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Symptom Management and Supportive Care

Frequency, Outcome, and Predictors of Success Within 6 Weeks of an Opioid Rotation Among Outpatients with Cancer Receiving Strong Opioids

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Pain • Opioid rotation • Outpatient • Palliative care • Opioid-induced neurotoxicity

Learning Objectives

Determine the frequency, indications, and outcomes of opioid rotation in cancer outpatients.

Describe the predictors of successful opioid rotation.

ABSTRACT

Background. Opioid rotation is used to treat uncontrolled pain and/or opioid-related adverse effects. Our aim was to determine the frequency, indications, outcomes, and predictors of successful opioid rotation in outpatients with cancer.

Methods. Medical records of consecutive outpatients with cancer who received strong opioids and returned for follow-up visit within ≤6 weeks to our supportive care center from January to December 2008 were reviewed. Data on patient characteristics, symptoms, opioid use, indications for opioid rotation, outcomes, and morphine equivalent daily dose were collected. Successful opioid rotation was defined as a two-point or 30% reduction in the symptom score or the resolution of opioid-induced neurotoxicity and continuation of the new opioid at follow-up.

Results. Opioid rotation was performed in 120 of 385 patients (31%). The median patient age was 55 years. There were 6/120 patients with missing data. Of the 114 evaluable patients, 68 (60%) were men, 81 (71%) were white, 27 (24%) had gastrointestinal cancer, and 90 (80%) had advanced-stage disease. The median Eastern Cooperative Oncology Group score was 1 (interquartile range: 1–2) and the median time between opioid rotation and follow-up was 14 days (interquartile range: 7–21 days). The most common indications for opioid rotation were uncontrolled pain (95/114; 83%) and opioid-induced neurotoxicity (13/114; 12%). A total of 35 patients (31%) had partial opioid rotation. The median improvements in pain and symptom distress score were −2 (interquartile range: −4 to 0; $p < .001$) and −5 (interquartile range: −14 to 7; $p = .004$), respectively. The morphine equivalent daily dose did not change significantly after opioid rotation ($p = .156$). A total of 65% of patients (74/114) had successful opioid rotation. There were no clinically significant independent predictors for successful opioid rotation.

Conclusion. Opioid rotation was conducted in 31% of outpatients with cancer, with a 65% success rate. The most frequent reason for opioid rotation was uncontrolled pain. There were no independent predictors for successful opioid rotation. ***The Oncologist*** 2013;18:212–220

Implications for Practice: Opioid rotation (OR) is the replacement of one opioid by another using an equianalgesic dose. The strategy is used to treat uncontrolled pain and intolerable opioid-related side effects like opioid-induced neurotoxicity (OIN). In this study, OR was administered in about one third of cancer outpatients receiving strong opioids. The rate of success with OR was 65%, which parallels findings of previous studies in the inpatient setting. OR was associated with improvements in pain, symptom distress score, depression, well-being, and insomnia in addition to the resolution of symptoms associated with OIN. OR can effectively manage uncontrolled pain and OIN in cancer outpatients. Further prospective studies should aim at determining the predictors of successful OR.

INTRODUCTION

Cancer-related pain affects 80%–90% of patients with advanced cancer [1]. Opioids are the preferred treatment modality for cancer-related pain [2]. However, challenges such as inadequate pain control and suboptimal management of var-

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ious opioid-related side effects still persist. Apart from common side effects like nausea and constipation, opioid-induced neurotoxicity has garnered attention as a significant side effect. Opioid-induced neurotoxicity comprises symptoms such as excessive sedation, delirium, hallucinations, myoclonus, and seizures, which result from the accumulation of the parent opioid and its metabolites [3]. Moreover, opioid tolerance can result in dose escalation and treatment-limiting side effects, and rapid dose escalation and accumulation of opioid metabolites have been linked to poor analgesic response [4]. When performed in a safe and effective manner, opioid rotation, which is defined as substituting one opioid with another using equianalgesic ratios, is recommended for treating uncontrolled pain and intolerable side effects, including opioid-induced neurotoxicity [5–14].

