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Clinical Trial Results

OXFORD

Dose response relationship of medical cannabis and symptom control in patients with pancreatic cancer: an analysis of the CANPAN trial

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Abstract

Background: **In a pilot waitlist-control randomized trial, a personalized medical cannabis intervention improved certain symptoms among patients with pancreatic cancer over 8 weeks. Longer-term and dose-response data can guide future trial design.**

Methods: **CANPAN enrolled 32 cannabis-naïve patients with newly diagnosed locally advanced/metastatic pancreatic adenocarcinoma (NCT06605430). Patients were randomized to early (0-8 weeks) or delayed (9-16 weeks) cannabis intervention. Primary efficacy results over the first 8 weeks were previously reported. We investigated cannabis use and patient-reported outcome (PRO) completion over 9-16 weeks, and the relationship between tetrahydrocannabinol (THC) dose and symptom efficacy.**

Results: **Among 32 participants, 23 (72%) used cannabis during their assigned 8-week period (12/16 in early arm and 11/16 in delayed arm). Of these, 16 (50%) had both pre-cannabis and 8-week post-cannabis initiation PRO data available. At the end of the 16-week study period, PRO data were available for 16 (50%) participants (9/16 early arm, 7/16 delayed arm). Median daily THC dose 4 weeks after starting cannabis was similar in early vs delayed arms (10 mg vs 9.3 mg). A higher average daily THC dose was associated with improvements in anxiety ($r = 0.52$, $P = .038$) and insomnia ($r = 0.53$, $P = .033$). A $\geq$ 10 mg daily THC dose (vs <10 mg) was associated with mean improvement in 4 vs 2.1 symptoms.**

Conclusions: **The 50% complete data availability at 16 weeks, dose-response relationship with psychological symptoms, and threshold dose for multi-symptom efficacy will guide future trials. Similar cannabis use patterns across arms raise confidence in the waitlist-control design.**

Key words: cannabis; pancreatic cancer; symptom; clinical trial; dose response

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Lessons learned

- In a waitlist-control trial of medical cannabis among patients with pancreatic cancer initiating cytotoxic chemotherapy, 72% participants accessed cannabis through a State-licensed program, and 50% had evaluable patient-reported outcome data at 16 weeks.
- Cannabis access rates and use patterns were similar in the early vs delayed cannabis intervention arm, raising confidence in intervention fidelity across arms using the waitlist-control design.
- Higher daily THC use was associated with improvements in psychological symptoms such as anxiety and insomnia, and participants who used ≥10 mg daily average THC experienced improvement in a greater number of symptoms.

TRIAL INFORMATION

Disease	Newly diagnosed pancreatic adenocarcinoma
Stage of disease/treatment	Locally advanced/metastatic with ≥1 eligible symptom
Prior therapy	Initiating first line standard-of-care systemic cytotoxic chemotherapy
Type of study	Phase II
Primary endpoints	Feasibility (of randomization, conduct, adherence to arm, PRO collection) of 0-8 weeks, reported previously
Secondary endpoints	Efficacy via changes in individual symptom scores (PRO-CTCAE) (pain, nausea, vomiting, appetite, insomnia, anxiety, neuropathy, and possible harms such as dry mouth, dizziness, and concentration problems). Primary efficacy data for 0-8 weeks reported previously. Secondary outcomes reported now include cannabis use and PRO completion through 16 weeks, attrition patterns, cannabis dose in the early and delayed cannabis access arms, change from baseline (pre-cannabis use) in individual PRO-CTCAE symptom severity scores, and associations between mean daily THC exposure and symptom response (threshold dose for and dose-response relationship with symptom efficacy).

Additional details of endpoints or study design

Pilot randomized waitlist-control trial of medical cannabis for 32 adult patients with newly diagnosed locally advanced or metastatic pancreatic cancer who were initiating standard-of-care systemic chemotherapy with at least one self-reported qualifying symptom (pain, nausea, vomiting, anorexia, or cachexia). Minnesota residency was required for Minnesota Medical Cannabis Program (MMCP) participation. Randomized 1:1 to early (0-8 weeks) or delayed (9-16 weeks) cannabis intervention. Intervention included MMCP certification, personalized education regarding cannabis use by the study team and MMCP pharmacists to address routes of administration, side effects, titration strategies, safety considerations, and provision of cannabis products at no cost during assigned interventional period. When appropriate (immediately in the early arm; at week 9 in the delayed arm), participants visited a MMCP dispensary and picked up personalized products.

