Brief Report

Levorphanol as a Second Line Opioid in Cancer Patients Presenting to an Outpatient Supportive Care Center: An Open-label Study

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Abstract

Context. Levorphanol is a potent opioid agonist and NMDA receptor blocker with minimal drug interactions, and there are few reports of its use in cancer patients.

Objectives. We aimed to determine the frequency of successful opioid rotation (OR) to levorphanol and the median opioid rotation ratio (ORR) from Morphine Equivalent Daily Dose (MEDD).

Methods. This is a prospective, single-group, interventional study. Cancer outpatients requiring an OR and receiving a MEDD of 60−300 mg were rotated to levorphanol using a ratio of 10:1 and assessed daily for 10-day. Successful OR was defined as a 2-point improvement in the Edmonton Symptom Assessment System (ESAS) pain score on day 10 or achieving the personalized pain goal between days 3−10 in patients with uncontrolled pain or resolution of opioid side effects (OSE) in those undergoing OR for OSE alone. The ORR to levorphanol was calculated using net-MEDD (MEDD before OR minus the MEDD of the breakthrough opioid used along with levorphanol after OR).

Results. Forty patients underwent OR to levorphanol, and uncontrolled pain 35/40 (87.5%) was the most common indication. The median net-MEDD and levorphanol doses were 95 and 10 mg, respectively, and 33/40 (82.5%) had a successful OR with a median (IQR) ORR of 8.56 (7.5−10). Successful OR was associated with significant improvement in ESAS and OSE scale scores. There was a strong association between MEDD and levorphanol dose.

Conclusion. This study provided preliminary data that cancer patients could be successfully rotated to levorphanol using an ORR of 8.5. Levorphanol was associated with improved pain and symptom control and was well- tolerated. J Pain Symptom Manage 2023;65:e683−e690.

Key Words

Cancer pain, levorphanol, opioid rotation, opioid rotation ratio, morphine equivalent daily dose, conversion ratio, and palliative care

Introduction

More than 80% of advanced cancer patients experience pain[1−3] and may require treatment with opioids.[4] Opioid metabolites may accumulate in patients and cause symptoms of opioid-induced neurotoxicity (OIN).[5,6] OIN includes symptoms such as excessive drowsiness, confusion, myoclonus, hallucinations, and seizures. Opioid rotation (OR), substituting one opioid with another, is recommended to treat OIN and uncontrolled pain despite opioid up-titration.[7]

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Approximately 30%−50% of cancer patients treated by palliative care (PC) teams will require an OR.[7,8] Methadone is the most common second-line opioid used in cancer pain management and most frequently used for OR.[7,8] In addition to being a potent mu-opioid agonist, methadone has unique properties as an NMDA (N-methyl-D-aspartate) receptor blocker and reuptake inhibitor of both serotonin and norepinephrine.[9] These unique properties make it the preferred drug for uncontrolled pain, hyperalgesia, neuropathic pain syndromes, and OIN.[9,10] However, methadone has been associated with numerous drug interactions and increased morbidity and mortality in patients with chronic pain.[11] Methadone can cause QTC prolongation and arrhythmias, and the risk substantially increases in the presence of electrolyte abnormalities or the concurrent use of cytochrome P-450 inhibitor drugs.[12] Cancer patients would benefit immensely from a safer alternative to methadone to treat complex chronic pain.

Levorphanol, like methadone, is an NMDA receptor antagonist and reuptake inhibitor of both norepinephrine and serotonin. It is metabolized by conjugation to a 3-glucuronide, bypassing the cytochrome P-450 system.[13−17] Unlike methadone, levorphanol has very few drug interactions,[16] and no known effect on QTC interval, making it an attractive alternative to methadone as it possesses several of its unique properties minus the risks.[13,16,18] Moreover, levorphanol has a shorter plasma half-life (11−16 hours) but a more prolonged duration of action (6−15 hours) compared to methadone and may have a substantially lower risk of drug accumulation.[16,17,19]