Opioid rotation was originally described in 1995 as a means of reducing toxicity and improving pain control [9]. This intervention was initially met with great resistance because many aspects of opioid-induced neurotoxicity were not well characterized, and a change in the μ-agonist was considered to have limited value [15, 16]. Since then, several publications and consensus conferences have endorsed opioid rotation as a useful method of reducing pain and opioid-induced neurotoxicity [13, 17–20]. Although the reasons for the success of opioid rotation are not fully known, incomplete cross-tolerance between opioids and higher cross-tolerance to adverse effects than to analgesic effects have been proposed [17]. Although opioid rotation is an established treatment modality for cancer-related pain, information regarding opioid rotation in ambulatory patients with cancer presenting to an outpatient supportive care center is limited. Recent studies indicated that patients with cancer have a median of only one or two follow-up visits after an initial consultation in an outpatient supportive care center because of late referrals and issues related to receiving care in a comprehensive cancer center away from home, [21, 22]. Half of the patients with cancer with moderate to severe pain did not achieve adequate analgesia after their initial palliative care consultation in an outpatient supportive care center [23]. These findings highlight the importance of controlling cancer-related pain in a short period of time, during which opioid rotation is an important tool. Previous studies have shown clinical improvement in 50%–84% of patients with cancer who are undergoing opioid rotation [12, 13, 18–20, 24].

The purpose of our study was to determine the frequency, indications, outcomes, and predictors of successful opioid rotation in consecutive patients with cancer receiving strong opioids who presented to our outpatient supportive care center. Our findings could provide preliminary data for future prospective studies aimed at effectively managing cancer-related pain.

Methods

Patient Eligibility

This study was approved by the Institutional Review Board at the University of Texas MD Anderson Cancer Center, which waived the requirement of informed patient consent. Consecutive electronic medical records of patients who visited our outpatient supportive care center from January 1, 2008, until December 31, 2008, were reviewed retrospectively to determine whether they received strong opioids and attended a follow-up visit within a 6-week period. To adequately evaluate the success of opioid rotation, the follow-up period was limited to 6 weeks to avoid attrition and account for possible changes in pain mechanism due to disease progression. These patient visits were then screened for opioid rotation as outlined in Figure 1.

Patient Assessment

The following information was obtained for each patient: demographics; Eastern Cooperative Oncology Group (ECOG) performance status; scores on the Edmonton Symptom Assessment Scale (ESAS) [25] Symptom Distress Scale (SDS), Memorial Delirium Assessment Scale (MDAS) [26], and Cut-down, Annoyed, Guilty, Eye-opener (CAGE) [27] questionnaire; pain characteristics (nociceptive, neuropathic, or both); tobacco and illicit substance use; constipation; opioid use; morphine equivalent daily dose; indications for opioid rotation; counseling; delirium; and opioid-induced neurotoxicity.

The interdisciplinary care provided to the patients in our outpatient supportive care center was previously described [28]. Briefly, the center provides care daily via an interdisciplinary approach led by one of our board-certified palliative care physicians. The other members of our team include palliative care-certified nurses, a social worker, a counselor, a chaplain, a clinical pharmacy specialist, and a nutritionist. A standardized model of care is practiced [29]. Patients and their family members are initially assessed by the registered nurses trained in palliative care using validated tools such as the ESAS, MDAS, and CAGE questionnaire. Other members of our interdisciplinary team are then consulted according to the needs of the patient and his or her family members. Assessments and management of cancer-related symptoms along with counseling, discussions about the goals of care, and assistance with decision making and coping are provided by the interdisciplinary team.

Morphine, hydromorphone, oxycodone, methadone, oxymorphone, and fentanyl were defined as strong opioids. The morphine equivalent daily dose is the total dose of opioids administered in 24 hours converted to an equivalent dose of oral morphine. The morphine equivalent daily dose was calculated using the standard conversion ratios [29] and a conversion factor of 5 was used for methadone [30].

The ESAS was used to assess 10 symptoms that are common in patients with cancer during the 24 hours preceding its administration: pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, insomnia, and well-being. The severity of each symptom is rated from 0 to 10 on a numerical scale (0 = absence of that symptom; 10 = worst possible severity of that symptom). The instrument is both valid and reliable for assessing the intensity of symptoms in patients with cancer [25, 31]. The SDS score is a composite score (sum) of all the symptoms in the ESAS except insomnia (i.e., nine symptoms scored from 0 to10 on a numerical scale).

