Use of Oral and Transdermal Opioids Among Patients with Metastatic Cancer During the Last Year of Life

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Abstract
This study documents the use of oral and transdermal opioids among patients with metastatic cancer during their final year of life. Using a large, integrated health-insurance claims database, we identified all patients who had metastatic lung, breast, colorectal, prostate, or breast cancer and who also died in 1998 or 1999. We then examined all pharmacy claims for these patients over their final 12 months of life. A total of 2,132 patients were identified who met study entrance criteria. Among patients with bone metastases \( (\text{number} = 717) \), 86.9% received opioids at some point during their final year of life; 71.2% of those without bone metastases \( (\text{number} = 1,415) \) received them. Corresponding figures for long-acting opioids were 52.9% and 23.5%. Coverage ratios (total days supplied/total noninstitutionalized days) for any opioids and long-acting opioids were 25.1% and 12.5%, respectively, among patients with bone metastases, and 13.9% and 4.2% for those without bone metastases. During the final month of life, these ratios were 50.8% and 31.3%, and 28.7% and 13.1%. These relatively low rates of opioid use among patients with metastatic cancer in their final year of life suggest that pain in many cases may be suboptimally treated.

Key Words
Neoplasms, pain, opioid analgesics, palliative care, neoplasm metastases, terminal care

Introduction
The causes of pain in patients with metastatic cancer are multiple in nature, and include tumor infiltration of bone, tumor impingement on nerves, and cancer treatment itself.\(^1\) Between 50% and 95% of patients with metastatic cancer experience pain of moderate-to-severe intensity.\(^2\) Bone metastases are probably the most common cause of moderate-to-severe pain among patients with metastatic disease;\(^1,4,10-12\) 85% of such patients report pain.\(^13\) For many patients, the pain resulting from bone metastases is persistent and increases in severity over time.\(^1\) For one-half of all patients with terminal cancer, the duration of persistent moderate-to-severe pain has been reported to be one to four
months; for one-third of such patients, it is five to eight months. Patients with metastatic disease who experience persistent pain report a significant reduction in their ability to perform daily activities, ability to sleep, relations with others, and enjoyment of life.

Opioids (e.g., morphine, hydromorphone, oxycodone, fentanyl) are “an essential part of a pain-management plan” and play a particularly critical role in the effective management of pain in patients with advanced cancer. Effective pain relief may be achieved in up to 90% of patients with metastatic cancer through the use of short- and/or long-acting opioids. The latter agents are generally preferred in these patients, because the relatively constant blood levels achieved with them provide better pain control than the “peaks” and “troughs” associated with short-acting opioids. Published clinical practice guidelines for the treatment of pain in patients with metastatic cancer recommend that long-acting opioids be administered on a regularly scheduled, “around-the-clock” basis to avoid undermedication.

Despite these guidelines, a variety of factors often limit the use of opioids in patients with advanced cancer, including inadequate education of health-care providers, patient reluctance to report pain, an inappropriate fear of opioid addiction (expressed by both health-care providers and patients), and cumbersome legal regulations governing opioid prescribing. Prior studies have identified specific groups of patients with cancer who are less likely to receive opioids, including the elderly, minorities, and females. As a result of these barriers, the pain associated with terminal cancer is frequently undertreated.

Data are limited on the magnitude of undertreatment of pain in metastatic disease, especially in the outpatient setting. Outpatient pharmacy claims potentially are an important source of information on opioid utilization in patients with advanced cancer, and probably capture the bulk of pain management for most such patients. The aim of this study was to examine the use of oral and transdermal opioids among patients with metastatic cancer during their final year of life, using a large, geographically-diverse, health insurance claims database.

**Methods**

**Overview**

Using a large, integrated, health-care claims database, we selected all patients with metastatic breast, colorectal, lung, prostate, or gynecological cancer who died between January 1, 1998 and December 31, 1999. Patients were identified based on: (1) the presence of one or more inpatient or outpatient claims with a diagnosis of breast, colorectal, lung, prostate, or gynecological cancer; and (2) one or more such claims with a diagnosis of metastases. For each such patient, all pharmacy claims were compiled over the 12-month period prior to date of death. The use of short- and long-acting opioids was then examined over this period, stratifying patients according to whether or not they had bone metastases.