Levorphanol has not been studied extensively in cancer patients.[13,15,18,20] There are no known large studies on levorphanol, and there is insufficient evidence to support its use in many pain settings. The currently used opioid rotation ratio (ORR) for OR from Morphine Equivalent Daily Dose (MEDD) to levorphanol is unknown. Experts suggest ranges from 4:1 to 20:1.[15] Our objective was to determine the proportion of successful OR from MEDD to levorphanol and the median ORR from MEDD to levorphanol in cancer patients with successful OR. Determining the frequency of successful OR and a safe and effective ORR would enable researchers to design future randomized clinical trials (RCTs) successfully.

Methods

This is an investigator-initiated, open-label intervention study. Patients were enrolled in the outpatient supportive care clinic (SCC) at The University of Texas M. D Anderson Cancer (UTMDACC). The institutional review board of UTMDACC approved this study (2017−0925), and all participants signed informed consent. The study was activated on November 29, 2018 and was closed on January 30, 2020. Clinicaltrials.gov trial registration: NCT03927885.

Participants

Patients were eligible if they were on first-line potent oral opioids (morphine, oxycodone, oxymorphone, fentanyl, hydromorphone, or hydrocodone), opioid-tolerant (MEDD of ≥60 mg), 18 years or older, and had an Eastern Cooperative Oncology Group Performance Status (PS) of ≤3. Patients with cognitive impairment, renal or hepatic insufficiency, and neuropathic pain without any nociceptive pain were excluded, along with those on methadone (due to long and variable half-life), benzodiazepines (risk for excessive sedation and respiratory depression), and baseline MEDD >300 mg. Patients with a history of or at high-risk for alcohol or substance use disorders were excluded.

SCC Workflow

Standardized interdisciplinary care is provided in our SCC.[21] The team includes board-certified PC physicians, nurses, counselors, a social worker, a chaplain, and a pharmacist. Patients are assessed using validated tools like the Edmonton Symptom Assessment Scale (ESAS),[22,23] Memorial Delirium Assessment Scale (MDAS),[24] and The Cut-Down, Annoyed, Guilty, and Eye Opener questionnaire Adapted to Include Drug Use (CAGE-AID).[25] Interdisciplinary team members are consulted according to the patient's or caregivers' needs. The team provides assessment and management of cancer-related symptoms, counseling, and assistance with decision-making and coping.

Experimental Approach

Patients taking potent opioids and experiencing uncontrolled pain, opioid-related side effects, or a combination were approached by research staff with an invitation to participate in the study, and informed consent was obtained if agreeable. Levorphanol was prescribed using a conservative MEDD to levorphanol ratio of 10:1, rounded to dose availability, and divided into three doses eight hours apart. An immediate-release opioid (either previously used or a new one) dosed at 5%−20% of the baseline MEDD was prescribed for breakthrough pain as per the clinical judgment of the PC specialist.[26] Levorphanol was obtained from Sentynl Therapeutics, Inc. in 2 mg tablets. The maximum baseline MEDD for study enrollment was capped at 300 mg to ensure patients would not require taking more than 15 of the 2 mg tablets (five tablets every eight hours for MEDD of 300) daily. Patients were contacted daily by the research team for 10 days to monitor for symptoms and side effects. Levorphanol doses were titrated on days 3, 5, and 7 depending on

the response to the drug and any associated side effects. On day 5 (taking advantage of the rapid onset of analgesia (30 minutes) and peak analgesia of one hour[17,18]), the breakthrough opioid was also switched to levorphanol, dosed at around 10% of the daily levorphanol dose. All patients continued to have access to previously used immediate-release opioid for breakthrough pain not responding to as-needed levorphanol. The study intervention duration was 10 days, after which patients returned to usual care and could continue receiving levorphanol for up to six months.