The MDAS was used to measure the presence and severity of delirium. A score of $\geq$7/30 has been recommended as a cut-off for establishing a diagnosis of delirium [26]. The CAGE score was used to screen for alcoholism. The threshold varies according to sex. On a 4-point scale, a score of $\geq$2 is considered positive for men, whereas a score of $\geq$1 is considered positive for women [27]. Symptoms such as excessive sedation, confusion (delirium), hallucinations, and myoclonus

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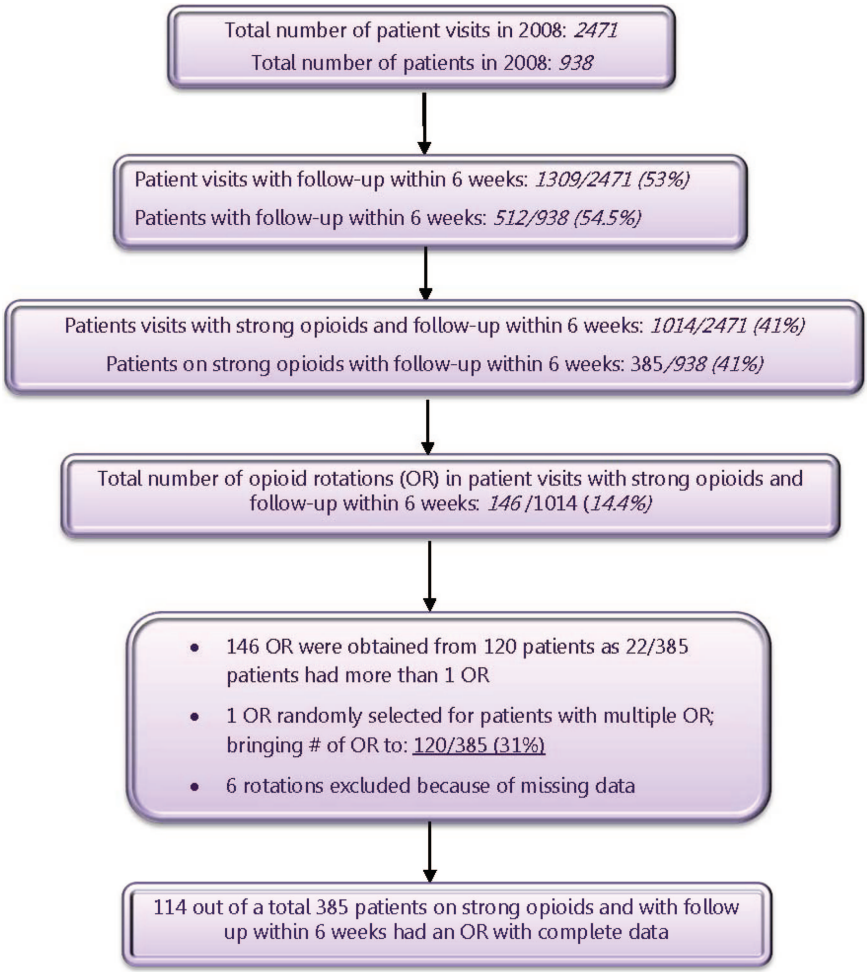

Figure 1. Data collection flow chart of patients seen in the outpatient supportive care center in 2008.
Abbreviation: OR, opioid rotation.

were recorded and defined as opioid-induced neurotoxicity [17].

Successful complete opioid rotation was defined as either

1. Evidence of resolution/improvement of side effects at the first follow-up visit for cases in which the reason for opioid rotation was side effects of the previous opioid (e.g., a 2-point reduction in nausea at the follow-up visit was considered a successful opioid rotation if the reason for opioid rotation was nausea); or
2. Improvement in pain defined as a 30% or 2-point reduction in the ESAS pain score [32] if uncontrolled pain prompted opioid rotation and continued use of the new opioid at the follow-up visit.

Successful partial opioid rotation was defined as the continuation of at least one of the previous opioids with criteria 1 and 2 for complete opioid rotation. For example, a patient treated with fentanyl and hydromorphone as needed for breakthrough pain was switched to methadone as a long-acting opioid, and hydromorphone was retained as a short-acting opioid.

