to utilize for any after-hour cannabis-related issues) [14]. Third, we reviewed any emergency room/

urgent care visits and/or hospital admission for a potential attribution to cannabis use based on clinician notes. Finally, patients and their certifying oncology provider completed study close-out questionnaires with questions regarding cannabis benefits and harms on a 7-point Likert scale. Regarding harms, patients were asked, "how much negative impact, if any, have you experienced by taking medical cannabis?," while providers were asked, "how much negative impact, if any, do you believe the patient experienced by taking medical cannabis?" To assess possible benefits, patients were asked, "how much benefit, if any, have you experienced by taking medical cannabis?".

Plasma THC and CBD concentrations were measured at two time points: pre-cannabis dose and within 7 days of planned cessation of medical cannabis (in attempts to obtain a steady-state measurement) by a validated assay via high-performance liquid chromatographic tandem mass spectroscopy (LC–MS/MS) (Birnbaum Laboratory, University of Minnesota) [15].

Cannabis registration and dosing

Prior to receiving cannabis, patients were certified by their oncology clinician and registered for the MMCP. The state registration fee was paid for by the study, and all cannabis-based medicine (CBM) were provided by MMS and LLL at no cost to the patient. Patients met with pharmacists at their choice of one of eight cannabis dispensaries to determine the initial CBM dosing and titration plan based on clinical goals, formulation, and route (see Appendix 1). The Minnesota licensed cannabis pharmacists have robust internal training on medical cannabis products and dosing and are required by state law to consult the commissioned, "Review of Medical Cannabis Studies Relating to Chemical Compositions and Dosages for Qualifying Medical Conditions" document available on the MMCP website for additional guidance (https://www.health.state.mn.us/people/cannabis/docs/practitioners/dosagesandcompositions2019.pdf). Patients were advised to begin dosing at 2.5–5 mg/2.5–5 mg (THC/CBD), respectively, with a titration plan to escalate to a maintenance dose of 30–40 mg of THC and 30–40 mg of CBD per day over 2–4 weeks (Table 1). Doses were adjusted with pharmacist guidance up to twice a month based on symptom goals and tolerance. Dispensaries provided records of all cannabis products dispensed to patients. A low- and high-dose estimate was calculated based on the dosing instructions provided by the cannabis pharmacist.

Data analysis

Feasibility was assessed by reporting the number of patients screened and enrolled. The primary feasibility aim was to enroll 50 patients with metastatic cancer from a single healthcare organization within 6 months. Detailed screening logs were kept to capture reasons that patients declined enrollment in the study. Descriptive summaries were generated for pain, daily oral morphine equivalents (OME), and cannabis dosage data by month of the study. Month 1 OME calculations were used for baseline data in the DC patients as they did not complete an opioid diary until day 21. Means and standard deviations were used for continuous variables; counts and percentages were used for categorical variables. Analysis was conducted in SAS v9.4 (SAS Institute, Inc., Cary, NC).

Table 1 Initial 2-week cannabis-based medicine (CBM) dosing titration algorithm. After initial dose on day 1 (which should be divided BID on that first day), assess effect/side effect. On day 2, start with day 1 initial dose, and then the next dose in 4–8 h is adjusted upwards based on initial dose response. Upwards adjustments should occur in single spray/inhalation/pill increments per dose. For oral solutions, a patient can double the previous mg dose when titrating upwards. Repeat this same reassessment and re-dosing again after an additional 4–8 h and again 4–8 h later, etc. until side effects are noted or until max daily dose for days 2–4. When limiting side effects are noted, the patient should return to the previously tolerated dose amount for the next dose and remain at that dose amount every 4–12 h until the next step up period. Continue this process at each step up period until the 2-week pharmacist visit

Initial titration period	Standard titration daily THC/CBD dose in mg	Low dose titration daily THC/CBD dose in mg
Day 1	5 mg/5 mg*	2 mg/2 mg*
Days 2–4	5–10 mg/5–10 mg	2–5 mg/2–5 mg
Days 5–8	10–20 mg/10–20 mg	5–10 mg /5–10 mg
Days 9–11	10–30 mg/10–30 mg	5–20 mg/5-20 mg
Days 12–14	10–40 mg/10–40 mg	5–30 mg/5-30 mg
Days 15 +	Pharmacist guided based on patient results initial titration	Pharmacist guided based on patient results initial titration
	*Initial dosing amount depends on the exact format of CBM (vaporized oil, tincture (i.e., for sublingual administration), oral solution, pill) formulation limitations. Range is 4.2–5.0 mg)	*Initial dosing amount depends on the exact format of CBM (vaporized oil, tincture, oral solution, pill) formulation limitations. Range is 1.3–2.2 mg)

