JAMA Oncology | Original Investigation

Global Variation in Opioid Use in Prostate Cancer Trials

Jessica K. Roydhouse, PhD; Daniel L. Suzman, MD; Laurel A. Menapace, MD; Pallavi S. Mishra-Kalyani, PhD; Rajeshwari Sridhara, PhD; Gideon M. Blumenthal, MD; Julia A. Beaver, MD; Richard Pazdur, MD; Paul G. Kluetz, MD

IMPORTANCE Regional variation in opioid use may be attenuated when pharmaceutical-sponsored trials include care that is often standardized by protocols. Understanding such variation is important for global trials that sometimes include time to opioid use as an end point.

OBJECTIVE To identify whether regional and country-level variation in opioid use exists among prostate cancer clinical trials across the world.

DESIGN, SETTING, AND PARTICIPANTS International phase 3 randomized clinical trials with patients with metastatic prostate cancer and initiation from January 1, 2008, or later were identified through internal databases of the US Food and Drug Administration. Data of patients in the intention-to-treat population from each trial were pooled. Descriptive and regression analyses of the collected data were conducted from September 2018 to February 2019.

EXPOSURES Cancer therapy.

MAIN OUTCOMES AND MEASURES Opioid use data were from concomitant medications reported in the database for each trial. Logistic regression models, descriptive statistics, and χ^2 tests were used to compare opioid use across world regions while adjusting for patient age, presence of visceral disease, bony disease, and baseline Eastern Cooperative Oncology Group Performance Status score and pain score.

RESULTS In total, 9670 patients (mean [SD] age of 69.2 [8.3] years) from 8 prostate cancer clinical trials in 46 countries were included. Patients in Eastern Europe (adjusted odds ratio [AOR], 0.19; 95% CI, 0.16-0.22) and Asia (AOR, 0.31; 95% CI, 0.25-0.38) were less likely to use opioids compared with patients in North America. These findings held even when the analysis was restricted to patients who reported moderate to high pain levels at baseline (Eastern Europe: AOR, 0.16 [95% CI, 0.12-0.22]; Asia: AOR, 0.47 [95% CI, 0.29-0.79]). Within North America, rates of opioid use were similar between the United States and Canada (AOR, 1.13; 95% CI, 0.93-1.37).

CONCLUSIONS AND RELEVANCE This study found that, despite the clinical trial setting, opioid use appeared to vary by world regions, suggesting that this variability should be considered in international clinical trials.

JAMA Oncol. 2019;5(11):e192971. doi:10.1001/jamaoncol.2019.2971
Published online September 12, 2019.

Supplemental content

Author Affiliations: Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland (Roydhouse, Suzman, Menapace, Beaver); Office of Biostatistics, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland (Mishra-Kalyani, Sridhara); Oncology Center of Excellence, Food and Drug Administration, Silver Spring, Maryland (Blumenthal, Pazdur, Kluetz).

Corresponding Author: Jessica K. Roydhouse, PhD, Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, MD 20993 (jessica.roydhouse@fda.hhs.gov).

Pain is a common symptom in cancer, particularly when disease has metastasized to the bone.[1] Undertreatment of cancer pain has been described in previous studies,[2,3] and access to opioid analgesics varies around the world,[4-10] with poorer access reported in lower- and middle-income countries.[11,12]

Only a small proportion of patients with cancer participate in clinical trials,[13] and patients in these trials often differ from the general patient population both sociodemographically[14-16] and clinically.[17,18] Furthermore, in industry-sponsored trials of products seeking regulatory approval, some aspects of care may be standardized by protocols. Thus, to our knowledge, whether previously documented variability in opioid analgesic use in clinical practice also occurs in the clinical trial setting is unknown. This variability is an important consideration because opioid use is associated with adverse effects, and delay of opioid initiation can be a trial end point, particularly in prostate cancer.[19,20] Given that industry-sponsored trials are often global, understanding the variations in opioid use among patients with cancer enrolled in clinical trials is important.

Key Points

Question Do regional variations in opioid use exist in a controlled clinical trial setting?

Findings In this study of 8 randomized clinical trials for prostate cancer conducted in 46 countries involving 9670 participants, fewer patients in Eastern Europe and Asia received opioids compared with patients in North America, a pattern that persisted even after adjustment for clinical and sociodemographic characteristics. Within North America, opioid use was similar between the United States and Canada.

Meaning This study suggests that global variability in opioid use should be considered in international clinical trials using delay in opioid initiation as a trial end point.

Methods

Data were acquired from 8 phase 3 randomized clinical trials with initiation from January 1, 2008, or later that provided primary or postmarketing confirmatory support for new metastatic prostate cancer indications. The internal databases of the US Food and Drug Administration (FDA) were used to identify the trials. The FDA Oncology Center of Excellence approved the conduct of this retrospective review of clinical trial data housed in the FDA clinical trial repository. The FDA project lead and/or the Center for Drug Evaluation and Research Human Subject Protection liaison to the FDA institutional review board determined that this study was consistent with a "not human subject research" designation and thus did not require institutional review board approval.

