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Medical Marijuana for Pain Management in Hospice Care as a Complementary Approach to Scheduled Opioids: A Single Arm Study

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Abstract

Background: Opioid therapy is critical for pain relief for most hospice patients but may be limited by adverse side effects. Combining medical cannabis with opioids may help mitigate adverse effects while maintaining effective pain relief. **Aim**: This single-arm study investigated the impact of combined medical cannabis/opioid therapy on pain relief, opioid dose, appetite, respiratory function, well-being, nausea, and adverse events in hospice inpatients. **Design**: Adult hospice inpatients using scheduled oral, parenteral, or transdermal opioids for pain were administered standardized oral medical cannabis, 40 mg CBD/1.5 mg THC or 80 mg CBD/3 mg THC. Descriptive statistics detailed demographic and clinical baseline characteristics, the Mann-Whitney test compared outcomes, and the longitudinal mixed effects regression model analyzed longitudinal effects of combined therapy. **Setting/Participants**: Sixty-six inpatients at The Connecticut Hospital, Inc. were assessed over 996 treatment days; average age was 68.2 ± 12.9 years, 90.9% were white. Cancer was the most common diagnosis. **Results**: The medical cannabis/opioid combination showed a significant longitudinal reduction in pain intensity (P = .0029) and a non-significant trend toward lower opioid doses. Well-being, appetite, nausea, and respiratory function showed non-statistically significant changes. Three patients (4.5%) experienced minor, reversible adverse events potentially related to medical cannabis. No serious or life-threatening adverse events were seen. **Conclusion**: Combination medical cannabis/opioid therapy showed statistically significant pain relief and may have the potential for reducing opioid dose and mitigating opioid toxicity, offering a safe pain management alternative to opioids alone for patients in end-of-life care settings, and warrants further investigation in larger controlled trials.

Keywords

pain management, medical marijuana, medical cannabis, hospice, opioids, medical cannabis/opioid

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Introduction

Pain management is central to hospice care, which emphasizes improving quality of life for patients with a life expectancy of six months or less (Kruse et al.[1]). A study of 400 hospice inpatients revealed a high incidence of chronic pain (62%), anorexia (58%), nausea (37%), sleep problems (22%), and anxiety (19%) (Potter et al.[2]). Opioids are the standard of care for pain management in hospice patients (Sinha et al.[3]), but use may be limited by adverse side effects and concerns regarding tolerance, dependence, and opioid use disorder (Benyamin et al.[4]). Common adverse side effects include constipation, nausea, sedation, and rarely respiratory depression, dependence, and death (Bruehl et al.[5]). As a result, careful opioid dose titration is imperative to effect adequate pain relief while minimizing adverse side effects.

Medical cannabis has emerged as a promising adjunctive medication for pain management, with several studies supporting its efficacy in controlling both nociceptive and neuropathic pain (Karst and Wippermann[6]). The most extensively studied constituents of cannabis for therapeutic purposes are delta 9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD) (Fine and Rosenfeld[7]). Δ9-THC acts primarily on Cannabinoid-1 receptors (CB1), which are most densely concentrated in central nervous tissue, while CBD primarily acts on Cannabinoid-2 receptors (CB2), which exist mostly in peripheral tissues (Fine and Rosenfeld[7]). Both CB1 and CB2 receptors are involved in regulating inflammatory pain (Anthony et al.[8]). The activation and inhibition of cannabinoid receptors affects pain perception, cognition, memory, locomotor activity, endocrine functions, temperature control, heart rate, nausea, inflammation, and immune activity (Burggren et al.,[9] Bogáthy et al.,[10] Fine and Rosenfeld.,[7] Meah et al.,[11] Rawls and Benamar.,[12] Vivian et al.,[13] Bruni et al.[14]). Δ 9-THC and CBD's actions on cannabinoid receptors may reduce inflammation and pain (Miller, Bonawitz, and Ostrovsky[15]). While higher doses of Δ 9-THC have been associated with adverse psychological effects such as psychosis-like symptoms and motor and cognitive impairment, CBD may mitigate these effects (Solowij et al.[16]). Evidence of a physiological basis for the opposing effects of Δ 9-THC and CBD was demonstrated in study cross-referencing their behavioral effects with their respective functional MRI (fMRI) images (Bhattacharyya et al.[17]).