Results

Feasibility and patient demographics

Of the 148 patients screened for this study, 84 met all inclusion/exclusion criteria and were invited to participate (Fig. 1). Ultimately, 30 patients (36% of eligible patients) were randomized to EC (n = 15) and DC groups (n = 15), with 24 patients enrolled in the first 6 months; thus, the primary feasibility endpoint was not reached. Of the 18 patients who appeared eligible and were approached, 8 declined enrollment because they wanted access to cannabis immediately and 5 declined enrollment because their pain was stable or improving. Patients in the EC group were similar to DC group with respect to mean age (57 (SD = 9) years vs 55 (SD = 13) years) and percentage female (47% vs 53%), respectively. The most common cancer diagnoses included the pancreas (n = 6), lung (n = 5), colon/rectum (n = 5), breast (n = 4), and myeloma (n = 3). Due to early death (n = 2), withdrawal from the study (n = 3), and poor compliance (n = 7) with documentation/logs, 18 patients were ultimately analyzed for key clinical outcomes at 3 months pertaining to pain and opioid utilization (EC = 9, DC = 9). Overall, 23 total patients received at least one cannabis prescription (EC = 14 (during months 1–3), DC = 9 (during months 4–6)), but two DC patients had insufficient data to verify dosing.

Cannabis dosing and utilization patterns

Choosing an appropriate cannabis product and dose is challenging for patients, and dose escalation may be required to achieve maximum effectiveness. We analyzed cannabis utilization patterns to determine types and formulations dispensed as well as approximate THC and CBD dosing (Fig. 2). Of the 21 patients who tried cannabis during the trial and had verifiable pharmacy-related data (EC = 14, DC = 7), 71% and 48% used cannabis for at least 60 and 90 days, respectively. Overall, the amount of THC and CBD dispensed was relatively constant over 90 days (Fig. 2). On average, the amount of THC dispensed per patient each month was nearly twice that of CBD (average 34.3 mg THC vs 16.6 mg CBD).

In addition, a variety of formulations (e.g., oral, inhalational, topical) with differing ratios of THC/CBD were