Participants

Primary analyses of patients in the intention-to-treat population were conducted. Patient data were pooled across trials. Patient eligibility varied across the trials, but trial criteria consistently excluded patients with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) scores (range: 0 [no restrictions on activity] to 5 [dead]) above 2 or with known brain metastases. Trials also excluded patients with major laboratory result abnormalities, previous malignant neoplasms other than nonmelanoma skin cancer within the past 5 years, and severe cardiovascular disease. Inclusion or exclusion criteria for baseline pain scores, the presence of bone metastases, and the use or nonuse of previous or concurrent therapies varied depending on trial objectives. Noninvestigational arms also varied across the trials, although all contained a backbone of androgen deprivation therapy. These arms included placebo and supportive therapies (n = 6), which generally included corticosteroids, and active agents that had previously been demonstrated to prolong overall survival (n = 2).

Overall survival was a primary end point for all trials, although some trials also included radiographic progression-free survival as a co-primary end point. Secondary end points varied by trial, although all trials evaluated time to prostate-specific antigen progression. Opioid use was a secondary end point for 3 trials either on its own or as part of a composite end point evaluating pain. Stratification factors for randomization likewise varied by trial, with 3 trials stratified by region and/or study site.

Several subpopulations were also considered in this analysis. The first subgroup analysis included only patients with a higher tumor burden, as determined by the extent of bony disease. This information was available from 5 trials. High tumor burden was defined as 6 or more bone lesions. This threshold is supported by previous studies that have identified improved survival for patients with fewer than 6 lesions.[21,22]

In addition, subgroup analyses were conducted that compared patients with more advanced disease (enrolled in later-line postchemotherapy trials) with patients with less advanced disease and those with moderate to high levels of pain at baseline.

Outcomes

The outcome of interest was the use of opioids at any point before, during, or after the trial. In a sensitivity analysis, the outcome of interest was limited to opioid use during the trial. Data on opioid use were captured through the concomitant medication data sets submitted to the FDA. Drugs in these data sets are categorized using the World Health Organization Anatomical Therapeutic Chemical (ATC) Classification System. Opioids were identified as all medications with the ATC codes N02A (opioids), N01AH (opioid anesthetics), and R05DA (opium alkaloids and derivatives). Observations with prophylactic and/or procedural indications (ie, colonoscopy) were excluded. Exclusion decisions were reviewed by one of us (L.A.M.). All other instances of opioid use were retained, even when an indication specific to cancer pain was not provided. Long-term use was not considered in this analysis; if a patient was recorded as having used opioids at least 1 time, this was defined as opioid use.

Statistical Analysis

Global and regional variations in opioid use were defined with descriptive statistics, χ^2 tests, and binary logistic regression models. In this exploratory study, no adjustment was made for multiple statistical testing. The primary logistic regression model for geographic region as the independent variable was

adjusted for bony disease (yes or no), baseline ECOG PS score, patient age, baseline pain level (unknown or missing, less than moderate pain, or moderate to high pain), and presence of visceral disease (yes or no). Differences in opioid use for each comparison are described using adjusted odds ratios (AORs). Because the instruments for evaluating pain varied across the trials, existing categorizations were used when available. If categorizations were not available, the higher end of the score range was considered moderate to high.

Countries were classified as high income or not high income according to the World Bank definition,[23] and the difference in opioid use was evaluated on the basis of country income level. A subgroup analysis adjusting for the extent of bony disease (≥6 vs <6 lesions) was conducted in the 5 trials for which this information was available. In a sensitivity analysis, a threshold of 10 lesions was also considered, following the approach taken in a clinical trial.[24] The primary model was rerun with on-trial (rather than any) opioid use as the dependent variable as well as in the pooled safety population (at least 1 dose of drug) rather than the intention-to-treat population (with any and with on-trial opioid use).

For descriptive country-level analyses, countries with at least 50 patients were included. All analyses were conducted in R Studio, version 1.1.423 (R Foundation for Statistical Computing). Descriptive and regression analyses of the collected data were conducted from September 2018 to February 2019.

Results

Patients

The combined total of the intention-to-treat population from the 8 trials was 9687 patients. Patients who had protocol violation or unknown ECOG PS scores (n = 5) or who lacked information about bone involvement (n = 12) were excluded. The analysis population consisted of 9670 patients (mean [SD] age of 69.2 [8.3] years) from 46 countries. The advanced disease trials comprised 4502 patients (46.6%), and 2353 patients (24.3%) had moderate to high levels of pain at baseline. Nearly all patients (8786 [90.9%]) had bony disease, and most (9115 [94.3%]) had ECOG PS scores of 0 or 1.

