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The Efficacy of Medical Marijuana in the Treatment of Cancer-Related Pain

Ian M. Pawasarat, DO, MA,[1] Emily M. Schultz, BS,[2] Justin C. Frisby, BS,[2] Samir Mehta, BS,[3] Mark A. Angelo, MD,[4] Samuel S. Hardy, MD,[4] and Tae Won B. Kim, MD[5]

Abstract

Background: The opioid epidemic has spurred investigations for nonopioid options, yet limited research persists on medical marijuana's (MMJ) efficacy in managing cancer-related symptoms.
Objective: We sought to characterize MMJ's role on symptomatic relief and opioid consumption in the oncologic population.
Design: Retrospective chart review of MMJ-certified oncology patients was performed. Divided patients into MMJ use [MMJ(+)] versus no use [MMJ(−)], and Edmonton Symptom Assessment System (ESAS)-reported pain cohorts: ''mild-moderate'' versus ''severe.''
Measurements: Medical records were reviewed for ESAS, to measure physical and emotional symptoms, and opiate consumption, converted into morphine milligram equivalents (MME). Minimal clinically important differences were determined. Wilcoxon signed-rank tests determined statistical significance between MMJ-certification and most recent palliative care visit.
Results: Identified 232 patients [95/232 MMJ(−); 137/232 MMJ(+)]. Pain, physical and total ESAS significantly improved for total MMJ(−) and MMJ(+); however, only MMJ(+) significantly improved emotional ESAS. MMJ(−) opioid consumption increased by 23% (97.5–120 mg/day MME, $p = 0.004$), while it remained constant (45–45 mg/day MME, $p = 0.522$) in MMJ(+). Physical and total ESAS improved in mild-moderate-MMJ(−) and MMJ(+). Pain and emotional symptoms worsened in MMJ(−); while MMJ(+)'s pain remained unchanged and emotional symptoms improved. MMJ(−) opioid consumption increased by 29% (90–126 mg/day MME, $p = 0.012$); while MMJ(+)'s decreased by 33% (45–30 mg/day MME, $p = 0.935$). Pain, physical, emotional, and total ESAS scores improved in severe-MMJ(−) and MMJ(+); opioid consumption reduced by 22% in MMJ(−) (135–106 mg/day MME, $p = 0.124$) and 33% in MMJ(+) (90–60 mg/day MME, $p = 0.421$).
Conclusions: MMJ(+) improved oncology patients' ESAS scores despite opioid dose reductions and should be considered a viable adjuvant therapy for palliative management.

Keywords: medical cannabis; oncology issues in palliative care; opioid analgesics; pain control

Introduction

As new therapeutic options improve survival, an increasing number of cancer patients will require prolonged management of their cancer-related pain.[1] Opioids have played a crucial role in the World Health Organization's (WHO) stepwise ladder to reduce the burden of pain.[2,3] Yet, even with increasing dosages, nearly 40% of patients' pain is poorly controlled.[4] Furthermore, these patients suffer from adverse effects, including addiction, overdose, and increased pain sensitivities, associated with high-dose opioids.[5–7] As such, management of cancer-related pain remains a challenge for patients and health care providers alike.

The antinociceptive, inflammatory, and emetic effects of delta-9-tetrahydrocannabinol (THC), the main psychoactive cannabinoid derived from cannabis, have been of great interest

[1]Inspira Health Network, Vineland, New Jersey, USA.
[2]Cooper Bone and Joint Institute, Camden, New Jersey, USA.
[3]Rowan University School of Osteopathic Medicine, Stratford, New Jersey, USA.
[4]MD Anderson Cancer Center at Cooper University Health Care, Camden, New Jersey, USA.
[5]Cooper Bone and Joint Institute, Cooper University Hospital, Camden, New Jersey, USA.
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in the treatment of concomitant cancer symptoms. Currently, the Food and Drug Administration (FDA) has approved few synthetic cannabinoids in the United States, such as the synthetic THC drugs, dronabinol (Marinol) and nabilone for cancer-induced nausea and emesis.[8–11] However, in states with legalized medical marijuana (MMJ), patients have access for the treatment of qualifying conditions. Due to the varying ratios of cannabinoids, the effects of smoked or consumed marijuana may differ from those of synthetic cannabinoids, as THC derivatives only comprise one of the hundreds of cannnabinoids extracted from cannabis.[9,10]

Despite the growing interest, potential benefits, and pharmacologic commonalities, limited research on the efficacy of MMJ to treat chronic cancer-related symptoms persists. Thus, our study sought to characterize the therapeutic efficacy of MMJ on symptomatic relief, especially pain, and opioid consumption in oncology patients.