The primary study period was 0-8 weeks when only the early arm received the intervention, and the secondary study period was 9-16 weeks when the delayed arm received the intervention. The early arm could continue the intervention during the secondary period (though cannabis products were no longer covered by the study).

Trial assessments were conducted remotely with no additional in-person study-specific visits after the initial consent visit. Participants could initiate, continue, or modify supportive care treatments and any modifications to their cancer—directed treatment were per standard-of-care.

We collected electronic patient-reported outcomes (ePROs): The NCI-Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) survey customized for cancer-associated and potential cannabis-related symptoms as well as the PROMIS Global assessment of mental and social health in patients with cancer (QOL). Early participants completed the PRO-CTCAE (weekly) and QOL (every 4 weeks) through week 8, then PRO-CTCAE/QOL every 4 weeks through week 16. Delayed participants completed PRO-CTCAE weekly and QOL every 4 weeks throughout the 16 weeks.

Drug information

DRUG INFORMATION	
Generic/working name	Medical cannabis products accessed through state-licensed dispensary
Company name	Cannabis was dispensed by Vireo Health (GreenGoods Minnesota), a licensed MMCP manufacturer.
Dose	See dosing table below: followed "start low, go slow" approach with exact products/dosing strategy individualized to each patient and the dominant symptom(s). See below.
Route	Oral and/or inhaled and/or topical
Schedule of administration	Flexible, patient-directed with guidance from study team and MMCP pharmacists. Educational material provided, and patients self-titrated dose/route/schedule with study team and MMCP pharmacist guidance. Early arm accessed cannabis from 0-8 weeks with option to continue from 9-16 weeks. Delayed arm accessed cannabis from 9-16 weeks.

DOSE TITRATION GUIDELINES AND TABLE-PART 1			
Product type	**Week 1**	**Week 2**	**Week 3**
THC-dominant product	Day 1: 3-5mg at night	Up to 10 mg at night if needed	Adjusted per oncology care team and pharmacist guidance, and personal tolerance.
THC-to-CBD balanced product	Day 2: 2.5 mg THC to 2.5 mg CBD with morning and evening meal	5mg THC to 5 mg CBD for each mealtime dose as needed	
Short-acting THC-dominant product[a]	Day 3: 2-3mg if needed. Limit to 5 doses (approx. 10 mg THC) in a 24-hour period	As needed	

Abbreviations: THC = tetrahydrocannabinol; CBD = cannabidiol.
[a]An oral spray or inhaled product.

DOSE TITRATION GUIDELINES AND TABLE-PART II			
Symptom	**THC/CBD cannabinoid ratio**	**Route**	**Starting dose**
Insomnia	High (THC-dominant and/or CBN)	Oral	2.5 to 5 mg THC at night and/or 5 to 10 mg CBN
Pain (chronic)	Balanced[a]	Oral	2.5 to 5 mg up to 3 times per day with meals
Pain (breakthrough)	High (THC-dominant)	Inhaled (Vaporizer or Spray)	1 to 2 mg each dose up to 6 times per day
Pain (localized)	High (THC-dominant)	Topical (Ointment or Cream)	Apply to the affected areas 2 to 3 times per day
Nausea, vomiting or anorexia (cachexia)	Balanced	Oral	2.5 to 5 mg up to 3 times per day with meals
Nausea or vomiting (breakthrough)	High (THC-dominant)	Inhaled (Vaporizer or Spray)	1 to 2 mg each dose up to 6 times per day
Anxiety	Low (CBD-dominant)	Oral	20 to 50 mg each dose up to 2-3 times per day with meals

Abbreviations: THC = tetrahydrocannabinol; CBN = cannabinol; CBD = cannabidiol.
[a]Equal ratio of THC and CBD.