Most patients (8367 [86.5%]) resided in high-income countries. Recruitment was global, with just 2353 (24.3%) of patients from North America (1661 [17.2%] from the United States) (eTable in the Supplement). Patient characteristics were broadly similar across the primary analysis population and the subpopulations of interest. Higher (worse) ECOG PS scores and opioid use were more common in patients with moderate to high levels of pain at baseline (**Table 1**). The percentage of patients with moderate to high pain at baseline was greatest in the Middle East and Africa at 34.6% and Eastern Europe at 32.9% and was lowest in Asia at 17.6% (**Table 2**).

Outcomes

Unadjusted Comparison of Opioid Use

More than half of the analysis population used opioids (4983 [51.5%]), and 4877 patients (50.4%) used opioids while on trial. Opioid use was less common in Asia (174 of 528 [33.0%]) and Eastern Europe (367 of 1196 [30.7%]) compared with North America (1391 of 2353 [59.1%]), Oceania (451 of 834 [54.1%]), and Western Europe (2321 of 4140 [56.1%]). Across all regions, opioid use was more common in patients with high tumor burden and more advanced disease (**Table 3**).

Variation in opioid use was seen across countries within a region (**Table 4**). In Asia and Eastern Europe, a higher percentage of patients from high-income countries used opioids compared with those from not-high-income countries. However, variations were also seen across high-income countries within a region. For example, in Asia, opioid use was higher in Korea (85 of 167 patients [50.9%]) than Japan (35 of 149 patients [23.5%]). In Western Europe, rates of use ranged from 36.4% (20 of 55 patients) in Austria to 83.2% (114 of 137 patients) in Norway, with approximately 40% to 60% of patients in most Western European countries using opioids (median of approximately 50%). Opioid use in the United States and Canada was similar (989 of 1661 patients [59.5%] vs 402 of 692 patients [58.1%]).

Adjusted Comparison of Opioid Use

After adjustment for bone involvement, visceral disease, baseline ECOG PS and pain categories, and age, patients in Asia (AOR, 0.31; 95% CI, 0.25-0.38) and Eastern Europe (AOR, 0.19; 95% CI, 0.16-0.22) remained less likely to use opioids compared with patients in North America (**Table 5**). Similar results were found when the dependent variable was on-trial use rather than any opioid use. When the variation in North America specifically was examined, no substantial difference was found between the United States and Canada after adjustment for clinical and demographic characteristics (AOR, 1.13; 95% CI, 0.93-1.37). Patients in high-income countries were more likely to use opioids compared with those in not-high-income countries (AOR, 5.29; 95% CI, 4.59-6.10).

With adjustment for the extent of bony disease rather than presence or absence of bone involvement, the findings were similar for both Asia (AOR, 0.24; 95% CI, 0.18-0.30) and Eastern Europe (AOR, 0.15; 95% CI, 0.12-0.19). Defining high disease burden as at least 10 lesions rather than at least 6 lesions did not change the findings. When the analysis was restricted to patients with at least 6 bone lesions, the results were not substantially changed for Asia (AOR, 0.23; 95% CI, 0.16-0.31) or Eastern Europe (AOR, 0.14; 95% CI, 0.11-0.18) (Table 5).

In analyses restricted to patients with moderate to high levels of pain at baseline, the results of regional variation were consistent with those of the primary analytic population. Patients in Asia (AOR, 0.47; 95% CI, 0.29-0.79) and Eastern Europe (AOR, 0.16; 95% CI, 0.12-0.22) used opioids less frequently than those in North America.

Discussion

In this pooled analysis of 8 different international clinical trials in metastatic prostate cancer, regional variations in opioid use were evident. Patients in Asian and Eastern European countries were less likely to use opioids compared with patients in North America. This disparity persisted after adjusting for

