Trends in Opioid Use Over Time: 1997 to 1999

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ABSTRACT

Substantial resources have been spent to improve pain control for dying patients, and increased opioid administration has been presumed. Oregon has been a consistent leading state in per capita use for morphine for the past 10 years, as recorded by the Automation of Reports and Consolidated Orders System (ARCOS). Health policy experts, extrapolating from World Health Organization methods, have suggested these data are indicative of the quality of end-of-life care in Oregon. To determine whether trends in opioid prescription at the state and national levels reflect increased opioid use for inpatients during the final week of life, chart reviews were conducted to record all opioid medications administered in the last week of life to 877 adult inpatients who died from natural causes between January 1, 1997 and December 31, 1999. Inpatient morphine use did not increase significantly for dying patients from 1997 to 1999. However, overall morphine use for both Oregon and the United States as measured by ARCOS data increased significantly. Comparisons revealed no significant difference between linear trends for Oregon and U.S. morphine use, but both were significantly greater than the dying inpatients. This pattern was also found for all other opioids. These findings suggest that ARCOS data do not necessarily provide information about opioid use for specific subpopulations of patients and raise questions about the meaning of observed increases in ARCOS data.

INTRODUCTION

ADEQUATE PAIN MANAGEMENT is vital to quality end-of-life care.[1] Opioid analgesics are a mainstay in the treatment of moderate to severe pain for patients who are dying.[2] Their efficacy in managing pain has been demonstrated in controlled studies and meta-analyses in patients with cancer and other painful conditions, and studies of the World Health Organization (WHO) cancer pain treatment protocol confirm that treatment is effective in as many as 90% of cancer patients.[3] However, despite the existence of proven, efficacious therapies, many dying patients continue to experience significant pain.[3,4] The SUPPORT study found that 50% of seriously ill patients hospitalized in five academic medical centers were reported to be in moderate to severe pain during the last 3 days of their lives.[5]

Over the past decade, substantial resources have been directed toward improving the care of dying patients, with specific efforts aimed at pain management. However, measurement of the degree to which these strategies have been effective in decreasing pain in the dying is challenging. Trends in total opioid purchasing are one surrogate measure of efforts to improve pain management. The WHO regards a country's morphine purchasing to be an important indicator of the progress of its worldwide effort to improve can-

cer pain relief.[6] Within the United States, this thinking has been extrapolated to the state level. A recent *New England Journal of Medicine* Health Policy Report[7] favorably characterized palliative care in Oregon, citing the fact that Oregon ranks first among the states in medical use of morphine as one piece of support.

However, it is unclear whether trends in a state's total medical opioid use, as reflected by purchasing data, can be used as an indicator of efforts to improve end-of-life care. Opioids can be used for a range of purposes and it is not possible within existing data to identify how much of the opioids used are actually administered to dying patients. In order to determine whether trends in opioid use are reflective of pain management for dying patients, we conducted a chart review to extract information about the type and amount of opioids administered to dying hospitalized inpatients at an academic medical center during the last week of life over a 3-year period. These data were then compared with statewide and national trends in medical opioid use to better understand the relationship between trends in opioid use and opioid administration to the dying.

METHODS

Setting

Oregon Health & Science University (OHSU) is an urban, academic hospital with 411 beds. Since 1995, OHSU has had both a palliative care team and two pain services. The University has a diagnostically and geographically diverse patient population with approximately one third of all patients referred from outside the Portland metropolitan area.[8]

Procedures

After approval from the Institutional Review Boards at both OHSU and the Oregon Department of Human Services, OHSU hospital death logs were used to identify adults who died in the hospital between January 1, 1997 and December 31, 1999. In collaboration with the Oregon Department of Human Resources, this information was used to pull each death certificate. Deaths caused by accident, homicide, suicide, undetermined causes under investigation, or in emergency departments were excluded from the sample.