Materials and Methods

In August 2012, the State of New Jersey Medicinal Marijuana Program Registry (NJMMPR) became active. After obtaining Institutional Review Board (IRB) approval, a retrospective chart review of all oncology patients under the care of NJMMPR-approved palliative medicine physicians at our institution was conducted, to coincide with registration opening, between August 1, 2012 and December 31, 2017. To identify patients, physicians' NJMMPR patient certification ledgers were utilized; ledger information includes patient registration status, date of the most recent purchase, and amount (g) purchased.

During this period, 575 patients were certified at our institution. Two hundred eighty-two of these patients were excluded for the following criteria: nononcologic diagnosis, incomplete medical records, cannabis use at the time of certification, inpatient status, and patients without both certification and most recent visit data. Of the remaining 293 patients, 61 eligible patients did not buy MMJ; thus, leaving 232 included patients to be assigned into two cohorts, based upon their reported, routine cannabis use after their initial certification visit: MMJ use [MMJ (+)] or no MMJ use [MMJ (−)]. These cohorts were further subdivided into Edmonton Symptom Assessment System (ESAS)-reported pain cohorts: ''mild-moderate'' versus ''severe.'' Mild-moderate is classified as certification pain scores 6 or less and severe pain representing anything higher. Electronic medical records of included patients were reviewed for palliative care visits and standardized events were recorded: cancer diagnosis, treatment history, a patient-completed ESAS score, a medication review (dosage, frequency, route of administration), and review of MMJ use. Specifically, certification and most recent visit were utilized to capture the following outcomes: ESAS pain, physical ESAS, emotional ESAS and total ESAS scores, and daily opiate consumption. Certification visit was defined as the office visit the patient became MMJ-certified; and most recent visit as the last office visit with MMJ documentation.

MMJ(−) and MMJ(+) pain, physical, emotional, and total ESAS scores were compared at certification, most recent and between visits. ESAS uses nine visual analog scales to evaluate current levels of physical (pain, tiredness, nausea, appetite, drowsiness, and shortness of breath), emotional (depression, anxiety), and well-being symptoms.[12–15] Well-being was excluded from analysis. Each component is ranked from 0 to 10, with lower scores indicating lesser symptom distress. Total ESAS score was the sum of physical and emotional ESAS scores. To account for fluctuations in patients' ESAS scores, minimal clinically important differences (MCID) were utilized to account for the smallest amount of change required to impact treatment.[12] The established MCID improvement and deterioration score for an individual ESAS category is ≥1/10.[13,14] Physical ESAS MCID values are ≥3/60 points for improvement and ≤–4/60 points for deterioration. Emotional ESAS MCID values are ≥2/20 points for improvement and ≤–1/20 point for deterioration. Total ESAS MCID values are ≥3/90 for improvement and ≤–4/90 for deterioration.[13,14]

MMJ(−) and MMJ(+) opiate consumption was also compared at certification, most recent and between visits. As palliative care physicians serve as the primary ordering provider for all analgesic medications of patients under their care, prescribed opioid dosages were used as proxy for opioid consumption. Opiates were converted to oral morphine milligram equivalents (MME) using the Centers for Disease Control and Prevention's (CDC) MME conversion factors, allowing for the comparison of opiates with different potencies.[15]

For non-normal distributions of continuous variables and ordinal variable analysis, Wilcoxon signed-rank tests were used to evaluate differences within each study cohort (from certification to most recent visit) and Mann–Whitney *U*-tests were used to assess differences across study cohorts. Normally distributed variables were evaluated using paired samples *t*-tests to evaluate mean differences within each study cohort and independent sample *t*-tests were used to evaluate mean differences across study cohorts. Binary data were analyzed using Pearson's chi-squared tests. Statistical analysis was performed utilizing SPSS.

