Key opioid prescription concerns in cancer patients: A nationwide study

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Abstract

Background: Opioids are crucial in cancer pain management. We examined the nationwide prescription patterns of opioids in Taiwan cancer patients to find the potential concerns.

Methods: We reviewed the claims database of the National Health Insurance of Taiwan for patients diagnosed with cancer from 2003 to 2011. The use and cost of analgesics were analyzed. Opioids were classified into recommended strong opioids (morphine and transdermal fentanyl), recommended weak opioids (tramadol, buprenorphine, and codeine), and unrecommended opioids (propoxyphene, nalbuphine, and meperidine).

Results: We enrolled 1,424,048 patients with cancer, and ~50% of them took analgesics. Among analgesic users, patients who used opioids increased from 48.2% in 2003 to 52.0% in 2010. Approximately 92% of the opioid use came from recommended opioids, either strong (51%) or weak opioids (41%). The ratio of the use of short-acting strong opioids to that of long-acting opioids increased from 0.41 in 2003 to 0.63 in 2011. Transdermal fentanyl accounted for >50% of the use of strong opioids. Among weak opioids, the use of tramadol gradually increased to 71% in 2011. On average, opioids contributed to 0.79‰ of all medical expenditures and 2.94‰ of all medication costs.

Conclusion: The use of short-acting strong opioids increased during the study period. Instead of oral opioids, transdermal fentanyl was the most commonly used opioid among Taiwan cancer patients. The use of weak opioids, particularly tramadol, was high. These concerns should be the focus of pain management education.

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1. Introduction

Pain is one of the most common symptoms of cancer.⁴, ⁵ For example, >90% of patients with pancreatic or bone cancers have experienced pain.⁴ Approximately one-third of patients who completed curative cancer treatment continue to experience pain.⁶ Cancer pain can generally be controlled using adequate medications.⁷ An efficient management of pain ensures patient comfort. Studies have reported that early and aggressive management of symptoms, including pain, may improve patient survival.⁵, ⁶

Although opioid use for noncancer-related pain might be controversial, opioids are crucial in cancer pain management, taking into account their potency and safety.⁸, ⁹ However, not all opioids are suitable for patients with cancer. Meperidine, propoxyphene, and nalbuphine are not recommended under recent guidelines because of their mechanisms, toxicities, or addictiveness.⁸, ¹⁰ Apart from these opioids, various opioids with

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different intervals, administration routes, and potency are available in the market. Adequate pain control in patients depends on the prescription and adjustment of different opioids by physicians. However, according to recent reports from Western and Eastern countries, not all oncologists have an adequate knowledge of pain management.11–13

Previous studies on nationwide opioid use have not focused on patients with cancer.14,15 These analyses are useful for narcotic controls at government level, but may not ensure an effective understanding of the treatment of cancer pain. Therefore, a detailed examination of patients with cancer is necessary. We used the database of a mandatory, single-player, national health insurance system in Taiwan for a nationwide analysis of opioid use among patients with cancer. We aimed to identify key issues in opioid prescriptions in Taiwanese cancer patients.

2. Methods

2.1. Data sources

The National Health Insurance program in Taiwan is a mandatory single-payer system covering > 98% of the population.16 Outpatient clinic and inpatient hospitalization services provided by private and public sectors are included in a unified reimbursement system. All medical claims are electronically submitted and captured. The National Health Insurance Research Database (NHIRD) has been established for research purposes, based on the accumulated claims. The NHIRD contains a complete history of diagnoses, outpatient visits, hospital admissions, medical procedures, and medication prescriptions for all beneficiaries. To comply with personal electronic data privacy regulations, personal identities were encrypted, and all data were anonymously analyzed. Furthermore, study data were approved for release by the Data Release Review Board of the Collaboration Center of Health Information Application, Ministry of Health and Welfare, Executive Yuan. The study protocol was approved by the Research Ethics Committee of the National Taiwan University Hospital, Taipei, Taiwan.

2.2. Study population

All in- or outpatient clinical visits with the diagnosis of cancer (ICD-9-CM: 140–208) from January 1, 2003 to December 31, 2011 were included. If patient clinical visits were in different calendar years, every annual record was considered to be an independent case. Thus, we constructed a total of nine cohorts according to the calendar years.

2.3. Definitions of analgesic use

All drug prescription records were mapped to the World Health Organization (WHO) anatomical therapeutic chemical (ATC) classification system. Analgesics, both opioids and non-opioids were analyzed. We classified all available opioids into three categories (recommended strong opioids: morphine and transdermal fentanyl; recommended weak opioids: tramadol, buprenorphine, and codeine; and unrecommended opioids: propoxyphene, nalbuphine, and meperidine; Table 1). Hydromorphone, oxycodone, methadone, hydrocodone, and oxymorphone were unavailable during the study period.

Patients who received at least one prescription for a particular analgesic (both opioid and non-opioid) were categorized as its user. We used the defined daily dose (DDD) published by WHO to calculate and compare the use of various opioids. DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.17 For instance, DDD for oral morphine is 100mg, thus, a patient who received 60 mg of long-acting morphine per day was defined as receiving 0.6 DDD per day. The cumulative opioid use was calculated as the total prescribed DDD in the same calendar year.