Statistical Analysis

Descriptive analyses were carried out on patient characteristics. Medians and ranges were used to summarize continuous demographic and clinical characteristics such as age and ESAS, SDS, MDAS, and morphine equivalent daily dose scores. Counts and proportions of categorical demographic and patient characteristics, characteristics of pain, delirium, reason for opioid rotation, opioid rotation type, visit type (i.e., follow-up vs. consult) and morphine equivalent daily dose category were calculated. To determine the factors associated with opioid rotation success, we applied univariate logistic regression models to individual baseline factors such as sex; race; disease type; cancer type; ECOG performance status; constipation; characteristics of pain; delirium, reason for opioid rotation; opioid rotation type; visit type; and ESAS; MDAS; SDS, and CAGE scores; and morphine equivalent daily dose.

Odds ratios, associated 95% confidence intervals (CIs), and *p* values are reported. Univariate logistic regression models were used to predict opioid rotation success using the paired difference in ESAS, MDAS, and SDS scores and morphine equivalent daily dose between the baseline and follow-up measurements. The baseline morphine equivalent daily dose was analyzed via Kruskal-Wallis one-way analysis of variance on categorical factors. Spearman correlation coefficients were used to determine the associations between the baseline morphine equivalent daily dose and ESAS scores. Wilcoxon signed rank tests were carried out on the paired difference in ESAS, MDAS, and SDS scores and morphine equivalent daily dose between baseline and follow-up visits. To correct for multiple comparisons to determine the associa-

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tion of baseline morphine equivalent daily dose with patient characteristics, opioid rotation success with baseline patient characteristics and opioid rotation success with changes of symptoms, morphine equivalent daily dose and opioid rotation success or opioid rotation failure, we used Bonferroni correction. A p value of $< .05$ was considered statistically significant. All statistical analyses were done using R: A Language and Environment for Statistical Computing (R-2.13.0; R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 1,014 of 2,471 consecutive patient visits with a 6-week follow-up period (41%) or 385 of 938 patients (41%) included a strong opioid prescription. In all, 146 of 1,014 patient visits had an opioid rotation (14%; Fig. 1).

During the evaluation period, 22 of 385 (6%) patients had more than one opioid rotation. In these cases, one opioid rotation was randomly sampled for each patient, so the number was reduced to 120 opioid rotations in 385 patients (31%). Six opioid rotations were excluded because significant information, such as the baseline or follow-up morphine equivalent daily dose score, was unavailable. Therefore, 114 opioid rotations were available for analysis.

Patient characteristics are summarized in Table 1. The median age was 55 years. In all, 60% (68/114) were men, 71% (81/114) were white, 24% (27/114) had gastrointestinal cancers, 79% (90/114) had advanced cancer, 12% had history of drug abuse, 58% were smokers or ex-smokers, and 18% (20/114) had a CAGE score of >0. The median ECOG score was 1 (interquartile range: 1–2). The median time between opioid rotation and follow-up was 14 days (interquartile range: 7–21 days). Of the 114 patients evaluated, 57 (50%) had nociceptive pain, 12 (11%) had neuropathic pain, and 27 (24%) had both. Uncontrolled pain, experienced by 95 (83%) patients, was the most common indication for opioid rotation, followed by opioid-induced neurotoxicity, which was experienced by 13 (12%) patients. Other reasons for opioid rotation were nausea (2 patients), itching (1 patient), renal failure (1 patient), and dysphagia (1 patient). Opioid rotation was initiated for more than one reason in 27 of 114 (24%) patients for whom a clearly identified reason in the patient's medical record was recorded as the primary reason for opioid rotation; 35 (31%) underwent a partial opioid rotation. A total of 44% (50/114) were consultation visits, with the remainder being follow-up visits. The most common opioid prior to opioid rotation was fentanyl (42%), and the most common opioid after opioid rotation was methadone (57%).

We observed no statistically significant differences in baseline morphine equivalent daily dose on the basis of patient characteristics. The baseline morphine equivalent daily dose was significantly associated with cancer type ($p = .009$). Patients with sarcoma or breast cancer had the highest morphine equivalent daily dose (Table 2).

Table 3 shows the univariate association between factors measured at baseline and the success of opioid rotation. There were no clinically significant independent predictors for successful opioid rotation. Of the 114 patients who had opioid rotation and a follow-up visit within 6 weeks, 74 (65%) had a successful opioid rotation. The success of opioid rotation was not significantly different between non-Hispanic whites and patients of other races ($p = .539$).