Results

Two hundred thirty-two patients were included. MMJ(+) group consisted of 137 (59.1%) patients who used cannabis after their initial certification visit; whereas, the MMJ(−) group was comprised of 95 patients (40.9%) (Table 1). The sub-cohort analyses were comprised of 46/95 MMJ(−) and 76/137 MMJ(+) who reported mild-moderate pain; and 49/95 MMJ(−) and 61/137 MMJ(+)with severe pain.

As all patients possessed an oncological diagnosis and satisfied the NJMMPR requirements for MMJ certification, all cohorts were relatively homogenous (Table 1). After testing for cohort differences, unrelated to MMJ consumption, the only significant difference was time from certification to most recent visits (Table 1). Of the MMJ(+) group, 58.4% (80/137) patients' last visit was between 9 and >12 months; whereas, majority of the MMJ(−) group (60/95, 63.2%) last visit was <6 months after certification ($p = 0.008$). The 61 patients who did not purchase MMJ reported these common barriers: difficulty with registration, cost, and deteriorating health (Table 2).

Opiate consumption

Total MMJ(+) cohort used significantly less MME at certification ($p = 0.015$) and most recent visit ($p < 0.001$) compared to MMJ(−). While MMJ(−) experienced a significant

Table 1. Cohort Demographics

	MMJ (−), N *(%)*	*MMJ (+),* N *(%)*	*Total,* N *(%)*	
	n = *95*	n = *137*	n = *232*	p
Age (IQR)	58 (18)	57 (14)	58 (14.75)	0.062
Gender				
Male	42 (44.2)	61 (44.5)	103 (44.4)	0.962
Female	53 (55.8)	76 (55.5)	129 (55.6)	
Ethnicity				
Caucasian	67 (70.5)	114 (83.2)	101 (78)	0.064
African American	20 (21.1)	15 (10.9)	35 (15.1)	
Other/unspecified	8 (8.4)	8 (5.8)	16 (6.9)	
Mortality				
No	55 (57.9)	92 (67.2)	147 (63.4)	0.15
Yes	40 (42.1)	45 (32.8)	85 (36.6)	
History of metastatic disease				
No	25 (26.3)	29 (21.2)	54 (23.3)	0.362
Yes	70 (73.7)	108 (78.8)	178 (76.7)	
History of radiation treatment				
No	24 (25.3)	51 (37.2)	75 (32.3)	0.055
Yes	71 (74.7)	86 (62.8)	157 (67.7)	
History of chemotherapy				
No	3 (3.2)	13 (9.5)	16 (6.9)	0.061
Yes	92 (96.8)	124 (90.5)	216 (93.1)	
Cancer type				
Gastrointestinal cancer	23 (24.2)	30 (21.9)	53 (22.8)	0.949
Lung cancer	22 (23.2)	31 (22.6)	53 (22.8)	
Genitourinary cancer	22 (23.2)	27 (19.7)	49 (21.1)	
Breast cancer	14 (14.7)	23 (16.8)	37 (15.9)	
Head and neck cancer	6 (6.3)	7 (5.1)	13 (5.6)	
Leukemia/lymphoma	4 (4.2)	9 (6.6)	13 (5.6)	
Musculoskeletal tumor	2 (2.1)	7 (5.1)	9 (3.9)	
Skin cancer	1 (1.1)	2 (1.5)	3 (1.3)	
Nervous system tumor	1 (1.1)	1 (0.7)	2 (0.9)	
Distance from MMJ dispensary in miles (SD)	21 (16.2)	18.5 (13.9)	19.6 (14.9)	
MMJ certification date to most recent follow-up				
0–3 Months	32 (33.7)	21 (15.3)	53 (22.8)	0.008
3–6 Months	28 (29.5)	36 (26.3)	64 (27.6)	
6–9 Months	10 (10.5)	21 (15.3)	31 (13.4)	
9–12 Months	10 (10.5)	23 (16.8)	33 (14.2)	
>12 Months	15 (15.8)	36 (26.3)	51 (22)	

MMJ, medical marijuana; SD, standard deviation.

increase between visits (97.5–120 mg/day MME, $p = 0.004$), MMJ(+) remained unchanged (45–45 mg/day MME, $p = 0.522$) (Table 3). Additionally, analysis of the rate of escalation of MME consumption displayed a decreased rate in MMJ(+) compared to MMJ(−) (Fig. 1).