PATIENT CHARACTERISTICS				
	N = 32 (whole cohort)	*N* = 23 (′annabis users)	*N* = 16 (PRO data available)	*N* = 7 (PRO data not available)
Age, median (IQR) years	71 (64-76)	71 (64-76)	70 (64-76)	72 (64, 76)
Female sex, *N* (%)	17 (53%)	15 (65%)	10 (63%)	5 (71%)
White race, *N* (%)	29 (91%)	22 (96%)	16 (100%)	6 (86%)
Urban residence, *N* (%)	28 (88%)	20 (87%)	14 (88%)	6 (86%)
Locally advanced stage, *N* (%)	14 (44%)	13 (57%)	10 (63%)	3 (43%)
Body mass index at diagnosis, kg/m^2, median (IQR)	25 (22-29)	26 (22-30)	25 (22-29)	25 (22, 29)
Chemotherapy at enrollment				
5-Flourouracil based	17 (53%)	13 (57%)	9 (56%)	4 (57%)
Gemcitabine based	12 (38%)	9 (39%)	6 (38%)	3 (43%)
None	3 (9%)	1 (4%)	1 (6%)	0

Primary assessment method

PRIMARY ASSESSMENT METHOD	
Number of patients screened	72
Number of patients enrolled	34 (2 patients were unable to start study and were replaced before initiating study activities)
Number of patients assigned to early cannabis access arm	16
Number of patients assigned to delayed cannabis access arm	16
Cannabis use during assigned 8-week use window	
Cannabis use	23/32 (72%)
Early arm	12/16 (75%)
Delayed arm	11/16 (69%)
PRO completion among cannabis users	
PRO data available at 16 weeks (end of study)	16/32 (50%); 9/16 early cannabis, 7/16 delayed cannabis
Baseline survey at cannabis start	22/23 (96%)
4-week survey after cannabis start	17/23 (74%)
8-week survey after cannabis start	16/23 (70%)
Elective self-pay cannabis continuation among early arm participants during 9-16 weeks	4 (of 9 eligible)
Final analysis sample for dose-response analysis (per-protocol cannabis users with baseline and 8-week after cannabis start PRO data available)	16
Cannabis exposure over the 8 weeks of use among dose-response cohort	
Median THC dose, early arm	10.0 mg
Median THC dose, delayed arm	9.3 mg

Cannabis dose and improvement in number of symptoms		
	Mean number of symptoms improved	**Mean percentage of symptoms improved**
Mean THC daily dose, <10 mg	2.1	18.2%
Mean THC daily dose, ≥10 mg	4	33.5%
Evaluation method	Symptom severity and PRO completion assessed through self-reported ePRO data. Cannabis use was assessed via self-report to the study team during interventional periods. Cannabis purchase logs available through MMCP were used to assess the optional continuation of cannabis use of early participants during the secondary period. At weeks 4 and 8 of the cannabis administration period (day 28/week 4 and day 56/week 8 for the early cohort; and day 84/week 12 and day 112/week 16 for the delayed cohort), study coordinators contacted the participant who completed a 24-hour recall of their cannabis use. This included documenting the dose, frequency, route, and name of each cannabis product used. Details were recorded in the electronic data capture tool (REDCap), which contained pre-loaded information on the cannabinoid content of each cannabis product from the GreenGoods dispensary (Vireo Health). Once the cannabis use details were inputted for each product used, REDCap then calculated a combined daily total mg for each cannabinoid across all products documented (THC, CBD, CBG, CBN, CBC). Given that THC was the dominant cannabinoid used, we considered mean daily THC use (in mg) as the primary exposure.	
Outcome notes	Figure 1 shows the CONSORT diagram with enrollment, allocation, follow-up, and analysis, and explanation of cannabis users across both arms included in dose response analysis. Figure 2 shows correlations between THC exposure and change from baseline PROs at each time point. Line shows general correlation between dose and change in symptom severity. Correlation co-efficient (r) with p-value indicates the strength and direction of association. Control benchmark (average change in symptom with no cannabis use) added using data from delayed arm in first 8 weeks (those not using cannabis). We observe a statistically significant, positive correlation between higher THC dose and improvements in anxiety and insomnia. The control arm (non-cannabis users) experienced minimal-to-no improvement in these symptoms. Figure 3 shows heatmap of each cannabis use participant (each participant is 1 row) ordered by highest to lowest average THC dose over 8 weeks of use, with changes in individual symptoms for each participant. We observe a threshold mean daily THC dose (of 10 mg) at and above which the number of symptoms that improve increases.	