This paper presents a single-arm study assessing the impact of combined medical cannabis/opioid therapy on pain scores, opioid dose, appetite, nausea, well-being, and respiratory function in hospice inpatients, and the safety and tolerability of this combination, and seeks to explore not only whether combination therapy is safe and effective for pain management, but whether opioid dose might be stabilized or reduced, potentially mitigating opioid-related adverse side effects.

Methods

Patients and Study Design

The study, conducted at The Connecticut Hospice, Inc.'s inpatient facility in Branford, Connecticut, recruited non-pregnant, alert, oriented, adult (18+ years of age) hospice inpatients with a terminal illness (defined as having a life expectancy of six months or less if the illness followed its natural course as assessed by a physician) with a minimum 3-day life expectancy. All patients using scheduled opioids (measured in oral morphine milligram equivalents – MMEs, Supplemental File 1, Yale New Haven Health System [YNHHS] Opioid Conversion Chart) for pain who were able to take oral medications were offered medical cannabis. Opioids were administered by the oral, intravenous, subcutaneous, and transdermal routes (see below). Terminal diagnoses included cancer and non-cancer illness. The study was open-label and all participating patients were provided standardized medical cannabis. Patients were invited to participate at admission to inpatient hospice and were enrolled after providing informed consent detailing the potential risks, benefits, and outcomes of the study (Supplemental file 2. Informed Consent Form – Marijuana in Combination with Opioids in Palliative and Hospice Care). Patients and authorized caregivers/surrogates/family members were provided ongoing counseling and the opportunity to ask questions about the protocol, and could end participation at any time.

Intervention Description, End Points, and Assessments

Medical cannabis, 40 mg CBD/1.5 mg THC ("40 mg") or 80 mg CBD/3 mg THC ("80 mg") compounded into gelatin capsules by hospice pharmacy staff was supplied by the Research Triangle Institute at no cost as authorized by the National Institute for Drug Abuse (NIDA's Role in Providing Cannabis for Research[18]). Cannabis naive patients (no recreational or medical cannabis use within the last 30 days) received the lower dose product and cannabis tolerant patients (recreational or medical cannabis use within the last 30 days) received the higher dose product, which was administered orally three times daily without food. Patients experiencing three or more increases of scheduled opioid doses were eligible to receive the higher dose of medical cannabis. Opioids used in combination with medical cannabis included oral oxycodone, oral and parenteral morphine, hydromorphone, and methadone, and transdermal fentanyl (also see *Discussion* and *Limitations*). Primary measured outcomes were total scheduled and as needed (or PRN) opioid dose in MMEs (Supplemental File 1, YNHHS Opioid Conversion Chart) and pain score on a 0 – 10 scale (0 = no pain, 10 = worst possible pain on the Edmonton Symptom Assessment Scale [ESAS], Bruera et al.,[19] Chang et al.[20]); secondary measured outcomes were appetite on a

1- 4 scale (measured as percent of meals consumed; 1 = 0%–25% of the most recently offered meal consumed, 2 = 25%–50%, 3 = 50%–75%, and 4 = 75%–100%.), well-being on a 0-10 scale (0 = best possible feeling of well-being, 10 = worst possible feeling of well-being on the ESAS scale), nausea on a 0-10 scale (0 = no nausea, 10 = worst possible nausea on the ESAS scale), and respiratory function (measured as percent oxygen saturation). Adverse events potentially attributable to medical cannabis and typically unassociated with opioids, including dysphoria, panic attack, paranoia, psychosis, ataxia, and impaired motor coordination, and nausea and dizziness, which might be attributable to opioids, were recorded at baseline and three times daily by inpatient hospice nursing staff (Supplemental file 3. Data Sheet for Medical Marijuana Study). For patients unable to talk but able to swallow oral medications, pain levels were determined by a validated nursing assessment tool for nonverbal cues to pain (Supplemental file 4. Pain Flow Sheet Non-Verbal Patients).