Table 2. Reasons for Not Purchasing Medical Marijuana

	Frequency	*%*
Cost	11	18
Lack of education surrounding use effects of MMJ	10	16
Registration/re-certification difficulty	32	52
Rejected by NJMMP	1	2
Transportation difficulties to dispensary	1	2
Unable due to deteriorating condition	6	10
Total	61	100

NJMMP, New Jersey Medicinal Marijuana Program.

Both severe pain MMJ(+) (90–60 mg/day MME, $p = 0.421$) and MMJ(−) (135–106 mg/day MME, $p = 0.124$) sub-cohorts reduced daily opiate consumption between visits.

Mild-moderate pain sub-cohort analysis also displayed statistically significant differences between MMJ (−) and MMJ(+) at certification ($p = 0.01$) and most recent visit ($p < 0.001$). MMJ(−)significantly increased daily opiate consumption between visits (90–126 mg/day MME, $p = 0.012$); while, MMJ(+) decreased dosages (45–30 mg/day MME, $p = 0.935$) (Table 3).

ESAS components

ESAS pain. Both, total MMJ(−) (7/10–5/10, $p = 0.044$) and MMJ(+) (6/10–6/10, $p = 0.001$), cohorts experienced significant improvements in pain scores between visits. MCID improvement ($p = 0.950$) and deterioration ($p = 0.889$) were not significant (Table 3).

Both severe pain sub-cohort MMJ(−) (8/10–7/10, $p < 0.001$) and MMJ(+) (8/10–7/10, $p < 0.001$) improved between visits.

Table 3. Entire Cohort, Severe Pain Sub-Analysis and Mild to Moderate Pain Sub-Analysis Primary Outcomes with Minimal Clinically Important Differences Improvement and Deterioration Values

	MMJ (−)	*MMJ (+)*	
Total cohort	n = *95*	n = *137*	p
Pain, median (IQR)			
Certification	7 (4)	6 (10)	0.126
Most recent	5 (6)	5 (7)	0.142
p	0.044	0.005	
MCID improvement	42 (44.2)	60 (43.8)	0.95
MCID deterioration	29 (30.5)	43 (31.4)	0.889
Physical, median (IQR)			
Certification	26 (18)	24 (14)	0.075
Most recent	22 (20)	20 (18)	0.258
p	0.001	0.003	
MCID improvement	56 (58.9)	80 (58.4)	0.933
MCID deterioration	24 (25.3)	39 (28.5)	0.589
Emotional, median (IQR)			
Certification	6 (10)	6 (11)	0.421
Most recent	4 (10)	5 (10)	0.817
p	0.193	0.01	
MCID improvement	37 (38.9)	60 (43.8)	0.462
MCID deterioration	35 (36.8)	39 (28.5)	0.178
Total ESAS, median (IQR)			
Certification	40 (29)	36 (25)	0.234
Most recent	31 (28)	29 (22)	0.459
p	0.001	0.002	
MCID improvement	58 (61.1)	74 (54)	0.287
MCID deterioration	27 (28.4)	45 (32.8)	0.474
Total morphine eq., median (IQR)			
Certification	97.5 (150)	45 (135)	0.015
Most recent	120 (218)	45 (157.5)	<0.001
p	0.004	0.522	
Severe pain	*n* = 49	*n* = 61	
Pain, median (IQR)			
Certification	8 (2)	8 (2)	0.131
Most recent	7 (6)	7 (6)	0.404
p	<0.001	<0.001	
MCID improvement	28 (57.1)	38 (62.3)	0.584
MCID deterioration	8 (16.3)	10 (16.4)	0.992
Physical, median (IQR)			
Certification	34 (17)	28 (15)	0.028
Most recent	22 (21)	23 (17)	0.876
p	<0.001	<0.001	
MCID improvement	34 (69.4)	39 (63.9)	0.547
MCID deterioration	5 (10.2)	17 (27.9)	0.021
Emotional, median (IQR)			
Certification	7 (12)	7 (8)	0.978
Most recent	6 (10)	6 (12)	0.792
p	0.178	0.055	
MCID improvement	25 (51)	29 (47.5)	0.717
MCID deterioration	17 (34.7)	18 (29.5)	0.562
Total ESAS, median (IQR)			
Certification	48 (19)	42 (19)	0.1
Most recent	33 (33)	33 (26)	0.942
p	<0.001	0.077	
MCID improvement	35 (71.4)	33 (54.1)	0.063
MCID deterioration	11 (21.4)	18 (29.5)	0.404
Total morphine eq., median (IQR)			
Certification	135 (157.5)	90 (172.5)	0.454
Most recent	106 (202.2)	60 (236.25)	0.17
p	0.124	0.421	
Mild to moderate pain	*n* = 46	*n* = 76	
Pain, median (IQR)			
Certification	3.5 (5)	3 (5)	0.721
Most recent	4 (4)	3 (6)	0.319
p	0.078	0.316	
MCID improvement	14 (30.4)	22 (28.9)	0.861
MCID deterioration	21 (45.7)	33 (43.4)	0.81
Physical, median (IQR)			
Certification	22 (15)	21.5 (16)	0.705
Most recent	19.5 (15)	17 (17)	0.109
p	0.943	0.075	
MCID improvement	22 (47.8)	41 (53.9)	0.512
MCID deterioration	19 (41.3)	22 (28.9)	0.161
Emotional, median (IQR)			
Certification	2.5 (10)	6 (10)	0.19
Most recent	3 (10)	4 (8)	0.777
p	0.903	0.073	
MCID improvement	12 (26.1)	31 (40.8)	0.099
MCID deterioration	18 (39.1)	21 (27.6)	0.187
Total ESAS, median (IQR)			
Certification	32 (23)	30.5 (27)	0.994
Most recent	30.5 (24)	26.5 (22)	0.348
p	0.642	0.077	
MCID improvement	23 (50)	41 (53.9)	0.672
MCID deterioration	16 (34.8)	27 (35.5)	0.934
Total morphine eq., median (IQR)			
Certification	90 (150)	45 (108.75)	0.01
Most recent	126 (230.63)	30 (120)	<0.001
p	0.012	0.935	