**Database**

Data for this study were obtained from the Protocare Sciences Managed Care Database (MCD). The database comprises paid institutional, health-care provider, and pharmaceutical claims derived from a variety of private health-care benefit plans. The database contains private health-care claims and enrollment data representing health-care services provided through health maintenance organizations (HMO), preferred provider organizations (PPO), and specialty products (e.g., workers’ compensation) to approximately three million members annually. The plans cover a wide geographic distribution with members residing in over 20 states, primarily the South Atlantic and South Central (65%) and North Central (31%) regions of the US. These products are marketed to employer and other commercial groups as well as Medicare-eligible individuals.

and associated therapy-days dispensed, and dates of service for drugs and medical services. All claims for a given patient can be linked using unique identifiers and arrayed in chronological order to provide a detailed longitudinal profile of all medical and pharmacy services. Mortality also can be tracked using a combination of information provided by participating plans as well as records from the US Social Security Administration (available only for primary subscribers).

The database for this study encompassed the period from January 1, 1997 through December 31, 1999. All patients who met the sample-selection criteria set forth below were included in the study sample.

Sample Selection
All institutional and health-care provider claims during calendar years 1998 and 1999 were scanned to identify all patients with: (1) at least one paid facility or health-care provider claim in which a diagnosis of breast (ICD-9-CM diagnosis code 174.XX), prostate (185.XX), colorectal (153.XX, 154.0X, 154.1X), lung (162.XX), or gynecological (179.XX-184.XX) cancer was recorded as the reason for the visit or admission; and (2) at least one medical encounter (i.e., facility or health-care provider claim) in which a diagnosis of metastasis (196.XX-198.XX) cancer was recorded as the reason for the visit or admission; and (2) at least one medical encounter (i.e., facility or health-care provider claim) in which a diagnosis of metastasis (196.XX-198.XX) cancer was noted. Patients with multiple primary tumor sites (e.g., breast and colorectal) (n = 532) were excluded from the sample.

Among all such patients, attention was limited to those who died during calendar year 1998 or 1999. Deaths (and dates thereof) were ascertained on the basis of information contained in the patient eligibility file, data from inpatient facility claims (as discharge status “dead” for patients who died in hospital), and the records of the Social Security Administration.

Patients also were excluded from the study sample if they were not continuously eligible for health and drug benefits throughout the 12-month period preceding date of death, or if they were enrolled in a Medicare Supplemental Plan or capitated plan, since the Protocare Sciences MCD does not include complete claims histories for these patients.

For all remaining patients, all outpatient pharmacy claims were compiled over the 12-month period ending with the date of death. Measures and Analyses
Measures of interest included the use of short- and long-acting oral and transdermal opioids during the last year of life. Short-acting opioids were defined to include any products containing: (1) immediate-release morphine; (2) immediate-release oxycodone; (3) meperidine; (4) propoxyphene; (5) codeine; (6) tramadol; (7) pentazocine; (8) dihydrocodeine; (9) levorphanol; (10) hydrocodone; or (11) hydromorphone. Long-acting opioids were defined to include: (1) controlled-release morphine; (2) controlled-release oxycodone; (3) transdermal fentanyl; and (4) methadone hydrochloride.

The use of these medications was characterized in terms of the numbers of patients receiving them over the period of interest, as well as the corresponding numbers of prescriptions and associated days of therapy received. Medication use was assessed on the basis of information contained on paid pharmacy claims; days of therapy supplied were ascertained using the “Days Supply” field contained on each claim, which is entered by the pharmacist using directives noted by the prescribing physician (e.g., a prescription written for 90 pills to be taken three times daily would result in a prescription for 30 therapy-days).

As the Protocare Sciences MCD contains information only on prescriptions dispensed on an outpatient basis, to calculate the percentage of noninstitutionalized days that patients were “covered” by outpatient opioid therapy, we subtracted the number of days they spent in hospital or another institution from 365, and expressed the number of opioid therapy-days received as a proportion of this total number of noninstitutionalized days (“coverage ratio”). All opioid therapy-days received were assumed to be additive (e.g., two 30-day prescriptions received during a 45-day period were counted as 60 days of opioid therapy); we also assumed that therapy-days would carry over while patients were in hospital (e.g., a patient who received a 30-day prescription and was hospitalized 10 days subsequent would have 20 days of therapy remaining upon discharge from hospital).

Study measures were tabulated on an overall basis, as well as for subgroups of patients defined on the presence/absence of at least one paid claim with a diagnosis of bone metastases.
(ICD-9-CM 198.5) during their final year of life. Use of opioids was assessed in each month of the last year of life based on dates of service on paid claims.

Significance testing was not performed, as there were no prespecified hypotheses; analyses were descriptive in nature only. All analyses were performed using PC-SAS® v.8.0.