Table 1. Patient Characteristics and Outcomes Across Analytic Populations

Variable	Population, No. (%)				
	Analytic (N = 9670)	High Disease Burden, ≥6 Bone Lesions (n = 3715)	More Advanced Disease (n = 4502)	Less Advanced Disease (n = 5168)	Moderate to High Pain Level at Baseline (n = 2353)
Opioid use at any time	4983 (51.5)	2241 (60.3)	2937 (65.2)	2046 (39.6)	1646 (70.0)
Opioid use during trial	4877 (50.4)	2170 (58.4)	2854 (63.4)	2023 (39.1)	1616 (68.7)
Patient age, mean (SD), y	69.2 (8.3)	69.5 (8.6)	69.0 (8.1)	69.3 (8.6)	67.8 (8.2)
Bone involvement present at baseline	8786 (90.9)	3715 (100.0)	4204 (93.4)	4582 (88.7)	2250 (95.6)
Visceral disease present at baseline	1646 (17.0)	434 (11.7)	964 (21.4)	682 (13.2)	595 (25.3)
Baseline ECOG PS score					
0	4667 (48.3)	1751 (47.1)	1484 (33.0)	3183 (61.6)	603 (25.6)
1	4448 (46.0)	1741 (46.9)	2553 (56.7)	1895 (36.7)	1440 (61.2)
2	555 (5.7)	223 (6.0)	465 (10.3)	90 (1.7)	310 (13.2)
Pain status at baseline					
Not high or moderate	6934 (71.7)	2826 (76.1)	2695 (59.9)	4239 (82.0)	0 (0.0)
High or moderate	2353 (24.3)	764 (20.6)	1604 (35.6)	749 (14.5)	2353 (100.0)
Unknown or missing	383 (4.0)	125 (3.4)	203 (4.5)	180 (3.5)	0 (0.0)
Region					
Asia	528 (5.5)	250 (6.7)	95 (2.1)	433 (8.4)	93 (4.0)
Eastern Europe	1196 (12.4)	498 (13.4)	393 (8.7)	803 (15.5)	394 (16.7)
Middle East and Africa	205 (2.1)	94 (2.5)	76 (1.7)	129 (2.5)	71 (3.0)
North America	2353 (24.3)	755 (20.3)	1179 (26.2)	1174 (22.7)	537 (22.8)
Oceania	834 (8.6)	252 (6.8)	348 (7.7)	486 (9.4)	179 (7.6)
South and Central America	414 (4.3)	149 (4.0)	197 (4.4)	217 (4.2)	126 (5.4)
Western Europe	4140 (42.8)	1717 (46.2)	2214 (49.2)	1926 (37.3)	953 (40.5)
Recruited from high-income country	8367 (86.5)	3194 (86.0)	4140 (92.0)	4227 (81.8)	1927 (81.9)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group Performance Status (score range: 0 [no restrictions on activity] to 5 [dead]).

Table 2. Regional Comparison of Patient Baseline Characteristics and Outcomes

Variable	No. of Patients (%)						
	Asia (n = 528)	Eastern Europe (n = 1196)	Middle East and Africa (n = 205)	North America (n = 2353)	Oceania (n = 834)	South and Central America (n = 414)	Western Europe (n = 4140)
Patient age, mean (SD), y	69.2 (8.1)	66.7 (8.2)	67.5 (9.0)	70.1 (8.8)	70.2 (8.4)	69.1 (8.1)	69.3 (8.0)
Bone involvement present	503 (95.3)	1142 (95.5)	195 (95.1)	2061 (87.6)	744 (89.2)	403 (97.3)	3738 (90.3)
Visceral disease present	96 (18.2)	244 (20.4)	47 (22.9)	419 (17.8)	128 (15.3)	85 (20.5)	627 (15.1)
Baseline ECOG PS score							
0	299 (56.6)	415 (34.7)	99 (48.3)	1172 (49.8)	416 (49.9)	153 (37.0)	2113 (51.0)
1	198 (37.5)	713 (59.6)	97 (47.3)	1061 (45.1)	363 (43.5)	228 (55.1)	1788 (43.2)
2	31 (5.9)	68 (5.7)	9 (4.4)	120 (5.1)	55 (6.6)	33 (8.0)	239 (5.8)
Pain status at baseline							
Not high or moderate	433 (82.0)	766 (64.0)	123 (60.0)	1774 (75.4)	638 (76.5)	248 (59.9)	2952 (71.3)
High or moderate	93 (17.6)	394 (32.9)	71 (34.6)	537 (22.8)	179 (21.5)	126 (30.4)	953 (23.0)
Unknown or missing	2 (0.4)	36 (3.0)	11 (5.4)	42 (1.8)	17 (2.0)	40 (9.7)	235 (5.7)
Residing in high-income countries[a]	375 (71.0)	501 (41.9)	77 (37.6)	2353 (100.0)	834 (100.0)	87 (21.0)	4140 (100.0)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group Performance Status (score range: 0 [no restrictions on activity] to 5 [dead]).

[a] Per World Bank definition.

clinical and demographic characteristics and was seen in patients with moderate to high pain levels. Possible explanations for the disparity include local attitudes and practices as well as lack of access to opioids and potential undertreatment for patients in some cases.

Although higher percentages of patients in high-income countries used opioids compared with those in not-high-income countries, use varied across high-income countries. These findings of lower opioid use in specific countries are generally consistent with previous reports in nontrial settings. The Global

Table 3. Regional Comparison of Opioid Use by Analytic Population[a]

Region	Population, No. (%)				
	Analysis (N = 9670)	High Disease Burden, ≥6 Bone Lesions (n = 3715)	More Advanced Disease (n = 4502)	Less Advanced Disease (n = 5168)	Moderate to High Pain Level at Baseline (n = 2353)
Asia	174 (33.0)	91 (36.4)	64 (67.4)	110 (25.4)	64 (68.8)
Eastern Europe	367 (30.7)	169 (33.9)	185 (47.1)	182 (22.7)	182 (46.2)
Middle East or Africa	97 (47.3)	51 (54.3)	45 (59.2)	52 (40.3)	39 (54.9)
North America	1391 (59.1)	519 (68.7)	824 (69.9)	567 (48.3)	439 (81.8)
Oceania	451 (54.1)	176 (69.8)	220 (63.2)	231 (47.5)	122 (68.2)
South or Central America	182 (44.0)	80 (53.7)	98 (49.7)	84 (38.7)	71 (56.3)
Western Europe	2321 (56.1)	1155 (67.3)	1501 (67.8)	820 (42.6)	729 (76.5)

[a] Denominator for each cell is the total number of patients within each region.