eq., equivalent; ESAS, Edmonton Symptom Assessment System; IQR, interquartile range; MCID, minimal clinically important differences.

MCID improvement ($p = 0.584$) and deterioration ($p = 0.992$) were not significant (Table 3).

Mild-moderate sub-cohort MMJ(+)'s pain remained consistent (3/10–3/10, $p = 0.316$); whereas, MMJ(−) slightly increased (3.5/10–4/10, $p = 0.078$) between visits. MCID improvement ($p = 0.861$) and deterioration ($p = 0.810$) were not significant (Table 3).

Physical ESAS score. Physical symptoms in both total MMJ(−) (26/60–22/60, $p = 0.001$) and MMJ(+) (24/60–20/60, $p = 0.003$) improved between visits. MCID improvement ($p = 0.933$) and deterioration ($p = 0.589$) were not significant (Table 3).

Both severe pain MMJ(−) (34/60–22/60, $p < 0.001$) and MMJ(+) (28/60–23/60, $p < 0.001$) significantly improved between visits. MCID improvement ($p = 0.547$) was not significant; however, greater deterioration was demonstrated in MMJ(+) (17/61, 27.9%) than MMJ(−) (5/49, 10.2%) ($p = 0.021$) (Table 3).

Neither, mild-moderate sub-cohorts, MMJ(−) (22/60–19.5/60, $p = 0.943$) nor MMJ(+) (21.5/60–17/60, $p = 0.075$) significantly improved between visits. MCID improvement ($p = 0.512$) and deterioration ($p = 0.161$) were not significant (Table 3).

Emotional ESAS score. While the change between visits in total MMJ(−) was not significant (6/20–4/20, $p = 0.193$); total MMJ(+) cohort's improvement was significant (6/20–5/20, $p = 0.010$). MCID improvement and deterioration ($p = 0.178$) were not significant (Table 3).