Table 1. Table of Demographic and Clinical Characteristics of Patients Enrolled in the Connecticut Hospice Medical Cannabis Study.

	Overall (N = 66)
Age	
Mean (SD)	68.2 (12.9)
Median [min, max]	66.0 [37.0, 95.0]
Sex	
F	41 (62.1%)
M	25 (37.9%)
Race/Ethnicity	
Black	4 (6.1%)
Hispanic or latino	2 (3.0%)
White	60 (90.9%)
Diagnosis (most freq)	
Lung cancer	7 (10.6%)
Colon cancer	7 (10.6%)
Pancreatic cancer	5 (7.6%)
Prostate cancer	5 (7.6%)
Bladder cancer	3 (4.5%)
Heart failure	3 (4.5%)
Breast cancer	2 (3.0%)
Endometrial cancer	2 (3.0%)
Ovarian cancer	2 (3.0%)
Rectal cancer	2 (3.0%)
Medical morphine equivalent dose (MME) at baseline	
Mean (SD)	309.84 (775.62)
Length of enrollment in study (days)	
Mean (SD)	15.33 (19.57)
Median [min, max]	8 [3, 114]
CBD dose	
40	63 (95.5%)
40 -> 80	3 (4.5%)

Characteristics of Patients Enrolled in Study

Sixty-six of 74 enrolled patients completed the study between May 2017 and September 2022, 41 female (62%) and 25 male (38%). Six enrolled patients died in 3 days or less, and 2 patients with adverse side effects potentially related to medical cannabis disenrolled from the study. Sixty patients were white (90.9%), 4 were Black (6.1%), and 2 were Latino (3%). Average age was 68.2 ± 12.9 years (37 to 95 years). Diagnoses included lung cancer (7), colon cancer (7), pancreatic cancer (5), prostate cancer (5), bladder cancer (3), and heart failure (3). Mean length of observation was 15.33 days (±19.57 days). Average opioid dose was 309.84 ± 775.62 MME per day for initial pain management. Medical cannabis dose was 40 mg for 63 patients (95%), and increased to 80 mg for 3 patients (5%) (Table 1). Medical cannabis was administered on 996 treatment days.

Study Oversight

The study was registered with ClincalTrials.gov (NCT #03233633) and Western Institutional Review Board (WIRB Protocol 20161880-1167645). Ethical oversight was provided by Western Institutional Review Board (WIRB Protocol 20161880-1167 645, Protocol Approval Date: 10/21/16). Additional ethical resources were available through the Connecticut Hospice Ethics Committee. Study product supply, storage, access, and dispensing was overseen by inpatient hospice pharmacy staff per Federal and state regulations (CFR – Code of Federal Regulations Title 21,[21] United States Department of Justice Drug Enforcement Administration, 2022[22]). Participating patients were provided with a human study number and data then de-identified. This information was stored in a HIPPA-compliant password-protected database and will be maintained for three years after study completion (available on authorized request until September 2025).

Statistical Analysis (Also see below, "A Brief Description of Statistical Methods")

General Methodology, Exploratory Analysis, and Preliminary Comparisons. Patients were assessed using intent-to-treat (ITT), with one patient as the unit of analysis, and R software for data processing including data cleaning, exploratory analysis, and statistical analysis. Descriptive statistics (mean and standard deviation for continuous variables; percent prevalence for categorical variables) were used to characterize patients' baseline characteristics. Differences in the measured outcomes between the baseline and end-of-study were compared using the Mann-Whitney test. Statistical significance was determined at the Bonferroni-adjusted alpha level of .025 for the primary outcomes of pain and opioid dose and .0125 for the secondary outcomes of appetite, well-being, nausea, and oxygen saturation. These cut offs accounted for multiple

hypothesis testing, with the two primary outcomes, pain level and opioid dose, tested at an adjusted alpha level of .05, yielding statistical significance at .025, and the four secondary outcomes of appetite, well-being, nausea, and oxygen saturation, also tested at an adjusted alpha level of .05, yielding statistical significance at .0125.