Table 4. Country-Level Percentages of Opioid Use[a]

Country	No. in Population	Any Opioid Use, No. (%)	Income Status[b]
Asia			
Japan	149	35 (23.5)	High income
Korea	167	85 (50.9)	High income
China	147	22 (15.0)	Not high income
Eastern Europe			
Czech Republic	98	54 (55.1)	High income
Hungary	91	30 (33.0)	High income
Poland	218	114 (52.3)	High income
Slovakia	80	41 (51.3)	High income
Romania	161	44 (27.3)	Not high income
Russia	366	65 (17.8)	Not high income
Ukraine	145	13 (9.0)	Not high income
Middle East or Africa			
Israel	77	36 (46.8)	High income
South Africa	60	36 (60.0)	Not high income
Turkey	52	17 (32.7)	Not high income
North America			
Canada	692	402 (58.1)	High income
United States	1661	989 (59.5)	High income
South and Central America			
Brazil	198	103 (52.0)	Not high income
Mexico	74	11 (14.9)	Not high income
Western Europe			
Austria	55	20 (36.4)	High income
Belgium	288	160 (55.6)	High income
Denmark	199	85 (42.7)	High income
Finland	77	36 (46.8)	High income
France	885	522 (59.0)	High income
Germany	429	191 (44.5)	High income
Italy	202	95 (47.0)	High income
The Netherlands	176	85 (48.3)	High income
Norway	137	114 (83.2)	High income
Portugal	73	36 (49.3)	High income
Spain	423	186 (44.0)	High income
Sweden	215	132 (61.4)	High income
United Kingdom	953	643 (67.5)	High income

[a] To avoid small cell problems, we analyzed data from only the countries with at least 50 patients.

[b] Per World Bank definition.

Table 5. Results of Logistic Regression Models of Opioid Use[a]

Variable	Adjusted Odds Ratio (95% CI)				
	Population		Patients		
	Analysis (N = 9670)	High Tumor Burden, ≥6 Bone Lesions (n = 3715)	More Advanced Disease (n = 4502)	Less Advanced Disease (n = 5168)	Moderate to High Pain Level at Baseline (n = 2353
Region					
Asia	0.31 (0.25-0.38)	0.23 (0.16-0.31)	0.73 (0.46-1.18)	0.31 (0.24-0.40)	0.47 (0.29-0.79)
Eastern Europe	0.19 (0.16-0.22)	0.14 (0.11-0.18)	0.25 (0.19-0.32)	0.21 (0.17-0.26)	0.16 (0.12-0.22)
Middle East and Africa	0.47 (0.34-0.63)	0.42 (0.27-0.67)	0.48 (0.29-0.80)	0.55 (0.38-0.81)	0.26 (0.15-0.44)
North America	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Oceania	0.79 (0.67-0.93)	1.04 (0.75-1.43)	0.60 (0.46-0.78)	0.97 (0.78-1.20)	0.43 (0.29-0.64)
South and Central America	0.39 (0.31-0.48)	0.35 (0.24-0.51)	0.34 (0.25-0.48)	0.50 (0.36-0.67)	0.25 (0.16-0.38)
Western Europe	0.84 (0.75-0.93)	0.85 (0.70-1.02)	0.88 (0.75-1.04)	0.76 (0.66-0.89)	0.71 (0.54-0.93)
Bone involvement present (vs not)	2.12 (1.82-2.47)	NA; all patients have bone involvement by population definition	2.60 (2.01-3.37)	1.77 (1.47-2.15)	2.29 (1.49-3.48)
Visceral disease present (vs not)	0.94 (0.83-1.05)	0.86 (0.69-1.08)	0.85 (0.72-1.00)	0.97 (0.81-1.15)	0.95 (0.77-1.18)
Baseline ECOG PS score					
0	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
1	1.98 (1.81-2.17)	2.06 (1.77-2.40)	2.05 (1.78-2.37)	1.54 (1.35-1.75)	1.88 (1.52-2.32)
2	4.06 (3.26-5.09)	3.91 (2.70-5.77)	3.73 (2.84-4.94)	2.34 (1.49-3.67)	3.24 (2.30-4.62)
Pain category at baseline					
Not moderate or high	1	1	1	1	NA; all patients have high pain level by population definition
Moderate or high	2.38 (2.13-2.66)	2.71 (2.21-3.33)	2.79 (2.39-3.26)	1.58 (1.33-1.88)	NA
Missing	0.96 (0.77-1.19)	1.27 (0.85-1.91)	0.96 (0.71-1.31)	0.91 (0.66-1.24)	NA
Age (continuous)	0.98 (0.97-0.98)	0.97 (0.97-0.98)	0.97 (0.96-0.97)	0.98 (0.98-0.99)	0.99 (0.97-0.997)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status (score range: 0 [no restrictions on activity] to 5 [dead]); NA, not applicable.