Sample

The OHSU medical records department located complete medical records for all but 11 of the 900 deceased patients. Another 9 patients were eliminated from the sample because they received epidural opioids. Patients given medication via this route were excluded because there is no clear consensus on the relative potency of oral and epidural opioids. Furthermore, as epidural opioids are from 10 to 100 times more potent than intravenous medications, the amounts of opioids excluded from our totals (measured in grams) are comparatively miniscule.[9,10] An additional 3 patients were eliminated because data were inadvertently collected for more than 7 days. This left a sample of $n = 877$, 97.4% of all potentially eligible decedents.

Data sources

OHSU inpatient data. Once each record was located, demographic data from the death certificate were recorded onto a data collection form and the death certificate was then shredded to protect the anonymity of the decedent. Patient characteristics are presented in Table 1. All data collection was conducted by a clinical pharmacist (J.B.). The exact time of death was used in combination with the date and time of admission in order to determine the precise time period included in the chart review. For patients who died less than a week after admission to an inpatient unit, opioid data were recorded for their entire stay. For patients who died after more than 1 week as an inpatient, opioid data were recorded for the 7 days (168 hours) prior to death. The total amount of opioid administered each calendar day was recorded onto a data collection form and converted individually into oral morphine equivalencies.

Oregon and United States medical use data. The U.S. Drug Enforcement Administration collects and reports all Schedule II opioids purchased for medical use by retail pharmacies, hospitals, and physicians across the United States through the Automation of Reports and Consolidated Orders System (ARCOS).[11] These data are reported quarterly for all opioids used in grams per 100,000 population. Quarterly totals reflect the total amount of drug in grams without any conversions performed to take formulation (and differences in potency) into account. This is important to note because oral/sublingual formulations of

TABLE 1. INPATIENT DECEDENT CHARACTERISTICS

Year of death	1997	1998	1999
Number of deaths	289	251	337
Average age (in years)	59.1	59.4	59.5
Gender (% female)	49.5%	51.0%	44.2%
Race (% white)	94.4%	89.2%	89.3%
Cause of death			
Cancer	15.6%	16.7%	14.2%
Cerebrovascular disease	9.0%	10.4%	16.6%
Heart disease	22.5%	20.3%	19.0%
Liver disease	10.7%	8.4%	8.0%
Pneumonia	8.3%	9.6%	7.1%
Septicemia	17.6%	18.5%	15.1%
Other	16.3%	16.1%	20.0%
Average length of review period (in days)[a]	4.7	5.0	4.6
Patients receiving any opioid during the final week of life	86.9%	90.4%	91.4%

[a]Review period length was capped at a maximum of 7 days.

medications may require higher amounts of medication to achieve the same effect as intravenous/subcutaneous formulations. For example, 30 mg of oral morphine has approximately the same potency as 10 mg of intravenous morphine.[3] However, in the ARCOS data, 300 mg of oral morphine and 100 mg of intravenous morphine would be added together and presented as 400 mg (or 0.4 grams) of morphine used.

Oregon and United States opioid medical use data from January 1, 1997 to December 31, 1999 were used in the analyses. It should be noted that opioids used to treat dying hospitalized patients at OHSU would have been included in overall use totals as reflected by the United States and Oregon medical use data. Also, Oregon is one of the states included in the United States ARCOS medical use data.

Data analysis

In order to compare pain medication trends over time, several steps were taken to facilitate comparison between these three data sets (OHSU inpatient use, Oregon medical use, United States medical use). First, the total number of milligrams of each opioid administered to OHSU inpatients was added together by drug, irrespective of formulation, similar to the way that Oregon and United States medical use data are calculated. This step was necessary to achieve as similar a unit of analysis as possible between the three data sets.