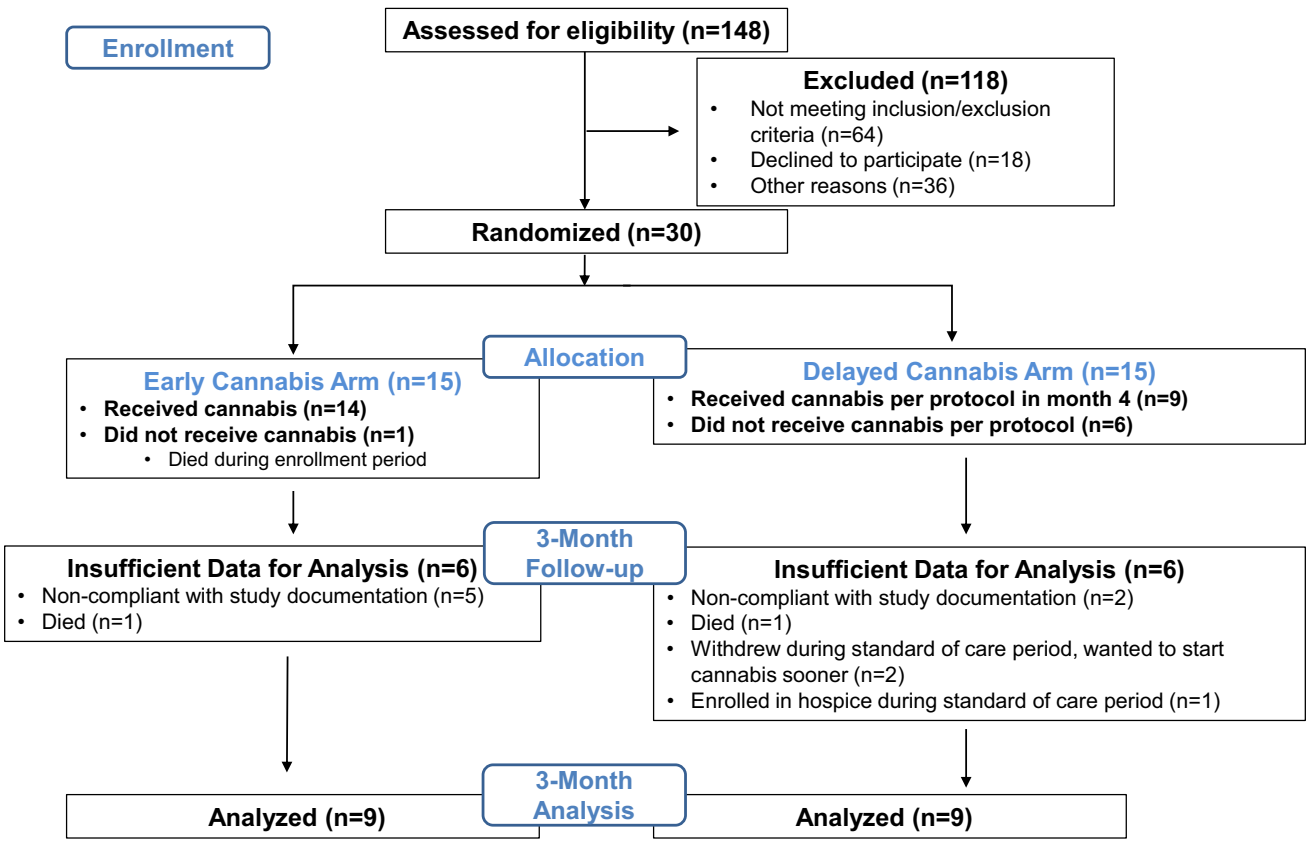

Fig. 1 Enrollment and analysis of patients in early and delayed cannabis groups during the first 3 months of the study. Patients in the delayed cannabis group received cannabis beginning in month 4, but no formal analysis between groups was done after month 3

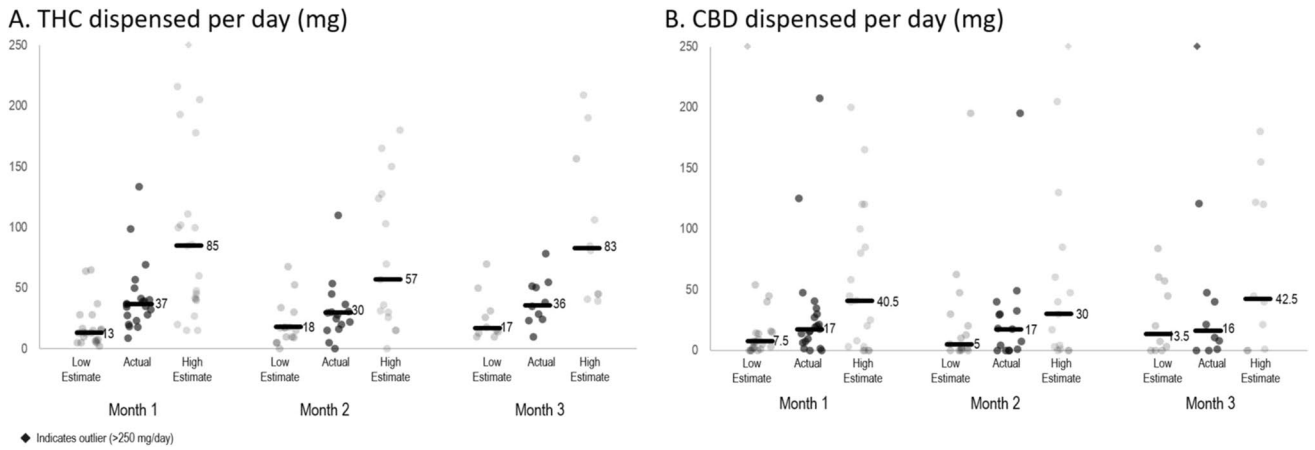

Fig. 2 Cannabis utilization patterns over 3 months of use for (**A**) THC and (**B**) CBD for each patient. Actual is determined by the total amount of cannabinoid dispensed to a patient in a given month. The low and high estimates were calculated based on the dosing instructions provided by the cannabis pharmacist