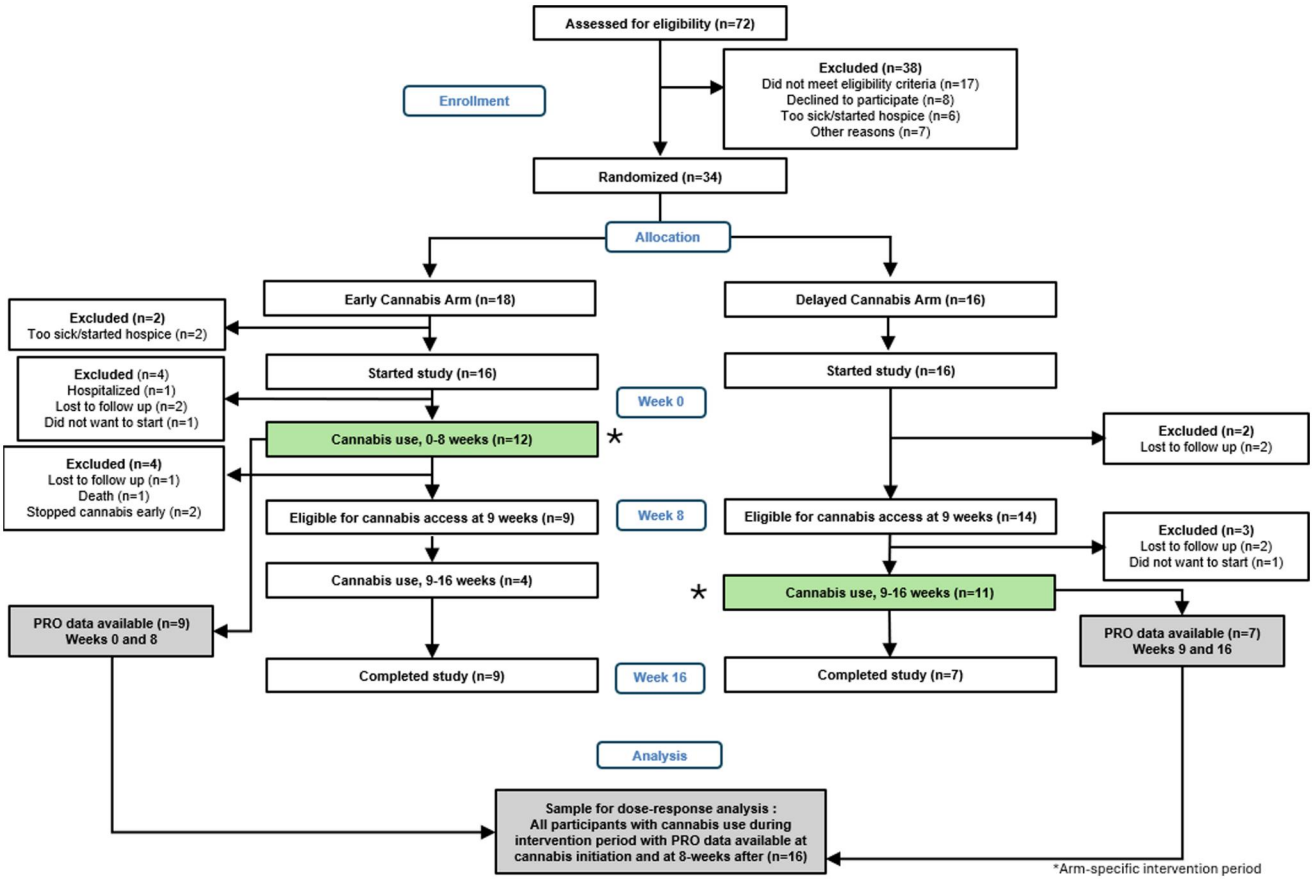

Figure 1. CONSORT diagram of participant enrollment, randomization, cannabis use, and data availability, with identification of the analytic sample for dose-response analysis ($N = 16$). Green boxes indicate the arm-specific intervention period used to determine cannabis use for the dose-response analysis; PRO = patient reported outcome.

Discussion

We have previously reported the feasibility of partnering with a State cannabis program to overcome regulatory and legal barriers to conducting interventional cannabis trials, and preliminary efficacy in managing symptoms among patients with pancreatic cancer.[1] The current analysis provides 3 methodological insights and clinical signals that can guide future interventional cannabis trials among patients with advanced cancer.