Second, opioids in the OHSU inpatient data, Oregon medical use data, and United States medical use data were converted into oral morphine equivalencies using an equianalgesic table (Table 2). Because the calculated totals for each drug were not formulation-specific, the most commonly administered formulation (based on OHSU inpatient data) was assumed in making conversions to oral morphine equivalencies for drugs available in more than one formulation. Table 2 shows equianalgesic potency conversions and provides a reference to convert one medication given by a specific route to the equipotent amount of another given by the same or different route. For example, 60 mg of oral morphine is equivalent in potency to 20 mg of parenteral morphine, 15 mg of oral hydromorphone, or 600 mg of oral meperidine. Similarly, 60 mg of oral morphine would be equivalent in potency to 3 mg of intravenous hydromorphone, or 0.2 mg of parenteral fentanyl. Methodologic uncertainties surrounding equianalgesic dosing were minimized by using the same conversion ratios for each data set.[12,13]

Third, to compare changes over time in the three data sets, OHSU inpatient data were converted to grams per 100,000 dying hospitalized patients, similar to the Oregon and United States medical use data. The total amount of drugs per quarter in oral morphine equivalencies was divided by the number of patients per quarter and multiplied by 100,000 to obtain the total grams per 100,000 population.

TABLE 2. EQUIANALGESIC POTENCY CONVERSION CHART

Opioid	IM/IV dose	Oral dose
Fentanyl[22]	0.1	N/A
Hydromorphone[3]	1.5	7.5
Meperidine[22]	75	300
Methadone[3]	10	20
Morphine[3]	10	30
Oxycodone[3]	N/A	30
Sufentanil[3]	0.02	N/A
Fentanyl patch conversions[23]		
Fentanyl patch delivery (in mcg/hr)	Morphine oral equivalent (mg/24 hr)	Morphine parenteral equivalent (mg/24 hr)
25	45–134 (~90)	8–22 (~15)
50	135–224 (~180)	23–37 (~30)
75	225–314 (~270)	38–52 (~45)
100	315–404 (~360)	53–67 (~60)

Multiples of the above fentanyl increments could be used to find the appropriate morphine dose or vice versa
IM, intramuscular; IV, intravenous.

Statistics. Data were analyzed using SPSS 11.0 (SPSS Inc., Chicago, IL). We were specifically interested in comparing morphine to all other opioids in the study. Using this approach, we were able to calculate the total amount of morphine (in oral morphine grams per 100,000 population) and all other opioids (in oral morphine grams per 100,000 population). After initial inspection of means, regressions were performed. The slope was used to assess whether changes over time were statistically significant in each of the three data sets. Pairwise R to Z transformations, in which the regression correlation for each set of data serves as the basis of comparison, were used to determine whether the linear trends for each data set were significantly different from each other.[14] The regression correlation was used as the basis of comparison rather than the slope, because slopes are affected by the standard error while regression correlations are not. The α was set at $p < 0.05$ for these analyses. The opioids included in this study were morphine, fentanyl, hydromorphone, meperidine, methadone, oxycodone, and sufentanil. Alfentanil, tramadol, and propoxyphene were excluded from analyses because each drug was administered to fewer than four OHSU inpatients over the 3-year study period.

RESULTS

Regressions were performed on the OHSU inpatient, Oregon, and United States morphine use data with time period ($n = 12$ quarters) as the independent variable and average grams per 100,000 population as the dependent variable. OHSU inpatient morphine use did not increase significantly from 1997 to 1999 ($\beta = 0.139$, $p = 0.666$). However, statewide Oregon morphine use did increase significantly between 1997 and 1999 ($\beta = 0.837$, $p = 0.001$) as did United States morphine use ($\beta = 0.885$, $p < 0.001$).

Analysis indicated that the linear trend for OHSU inpatient use of morphine was significantly different from both Oregon morphine use ($z = -2.27$, $p = 0.011$) and United States morphine use ($z = -2.68$, $p = 0.003$). This suggests that morphine use in the United States and Oregon were increasing at significantly greater rates than OHSU inpatient use during the final week of life. However, the Oregon and United States morphine linear trends were not significantly different from each other ($z = 0.41$, $p = 0.35$), suggesting that the increased rate of change in morphine use was similar in Oregon and the United States.