Results

Patient Characteristics

A total of 2,132 patients were identified in the study database who died in 1998 or 1999 and had at least one paid facility or health-care provider claim in which a diagnosis of breast, colorectal, lung, prostate, or gynecological cancer was noted and at least one paid facility or health-care provider claim in which a diagnosis of metastasis was noted. Most patients were over the age of 65 years (Table 1). One-third (33.6%) had one or more claims for bone metastases; most such patients had lung, prostate, or breast cancer.

Use of Opioids

The proportion of patients receiving opioids increased from 16.5% in the 12th month prior to death to 39.6% in the last month of life. Among patients with bone metastases, the percentage receiving opioids increased from 19.4% to 47.8%; corresponding values for those without bone metastases were 15.0% and 35.5% respectively (Fig. 1). The percentage of patients with and without bone metastases who had no pharmacy claims for opioids over the entire 12-month period preceding death was 13.1% and 28.8% respectively.

The proportion of patients receiving long-acting opioids increased from 2.1% in the 12th month prior to death to 16.8% in the last month of life. Among patients with bone metastases, the percentage receiving long-acting opioids increased from 3.9% to 25.0%; corresponding values for those without bone metastases were 1.2% and 12.7% respectively (Fig. 2). Approximately one-half (47.1%) of patients with bone metastases and 76.5% of those without bone metastases had no pharmacy claims for long-acting opioids during their final year of life.

The mean percentage of noninstitutionalized days on which patients were covered by opioids increased steadily throughout the last year of life, from 6.4% during the 12th month prior to death to 36.2% during the final month of life. Among patients with bone metastases, these percentages were 7.8% during the 12th month prior to death and 50.8% during

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic Characteristics of Patients with Metastatic Cancer By Presence of Bone Metastases</th>
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<tbody>
<tr>
<td></td>
<td>Bone Metastases $(n = 717)$</td>
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<tr>
<td>Age, years, n(%)</td>
<td>12</td>
</tr>
<tr>
<td>&lt;35</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>35–45</td>
<td>13 (1.8)</td>
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<tr>
<td>45–55</td>
<td>39 (5.4)</td>
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<td>55–65</td>
<td>108 (15.1)</td>
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<td>65–75</td>
<td>260 (36.3)</td>
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<tr>
<td>75–85</td>
<td>225 (31.4)</td>
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<tr>
<td>85+</td>
<td>70 (9.8)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>71.1 (10.6)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>436 (60.8)</td>
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<tr>
<td>Primary Tumor Site, n (%)</td>
<td>12</td>
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<tr>
<td>Breast</td>
<td>125 (17.4)</td>
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<tr>
<td>Colorectal</td>
<td>37 (5.2)</td>
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<tr>
<td>Gynecological</td>
<td>15 (2.1)</td>
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<tr>
<td>Lung</td>
<td>327 (45.6)</td>
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<tr>
<td>Prostate</td>
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<td>Payer type, n (%)</td>
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<tr>
<td>Indemnity</td>
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<td>Medicare HMO</td>
<td>520 (75.5)</td>
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<td>PPO</td>
<td>65 (9.1)</td>
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<tr>
<td>Other</td>
<td>21 (2.9)</td>
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</table>
Fig. 1. Percentage of patients with metastatic cancer receiving any opioids, by presence of bone metastases and one month prior to death.

the last month of life; corresponding values for patients without bone metastases were 5.6% and 28.7% respectively (Fig. 3).

The mean percentage of noninstitutionalized days on which patients were covered by long-acting opioids increased from 1.0% in the 12th month prior to death to 19.2% in the final month of life. Among patients with bone metastases, these percentages were 1.9% during the 12th month prior to death and 31.3% in the last month of life; corresponding values for patients without bone metastases were 0.6% and 13.1% respectively (Fig. 4).

Discussion

Patients with metastatic cancer often experience chronic, moderate to severe pain.2–9 While published clinical guidelines recommend the use of opioids in this setting, many patients may not be appropriately treated. We used a large, geographically diverse, health insurance claims database to examine the use of oral and transdermal short- and long-acting opioids among patients with metastatic breast, colorectal, lung, prostate, and gynecological cancer in their final year of life.

Our findings corroborate those of prior studies that have reported that cancer pain is often poorly managed during the terminal phase of the illness.1,5,12,13,16,25,26 While the number of patients receiving oral and/or transdermal opioids increased steadily throughout the final year of life, only one-third ever received a long-acting opioid. While our results indicate that patients with bone metastases were more likely to receive long-acting opioids than those without bone metastases, only one-half of the former and one-fifth of the latter received such therapy during the final year of life. After adjusting for the number of days that subjects spent in hospital, we found that those with and without bone metastases only received enough days of therapy with long-acting opioids to cover one-third and one-tenth of all noninstitutionalized days respectively during the final month of life.