Neither, severe pain sub-cohorts, MMJ(−) (7/20–6/20, $p = 0.178$) nor MMJ(+) (7/20–6/20, $p = 0.055$ significantly

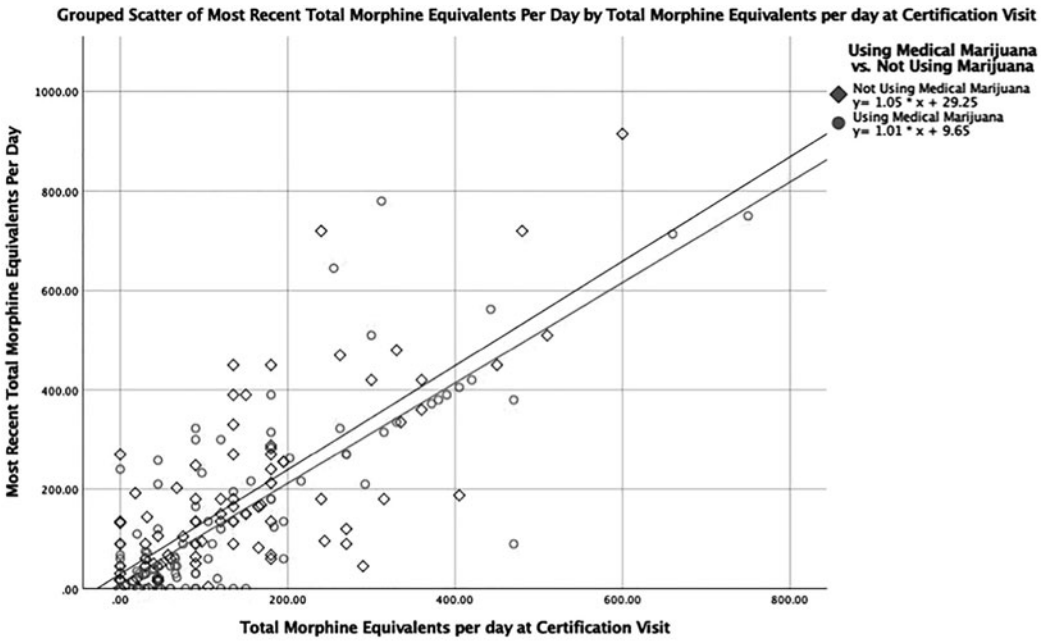

FIG. 1. Rate of MME escalation. MME, morphine milligram equivalents.

improved between visits. MCID improvement ($p=0.717$) and deterioration were not significant ($p=0.562$) (Table 3).

Mild-moderate MMJ(−) (2.5/20–3/20, $p=0.903$) slightly increased; whereas, MMJ(+) (6/20–4/20, $p=0.073$) scores improved between visits. MCID improvement ($p=0.190$) and deterioration ($p=0.073$) were not significant (Table 3).

Total ESAS. Both total MMJ(−) (40/80–31/80, $p=0.001$) and MMJ(+) (36/80–29/80, $p=0.002$) significantly improved between visits. MCID improvement ($p=0.287$) deterioration ($p=0.474$) were not significant (Table 3).

While both severe pain sub-cohorts' improved between visits, MMJ(−) (48/80–33/80, $p<0.001$) experienced a significant reduction; whereas, MMJ(+) (42/80–33/80, $p=0.077$) did not. MCID improvement ($p=0.063$) and MCID deterioration ($p=0.404$) were not significant (Table 3).

Mild-moderate MMJ(−) (32/80–30.5/80, $p=0.642$) and MMJ(+) (30.5/80–26.5/80, $p=0.077$) improved between visits. MCID improvement ($p=0.672$) and deterioration ($p=0.934$) were not significant (Table 3).

Discussion

Compared to patients solely utilizing opioids, MMJ as an adjunctive therapy provided analogous symptomatic relief without the additional burden of opioid dose escalation. As health care providers are caught between providing satisfactory symptomatic reliefs and protecting against addiction, MMJ should be considered a viable adjuvant therapy for palliative management in the oncologic population.[3]

Cancer survivors, as many as 10 years after remission, maintain higher opioid prescription rates than patients without a prior oncological diagnosis.[16,17] After a threshold of 29 mg/day MME, every additional 3–4 mg/day demonstrates a significant dose response relationship with subsequent opioid-attributed adverse clinically meaningful events.[18] At the time of MMJ certification, patients who did not use MMJ [MMJ(−)] and those who used MMJ [MMJ(+)] had a daily opiate consumption of nearly four times and twice this threshold, respectively, placing these patients at risk for serious adverse events.