provided depending on individual patient symptoms. The median number of different products tried was 5 (range 1–14). After 30 days of cannabis use, 108 different products were dispensed to patients; 63% had a high THC:CBD ratio, 30% were balanced in THC:CBD, and 7% were high CBD:THC. Routes of administration also varied. Oral products were the most common (26% pills and 25% liquid), followed by inhaled (35%) and topical (14%).

We attempted to correlate cannabis dosing with plasma levels of THC and CBD by conducting an end-of-treatment blood draw during month 3. Blood was collected during routine clinic encounters (i.e., the concentrations were not collected at precise time points after dosing or standardized to last meal), thus limiting the ability to correlate drug concentration with a specific THC/CBD dose. The mean, median, and range at study close-out were 7.3, 1.2, and 0.6–52.4 ng/mL for THC and 6.0, 1.9, and 0.11–35.9 ng/mL for CBD, respectively. Since all patients had undetectable values before starting cannabis, this confirms that patients (a) were not using cannabis sourced outside of the MNCP prior to study initiation and (b) actively used cannabis while in study.

Cannabis impact on pain and opioid use

Obtaining adequate pain control while minimizing opioid utilization is a goal for both patients and clinicians. Since cannabis may improve pain and may lower opioid requirements in non-cancer-related pain [16], we analyzed pain and total OME over the first 3 months of the trial in all patients. Baseline pain levels and personalized pain goals were similar (Table 2). From the study entry to 3 months, the overall mean pain scores remained similar; however, the number of patients who reported meeting their personalized pain goal increased from 2/9 (22%) to 4/9 (44%) in EC cohort and dropped from 3/9 (33%) to 1/9 (11%) in the DC cohort. During the 3-month study period, EC patients had stable levels of opioid utilization, whereas the DC patients average daily OME increased by 57%. Furthermore, only patients using cannabis reduced their daily OME by at least 20%.

Safety of cannabis use

During the trial period, no cannabis-related adverse events were reported by study the participants to the call center. In addition, 18 of the 23 patients who utilized cannabis completed a study close-out questionnaire. The average "negative impact" score reported by patients was 2.8 (median 2.0) (1 = no negative effects; 4 = some negative effects; 7 = a great deal of negative effects). Two patients reported a score of 7 (with reasons provided being "the smell would make me nauseous" and "I felt anxious and could not sleep….it gave me headaches"). The average "negative impact" reported by the patient's treating oncologist was 2.5 (median 2). Only one oncologist listing a score of 6 or higher states, "patient did not like the "high" feeling; dizzy and unable to concentrate." Finally, review of all emergency room/urgent care visits showed that none were attributed to cannabis use.

Patient satisfaction and cannabis continuation plan

While the overall quality of life and key symptom scores did not change significantly over a 3-month period for EC users (Table 2), patients reported a high degree of overall benefit from cannabis use at their study close-out. The average "benefit" score was 4.9, median 5, with over one-third of respondents reporting a "7" (1 = no benefit; 4 = some benefit; 7 = a great deal of benefit). Forty-four percent of respondents

Table 2 Analysis of pain, opioid utilization, and symptom scores between early cannabis and delayed cannabis patients between baseline and 3 months. Patients in the delayed cannabis group received only standard of care treatments through month 3

Outcomes	Early cannabis (n = 9)		Delayed cannabis (n = 9)	
	Baseline	3 months	Baseline	3 months
Mean pain, 0–10 (SD)	5 (1)	5 (2)	6 (3)	6 (2)
Mean personalized pain goal (PPG), (SD)	3 (2)	3 (3)	4 (2)	4 (3)
# patients meeting PPG (%)	2 (22)	4 (44)	3 (33)	1 (11)
Mean daily oral morphine equivalent (OME), (SD)*	53 (44)	57 (41)	35 (66)	55 (77)
Relative change in OME over 3 months, # of patients (%)*				
Increase of 20% or more	NA	3 (38)	NA	4 (67)
Decrease of 20% or more	NA	3 (38)	NA	0 (0)
No change of more than 20%	NA	2 (25)	NA	2 (33)
Overall quality of life score, mean/median**	2/2	2/3	3/3	3/3
Overall constipation score, mean/median***	2/2	1/1	2/1	1/1
Overall insomnia score, mean/median***	2/2	1/2	2/2	2/1
Overall decreased appetite score, mean/median***	2/2	1/1	1/1	2/1