Table 1. Patient characteristics

Characteristic	*n* (%)
Age, years[a]	55 (48–61)
Sex	
Female	46 (40)
Male	68 (60)
Race	
Asian	6 (5)
Black	14 (12)
Hispanic	12 (11)
White	81 (71)
Other	1 (1)
Advanced disease	
No	24 (21)
Yes	90 (79)
Cancer type	
Breast	10 (9)
Gastrointestinal	27 (24)
Genitourinary	7 (6)
Gynecologic	9 (8)
Head and neck	16 (14)
Lung	24 (21)
Sarcoma	10 (9)
Other	11 (10)
History of drug abuse	
No	84 (88)
Yes	11 (12)
Smoking status	
Current smoker	18 (16)
Ex-smoker	48 (42)
Nonsmoker	48 (42)
CAGE score	
0	94 (82)
1–4	20 (18)

[a]Data are median (interquartile range).
Abbreviation: CAGE, Cut-down, Annoyed, Guilty, Eye-opener questionnaire.

Compared with the baseline scores, the scores for pain ($p < .001$), well-being ($p = .010$), insomnia ($p = .013$), depression ($p = .040$), and SDS ($p = .004$) were significantly improved at follow-up (Table 4). However, the morphine equivalent daily dose did not significantly change from baseline to follow-up ($p = .157$).

The median change in the morphine equivalent daily dose in patients who underwent opioid rotation for opioid-induced neurotoxicity was -45 (-100 to 0), which was significantly different than the change of 17.5 (-40 to 90) in patients who underwent opioid rotation for uncontrolled pain ($p = .005$).

Compared with patients with unsuccessful opioid rotation, patients with successful opioid rotation had significant improvements in ESAS scores for pain ($p = .0014$), well-being

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Table 2. Association of baseline morphine equivalent daily dose with patient characteristics

Patient characteristic	Median baseline MEDD (interquartile range)	*p* value	*p* value (Bonferroni correction)
Sex		.819	>.2
Female	150 (65–348)		
Male	150 (98–224)		
Race		.971	>.2
Asian	170 (98–198)		
Black	165 (98–219)		
Hispanic	155 (94–309)		
White	150 (80–260)		
Other	125 (125–125)		
Cancer type		.001	.009
Breast	270 (144–424)		
Gastrointestinal	165 (120–243)		
Genitourinary	120 (57–120)		
Gynecologic	60 (50–75)		
Head and neck	187 (95–244)		
Lung	105 (72–196)		
Sarcoma	285 (174–393)		
Other	150 (105–214)		
Advanced disease		.746	>.2
No	176 (79–287)		
Yes	150 (90–224)		
Drug abuse history		.242	>.2
No	150 (80–238)		
Yes	160 (123–356)		
Smoking status		.692	>.2
Current smoker	123 (76–258)		
Ex-smoker	163 (90–263)		
Nonsmoker	150 (90–206)		
ECOG performance status		.243	>.2
0	128 (86–244)		
1	180 (105–335)		
2	135 (80–200)		
3–4	105 (79–231)		
CAGE score		.276	>.2
0	150 (80–233)		
1–4	150 (104–340)		
Constipation		.023	>.2
No	123 (75–200)		
Yes	180 (120–321)		

Data were calculated using the Kruskal-Wallis test of baseline MEDD on patient characteristics.
Abbreviations: CAGE, Cut-down, Annoyed, Guilty, Eye-opener questionnaire; ECOG, Eastern Cooperative Oncology Group; MEDD, morphine equivalent daily dose.

($p = .0014$), and sleep ($p = .0014$), as well as MDAS ($p = .042$) and SDS ($p = .0014$) scores (Table 5).

Discussion

In this study of consecutive patients with cancer who presented to our outpatient supportive care center, we found that 31% required an opioid rotation; the success rate was 65%. Opioid rotation was associated with significant improvements in pain, SDS, depression, well-being, and insomnia scores, as well as opioid-induced neurotoxicity. There were no clinically significant independent predictors for successful opioid rotation.

Compared with the patients who had unsuccessful opioid rotation, patients who had successful opioid rotation (65%) had significant improvements in well-being and significant reductions in pain and insomnia according to their ESAS scores and reductions in their SDS scores. Our findings that pain and SDS scores were significantly reduced confirm previous reports of inpatient studies regarding pain and overall symptom distress reduction when opioid rotation was administered [12, 19]. The association between the reduction in pain and improvements in depression, well-being and insomnia could be attributed to a general improvement in pain intensity, a reduction of side effects of the previous opioid, or the success of a palliative care intervention that also included nonpharmacologic interventions, such as counseling.