The prolonged utilization of opioids is also associated with the development of tolerance, the need for higher dosages to achieve the same degree of relief; however, the initial effects of tolerance have been postulated to begin after a single dose of orally administered oxycodone.[18] Diminishing the need for high-dose opioids could serve as a protective factor against severe adverse events, including tolerance development.[18–20] Our study found that the addition of MMJ to patients' palliative care regimen withstood the development of tolerance and reduced the rate of opioid use, over a significantly longer follow-up period than patients solely utilizing opioids. Both sub-analyses of patients using MMJ reduced daily opioid consumption by 33%. Furthermore, by the time of most recent visit, patients using MMJ who identified with mild-moderate pain reduced their daily opiate usage to a low-risk, low-dose consumption. Unfortunately, this was not demonstrated by their counterparts not using MMJ, as their daily opiate consumption was nearly five times this value. In fact, patients', who did not use MMJ, daily opiate consumption experienced a statistical and clinically significant median increase of nearly 23%. These findings were in accordance with prior observational and early clinical trials that demonstrated similar dose decreases after the administration of cannabinoids to preexisting opioid therapies.[21–23]

One-fourth of patients taking opioids achieve less than minimal pain relief.[24] One strategy patients with uncontrolled pain may benefit from is ''opioid switching'' to prevent adverse events and increase opioids' analgesic properties.[25] However, the advantages of ''opioid switch'' are highly unpredictable, varying independently between patients' symptoms. As such, nonopioid adjuvant analgesics, including acetaminophen, nonsteroidal anti-inflammatory drugs, and corticosteroids, are

utilized to bolster opioids to alleviate unresolved pain.[26] Yet, especially in vulnerable populations, these medications are affiliated with many renal, gastrointestinal, and cardiovascular risks.[26,27] Cannabinoids, such as delta-9-THC, produce antinociceptive and anti-inflammatory effects, provoking great interest in their adjunctive analgesic properties for cancer-related pain.[28–30] As mu opioid receptors and cannabinoid receptors are distributed in similar areas of the central nervous system, opioidergic and endocannabinoid systems' concurrent expression and interaction indicates a possible synergistic effect.[31] Utilizing these synergistic properties, adjunctive cannabinoids can decrease opioid dosages, and subsequent adverse side effects, without sacrificing analgesic efficacy.[28,32] Several preclinical and early clinical trials of inhaled and oromucosal spray cannabinoids proved effective as adjuvant therapies in the treatment of chronic pain.[21–23,29,33–36] Our findings provide additional evidence that MMJ can offer ''opioid-sparing'' effects. As both cohorts' pain significantly improved, those not using MMJ required 63% more daily opiate dosages to achieve significant pain alleviation than their counterparts utilizing adjunctive MMJ.

Besides pain, physical ESAS encompasses other debilitating cancer-related symptoms, including nausea, tiredness, drowsiness, appetite, and shortness of breath. While not life threatening, nearly 45% of patients experience a multitude of physically taxiing adverse events, especially gastrointestinal distress, immediately after opioid introduction.[24,25] These disturbances negatively impact patient quality of life.[24,25,37] In efforts to combat opioid-induced gastrointestinal nausea, preclinical studies have indicated the endocannabinoid system's role in the regulation of nausea and early clinical trials have further demonstrated cannabinoids' antiemetic effects to be as effective as several leading prescriptions.[34,38–40] In our study, both cohorts met the MCID for both physical symptoms improvement and deterioration. Interestingly, patients with severe pain who used MMJ displayed significantly more deterioration between visits. The sedating effects of cannabinoids (i.e., THC) could be a possible explanation for this deterioration, as drowsiness and tiredness are both components of the physical ESAS score and patients exposed to MMJ were reported ''naïve-users.''[38] This is in comparison to the opioid users where escalation of current medications may not cause the same level of drowsiness typically seen with a newly administered drug. While cannabinoid-induced sedation can greatly impact drowsiness, it does not pose risks for central nervous system depression, respiratory failure, and overdose-related deaths, as reported with high-dose opioids usage.[38,41] As opioid medications accounted for nearly 70% of all drug-related deaths, the rate of prescription opioid-related overdoses was five times that of 1999 in 2017.[41] Although the overdose rate is lower in the oncologic population, studies have established statistically significant associations between prescribing patterns and overdose risks in this vulnerable population.[42] Considering the nature of cannabinoid-related adverse effects and the unlikelihood of overdose, MMJ has favorable safety considerations compared to other analgesics during a time of increasing prescription opioid-related overdoses.[38]