[a] Adjusted for the variables shown.

Opioid Policy Initiative survey in Asia found that opioid consumption was highest in Korea, followed by Japan and then China,[8] a finding that was also observed in the present data set. Similarly, this study's finding of comparatively lower opioid use in Ukraine and Russia is consistent with results of previous research on country- and region-level opioid consumption.[25]

This study is unique in several ways. Previous research on disparities in global opioid use has examined formulary availability and cost[4] or evaluated data from the International Narcotics Control Board.[26] These studies provide information on country and regional issues, but they do not provide specific information on opioid use in patients with cancer. Single-site assessments of opioid use in patients with cancer exist,[27,28] and some multinational studies have been conducted in Europe.[29] However, to our knowledge, no study has compared opioid use across patients with cancer from a range of different countries within the clinical trial setting.

Strengths and Limitations

A strength of this study is the ability to assess patient-level data in a setting that has been unexplored, despite the use of end points involving opioids as well as the potential differences between a controlled trial setting and a community practice. This study also has several limitations. First, some instances of opioid use may have been missed if patients did not share information with study personnel; however, concomitant medication data sets in trials typically seek to record all nontrial medication use. In addition, opioids that were not classified using ATC codes were not captured, and the only excluded indications of opioid use were for pain prophylaxis associated with procedures. Second, attributing opioid use to cancer pain rather than to noncancer pain is challenging. A conservative approach was taken by including all nonprophylactic or procedural opioid use. Third, an indicator variable for missing pain data at baseline was used rather than multiple imputation. This approach assumes that the missing data are missing at random, which may not be verifiable. However, to date, simulations have not shown that multiple imputation is superior to simpler approaches, such as a missing indicator, for missing baseline covariates.[30]

Conclusions

This study documented the variability in opioid analgesic use across regions and countries in prostate cancer clinical

trials, suggesting the existence of disparities in oncologic pain management in the previously unexplored controlled trial setting. Although patients in US trials demonstrated a higher level of opioid use than those in several other regions, opioid use appeared similar between the United States and Canada. However, other regions had greater within-region variability in opioid use. These findings suggest that global variability in opioid use should be considered for international clinical trials using delay in opioid initiation as an end point or otherwise incorporating opioid use into trial end points. If region is not a stratification factor, then sponsors may wish to assess regional variability when analyzing these end points, depending on their countries of recruitment.

ARTICLE INFORMATION

Accepted for Publication: May 27, 2019.

Published Online: September 12, 2019. doi:10.1001/jamaoncol.2019.2971

Author Contributions: Dr Roydhouse had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Roydhouse, Mishra-Kalyani, Pazdur, Kluetz.
Acquisition, analysis, or interpretation of data: Roydhouse, Suzman, Menapace, Sridhara, Blumenthal, Beaver, Pazdur, Kluetz.
Drafting of the manuscript: Roydhouse, Mishra-Kalyani, Beaver, Pazdur.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Roydhouse, Mishra-Kalyani, Sridhara, Pazdur.
Administrative, technical, or material support: Sridhara, Blumenthal, Pazdur.
Supervision: Blumenthal, Beaver, Pazdur, Kluetz.
Other - Provided clinical expertise and interpretation of data: Menapace.

Conflict of Interest Disclosures: None reported.

Disclaimer: This paper reflects the views of the authors and should not be construed to represent the views or policies of the US Food and Drug Administration.

REFERENCES

1. Kane CM, Hoskin P, Bennett MI. Cancer induced bone pain. *BMJ*. 2015;350:h315. doi:10.1136/bmj.h315

2. Apolone G, Corli O, Caraceni A, et al; Cancer Pain Outcome Research Study Group (CPOR SG) Investigators. Pattern and quality of care of cancer pain management. Results from the Cancer Pain Outcome Research Study Group. *Br J Cancer*. 2009; 100(10):1566-1574. doi:10.1038/sj.bjc.6605053

3. Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment in cancer pain. A review of published literature. *Ann Oncol*. 2008; 19(12):1985-1991. doi:10.1093/annonc/mdn419

4. Cherny NI, Cleary J, Scholten W, Radbruch L, Torode J. The Global Opioid Policy Initiative (GOPI) project to evaluate the availability and accessibility of opioids for the management of cancer pain in Africa, Asia, Latin America and the Caribbean, and the Middle East: introduction and methodology. *Ann Oncol*. 2013;24(suppl 11):xi7-xi13. doi:10.1093/annonc/mdt498

5. Cleary J, Silbermann M, Scholten W, Radbruch L, Torode J, Cherny NI. Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in the Middle East: a report from the Global Opioid Policy Initiative (GOPI). *Ann Oncol*. 2013;24(suppl 11): xi51-xi59. doi:10.1093/annonc/mdt503