As previously reported [33], uncontrolled pain is more frequently the reason for opioid rotation in an outpatient setting; in contrast, opioid-induced neurotoxicity is the reason in the inpatient setting. This difference again probably reflects the fact that terminal delirium, infections, dehydration, and other such causes of delirium are more commonly seen in the inpatient setting where patients are more debilitated and deconditioned. Future research should identify patients with poor prognosis for opioid rotation who more likely to benefit from inpatient management than from an outpatient rotation, as well as patients with very good prognosis who should undergo early opioid rotation supported by their own oncologist or internist.

In our study, a patient visit with a palliative care specialist resulted in a frequent (31%) need to administer opioid rotation for pain and opioid-induced neurotoxicity. In a recent study, 33% of patients treated at an outpatient oncology facility received inadequate analgesia and had no improvement in pain control, even at subsequent visits [34]. These findings suggest that opioid rotation is underutilized by medical oncologists. Increased education regarding cautious approaches to opioid rotation among colleagues in fields such as oncology, palliative medicine, pain management, internal medicine, and family practice might facilitate better pain control and at the same time prevent adverse outcomes associated with opioid rotation, as outlined in recent publications [35, 36].

As reported in previous studies [19], transdermal fentanyl was used more commonly than morphine prior to opioid rotation, and methadone was the most common opioid used for opioid rotation in our study. Previous studies have shown that rotation to methadone was 84% successful in the outpatient setting [24] and 77% successful in the inpatient setting [37], and pain improvement was long lasting [38]. The high usage of transdermal fentanyl for pain control reflects the familiarity of oncologists with this medication, perhaps as an initial opioid of choice for uncontrolled pain prior to referral to supportive care. This finding is similar to the prescription pattern observed in Italy, where fentanyl was used as the first-choice strong opioid, even in the titration phase for uncontrolled pain [39].

Previous studies have shown that pain was significantly undertreated in minority groups in an outpatient oncology facility [34, 40]. We found no significant difference in the success of opioid rotation between non-Hispanic whites and patients of other

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Table 3. Univariate logistic regression of baseline factors predicting opioid rotation success

Factors	Opioid rotation, successful/total (%)	Odds ratio	95% confidence interval	Univariate *p* value	Univariate *p* value (Bonferroni correction)
Sex				.458	>.2
Female	28/46 (61)	1			
Male	46/68 (68)	1.34	0.62–2.93	.457	>.2
Race				.159	>.2
Asian	5/6 (83)	1			
Black	6/14 (43)	0.15	0.01–1.64	.12	>.2
Hispanic	9/12 (75)	0.6	0.05–7.41	.69	>.2
White	54/81 (67)	0.4	0.04–3.60	.414	>.2
Other	0/1 (0)			.991	>.2
Advanced disease				.839	>.2
No	16/24 (67)	1			
Yes	58/90 (64)	0.91	0.35–2.35	.839	>.2
Cancer type				.76	>.2
Breast	7/10 (70)	1			
Gastrointestinal	16/27 (59)	0.62	0.13–2.95	.551	>.2
Genitourinary	4/7 (57)	0.57	0.08–4.30	.587	>.2
Gynecologic	7/9 (78)	1.5	0.19–11.93	.702	>.2
Head and neck	12/16 (75)	1.29	0.22–7.50	.78	>.2
Lung	14/24 (58)	0.6	0.12–2.91	.526	>.2
Other	6/11 (55)	0.51	0.09–3.11	.469	>.2
Sarcoma	8/10 (80)	1.71	0.22–13.41	.608	>.2
History of drug abuse				.842	>.2
No	56/84 (67)	1			
Yes	7/11 (64)	0.88	0.24–3.24	.842	>.2
Smoking status				.123	>.2
Current smoker	13/18 (72)	1			
Ex-smoker	35/48 (73)	1.04	0.31–3.48	.955	>.2
Nonsmoker	26/48 (54)	0.45	0.14–1.48	.189	>.2
ECOG performance status				.092	>.2
0	3/6 (50)	1			
1	37/49 (76)	3.08	0.55–17.35	.201	>.2
2	19/30 (63)	1.73	0.30–10.08	.544	>.2
3–4	9/20 (45)	0.82	0.13–5.08	.83	>.2
CAGE score				.596	>.2
0	60/94 (64)	1			
1–4	14/20 (70)	1.32	0.47–3.76	.6	>.2
Constipation				.637	>.2
No	47/70 (67)	1			
Yes	27/43 (63)	0.83	0.37–1.83	.637	>.2
Pain characteristics				.311	>.2
Mixed	16/27 (59)	1			
Neuropathic	10/12 (83)	3.44	0.63–18.84	.155	>.2
Nociceptive	38/57 (67)	1.38	0.53–3.54	.509	>.2
Reason for opioid rotation				.002*	*.052**
Uncontrolled pain	57/95 (60)	1			
OIN	13/13 (100)			.988	>.2
Other	4/5 (80)	2.67	0.29–24.79	.389	>.2