Linear trends for morphine use are graphically displayed by quarter over the 3-year period in Figure 1. Standard units were used because, as expected, the grams of morphine per 100,000 population were very different for the OHSU inpatient data (average for first quarter of 1997 = 1816 grams per 100,000 population) as compared to the statewide Oregon (average first quarter of 1997 = 690 grams per 100,000 population) and United States data (average first quarter of 1997 = 494 grams per 100,000 population). In order to aid in interpretation, the standardized values were centered on time 1.
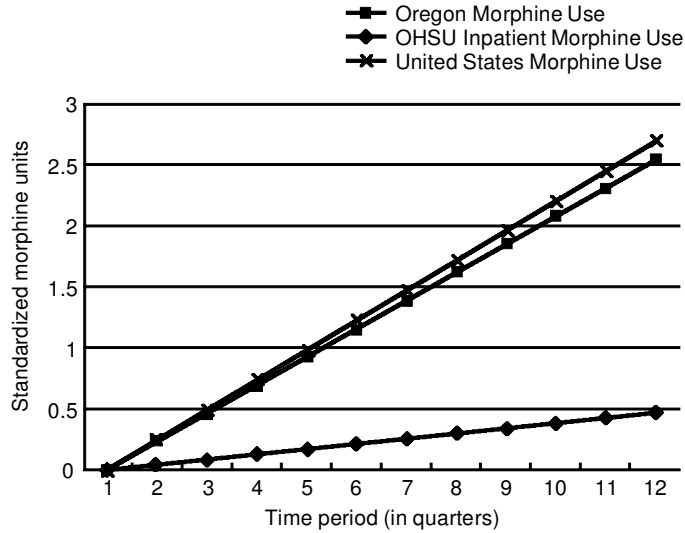
FIG. 1. Standardized regression coefficients reflecting the use of morphine for Oregon Health & Science University (OHSU) inpatients, Oregon, and the United States from 1997–1999.

Regressions were also performed with all other opioids in the study (fentanyl, hydromorphone, hydrocodone, meperidine, methadone, oxycodone, and sufentanil) in oral morphine equivalency as the dependent variable and time period ($n = 12$ quarters) as the independent variable. There was no significant change in the amount of other opioids administered to dying OHSU inpatients over the 3 years ($\beta = 0.161$, $p = 0.616$), although there was a nonsignificant upward trend over time. As with the morphine data, there was also a significant increase over time in the amount of other opioids used in Oregon ($\beta = 0.957$, $p < 0.001$) and in the United States ($\beta = 0.991$, $p < 0.001$).

Analysis indicates that the linear trend for OHSU inpatient use of other opioids was significantly different from the linear trends for both Oregon use of other opioids ($z = -3.8$, $p < 0.001$) and United States use of other opioids ($z = -5.3$, $p < 0.001$). However, there was no difference between the linear trends for Oregon use of opioids and United States use of opioids ($z = -1.5$, $p = 0.07$). Thus, overall medical use of opioids increased over the 3-year period in Oregon and the United States but remained stable at OHSU.

Linear trends for opioids are graphically displayed in Figure 2. Standard units were used because, as expected, the grams per 100,000 population were very different for the hospital data (e.g., average for first quarter of 1997 = 85,895 g per 100,000 population) compared to the Oregon

(average first quarter of 1997 = 2420 g per 100,000 population) and United States data (average first quarter of 1997 = 2323 g per 100,000 population). In order to aid in interpretation, the standardized values were centered on time 1.

DISCUSSION

Morphine use increased significantly in Oregon and the United States from 1997 to 1999. However, there was no significant increase in the amount of morphine administered to dying inpatients in our sample. The stable use of morphine could not be accounted for by a switch to other opioid agents, because like morphine, the trend for other opioids administered to dying inpatients was also relatively flat despite significant increases in use reflected in US and Oregon ARCOS data.