Assessments

Demographic characteristics, ESAS, CAGE-AID, MDAS, personalized pain goal (PPG; the patient-reported outcome for the goal of pain management on a 0−10 scale),[27] Douleur Neuropathique-4 (DN4) for diagnosis of neuropathic pain,[28] opioid side effect scale (OSES; xerostomia, nausea, constipation, drowsiness, confusion scale of 1−4, where 3 and 4 = severe),[9] and MEDD were recorded at baseline. ESAS, OSES, Global Perceived Effect (GPE) scale, and opioid doses were recorded on the day of meeting the primary outcome and day 30. GPE reflects a patient's belief about the efficacy of the treatment (complete pain relief, much improved, slightly improved, no change, slightly worsened, much worsened, or worse than ever).[29]

The primary outcome was the proportion of patients with a successful OR. The criteria for successful OR have been defined previously[30−34] and included:

Improvement in pain by 30% or two-point reduction in ESAS pain score on day 10 +/−1 or attainment of PPG between days 3−10 if OR was performed for uncontrolled pain,[35,36] or evidence of the disappearance of side effects on day 10 +/−1 if OR was performed for side-effects, or no worsening of pain score on day 10 +/−1 if OR was performed for other reasons such as drug interaction *and* the continued use of levorphanol after reaching the primary end point.

ORR from MEDD to levorphanol in patients with successful OR was calculated as baseline MEDD divided by the 24-hour total levorphanol dose. When patients used doses of another breakthrough opioid 24 hours before the assessments, net-MEDD (as previously defined) was calculated by subtracting the MEDD obtained from the breakthrough opioid from the baseline MEDD.[30,31,33]

Statistics

Based on our previous studies,[7,30−34] we anticipated that 60%−70% of the patients would undergo a successful OR. We planned for a sample size of 60 patients which would provide a two-sided 95% confidence interval (CI) of 0.127 for the proportion of patients with a successful OR. The actual enrollment was 40 patients due to funding limitations. We were able to estimate the proportion of patients with a successful OR with a two-sided 95% CI of 0.118.

Data were summarized using standard descriptive statistics such as mean, standard deviation, median, interquartile range for continuous and frequency and proportion for categorical variables. The Chi-Squared or Fisher's exact test examined the association between categorical variables. Wilcoxon rank-sum test and Wilcoxon signed-rank test were used to examine the difference in continuous variables between groups and within each group. A univariate logistic regression model was applied to assess the effect of variables on successful OR. All computations were performed in SAS 9.4 (SAS Institute Inc., Cary, NC, USA) using two-sided tests, and a *P*-value of ≤0·05 was considered statistically significant.

Results

We followed a referral system, as patients would be fully eligible only if they required an OR. Of the 5683 patients screened, 679 (12%) were eligible if they needed an OR on the day of the visit. Of those, 45 (7%) required an OR, and 43 enrolled in the study. Three patients did not start the study drug and dropped out due to hospice referral or planned hospital admission.

The median age was 55 years, 22/40 (55%) were female, 24 (60%) were white, lung (25%) was the most common cancer type, and 85% had metastatic disease. Uncontrolled pain (87.5%) was the most common indication for OR, and 37.5% had a component of neuropathic pain (Table 1). Of the 40 patients who underwent an OR to levorphanol, 33 (82.5%) had a successful rotation with 95% CI (70.7%, 94.3%). The univariate logistic regression models did not reveal any significant association between successful OR and the tested variables. The median (IQR) ORR from MEDD to levorphanol was 8.56 (7.5, 10) and did not vary according to MEDD or the presence of neuropathic pain (Table 3). There were no changes in the use of adjuvant analgesics during the 10-day study period.

The median net-MEDD and levorphanol doses were 95 mg and 10 mg, respectively. Fig. 1 shows the linear regression of levorphanol dose and MEDD and the strong association between both. Fig. 2 shows that the ORR was stable within a wide range of MEDD.

Table 2 shows an improvement in pain and multiple other symptoms in ESAS and OSES compared to baseline. A total of 26 patients underwent titration to the levorphanol dose; 23 had a dose increase, and three had a dose decrease. Of the 33 patients with successful OR, 27 continued levorphanol for 30 days. However, only 23 patients completed the 30-day assessments due

Table 1
Baseline Demographic & Clinical Characteristics.