6. Cleary J, De Lima L, Eisenchlas J, Radbruch L, Torode J, Cherny NI. Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in Latin America and the Caribbean: a report from the Global Opioid Policy Initiative (GOPI). *Ann Oncol*. 2013;24(suppl 11):xi41-xi50. doi:10.1093/annonc/mdt502

7. Cleary J, Simha N, Panieri A, et al. Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in India: a report from the Global Opioid Policy Initiative (GOPI). *Ann Oncol*. 2013; 24(suppl 11):xi33-xi40. doi:10.1093/annonc/mdt501

8. Cleary J, Radbruch L, Torode J, Cherny NI. Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in Asia: a report from the Global Opioid Policy Initiative (GOPI). *Ann Oncol*. 2013;24(suppl 11):xi24-xi32. doi:10.1093/annonc/mdt500

9. Cleary J, Powell RA, Munene G, et al. Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in Africa: a report from the Global Opioid Policy Initiative (GOPI). *Ann Oncol*. 2013; 24(suppl 11):xi14-xi23. doi:10.1093/annonc/mdt499

10. Cherny NI, Baselga J, de Conno F, Radbruch L. Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in Europe: a report from the ESMO/EAPC Opioid Policy Initiative. *Ann Oncol*. 2010;21(3):615-626. doi:10.1093/annonc/mdp581

11. Cleary J, Gelband H, Wagner J. Cancer pain relief. In: Gelband H, Jha P, Sankaranarayan R, Horton S, eds. *Cancer: Disease Control Priorities*. Vol 3. 3rd ed. Washington, DC: The International Bank for Reconstruction and Development/The World Bank; 2015:chap 9.

12. Seya MJ, Gelders SF, Achara OU, Milani B, Scholten WK. A first comparison between the consumption of and the need for opioid analgesics at country, regional, and global levels. *J Pain Palliat Care Pharmacother*. 2011;25(1):6-18. doi:10.3109/15360288.2010.536307

13. Unger JM, Cook E, Tai E, Bleyer A. The role of clinical trial participation in cancer research: barriers, evidence, and strategies. *Am Soc Clin Oncol Educ Book*. 2016;35:185-198. doi:10.1200/EDBK_156686

14. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA*. 2004;291(22): 2720-2726. doi:10.1001/jama.291.22.2720

15. Unger JM, Gralow JR, Albain KS, Ramsey SD, Hershman DL. Patient income level and cancer clinical trial participation: a prospective survey study. *JAMA Oncol*. 2016;2(1):137-139. doi:10.1001/jamaoncol.2015.3924

16. Unger JM, Hershman DL, Albain KS, et al. Patient income level and cancer clinical trial participation. *J Clin Oncol*. 2013;31(5):536-542. doi:10.1200/JCO.2012.45.4553

17. Kalata P, Martus P, Zettl H, et al; German Rectal Cancer Study Group. Differences between clinical trial participants and patients in a population-based registry: the German Rectal Cancer Study vs. the Rostock Cancer Registry. *Dis Colon Rectum*. 2009; 52(3):425-437. doi:10.1007/DCR.0b013e318197d13c

18. Jin S, Pazdur R, Sridhara R. Re-evaluating eligibility criteria for oncology clinical trials: analysis of investigational new drug applications in 2015. *J Clin Oncol*. 2017;35(33):3745-3752. doi:10.1200/JCO.2017.73.4186

19. Nussbaum N, George DJ, Abernethy AP, et al. Patient experience in the treatment of metastatic castration-resistant prostate cancer: state of the science. *Prostate Cancer Prostatic Dis*. 2016;19(2): 111-121. doi:10.1038/pcan.2015.42

20. Small EJ, Higano CS, Kantoff PW, Whitmore JB, Frohlich MW, Petrylak DP. Time to disease-related pain and first opioid use in patients with metastatic castration-resistant prostate cancer treated with sipuleucel-T. *Prostate Cancer Prostatic Dis*. 2014;17 (3):259-264. doi:10.1038/pcan.2014.21

21. Soloway MS, Hardeman SW, Hickey D, et al. Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. *Cancer*. 1988;61(1):195-202. doi:10.1002/1097-0142(19880101)61:1<195::AID-CNCR2820610133>3.0.CO;2-Y

22. Sabbatini P, Larson SM, Kremer A, et al. Prognostic significance of extent of disease in bone in patients with androgen-independent prostate cancer. *J Clin Oncol*. 1999;17(3):948-957. doi:10.1200/JCO.1999.17.3.948

23. The World Bank. High income. https://data.worldbank.org/income-level/high-income. Updated 2019. Accessed December 12, 2018.