Longitudinal Methods - Linear Mixed Effects Models: (Also see below, "A Brief Description of Statistical Methods"). Longitudinal regression analysis of patients' pain levels using linear mixed effects regression provided a more robust estimate of trends over time. Absent a control arm, the time covariate's statistical significance in the regression model was used to estimate treatment effect. We examined how changes in the outcome variable were associated with the passage of time while controlling for potential confounders like age and sex. This statistical approach enabled an assessment of temporal trends in outcomes and provided a means of evaluating the efficacy of the intervention over the study period. Linear Mixed Effects models with random intercept and random slope were used. To inform variable selection in the final regression model, 20 different models were fitted for the pain scales primary outcome dataset, and the final model was determined by the Akaike Information Criterion (AIC). The final model of patients' pain levels included the variables time, age, and diagnosis category (cancer vs noncancer).

Patient Subgroup Analysis. To better understand various demographic characteristics of patients whose pain levels and self-reported measures of wellness were the most improved over time, we conducted exploratory data analysis and visualized the trends of patient outcomes. We considered characteristics such as gender, primary diagnosis, and initial opioid dosage.

A Brief Description of Statistical Methods. Akaike Information Criterion: A means of comparing and choosing statistical models, with a lower AIC score being a more accurate model.

Bonferroni-adjusted alpha level: Used to control for multiple comparisons in statistical hypothesis testing, which sets .05 as the threshold for significance.

Linear mixed effects regression: Allows modeling within and between group variation, often used in social science and biology where data have complex structures.

Longitudinal regression analysis: Used to analyze data collected over time.

Mann-Whitney: Used to compare two samples or groups (Eg, differences in baseline and end of study measures).

Results

Baseline and End-of-Study Measurements

Baseline measurements were compared with the end-of-study measurements for opioid dose; pain, well-being, and nausea on the ESAS scale; and appetite as represented by percent of meals consumed and respiratory function as represented by oxygen saturation. The baseline mean for pain was 2.55 ± 2.46 (mild to moderate pain), which decreased to 1.40 ± 2.17 (no pain to mild pain, $P = .0029$) at the end of the study. This was a statistically significant reduction in pain intensity (Table 2). Reduction in pain was observed for patients observed for less than 7 days, from 7 to 15 days, from 15 days to 30 days, and for more than 30 days (Figure 1).

Baseline mean opioid dose was 309.84 ± 775.63 MME, which decreased to 285.54 ± 430.76 MME ($P = .326$) at the end of the study. This decrease was not statistically significant (Table 2) (also see *Discussion* and *Limitations*).

Baseline mean well-being was 3.31 ± 2.67 (mild to moderate distress) and 2.42 ± 2.73 (no distress to mild distress) at the end of the study ($P = .0394$), a non-statistically significant change in well-being. (Table 2)

Baseline nausea was .297 ± .98 (no nausea to mild nausea), which decreased to .17 ± .74 (no nausea to mild nausea) ($P = .176$), a non-statistically significant change (Table 2).

Table 2. Results of Mann-Whitney-Wilcox Test Comparisons Between Baseline and End-Of-Study in Primary and Secondary Outcomes.

	Baseline	End of Study	Mann-Whitney Test Statistic	*P*-value
Pain Scales				
Mean (SD)	2.55 (2.46)	1.40 (2.17)	W = 2770	$P = .0029$
Opioid dose (MME)				
Mean (SD)	309.84 (775.63)	285.54 (430.76)	W = 1017	$P = .326$
Well-being (ESAS)				
Mean (SD)	3.31 (2.67)	2.42 (2.73)	W = 2467.5	$P = .0394$
Appetite				
Mean (SD)	1.95 (1.05)	1.70 (1.07)	W = 2504.5	$P = .0498$
Oxygen saturation %				
Mean (SD)	94.86 (2.53)	94.10 (2.55)	W = 2581	$P = .0445$
Nausea				
Mean (SD)	.297 (.98)	.17 (.74)	W = 2038	$P = .176$