First, we observed 50% complete data availability at 16 weeks; this attrition highlights one of the challenges of conducting longitudinal, symptom-intervention studies in a population with potentially rapidly progressive disease like pancreatic adenocarcinoma. These data add to prior literature reporting approximate 70% complete PRO data availability at 8-weeks in advanced pancreatic cancer symptom intervention trials.[2] Additionally, in this waitlist-control design, 72% of participants were able to access and use cannabis during their assigned interventional period (early or late arm). Attrition from loss to follow-up combined with protocol non-adherence has implications for sample size calculations in future definitive trials.[3,4]

Second, a major methodological success is reflected in the finding that the average daily cannabis use doses were remarkably similar between cannabis users in the early and delayed arms. In addition, the number of cannabis users with complete PRO data available was similar across arms. In interventional cannabis research using flexible-dosing approaches with an open-label design, choosing an appropriate control arm can be controversial.[5] Using an "active" cannabis control arm is theoretically attractive but faces hurdles. Since current rules are prohibitive against academic investigators mandating specific cannabis product(s), the intervention itself is "dynamic" and "personalized," and even if it were not, creating a true placebo would require recreating complex terpene profiles and physical characteristics, which is logistically impossible. Thus, we opted for a waitlist-control design, especially considering medical cannabis was available as "standard of care" to interested patient-clinician dyads through the MMCP for Minnesota residents with cancer. Even then, ethical considerations could be raised that participants in the delayed arm were at risk of altered behavior, higher attrition and of receiving less-intensive intervention.[6] The consistency in numbers of cannabis users and patterns of cannabis use between the early and delayed arms is reassuring that this waitlist-control approach can reliably isolate the therapeutic effect of the intervention (during the early phase, when 1 arm accesses the intervention and the other does not) while maintaining ethical standards.

Lastly, analysis reveals an important dose-dependent signal for symptom management. Higher daily THC use was associated