Variable	Levels	Total	Success of Rotation		*P*-Value
			No	Yes	
All Patients		40 (100%)	7 (17.5%)	33 (82.5%)	
Gender	Female	22 (55%)	3 (13.6%)	19 (86.4%)	0.6798
	Male	18 (45%)	4 (22.2%)	14 (77.8%)	
Race	Asian	2 (5%)	1 (50%)	1 (50%)	0.2842
	Black	5 (12.5%)	1 (20%)	4 (80%)	
	Hispanic	7 (17.5%)	1 (14.3%)	6 (85.7%)	
	White	24 (60%)	3 (12.5%)	21 (87.5%)	
ECOG Performance Status	0	1 (2.5%)	0 (0%)	1 (100%)	0.6264
	1	6 (15%)	0 (0%)	6 (100%)	
	2	19 (47.5%)	5 (26.3%)	14 (73.7%)	
	3	14 (35%)	2 (14.3%)	12 (85.7%)	
Cancer Type	Breast	4 (10%)	0 (0%)	4 (100%)	0.3386
	Gastrointestinal	8(20%)	2 (25%)	6 (75%)	
	Genitourinary	7 (17.5%)	0 (0%)	7 (100%)	
	Gynecological	3 (7.5%)	1 (33.3%)	2 (66.7%)	
	Head & Neck	2 (5%)	1 (50%)	1 (50%)	
	Lung Cancer	10 (25%)	1 (10%)	9 (90%)	
	Sarcoma	5 (12.5%)	2 (40%)	3 (60%)	
Cancer Stage	Local/ Locally Advanced	6 (15%)	3 (50%)	3 (50%)	0.0547
	Metastatic	34 (85%)	4 (11.8%)	30 (88.2%)	
Indication for Opioid Rotation	Drug Interaction	1 (2.5%)	0 (0%)	1 (100%)	1.0000
	Opioid related adverse effect	4 (10%)	0 (0%)	4 (100%)	
	Uncontrolled Pain	35 (87.5%)	7 (20%)	28 (80%)	
Neuropathic Pain	Yes	15 (37.5%)	5 (33.3%)	10 (66.7%)	0.0812
Receiving Antineoplastic Treatment at Baseline	No	4 (10%)	1 (25%)	3 (75%)	0.5522
	Yes	36 (90%)	6 (16.7%)	30 (83.3%)	
Personalized Pain Goal	2/10	12 (30%)	3 (25%)	9 (75%)	0.6991
	3/10	24 (60%)	4 (16.7%)	20 (83.3%)	
	4/10	4 (10%)	0 (0%)	4 (100%)	
Baseline MEDD	<100	15 (37.5%)	2 (13.3%)	13 (86.7%)	0.6913
	≥100	25 (62.5%)	5 (20%)	20 (80%)	
Baseline Opioids	Fentanyl transdermal - Hydrocodone	1 (2.5%)	0 (0%)	1 (100%)	0.7718
	Fentanyl transdermal - Hydromorphone	4 (10%)	0 (0%)	4 (100%)	
	Hydrocodone	6 (15%)	0 (0%)	6 (100%)	
	Hydromorphone	5 (12.5%)	1 (20%)	4 (80%)	
	Morphine	15 (37.5%)	4 (26.7%)	11 (73.3%)	
	Oxycodone	9 (22.5%)	2 (22.2%)	7 (77.8%)	

to logistical issues, and some patients enrolled in hospice. There was a sustained improvement in pain, other ESAS symptom scores, and OSES on day 30 (Table 4).

Adverse events were assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4. Eight patients experienced adverse effects (somnolence, confusion, nausea, constipation, and dry mouth), mainly grade one and a few grade two. Six of the eight patients improved with dosage adjustments, supportive care, or observation. One patient with confusion and another with somnolence, both grade 2, withdrew from the study and had an unsuccessful OR.