2.4. Data analysis

SAS statistical software version 9.3 (SAS Institute, Cary, NC, USA) was used for all data analyses. To compare the use of different opioid categories, all opioid users were considered. To compare the use of specific opioids of an opioid category, we only analyzed patients who used opioids of the specific categories.

3. Results

In total, 1,424,048 patients with cancer were enrolled. Patient demographic data are listed in Table 2. The median age was 60 years. The most common primary sites of malignancy were the colon and rectum (14.8%), liver (12.4%), lung (9.8%), breast (8.9%), and prostate (5.0%). Among all patients, percentages of patients who used analgesics of all types and opioid analgesics (approximately 50% and 25%, respectively) were consistent during the study period. (Figures 1A and 1B). However, among patients who took analgesics, the percentage of opioid users increased from 48.2% in 2003 to 52.0% in 2010 (Figure 1C); although this percentage decreased to 51.0% in 2011, it was higher than that reported from 2003 to 2008.

Regardless of cumulative doses and drug potency, more patients received weak opioids than strong opioids. The percentage of patients who had used strong opioids (44.4–48.3%) remained consistent during the study period, whereas that of patients who had used weak opioids increased from 52.1% in 2003 to 69.1% in 2011 (Figure 1D). The percentage of patients who used unrecommended opioids decreased from 66.7% in 2003 to 45.7% in 2011.

Next, we calculated the annual cumulative opioid use according to the DDD. The use of all opioids increased from 41.8 in 2003 to 44.6 in 2009 but gradually decreased to 39.2 in 2011. This decrease was mainly caused by the decline in the use of strong opioids (Figure 2A). During the study, ~92% of opioid use was attributed to recommended opioids, either strong (51%) or weak opioids (41%; Figure 2A). Unrecommended opioids contributed little to the total opioid use; although the use of unrecommended opioids increased to 11% among all opioids in 2008 and 2009, it decreased to 2% in 2011. Transdermal fentanyl was the most commonly used strong opioid (Figure 2B). However, its use among the use of all strong opioids decreased from 60% in 2003 to 51% in 2011 (Table 3). Oral long-acting morphine contributed to only ~10% of the total use of strong opioids. The ratio of the use of short-acting strong opioids to long-acting strong opioids increased from 0.41 in 2003 to 0.63 in

<table>
<thead>
<tr>
<th>Categories</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended strong opioids</td>
<td>Long-acting morphine (interval ≥ 12 h) Transdermal fentanyl</td>
</tr>
<tr>
<td>Recommended weak opioids</td>
<td>Tramadol-containing medications Codeine Buprenorphine</td>
</tr>
<tr>
<td>Unrecommended opioids</td>
<td>Propoxyphene-containing medications Nalbuphine Meperidine</td>
</tr>
</tbody>
</table>
2011. Furthermore, tramadol and codeine equally contributed to the use of weak opioids from 2003 to 2006 (Figure 2C). The use of tramadol gradually increased to 71% of that of all weak opioids. Conversely, the use of codeine decreased since 2006 (Table 3). The use of buprenorphine remained limited. The use of unrecommended opioids was low (Figure 2D), and propoxyphene was the most frequently used among them. The use of propoxyphene considerably decreased in 2011 because its commercial use was banned by the government because of toxicity concerns.

All expenditures and medication costs of the NHI increased during the study period (Figure 3A). On average, opioid costs for patients with cancer contributed to 0.79‰ of all expenditures and 2.94‰ of all medication costs. Opioid costs for cancer patients compared with all medication costs fluctuated from 2003 to 2009 but decreased since 2009, reaching 2.55‰ in 2011 (Figure 3B). The average annual cost of all opioids for patients with cancer was United States (US)$10.8 million. Moreover, an average of US$7.5 million and US$2.9 million were spent on strong and weak opioids, respectively (Figure 3C). Transdermal fentanyl contributed the most (~80.5%) to the cost of strong opioids, and its average annual cost was US$6.0 million (Figure 3D). The costs of tramadol-containing medications increased from US$2.2 million in 2003 to US$3.4 million in 2011 (Figure 3E). The costs of unrecommended opioids were very limited (Figure 3F).

### Table 2

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>( n ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1,424,048 (100)</td>
</tr>
<tr>
<td>Male</td>
<td>751,797 (52.8)</td>
</tr>
<tr>
<td>Female</td>
<td>672,251 (47.2)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>210,761 (14.8)</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile ducts</td>
<td>177,119 (12.4)</td>
</tr>
<tr>
<td>Lung</td>
<td>139,069 (9.8)</td>
</tr>
<tr>
<td>Breast</td>
<td>127,336 (8.9)</td>
</tr>
<tr>
<td>Prostate gland</td>
<td>71,801 (5.0)</td>
</tr>
<tr>
<td>Oral cavity, oropharynx, &amp; hypopharynx</td>
<td>71,246 (5.0)</td>
</tr>
<tr>
<td>Renal pelvis &amp; bladder</td>
<td>55,239 (3.9)</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>53,856 (3.8)</td>
</tr>
<tr>
<td>Cervix of uterus</td>
<td>50,893 (3.6)</td>
</tr>
<tr>
<td>Stomach</td>
<td>49,257 (3.5)</td>
</tr>
<tr>
<td>Others</td>
<td>417,471 (29.3)</td>
</tr>
</tbody>
</table>