Major depression disorder is four times more prevalent in the oncologic population than the general population; as such, the impact of depression has pervasive effects on this population's health-related quality of life (HRQL) by inducing fatigue, insomnia, and appetite loss.[43–45] In conjunction with anxiety, the additive effects produce worse health outcomes and have been found to be predictive of physical functioning in breast cancer patients.[43,46] Yet, as nearly all cancer patients are treated with opioids, increases in both the duration and daily MME have been associated with the onset and progression of depression symptoms.[47,48] As evidence grows for the relationship between emotional ESAS components (depression and anxiety) and oncology patients' HRQL, an emphasis should be placed on detecting and controlling these symptoms,[43,44,46] Our study found that patients using MMJ benefitted from significant improvements in emotional ESAS (depression and anxiety components). In fact, patients who did not use MMJ with mild-moderate pain experienced an increase in their emotional distress scores between visits. Additionally, all evaluated subsets of patients who utilized MMJ experienced greater proportions of MCID improvements and lesser deterioration, compared to their counterparts. Prior observational and clinical studies have reported similar reductions in patient-reported depression and anxiety with additive cannabinoid therapy.[22,23,36]

Over 191 million opioid prescriptions were dispersed in 2017 as palliative care continues to rapidly evolve.[41,49,50] Advancements in cancer management and treatments have reduced mortality, between 1991 and 2011, by 22%; yet, cancer-related morbidity continues to plague patients as they are living with their oncologic diagnosis longer.[50,51] As such, the field of oncology has experienced a dramatic increase in the use of palliative care to relieve disease-related symptomatic distress and improve patient well-being.[50,51] In attempts to evaluate disease-related distress, the ESAS tool is utilized to assess nine frequently encountered physical (pain, tiredness, nausea, drowsiness, appetite), emotional (depression, anxiety), and well-being symptoms. ''Cancer Pain Relief'' guidelines and the ''analgesic ladder,'' developed by the WHO, have historically promoted opioids to address these cancer-related morbidities.[3,24,25] Currently, however, opioid utilization presents a challenge to palliative care providers as they must balance symptom relief with adverse effects and dependence. As there continues to be a void in the medications available to these providers, MMJ should be considered as an alternative.

There are limitations to this study. First, patients' MMJ use was obtained through patient-reported measures. Similarly, all prescribed opiates were assumed filled and utilized. Because these medications are in the best interest of the patient, it was reasonable to assume they were taken as prescribed. However, we cannot be certain that all medications, opioids, and MMJ were used as instructed. Second, as EMR were reviewed for patient consumption of MMJ and opioids, information regarding nonopioid adjuvant therapies was not collected. As such, the impact of these other nonopioid medications and therapies is unknown. Third, as MMJ is nonsynthetic, the exact concentration of cannabinoids may fluctuate and impact efficacy. However, as all MMJ(+) patients received MMJ from the NJMMPR, the authors believe the strain variations to be minimal. Also, due to the highly regulated nature of obtaining MMJ in New Jersey, the collected data in the registry is reliable, minimizing the limitations associated with utilizing a database. Fourth, ESAS is a subjective evaluation method and patient-reported scores could have been impacted by numerous confounding factors (i.e., family events, new treatments). Studies have also shown

patients' difficulty distinguishing between Tiredness and Drowsiness and between Depression and Anxiety symptoms. However, ESAS has been validated to assess the major symptoms of cancer patients seeking palliative care in different settings and as such is a standard of care practice.[52–54] Additionally, as these primary outcomes were qualitative in nature, MCID was utilized to quantitatively determine clinical impact.

When adjunctively utilized, our study suggests MMJ can effectively alleviate oncologic disease-related symptomatic distress. Although MMJ does not decrease the overall use of opioids, MMJ may have a role in delaying dose escalation. Despite growing evidence, mixed opinions persist and divide medical oncologists throughout the United States.[55] As such, further investigation is called for, as there is a paucity of sound prospective, randomized, double-blind studies on the subject.[56–58] At this time there are immense hurdles to conducting such research; this article and prior studies should serve as justification for future prospective studies.

Author Disclosure Statement

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Address correspondence to:
Tae Won B. Kim, MD
Cooper Bone and Joint Institute
Cooper University Hospital
3 Cooper Plaza, Suite 410
Camden, NJ 08103
USA

E-mail: kim-taewon@cooperhealth.edu