Thirty-four of the 40 enrolled patients reported either slightly improved pain, much-improved pain, or complete pain relief on the day of meeting the primary outcome. One patient reported a slight worsening of pain. Data was not available in five patients. All five patients had a failure of OR and were not reachable for assessment. The GPE was significantly associated with the success of OR ($P < 0.001$).

Of the seven patients who had unsuccessful OR, one did not meet the PPG and experienced only one point

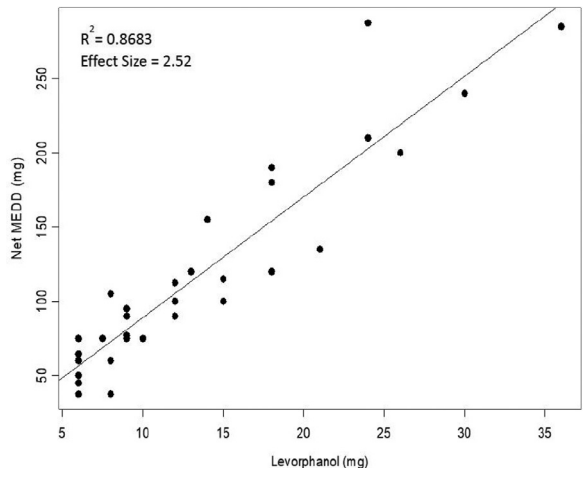

Fig. 1. Linear Regression of Daily Levorphanol Dose According to MEDD.

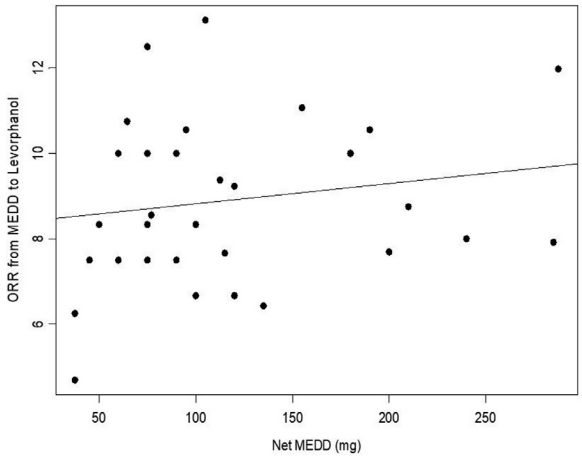

Fig. 2. Linear Regression of ORR According to MEDD.

reduction in pain score on the day 10 assessment. However, the patient indicated much-improved pain on GPE on day 10. Among the remaining six, three patients had unrelated admissions (infection, fracture, and deep vein thrombosis), one was noncompliant, one had increased drowsiness, and another had uncontrolled pain despite titration and developed confusion. A total of 27 of the 33 patients received a refill of levorphanol after one month, and nine continued levorphanol for six months.

Discussion

Our study provides preliminary evidence that levorphanol can provide successful pain control as a second-line opioid in cancer outpatients. A MEDD to levorphanol ratio of 8.5:1 can be used to calculate the dose of levorphanol. This information can be used by researchers when designing RCTs with levorphanol in various pain syndromes.

Compared to previous retrospective studies, a higher proportion of patients had a successful OR in our study.[7,30–34,37] In other studies, ORs to methadone were more successful (>69%) than ORs to other opioids (>60%).[7,10,37–40] In our study, many patients required titrations of levorphanol dose after rotation which likely increased the success of OR. A recent study from our group highlights the wide variation in ORRs used worldwide.[41] Our current study underscores the

Table 2
Summary of Changes in Edmonton Symptom Assessment System (ESAS) & Opioid Side Effect Scale from Baseline.