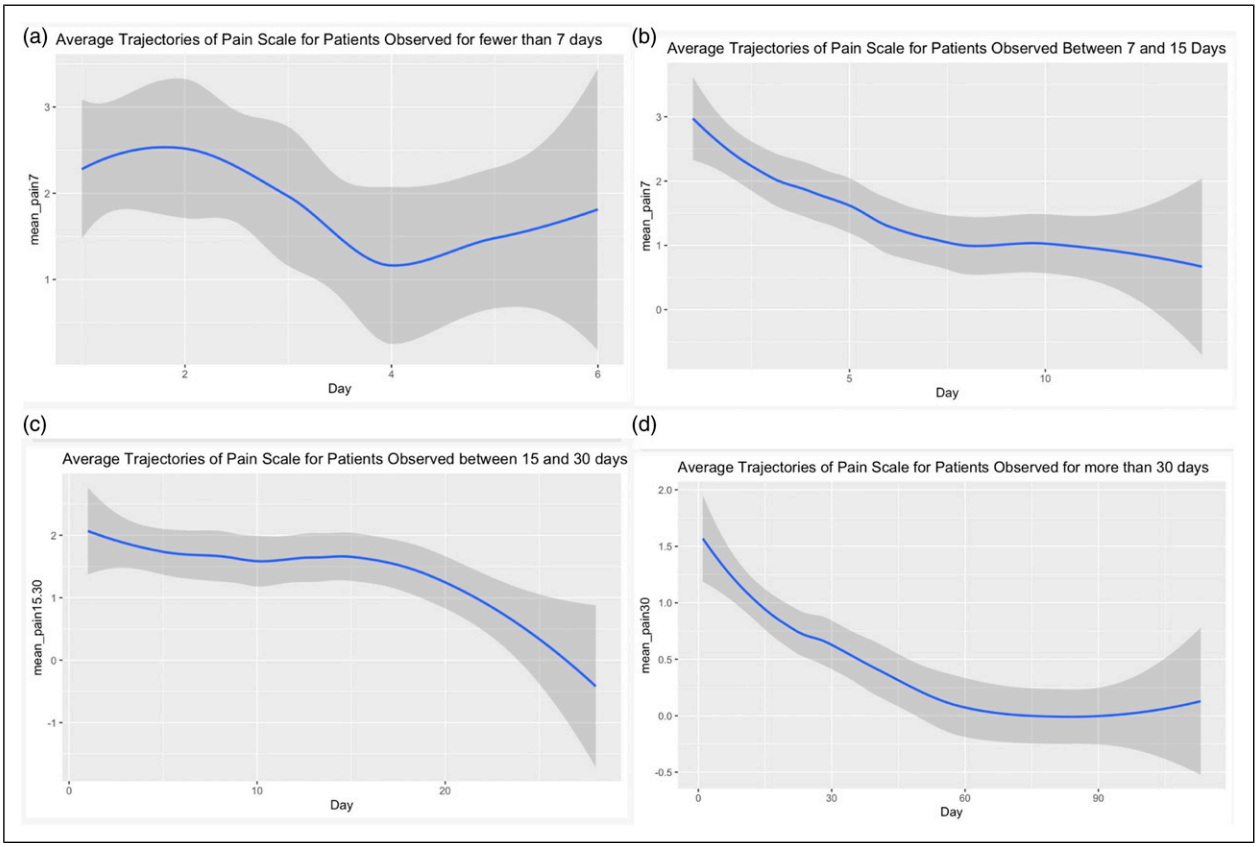

Figure 1. Average Trajectories of Pain Scale, stratified by length of observation. (A) Patients observed for less than 7 days, (B) observed for 7 – 15 days, (C) observed for 15 – 30 days, and (D) observed for >30 days.

Table 3. Results of the Longitudinal Mixed Effects Model. Reports a Statistically Significant Effect of Time on the Primary Outcome of Self-Reported Pain Level, Illustrating That Medical Cannabis Co-administration With Opioid Treatment Reduced Patients' Pain Levels Over Time.