(*continued*)

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Table 3. (Continued)

Factors	Opioid rotation, successful/total (%)	Odds ratio	95% confidence interval	Univariate *p* value	Univariate *p* value (Bonferroni correction)
Opioid rotation				.76	>.2
Full	52/79 (66)	1			
Partial	22/35 (63)	0.88	0.38–2.01	.76	>.2
Counseling				.463	>.2
No	15/21 (71)	1			
Yes	58/92 (63)	0.68	0.24–1.92	.47	>.2
Baseline MEDD				.615	>.2
High (>60)	62/94 (66)	1			
Low (≤60)	12/20 (60)	0.77	0.29–2.09	.613	>.2
Pain		0.99	0.84–1.17	.899	>.2
Fatigue		0.96	0.82–1.13	.662	>.2
Nausea		1.07	0.93–1.24	.318	>.2
Drowsiness		1.01	0.87–1.16	.938	>.2
Anxiety		1.02	0.90–1.16	.779	>.2
Well-being		0.97	0.84–1.12	.684	>.2
Dyspnea		0.99	0.87–1.13	.857	>.2
Sleep		0.89	0.77–1.03	.122	>.2
Depression		0.92	0.80–1.06	.242	>.2
Appetite		0.92	0.80–1.06	.257	>.2
MDAS		0.98	0.79–1.22	.876	>.2
SDS		1	0.97–1.02	.726	>.2

Abbreviations: CAGE, Cut-down, Annoyed, Guilty, Eye-opener questionnaire; ECOG, Eastern Cooperative Oncology Group; MEDD, morphine equivalent daily dose; MDAS, Memorial Delirium Assessment Scale; OIN, opioid-induced neurotoxicity; SDS, Symptom Distress Score.

Table 4. Changes in patient characteristics from baseline to follow-up

Variable	Change from follow-up to baseline, median (interquartile range)	*p* value
Pain	−2 (−4 to 0)	**<.001**
Fatigue	0 (−2 to 2)	.124
Nausea	0 (−2 to 1)	.464
Drowsiness	0 (−2 to 1)	.238
Anxiety	0 (−2 to 1)	.161
Well-being	0 (−3 to 1)	**.010**
Dyspnea	0 (−2 to 1)	.865
Sleep	0 (−3 to 1)	**.013**
Depression	0 (−2 to 1)	**.040**
Appetite	0 (−3 to 2)	.804
MDAS	0 (−1 to 2)	.070
SDS	−5 (−14 to 7)	**.004**
MEDD	10 (−45 to 79)	.157

All *p* values were calculated using Wilcoxon signed-rank test on paired numeric variables at baseline and follow-up. Bold values indicate statistical significance.
Abbreviations: MEDD, morphine equivalent daily dose; MDAS, Memorial Delirium Assessment Scale; SDS, Symptom Distress Score.

races in our study. This finding suggests that cancer pain in minorities is underdiagnosed rather than undertreated.

In this study, we also explored partial opioid rotation, which was 63% successful. Partial opioid rotation is very common in outpatient practice, as medications such as transdermal fentanyl and methadone are usually combined with another short-acting opioid for breakthrough pain. However, future prospective studies are needed to determine the efficacy of partial opioid rotation versus complete opioid rotation.