Variable	Success of Rotation	N	Median	IQR	*P*1	*P*2
Pain	Total	39	−3	(−5, −2)		
	No	6	−1.5	(−4, −1)	0.1250	0.0545
	Yes	33	−3	(−5, −3)	**<0.0001**	
Fatigue	Total	39	−2	(−4, 0)		
	No	6	2	(−2, 2)	0.7813	**0.0430**
	Yes	33	−2	(−4, 0)	**0.0005**	
Nausea	Total	39	−1	(−3, 0)		
	No	6	0.5	(−2, 1)	0.8125	0.2353
	Yes	33	−1	(−3, 0)	**0.0041**	
Drowsiness	Total	39	0	(−3, 2)		
	No	6	4.5	(3, 5)	**0.0313**	**0.0019**
	Yes	33	−1	(−3, 1)	**0.0202**	
Appetite	Total	39	−1	(−4, 0)		
	No	6	3	(2, 4)	0.3438	**0.0168**
	Yes	33	−2	(−4, 0)	**0.0010**	
Wellbeing	Total	39	−1	(−2, 0)		
	No	6	−0.5	(−4, 2)	0.8750	0.4926
	Yes	33	−1	(−2, 0)	**0.0001**	
Sleep	Total	39	−2	(−5, 0)		
	No	6	0	(−4, 5)	0.7500	0.1345
	Yes	33	−2	(−5, −1)	**<0.0001**	
ESAS Total Score	Total	39	−15.5	(−27.5, −6.5)		
	No	7	−8	(−19, 13)	0.6094	0.1572
	Yes	33	−16	(−29, -8)	**<0.0001**	
Nausea (opioid side effect scale)	Total	39	0	(−1, 0)		
	No	6	0	(−1, 1)	1.0000	0.2320
	Yes	33	0	(−1, 0)	**0.0079**	
Drowsiness (opioid side effect scale)	Total	39	0	(−1, 1)		
	No	6	2	(1, 2)	**0.0313**	**0.0010**
	Yes	33	−1	(−2, 0)	**0.0043**	
Confusion (opioid side effect scale)	Total	39	0	(−1, 0)		
	No	6	0	(0, 0)	1.0000	**0.0433**
	Yes	33	0	(−1, 0)	**0.0010**	

*P*1 = Wilcoxon signed rank test for changes within the group; *P*2 = Wilcoxon rank sum test for changes between groups.
Bold indicates statistical significance.

Table 3
Opioid Rotation Ratio (ORR) from Net-MEDD to Levorphanol in Patients with Successful Opioid Rotation (OR).

Variable	Baseline MEDD	N	Median ORR	IQR	Mean	SD	*P*-Value
MEDD	Total	33	8.56	(7.5, 10)	8.89	1.90	
	<100	13	8.33	(7.5, 10)	8.35	1.77	0.2380
	≥100	20	8.99	(7.8, 10.56)	9.24	1.95	
	Neuropathic Pain	N	Median	IQR	Mean	SD	*P*-value
Neuropathic pain	Total	33	8.56	(7.5, 10)	8.89	1.90	
	No	23	8.33	(7.5, 10)	8.76	1.84	0.5084
	Yes	10	10	(6.67, 10.75)	9.19	2.11	

Net-MEDD: Morphine Equivalent Daily Dose before OR minus the MEDD of the breakthrough opioid used along with levorphanol after OR.

importance of using evidence-based ratios, personalizing the dose to the patient's clinical situation, and the need for ongoing monitoring and access to PC teams to help improve the safety and success of ORs.

As previously reported, our study demonstrated not only an improvement in pain but in multiple other ESAS symptoms,[7,10,30,32] further solidifying the vital role OR plays in symptom management in PC. These improvements were persistent even at 30 days.

ORR from MEDD to levorphanol did not significantly differ in patients with neuropathic pain. Methadone is the go-to opioid in PC for complex pain syndromes and neuropathic pain, which may be present in about 40% of cancer patients.[42–44] The treatment of neuropathic pain remains a challenge, with a lack of well-conducted RCTs.[45–47] In a RCT, methadone was superior to fentanyl in treating neuropathic pain in cancer patients with head and neck cancer.[9] Levorphanol was beneficial in treating neuropathic pain, including phantom limb pain and brown-sequard syndrome.[20,48] Levorphanol must be studied in well-designed studies among patients with cancer-related neuropathic pain syndromes.