Why is statewide Oregon use of opioids increasing while opioid use for dying inpatients at an Oregon hospital is not? It is possible that increasing state opioid use reflects increased prescriptions to other patient populations, such as those with chronic pain or postsurgical patients. Another possibility is increasing diversion, though a study in Wisconsin between 1986 and 1990 found no evidence of increased diversion despite increases in morphine of 160% during that time period.[6] It is also possible that the inpatients in this sample were already receiving aggressive pain
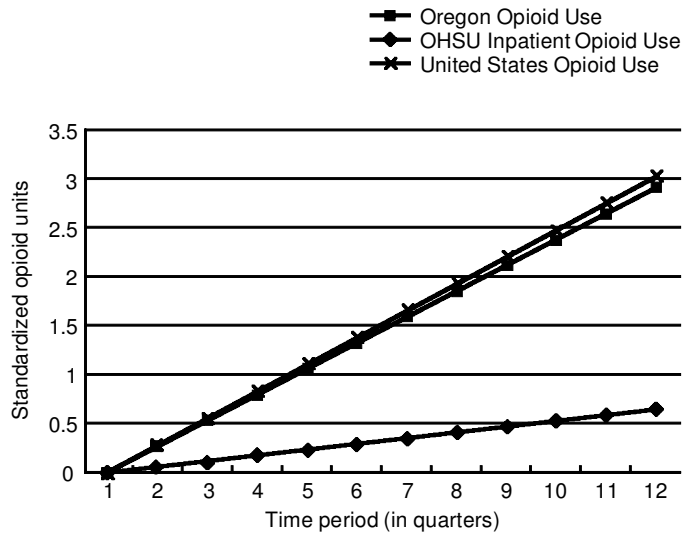
FIG. 2. Standardized regression coefficients reflecting the use of fentanyl, hydromorphone, meperidine, oxycodone, sufentanil, and methadone for Oregon Health & Science University (OHSU) inpatients, Oregon, and the United States from 1997–1999.

management and receiving the maximally necessary amounts of opioids. Self-reports by Oregon physicians indicate many were spurred into action in part by the 1994 vote to legalize physician-assisted suicide and voluntarily sought classes to improve their palliative care skills before the time period covered in this survey.[15]

Alternatively, dying inpatients may not be benefiting from increased statewide medical use of opioids because of the effects on prescribing of a complex political environment in Oregon surrounding end-of-life care issues.[16] In one survey of recently bereaved Oregon family members, family reports of moderate and severe pain increased in late 1997, following a second vote to legalize physician-assisted suicide.[17] When physicians and nurses were asked to explain the increase in family reports of pain, suggested reasons included increased family awareness of pain (endorsed by 96%), decreased physician prescribing of opioids (endorsed by 66%), and decreased nurse administration of opioids (endorsed by 57%). Fears of investigation were the most commonly cited reasons for decreased prescribing and administration.[18] Although Oregon had a historical reputation for aggressive investigation of over prescription of opioids, the Oregon Board of Medical Examiners announced its intent to investigate the under-treatment of pain as aggressively as the over-treatment of pain in 1998.[19]

Regardless of the reasons for the discrepancy between an academic hospital and ARCOS data,

these findings suggest that the ARCOS data alone do not provide adequate information about pain trends for specific patient populations. This is not surprising given that the ARCOS system was designed to monitor the legitimate distribution of controlled substances, not to assess the quality of clinical care.[20] The ARCOS data contains the total amount of opioids purchased by pharmacies and hospitals, not necessarily actual use by specific patient populations.[11]

The study has limitations that are important to note. First, the data on opioids administered to dying patients are from a single urban academic acute care health center in one state. There are no comparable data available about trends in opioid use in the final week of life for those dying in other hospitals or in community settings. This is particularly relevant in Oregon, which has among the lowest in-hospital death rates in the country.[21] It is possible that changes occurred in opioid administration to those dying at home and in long-term care facilities but not in the hospital where this study was conducted. These limitations affect the generalizability of findings. Second, the 3-year time frame may have limited the ability to identify changes in this single hospital that might be detectable over a longer time period. Third, in order to compare trends over time, state and national medical use data were compared to inpatient administration data. Changes were made to make these data sets as similar as possible, but this cannot change the fact that the data measure different (though related) constructs.

This 3-year study found opioid use to be unchanged in a population of dying hospitalized patients despite increases in national and state use of opioids. It is unclear which patient populations are receiving increases in opioid use. However, it is clear that trends in ARCOS data cannot be presumed to apply equally to all patient groups. Further research is needed to better measure and understand trends in opioid use for dying patients.