24. Fizazi K, Tran N, Fein L, et al; LATITUDE Investigators. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2017; 377(4):352-360. doi:10.1056/NEJMoa1704174

25. Duthey B, Scholten W. Adequacy of opioid analgesic consumption at country, global, and regional levels in 2010, its relationship with development level, and changes compared with 2006. *J Pain Symptom Manage*. 2014;47(2):283-297. doi:10.1016/j.jpainsymman.2013.03.015

26. Hastie BA, Gilson AM, Maurer MA, Cleary JF. An examination of global and regional opioid consumption trends 1980-2011. *J Pain Palliat Care Pharmacother*. 2014;28(3):259-275. doi:10.3109/15360288.2014.941132

27. Haider A, Zhukovsky DS, Meng YC, et al. Opioid prescription trends among patients with cancer referred to outpatient palliative care over a 6-year period. *J Oncol Pract*. 2017;13(12):e972-e981. doi:10.1200/JOP.2017.024901

28. Riechelmann RP, Krzyzanowska MK, O'Carroll A, Zimmermann C. Symptom and medication profiles among cancer patients attending a palliative care clinic. *Support Care Cancer*. 2007;15(12):1407-1412. doi:10.1007/s00520-007-0253-8

29. Paque K, Elseviers M, Vander Stichele R, et al. Changes in medication use in a cohort of patients with advanced cancer: the international multicentre prospective European palliative care cancer symptom study. *Palliat Med*. 2018;32(4):775-785. doi:10.1177/0269216317746843

30. Sullivan TR, White IR, Salter AB, Ryan P, Lee KJ. Should multiple imputation be the method of choice for handling missing data in randomized trials? *Stat Methods Med Res*. 2018;27(9):2610-2626. doi:10.1177/0962280216683570

Supplementary Online Content

Roydhouse JK, Suzman DL, Menapace LA, et al. Global variation in opioid use in prostate cancer trials. *JAMA Oncol.* Published online September 12, 2019. doi:10.1001/jamaoncol.2019.2971

eTable. Regional and Income Classification of Countries of Patient Recruitment

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable. Regional and Income Classification of Countries of Patient Recruitment (N=9,670)

Country^	N (%) of analytic population	Region	Income Status*
Argentina	46 (0.5%)	South/Central America	High-income
Australia	823 (8.5%)	Oceania	High-income
Austria	55 (0.6%)	Western Europe	High-income
Belarus	21 (0.2%)	Eastern Europe	Not high-income
Belgium	288 (3.0%)	Western Europe	High-income
Brazil	198 (2.0%)	South/Central America	Not high-income
Bulgaria	2 (0.02%)	Eastern Europe	Not high-income
Canada	692 (7.2%)	North America	High-income
Chile	41 (0.4%)	South/Central America	High-income
China	147 (1.5%)	Asia	Not high-income
Colombia	17 (0.2%)	South/Central America	Not high-income
Czech Republic	98 (1.0%)	Eastern Europe	High-income
Denmark	199 (2.1%)	Western Europe	High-income
Finland	77 (0.8%)	Western Europe	High-income
France	885 (9.2%)	Western Europe	High-income
Germany	429 (4.4%)	Western Europe	High-income
Greece	14 (0.1%)	Western Europe	High-income
Hong Kong (SAR)	21 (0.2%)	Asia	High-income
Hungary	91 (0.9%)	Eastern Europe	High-income
Israel	77 (0.8%)	Middle East/Africa	High-income
Italy	202 (2.1%)	Western Europe	High-income
Ireland (Rep. of)	14 (0.1%)	Western Europe	High-income
Japan	149 (1.5%)	Asia	High-income
Korea (Rep. of)	167 (1.7%)	Asia	High-income
Lithuania	14 (0.1%)	Eastern Europe	High-income
Malaysia	6 (0.1%)	Asia	Not high-income
Mexico	74 (0.8%)	South/Central America	Not high-income
Netherlands	176 (1.8%)	Western Europe	High-income
New Zealand	11 (0.1%)	Oceania	High-income
Norway	137 (1.4%)	Western Europe	High-income
Peru	38 (0.4%)	South/Central America	Not high-income
Poland	218 (2.3%)	Eastern Europe	High-income
Portugal	73 (0.8%)	Western Europe	High-income
Romania	161 (1.7%)	Eastern Europe	Not high-income
Russian Federation	366 (3.8%)	Eastern Europe	Not high-income
Singapore	14 (0.1%)	Asia	High-income
Slovakia	80 (0.8%)	Eastern Europe	High-income
South Africa	60 (0.6%)	Middle East/Africa	Not high-income
Spain	423 (4.4%)	Western Europe	High-income
Sweden	215 (2.2%)	Western Europe	High-income
Taiwan (POC)	24 (0.2%)	Asia	High-income
Tunisia	16 (0.2%)	Middle East/Africa	Not high-income
Turkey	52 (0.5%)	Middle East/Africa	Not high-income
Ukraine	145 (1.5%)	Eastern Europe	Not high-income
United Kingdom	953 (9.9%)	Western Europe	High-income
United States	1661 (17.2%)	North America	High-income

*Based on WorldBank classification of high-income countries; ^Designation of countries follows the abbreviations/country names provided in the datasets and/or World Bank website and should not be construed as a political statement