	Value	Standard Error	Degrees of Freedom	T-Statistic	*P*-Value
Intercept	5.043858	.8426457	852	5.985740	.0000
Category: Non-cancer	−.352139	.3942226	62	−.893250	.3752
Time	−.126731	.0337344	852	−3.756747	.0002
Age	−.038779	.0117202	62	−3.308727	.0016

Baseline mean appetite (percent of meals consumed) was 1.95 ± 1.05 (no oral intake to significantly reduced oral intake) and 1.70 ± 1.07 (no oral intake to significantly reduced oral intake) (P = .0498) at the end of the study, a non-statistically significant, change (Table 2).

Baseline mean oxygen saturation was 94.86 ± 2.53 (not suggestive of respiratory impairment), which slightly decreased to 94.10 ± 2.55 (not suggestive of respiratory impairment) at the end of the study (P = .0445), a non-statistically significant change (Table 2).

A total of five minor, reversible adverse events (dizziness, nausea, dysphoria, panic attack, and tremor) were noted in 3 of 66 patients (4.5%) over 996 treatment days. This represented an extremely small percentage of the total doses of the medical cannabis/opiod combination administered and was not subject to statistical analysis. Two patients dropped out of the study and all affected patients had resolution of adverse events within one day.

Longitudinal Regression Model of Pain Levels

Longitudinal trends assessed by a linear mixed effects regression analysis, adjusted for diagnosis category and age to account for potential confounding factors, demonstrated a significant time effect of combined medical cannabis/opioid therapy on reducing pain levels (P < .001). The regression coefficient for the time variable was −.127, with a standard error of .0337, indicating that the time-dependent trends in

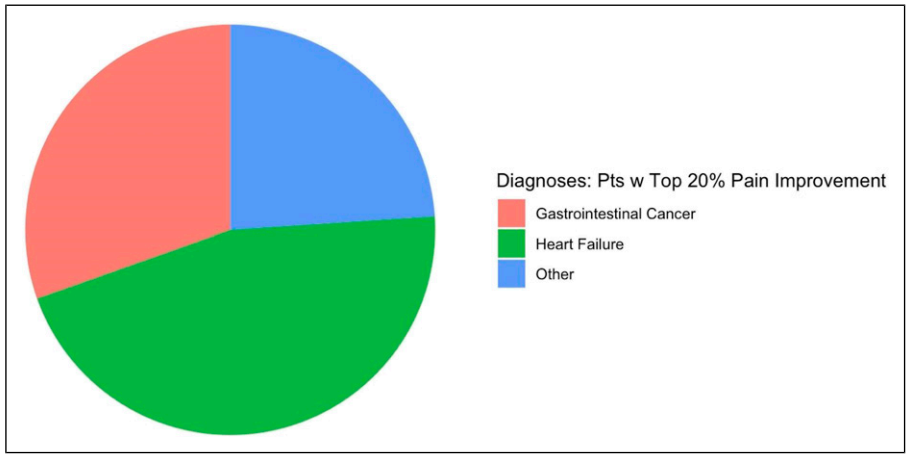

Figure 2. Patient subgroup analysis; diagnoses of patients with top 20% pain reduction.

pain levels decreased with statistical significance, reinforcing the evidence for the effectiveness of opioid and medical cannabis co-administration in reducing pain intensity over the course of the study. Table 3 shows results of the linear mixed effects regression analysis, including estimates, standard errors, and *P*-values for the time effect and other covariates. The coefficients and their standard errors further support the magnitude and precision of the observed effects.

Patient Subgroup Analysis

Exploratory data analysis was used to evaluate whether specific subgroups of patients benefited most from combined therapy. Half of the top 20th percentile of patients experiencing the most pain relief had heart failure, approximately a quarter had gastrointestinal cancer, and the remainder had other cancer diagnoses (thyroid, prostate, lung, and others), suggesting that medical cannabis may be particularly helpful for pain relief for heart failure and GI cancer patients, though follow-up studies with more rigorous evaluations are needed (Figure 2).