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REFERENCES

1. Singer PA, Martin DK, Kelner M: Quality end-of-life care: Patients' perspectives. JAMA 1999;1281:163–168.
2. Doyle D, Hanks GWC, MacDonald N: *Oxford Textbook of Palliative Medicine*, 2nd ed. New York: Oxford University Press, 1998.
3. Jacox A, Carr DB, Payne R, et al: Management of Cancer Pain. Clinical Practice Guideline No. 9. AHCPR Publication No. 94-0592. Rockville, MD. Agency for Health Care Policy and Research, U.S. Department of Health and Human Services, Public Health Service, March 1994.
4. Bernabei R, Bambassi G, Lapane K, Landi F, Gatsonis C, Dunlop R, Lipsitz L, Stcel K, Mor V: Management of pain in elderly patients with cancer. SAGE Study Group: Systematic Assessment of Geriatric Drug Use via Epidemiology. JAMA 1998;279:1877–1882.
5. The SUPPORT Principal Investigators: A controlled trial to improve care for seriously ill hospitalized patients. JAMA 1995;274:1591–1598.
6. Joranson DE: Availability of opioids for cancer pain: Recent trends, assessment of system barriers, new World Health Organization Guidelines, and the risk of diversion. J Pain Symptom Manage 1993;8:353–360.
7. Steinbrook R: Physician-assisted suicide in Oregon— An uncertain future. N Engl J Med 2002;346:460–464.
8. Oregon Health & Science University. OHSU At A Glance Page. <www.ohsu.edu/about/glance/html> (Last accessed February 14, 2003).
9. Krames ES: Intrathecal infusional therapies for intractable pain: Patient management guidelines. J Pain Symptom Manage 1993;8:36–46.
10. Mercadante S: Problems of long-term spinal opioid treatment in advanced cancer patients. Pain 1999;79:1–13.
11. Office of Diversion Control. DADS Quarterly Reports. Arlington VA: US Department of Justice, 1999.
12. Anderson R, Saiers, JH, Abram S, Schlicht C: Accuracy in equianalgesic dosing: Conversion dilemmas. J Pain Symptom Manage 2001;21:397–406.
13. Pereira J, Lawlor P, Vigano A, Dorgan M, Bruera E: Equianalgesic dose ratios for opioids. A critical review and proposals for long-term dosing. J Pain Symptom Manage 2001;22:672–687.
14. Cohen J, Cohen P: *Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences*. Hillsdale, New Jersey: Lawrence Earlbaum, 1975.
15. Ganzini L, Nelson HD, Lee MA, Kraemer DF, Schmidt TA, Delorit MA: Oregon physicians' attitudes about and experiences with end-of-life care since passage of the Oregon Death With Dignity Act. JAMA 2001;285:2363–2369.
16. Matesa J: A roundup of recent pain-policy avenues and trends. State Initiatives in End-of-Life Care 2002;14:6–8.
17. Tolle SW, Tilden VP, Hickman SE, Rosenfeld AG: Family reports of pain in dying hospitalized patients: a structured telephone survey. West J Med 2000;172:374–377.
18. Hickman SE, Tolle SW, Tilden VP: Physicians' and nurses' perspectives on increased family reports of pain in dying hospitalized patients. J Palliat Med 2000;3:413–418.
19. Tolle SW, Haley K: Pain management in the dying . . . successes and concerns. Oregon Board of Medical Examiners Report 1998; Fall:1,4.
20. Joranson DE, Ryan KM, Gilson AM, Dahl JL: Trends in medical use and abuse of opioid analgesics. JAMA 2000;283:1710–1714.
21. Center for Evaluative Clinical Sciences (2000). The Dartmouth Atlas. Dartmouth University. <www.dartmouthatlas.org> (Last accessed May 1, 2003).
22. Lacy CF, Armstrong LL, Goldman MP, Lance LL: *Drug Information Handbook*, 7th ed. Hudson, OH: Lexicomp, Inc., 1999.
23. Janssen Pharmaceuticals: Duragesic, fentanyl transdermal system prescribing information. Titusville, NJ, 1994.

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