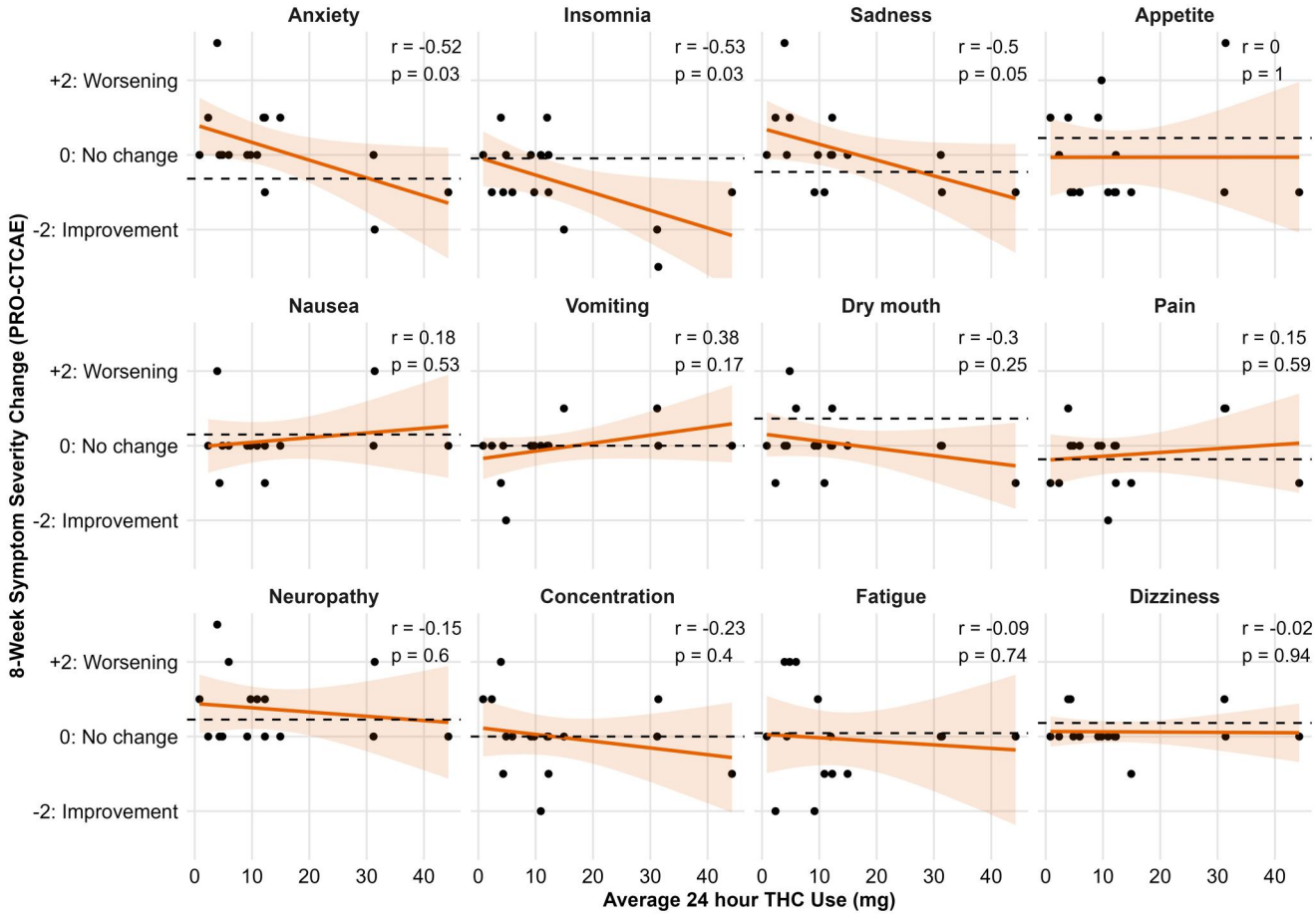

Figure 2. Correlation between average daily THC dose over the arm-specific intervention period and change in patient-reported symptom severity ($N = 16$). Dotted line represents the average symptom change over the untreated 8-week period for the subset of participants with data available during that period; solid orange line represents the linear regression fit with 95% confidence interval (shaded band); r = Pearson's correlation coefficient; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; THC = tetrahydrocannabinol.

with moderately strong improvements in psychological domains such as anxiety and insomnia (and non-significantly for sadness). We did not observe such an association for gastrointestinal or general symptoms such as nausea, pain, or fatigue despite cannabis use overall being associated with improvements in pain and appetite. Patients with pancreatic cancer can experience symptom clusters (eg, gastrointestinal, psychological, etc.) to differing degrees,[7] and palliative care interventions have greater efficacy in managing psychological symptoms than gastrointestinal or physical symptoms in prior work.[8] It may be that lower THC doses suffice for isolated non-psychological symptoms, whereas higher doses are needed to unlock improvements in psychological symptoms. Supporting a possible dose-response hypothesis, we additionally observed that ≥10 mg daily THC use was associated with broader, multi-symptom palliation. It is critical to note that in the current trial, participants were not randomized to lower or higher THC doses, and each participant used a personalized dose. Individuals experiencing early symptom benefit and/or excellent tolerance may thus have used higher THC doses and thus confounded the results. However, these data are hypothesis generating and can be considered in future trials. For example, future trials can focus more on psychological symptoms (affecting inclusion criteria and outcomes) versus "all-comers" with pancreatic cancer and any symptom, and aim for a target THC dose of at least 10 mg daily.

This analysis must be viewed within the context of its limitations, primarily the small sample size and the inherent open-label nature of the waitlist design. Given that our dose-response analysis was restricted to a small cohort of 16 participants, these findings are primarily exploratory and should be viewed as hypothesis-generating for future trial design rather than a basis for definitive clinical dosing recommendations. Additionally, in this pilot philanthropy-funded trial, we did not have detailed data on the cannabis dose (both clinically via specific cannabinoid ratios over time, and/or via formal laboratory-based pharmacokinetic monitoring) and could not account for the impact of cancer-directed treatments/complications (such as chemotherapy) and cancer progression over time on symptoms.

In conclusion, the results of this secondary analysis provide attrition and adherence metrics necessary to properly power future, larger-scale cannabis in cancer randomized controlled trials, support the fidelity and ethics of a waitlist-control approach, and generate preliminary data regarding a dose-response relationship between THC use and psychological symptom and multi-symptom relief.