The ORR from MEDD to methadone varies according to the MEDD.[49] In our study, the ORR from MEDD to levorphanol did not differ significantly according to MEDD. However, our study did not include patients with MEDD >300, and we had a small sample size. More studies must be conducted to determine if the ORR to levorphanol varies according to the MEDD.

Although some patients in our study were on both scheduled and as-needed doses of levorphanol and tolerated it well, further studies must examine the efficacy and safety of this practice. Our team does not recommend the use of levorphanol for breakthrough pain at this time.

Regular QTC monitoring may be necessary for treating pain in PC patients on methadone.[11,12,49] Levorphanol has no known QTC prolonging effect and may be a suitable alternative to methadone in patients with complex pain syndromes and a prolonged QTC. This is especially important for cancer patients in clinical trials, where methadone may be contraindicated due to drug interactions and QTC prolonging effects. Levorphanol is not affordable for most patients (> $2000 for a month's supply) and is not readily available in pharmacies.[16] Despite the high success rate of OR to levorphanol and the safe side effect profile, until it becomes more affordable and readily available, our patients will not be able to benefit from the drug. Drug manufacturers and payors must work together to make levorphanol available for patients who cannot undergo OR to methadone for safety, side effects, and drug interactions.

Limitations of our study include the prospective open-label design, small sample size, no placebo control group, and short duration of follow-up after OR. Our study was conducted at one tertiary cancer center, which may not be generalizable to other cancer patients or noncancer PC populations. We did not conduct urine drug screens to monitor for compliance and unreported use of other opioids. Future studies must

Table 4
Summary of Changes in Edmonton Symptom Assessment System (ESAS) & Opioid Side Effect Scale from Baseline to Day 30.

Variable	N	Median	IQR	*P*-value
Pain	23	−3	(−4, −2)	**<0.0001**
Fatigue	23	0	(−2, 1)	0.12
Nausea	23	−1	(−2, 0)	**0.045**
Depression	23	−1	(−3, 0)	**0.049**
Anxiety	23	−1	(−3, 0)	**0.0001**
Drowsiness	23	0	(−3, 1)	0.22
Appetite	23	−1	(−3, 0)	0.065
Wellbeing	23	0	(−2, 0)	0.29
Dyspnea	23	0	(−4, 0)	0.15
Sleep	23	−1	(−2, 0)	**0.0081**
ESAS Total Score	23	−10	(−25, −3)	**<0.0001**
Dry Mouth (opioid side effect scale)	23	0	(−2, 1)	0.22
Nausea (opioid side effect scale)	23	−1	(−2, 0)	**0.0045**
Constipation (opioid side effect scale)	23	−1	(−2, 0)	0.053
Drowsiness (opioid side effect scale)	23	−1	(−2, 0)	**0.019**
Confusion (opioid side effect scale)	23	0	(−1, 0)	**0.012**

P-values from Wilcoxon signed rank test for changes within the group.
Bold indicates statistical significance.

consider including drug screens in their design. The majority of the patients in our study had advanced cancer with a PS of 2−3 and a poor prognosis. Long-term benefits and side effects of levorphanol must be studied in patients with better PS and prognosis.

In conclusion, levorphanol effectively managed pain when used as a second-line opioid in cancer patients. An ORR of 8.5 may be used to calculate the levorphanol dose from MEDD. However, our team recommends an ORR of 10 to minimize errors in opioid dose calculations. Further studies on levorphanol are warranted, along with advocacy to make it affordable for patients.

Author contributions

All authors: Study concept and design; All authors: Analysis and interpretation of data; **AR, EB, AH, JA**, and **DH**: Drafting of the manuscript; All authors: Critical revision of the manuscript for important intellectual content; **JW**: Statistical analysis.

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The authors have no competing interests to declare relevant to this article's content.

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