*Complete oral morphine equivalent data unavailable for one early cannabis patient and 3 delayed cannabis patients

**5-point scale for quality of life (0 = excellent, 1 = very good, 2 = good, 3 = fair, 4 = poor)

***5-point scale for symptoms (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe)

who used cannabis stated that they planned to continue purchasing cannabis products through the state program after the trial; however, the cost was the biggest barrier listed as preventing ongoing use. When asked, "What is the most you are willing to pay per month for medical cannabis?," 28% reported up to $50, 39% reported up to $100, and 16% reported up to $200, with the remainder saying none.

Discussion

We successfully completed a pilot randomized, controlled trial of early vs delayed start medical cannabis obtained through a state-sponsored program in cannabis-naïve patients with advanced cancer. Patients used a variety of medical cannabis products and routes and increased doses over an initial 30-day period to an average daily THC dose of 34 mg and CBD dose of 17 mg. Medical cannabis use led to improvements in achieving personalized pain goals and lower overall opioid requirements. No serious adverse events with cannabis were reported, and most patients who used cannabis reported that benefits outweighed negative effects. This study demonstrates randomized trials incorporating state-sponsored medical cannabis products are feasible and could be utilized in larger, prospective studies.

The novel design of our study could have broad implications for treatment trials in cannabinoid research. Only 10 randomized trials incorporating cannabis in patients with cancer have been published in the past 20 years [4], although others may be in progress [17]. Creating pragmatic, cost-efficient cannabis treatment trials with strong safety oversight will help researchers address the risks and potential benefits in oncology and other disciplines. We partnered with MMCP and both state-licensed cannabis dispensaries to create a protocol that utilized medical cannabis products which were obtained following current standard practice under state law. This also allowed the ability to incorporate existing cannabis safety oversight with a third-party adverse effect reporting center. Our randomization functioned well with a control group initially receiving standard of care symptom management and then crossing over to obtain the cannabis intervention after 3 months. Allowing all patients an eventual opportunity to try cannabis likely improved accrual on this current trial. Of the 84 patients screened who met all inclusion/exclusion criteria, we enrolled 30 (36%) over 9 months. We did not meet our primary feasibility endpoint of enrolling 50 patients within 6 months; however, that goal may have been too ambitious for a single-center trial. Potential enrollment was also likely impacted by patients wanting immediate use of cannabis (n = 8) or being ineligible due to active cannabis use (n = 7). While we had significant patient drop-out mostly due to progressing cancer, we feel our trial design is feasible and should be considered by others wishing to do interventional studies with cannabinoids.

Another strength of our trial design was studying real-world dosing of cannabinoids by utilizing a patient-focused titration schedule in order to optimize symptom control and avoid side effects without cost factoring into a patient's choice of products. In 2019, patients with cancer spent an average of $236/month for cannabis medications in the MNCP [18]. While others have attempted to define safe and appropriate dosing protocols with cannabis, there are few prospective

dose escalation protocols specifically in cancer [19, 20]. In studies with nabiximols (an oromucosal product containing approximately 2.7 mg of THC and 2.7 mg of CBD per spray) for cancer-related pain, patients self-titrated to approximately 6 sprays/day (approximately 16 mg of THC and 16 mg of CBD each day) [21, 22]. Our data suggest (a) patients may try multiple products/formulations; (b) starting at 2.5 to 5 mg THC/day, patients were able to titrate up to higher levels of THC without significant side effects after 30 days; and (c) few patients required doses of THC above 36 mg. While cannabis dosing likely will remain somewhat individualized within state programs, our titration protocol (Appendix 1) provides a roadmap for dosing goals that could be further clarified with ongoing prospective, symptom-targeted trials.