This study is the first to our knowledge to focus on opioid rotation in outpatients with cancer presenting to a supportive care center while still receiving active antineoplastic treatment. Another novelty of this study is that it focuses on ambulatory cancer patients (with a median ECOG score of 1). Previous studies have included only inpatients with a median ECOG score of 3 and those admitted to an acute palliative care unit for end-of-life care or transition to hospice [19]. Unlike previous studies, in which inpatients were assessed frequently by nurses and physicians and were given opioid titrations along with psychosocial and spiritual support, our patient population underwent opioid rotation and continued taking the new opioids unmonitored at home until follow-up, although 35 of 114 patients (31%) communicated at least once by phone with the supportive care nurse after opioid rotation. In addition, the patients in our study were administered opioids via only the oral and transdermal routes, unlike those in inpatient studies that employ predominantly parenteral opioid administration. Our findings suggest that the safety and success of opioid rotation in the outpatient setting are comparable to the safety and success of opioid rotation in the inpa-

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Table 5. Changes in symptoms, MEDD, and performance status according to success or failure of opioid rotation

	Opioid rotation[a]				*p* value[b]	
Variable	Failure	Success	Odds ratio	95% confidence interval	Univariate	Bonferroni correction
Pain	0 (−1 to 1)	−3 (−4 to −2)	0.54	0.43–0.68	**<.001**	**<.0014**
Fatigue	0 (−1 to 2)	−1 (−3 to 1)	0.78	0.66–0.92	**.004**	.056
Nausea	0 (0–2)	0 (−2 to 1)	0.99	0.86–1.14	.857	>.2
Drowsiness	1 (−1 to 1)	−1 (−3 to 1)	0.85	0.74–0.98	**.023**	>.2
Anxiety	0 (−1 to 2)	−1 (−7 to 0)	0.8	0.69–0.94	**.005**	.07
Wellbeing	0 (−2 to 3)	−1 (−4 to 1)	0.73	0.62–0.87	**<.001**	**<.0014**
Dyspnea	0 (−1 to 2)	0 (−2 to 1)	0.88	0.77–1.00	**.056**	>.2
Sleep	0 (−1 to 2)	−1 (−3 to 1)	0.75	0.64–0.88	**<.001**	**<.0014**
Depression	0 (−1 to 1)	−1 (−2 to 0)	0.82	0.70–0.95	**.007**	.098
Appetite	0 (−3 to 2)	0 (−2 to 2)	0.91	0.80–1.05	.188	>.2
MDAS	1 (0–3)	0 (−1 to 1)	0.72	0.58–0.89	**.003**	**.042**
SDS	4 (−6 to 11)	−10 (−17 to 0)	0.85	0.92–0.98	**<.001**	**<.0014**
MEDD	30 (−11 to 90)	−6 (−69 to 74)	1	0.99–1.00	**.04**	>.2
ECOG performance status	0 (0–1)	0 (0–1)	0.94	0.62–1.43	.783	>.2

[a]Data are median paired difference (interquartile range).
[b]Data are logistic regression of paired patient characteristics between baseline and follow-up predicting success of opioid rotation. Bold values indicate statistical significance.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; MEDD, morphine equivalent daily dose; MDAS, Memorial Delirium Assessment Scale; SDS, Symptom Distress Score.

tient setting. Another positive aspect of this study was that the sample was obtained from a single institution cohort in which all patients underwent consistent assessment and management by board-certified palliative care specialists following a standardized protocol [29]. Our study also had several limitations. It was a retrospective study of prospectively collected data and, unlike other studies [24, 41], we included data from only one follow-up visit.

In the hands of palliative care specialists, 35% of the patients did not achieve successful opioid rotation. Our data are consistent with other studies that have shown a success rate of at least 50% for opioid rotation [9, 11–13, 19, 37, 42]. This implies that opioid rotation is not a simple intervention. Future prospective studies are needed to develop effective strategies for successful opioid rotation. Future studies should determine the success of opioid rotation after two or more follow-up visits and should focus on prospectively identifying the predictors of a successful opioid rotation in the outpatient setting. The role of opioid titration and aggressive management of side effects via regular telephone calls to the patient after opioid rotation should also be studied.

We conclude that opioid rotation was conducted in 31% of outpatients with cancer, with a 65% success rate. The most frequent reason for opioid rotation was uncontrolled pain. There were no independent predictors for successful opioid rotation.

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Disclosures

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