Results Summary

In sum, the study, in which medical cannabis was administered with opioids over 996 treatment days to 66 mostly white, female, older patients, demonstrated a statistically significant reduction in pain intensity over time, with pain falling from a narrative mean of mild to moderate to mild to none (also see *Limitations*), a possible enhanced impact in patients with GI cancers and heart failure, a non-statistically significant trend toward improved well-being, and non-statistically significant, negligible impacts on appetite, nausea, and oxygen saturation. Though not statistically significant, the down-trending of opioid dose from baseline to end of study may suggest that opioid dose is reduced or stabilized by its combination with medical cannabis (also see *Discussion* and *Limitations*). Adverse events were minor, non-life threatening, reversible, and very uncommon. These findings add to the data supporting medical cannabis/opioid combination therapy as safe and effective for pain management in hospice inpatients, with a possible potential to decrease opioid dose and associated adverse effects.

Discussion

Major Findings and Relevance to End of Life Care

This study evaluated the impact of combined medical cannabis and opioid therapy on pain, well-being, nausea, appetite, respiratory function and adverse side effects, and the potential of the combination to reduce or stabilize opioid dose in hospice inpatients. Combination therapy led to a statistically significant reduction in pain intensity over time, aligning with previous research suggesting that cannabinoids, the active compounds in medical cannabis, can modulate pain pathways and enhance the analgesic effects of opioids (Cooper et al.[23]). The study also showed a non-statistically significant trend toward reducing or stabilizing opioid dose by coadministration of medical cannabis. We considered a baseline daily MME of <300 mg as a low to moderate dose for the management of pain in patients at the end of life (Masman et al.[24]). While we intended to use a dose increase of 500 MME or less between study enrollment and end of study as indicative of dose stabilization, the average opioid dose used in combination with medical cannabis in our study decreased over time – while patients simultaneously showed statistically significant improved pain scores. While the decrease in opioid dose did not reach statistical significance, this trend may support a stabilizing effect of combination therapy on opioid dose. Should a larger scale study demonstrate statistical significance in this realm, such a finding might significantly impact end of life care in light of the common need to increase opioid dose over time to effect pain relief in this population (Masman et al.[23]) by potentially mitigating side effects such as

constipation, sedation, nausea, and delirium. This would have important implications for improved end-of-life care in all settings.

Longitudinal Robustness of Pain Management

The longitudinal regression analysis provided further evidence of the effectiveness of medical cannabis co-administration with opioid therapy in reducing pain levels over time. The statistical significance of the regression coefficient indicates that the time-dependent trends in pain levels were consistently decreasing throughout the study. This finding strengthens the case for the long-term effectiveness of this combination therapy and supports its adoption as a viable option for pain management in hospice care (also see *Limitations*).

Potential Impact on Secondary Outcomes

We examined secondary outcomes including patient well-being, appetite, nausea, and oxygen saturation. Though our results were not statistically significant, the positive, if negligible, trends in these realms merit further investigation in larger scale studies.

Potential Enhanced Effect in Subgroups

To explore potential patient subgroups that may benefit the most from combined medical cannabis/opioid therapy, we conducted a patient subgroup analysis. Our findings suggest that patients with heart failure and gastrointestinal cancer may particularly benefit from this combination therapy in terms of pain relief. However, as with the secondary outcomes, further studies with larger patient samples and more rigorous evaluations are needed to further investigate these preliminary findings.

Contribution to Preexisting Literature

Our study highlights the potential benefit of medical cannabis co-administration with opioid therapy for pain management in hospice inpatients, demonstrating statistically significant pain reduction over time with minimal adverse events. These findings contribute to the growing body of evidence supporting the use of medical cannabis as an adjunctive treatment for pain management. While not statistically significant, positive trends toward opioid dosage stabilization in our study are encouraging and support the need for larger, more robust studies to investigate this possibility, which, if proven, might significantly and positively impact end-of-life care.