It is possible that some patients who merited opioid therapy were not provided these agents due to health-care provider reluctance to prescribe them.25–27 It is equally plausible that patients did not report the severity of their pain to their health-care providers due to a fear of opioids, a feeling that they should not complain, and/or the belief that an admission of pain indicates a worsening of their disease and/or proximity of death.4 One survey of 40 patients with terminal cancer found that 60% believed that being given drugs for pain was harmful or that they should refrain from taking such therapy too often.14 Is also is possible that patients were indeed given prescriptions for opioids by their healthcare providers, but failed to fill them due to concerns about the use of these medications. Patients with metastatic cancer have been reported to be less than fully compliant with prescribed pain therapy.33–35

Pain in the elderly and among minorities appears to be particularly undertreated. In one large study of nursing-home residents with cancer who were aged 65 years or greater, only 32% of subjects who reported daily pain received one of the so-called “weak” opioids (e.g., propoxyphene) (World Health Organization
[WHO] Level 2); the number receiving one of the so-called "strong" opioids (e.g., morphine) (WHO Level 3) was only 26%.28 Eighty percent of patients in our study were 65 years of age or older. A study of the utilization of analgesia in patients with metastatic/recurrent cancer found that 65% of minorities did not receive guideline-recommended analgesia as compared with 50% of non-minority patients.5 Regrettably, the underlying reasons for low levels of opioid use among patients in our sample was beyond the scope of this investigation.

It also is possible that patients were provided with prescriptions for opioids, yet failed to fill them. Unfortunately, the study database only contained information on prescriptions filled by patients and not prescriptions written by health-care providers. Additional limitations of our study should be noted. For one, our findings are based on analyses of health insurance claims data. Of particular note, patients with metastatic cancer (as well as those with bone metastases) were identified based on a review of ICD-9-CM diagnosis codes on claims for reimbursement that were submitted by health-care providers to health insurers. Such diagnostic information is undoubtedly less accurate than that contained, for example, in patients’ medical records. Nonetheless, health-care claims data have been used in many studies to examine patterns and costs of care in patients with various disease conditions, including cancer, and have been shown to have reasonable sensitivity and specificity.36–39 Accordingly, while some patients undoubtedly were misclassified in our analysis, we suspect that the magnitude of resulting bias is small. Second, the study database contained information for approximately three million members of selected private health-care benefit plans (e.g., HMOs, PPOs) residing in 23 states; the generalizability of our findings to other health plans or settings is unknown. Third, the database that we employed contains information only on drugs that are dispensed through retail pharmacies. Thus, to the extent that patients received opioids through other channels (e.g., at physician offices and/or hospital outpatient departments, or while hospitalized), we would have underestimated their use. We believe, however, that most such medication is dispensed through retail pharmacies and that the magnitude of any bias that may have been introduced is small. Fourth, our study examined the utilization of oral and transdermal opioids only. Because of the nature of our database, we could not consider the use of subcutaneous, intravenous, and/or epidural opioids, which patients with
advanced cancer sometimes receive on an outpatient basis. We therefore may have underestimated the overall level of use of opioids in the study population. For reasons including cost, convenience, and ease of administration, however, the use of oral and transdermal opioid preparations is generally preferred.\textsuperscript{10,18,21} Furthermore, only a small percentage of patients with metastatic disease are unable to take drugs orally.\textsuperscript{10,21} We therefore do not believe that the magnitude of associated bias is large.

Finally, we lacked information on patients’ actual pain ratings. While the prevalence of moderate-to-severe pain is known to be high among those with metastatic cancer, we do not know how many patients in our sample actually experienced pain of this nature. We therefore do not know the extent to which patients in our study were actually appropriate candidates for treatment with short- and/or long-acting opioids. While all patients in our study sample had evidence of metastatic disease at some point during the year in which they died (1998 or 1999), we do not know whether they died as a result of advanced cancer versus some other unrelated cause. Accordingly, while the use of opioids—especially long-acting agents—was low in absolute terms and suggestive of suboptimal treatment, the precise magnitude of undertreatment is unknown.

In summary, our findings indicate that outpatient use of oral and transdermal opioid analgesics in patients with metastatic breast, colorectal, lung, prostate, or gynecological cancer is quite low in the final year of life. While published clinical guidelines recommend the use of opioids in this setting, many patients with advanced cancer may not receive adequate treatment for their pain.

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References