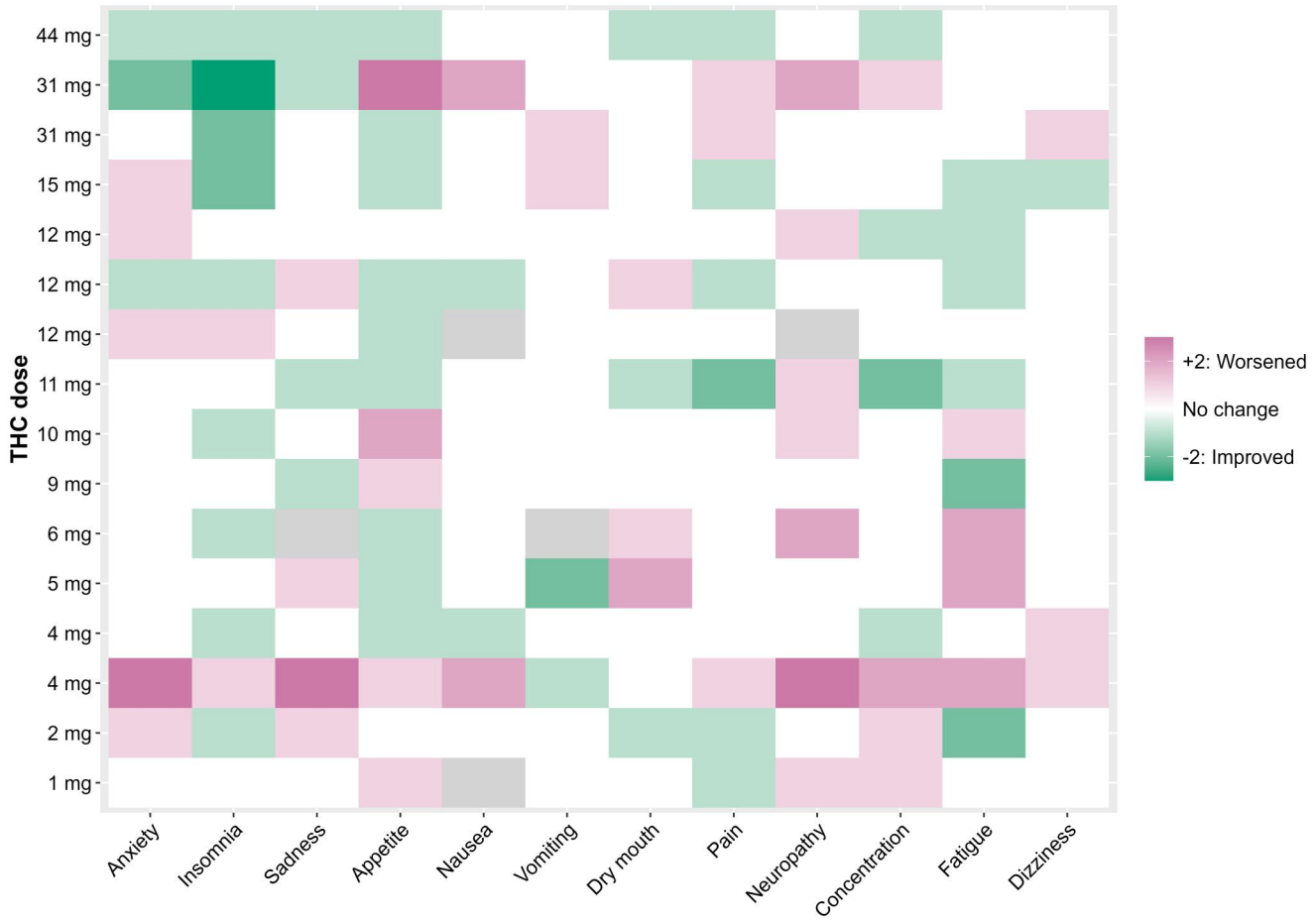

Figure 3. Participant-specific change in patient-reported symptom severity by average daily THC dose over the arm-specific intervention period. Each row represents an individual participant, ordered by average daily THC dose (mg); each column represents a symptom domain; Color indicates the magnitude and direction of change in symptom severity from baseline to the end of the intervention period, as captured by PRO-CTCAE; Gray cells indicate missing data; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; THC = tetrahydrocannabinol.

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Author contributions

All authors contributed to the design of the study. All authors directed the analyses, which were carried out by Ella Chrenka. All authors contributed to interpreting the results, drafting the manuscript, and critically revising the manuscript for important intellectual content. Dylan Zylla and Arjun Gupta obtained funding for the study. Arjun Gupta wrote the first draft of the manuscript. All authors approved the final version for submission. Dylan Zylla is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Conflicts of interest

None declared.

Data availability

Available upon reasonable request to corresponding author.

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