Our results support prior studies suggesting cannabis may improve pain and minimize opioid utilization in both cancer and non-cancer settings. Placebo-controlled trials with nabiximols in adult patients with incurable cancers not responding to optimized opioid therapy suggest a slight improvement in pain and opioid reduction in a subset of patients [21–24]. In a large prospective cannabis study involving patients with a wider variety of cancers (51% of cohort had stage IV cancers as in our study), the percentage of patients with severe pain was significantly improved after 6 months of cannabis [7]. In addition, opioid use after 6 months was discontinued (36%), decreased (10%), or remained stable (51%), suggesting patients responding to cannabis treatment can have meaningful improvements in both pain and opioid requirements. Our EC and DC groups were similar in baseline pain levels and pain goals, yet the EC group utilizing cannabis showed a better trend in achieving pain goals and minimizing opioid increases. Larger, prospective trials in patients with identical cancer diagnoses/pain types (e.g., newly diagnosed stage IV pancreatic cancer) are required to fully understand the potential impact of cannabis on pain and opioid use.

As our study was designed to assess feasibility, any conclusions regarding treatment effect of cannabis between EC and DC groups are limited. As a result, we did not conduct formal statistical analyses. The small sample size, diverse patient population, high study drop-out, and poor patient compliance with study symptom logs/diaries further limited our ability to closely analyze symptoms other than pain and opioid requirements. For example, patients struggled to clearly document the varying cannabis products and doses they took at the end of each month prompting us to calculate cannabis dosing based on total products dispensed by the pharmacist. Assuming patients actually ingested/inhaled all products dispensed may be inaccurate, but given the similar cannabinoid doses in month 2 and 3, we felt this was an appropriate surrogate. Furthermore, given the lack of clear dosing strategies in clinical practice, patients are often instructed to try multiple product formulations and choose the one that best addresses their symptoms with the least side effects. As such, determining the "right" product for each patient can involve much trial and error, further challenging the ability to conduct clinical trials in this space.

In addition, this was not a placebo-controlled, blinded RCT; thus, response bias may result in patients using cannabis reporting better pain levels. However, opioid utilization is more objective and seemed to support what patients were reporting. While no serious safety issues were identified, we did not conduct a formal toxicity analysis with validated patient-reported survey questions. Furthermore, we could not assess any impact cannabis may have had with chemotherapy interactions. While cannabis has generally been considered safe with traditional cytotoxic agents, there is concern that the anti-inflammatory properties of cannabis may negatively impact immunotherapy [25, 26]. Lastly, there is a large food effect with CBD, and information on administration of products with or without food was not collected [27].

Conclusion

In conclusion, we demonstrate a novel way to prospectively incorporate state-sponsored cannabis products into randomized controlled trials to better inform dose requirements, safety, and efficacy. The variability of cannabis products, doses (including content of THC and CBD), and routes remains a challenge for the reproducibility and generalization of results when conducting clinical trials. Incorporating cannabis into routine cancer care may improve pain control and minimize opioid requirements. Medical cannabis use appears safe with no serious adverse events reported. The time has come to move beyond the current reality of vulnerable populations self-medicating with cannabis-based products for medical use. Patients and their cancer care providers need robust evidence to guide them in appropriate ways to safely and effectively incorporate cannabis into treatment plans in the most cost-efficient manner. Conducting larger, prospective, pragmatic trials that incorporate cannabis in patients with similar cancer diagnoses, medical conditions, and cannabis products/doses will be needed. Without additional data, the true benefits and risks of cannabis may remain clouded in smoke.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Dylan Zylla, Justin Eklund, Grace Gilmore, Jordan Guggisberg, Gabriela BaazquezBenitez, Sara Richter, and Angela Birnbaum. The first draft of the manuscript was written by Dylan Zylla, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The authors have full control of all primary data and agree to allow the journal to review data if requested.

Code availability Not applicable.

Declarations

Ethics approval This research involved human participants and was performed in line with the principles of the Declaration of Helsinki. Approval was granted by HealthPartners Institutional Review Board.

Consent to participate Informed consent was obtained from all patients.

Consent for publication Not applicable.

Conflict of interest Dr. Dahmer has received personal compensation for serving as an employee of Vireo Health International. Matthew Tracy is employed by LeafLine Labs. The remaining authors have no conflict of interest to declare that are relevant to the content of this article.

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