Applicability of Findings Across Settings

While our study was limited to hospice inpatients, our results may be generalizable to end-of-life care for a broad spectrum of domestic and international inpatient, outpatient, hospice, and palliative care settings (also see *Limitations*). The ease of compounding and the oral route of administration of medical cannabis make it a viable option for enhanced pain management in resource constrained environments.

Limitations

While our study provides valuable insights, several limitations should be acknowledged. First, the study sample size was small and comprised almost entirely by white patients, which may limit generalizability of our findings. Future studies with larger and more diverse patient populations would enhance the robustness of the evidence. Second, the study's single-arm nature introduces the potential for confounding factors that may influence the outcomes. A randomized controlled trial design would offer stronger evidence and allow for better control of confounding variables including the potential for placebo effect. Additionally, the relatively short duration that our study subjects were enrolled in our study limits our understanding of the long-term effects of the combination on patients in longer-term hospice and other end-of-life care settings, including the outpatient setting. Duration of participation was limited by loss of ability to swallow oral formulations of medical cannabis, and short life expectancy, both common factors in hospice inpatients. We likewise recognize that opioids have varying potencies and pharmacokinetic and pharmacodynamic properties potentially relevant to our findings. However, because of our small sample size, we used MMEs to assess outcomes and did not analysis our primary and secondary outcomes by type of opioid used (also see *Pharmacokinetic Interactions between opioids and CBD/THC*). Further, our findings might have had more clinical relevance had we shown a more clinically impactful reduction in pain intensity, for example from severe to moderate (or mild). However, because we postulated that the opioid/cannabis combination would have a salutary effect on inpatients using opioids for pain, with improved pain relief and limited side effects, we elected to offer it to all patients meeting enrollment criteria regardless of the extent of pain, which averaged mild to moderate on enrollment to the study. Additionally, while some of our data was collected more than 5 years prior to final data analysis (data collected between May 2017 and June 2018), we believe that the findings not only remain relevant, as neither formulations of medical cannabis nor commonly used opioids have materially changed over this period, but find increased relevance as the legal use of medical cannabis has become broadly more common.

Pharmacokinetic Interactions Between Opioids and CBD/THC

While we did not subdivide and analyze our patients by the type of opioid used (morphine, oxycodone, hydromorphone,

methadone, and fentanyl), we recognize that pharmacokinetic interactions between medical cannabis and opioids may have influenced our results. For example, CBD inhibits enzyme UGHT2B7, which metabolizes morphine to morphine-6-glucuronide, potentially lowering the plasma morphine-6-glucuronide/morphine ratio (Vasquez et al.[25]). Because morphine-6-glucoride is considered a more potent analgesic than the parent compound, with potentially fewer side effects, this could potentially lessen the efficacy of morphine (Hain, et al.[26]). CBD and THC inhibit CYP2D6, involved in the metabolism of oxycodone, affecting oxymorphone formation and potentially reducing its analgesic effect (Vasquez et al.[25]). Notably, however, vaporized cannabis given to patients with pain using morphine or oxycodone increased their analgesic effect but found no significant differences in mean plasma concentration-time curves for morphine and oxycodone with and without cannabis treatment (Abrahms et al.[27]). CBD is a strong inhibitor of CYP2B6, the predominant enzyme responsible for methadone metabolism, so increased levels of this opioid and a greater analgesic potency might be observed (Vasquez et. al.[25]). Manini et al,[28] showed no interaction between intravenous fentanyl (not used by this route in our study) and cannabis; as such, fentanyl may be better suited to further study of the medical cannabis/opioid combination unconfounded by pharmacokinetic interactions.

It should also be noted that because many opioids and drugs commonly used in patients at the end of life, such as antidepressants, sedatives, and antipsychotics (also not tracked in our study), are metabolized by the cytochrome P450 enzyme system, pharmacokinetic interactions are likely to be common overall in hospice patients and may result in reduced or increased efficacy and potential toxicity of these agents (Pergolizzi,[29]).

Declaration of Conflicting Interests

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Board Protocol

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Supplemental Material

Supplemental material for this article is available online.

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