SD = standard deviation

Figure 1. (A) Total number of patients and patients who used analgesics (bars), and the percentage of patients who used analgesics (line); (B) total number of patients and patients who used opioids (bars), and the percentage of patients who used opioids (line); (C) percentage of patients who used opioids among all patients who used analgesics; (D) percentages of patients who have used the specific opioid categories among patients who used opioids.
4. Discussion

This nationwide study revealed several key concerns in opioid prescription for patients with cancer. Although most patients received guideline-recommended opioids, the use of short-acting strong opioids was high compared with long-acting strong opioids. Transdermal fentanyl was the most commonly used strong opioid. Weak opioids, particularly tramadol, were frequently used for Taiwanese patients with cancer. These concerns should be the focus of future educational programs.

As per our review of relevant literature, this study is the first to specifically focus on the nationwide opioid prescription to patients with cancer. Previous nationwide studies mostly analyzed opioid use in all patients, and may not be ideal in studying cancer pain management.4,15,18 Although our study is based in Taiwan, our findings may not be restricted to Taiwan. For instance, studies conducted in European countries have reported an extremely high use of transdermal fentanyl.19,20 Exploring whether the concerns identified in this study exist among physicians from different countries is crucial for improving the wellbeing of patients with cancer.

The ratio of the use of short-acting opioids to that of long-acting opioids gradually increased from 0.41 in 2003 to 0.63 in 2011. According to guidelines, the dose of short-acting opioids for breakthrough pain should be 10–20% of the daily dose of long-acting opioids. An adequate adjustment of long-acting opioids can avoid the breakthrough pain, and thus avoid the frequent use of short-acting rescue medications. In this study, an increasing proportion of patients used opioids for cancer pain management. However, the increase in the ratio of the use of short-acting opioids to that of long-acting opioids implied that these short-acting opioids were more commonly used in new opioid users, which may not be ideal.

### Table 3

<table>
<thead>
<tr>
<th>Drug class</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong opioids</td>
<td>51.1 (100)</td>
<td>46.9 (100)</td>
<td>46.4 (100)</td>
<td>47.5 (100)</td>
<td>46.0 (100)</td>
<td>45.9 (100)</td>
<td>49.2 (100)</td>
<td>46.1 (100)</td>
<td>41.3 (100)</td>
</tr>
<tr>
<td>Transdermal fentanyl</td>
<td>30.7 (60)</td>
<td>27.2 (58)</td>
<td>25.2 (54)</td>
<td>24.8 (52)</td>
<td>23.7 (51)</td>
<td>24.4 (53)</td>
<td>26.8 (55)</td>
<td>24.0 (52)</td>
<td>21.2 (51)</td>
</tr>
<tr>
<td>Long-acting morphine</td>
<td>5.4 (11)</td>
<td>4.8 (10)</td>
<td>4.6 (10)</td>
<td>4.7 (10)</td>
<td>4.5 (10)</td>
<td>4.2 (9)</td>
<td>4.5 (9)</td>
<td>4.2 (9)</td>
<td>4.2 (10)</td>
</tr>
<tr>
<td>Short-acting morphine</td>
<td>15.0 (29)</td>
<td>14.9 (32)</td>
<td>16.6 (36)</td>
<td>18.0 (38)</td>
<td>17.6 (39)</td>
<td>17.3 (38)</td>
<td>17.9 (36)</td>
<td>17.9 (39)</td>
<td>15.9 (38)</td>
</tr>
<tr>
<td>Weak opioids</td>
<td>33.3 (100)</td>
<td>32.0 (100)</td>
<td>31.8 (100)</td>
<td>32.1 (100)</td>
<td>30.9 (100)</td>
<td>30.3 (100)</td>
<td>28.5 (100)</td>
<td>27.5 (100)</td>
<td>26.9 (100)</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>1.1 (3)</td>
<td>1.1 (4)</td>
<td>0.8 (3)</td>
<td>0.7 (2)</td>
<td>0.6 (2)</td>
<td>0.5 (2)</td>
<td>0.4 (1)</td>
<td>0.3 (1)</td>
<td>0.2 (1)</td>
</tr>
<tr>
<td>Codeine</td>
<td>15.1 (45)</td>
<td>14.4 (45)</td>
<td>15.3 (48)</td>
<td>15.5 (48)</td>
<td>12.8 (41)</td>
<td>11.2 (37)</td>
<td>9.7 (34)</td>
<td>8.5 (31)</td>
<td>7.5 (28)</td>
</tr>
<tr>
<td>Tramadol-containing medication</td>
<td>17.1 (51)</td>
<td>16.5 (51)</td>
<td>15.7 (49)</td>
<td>15.9 (50)</td>
<td>17.6 (57)</td>
<td>18.6 (61)</td>
<td>18.4 (63)</td>
<td>18.7 (68)</td>
<td>19.3 (71)</td>
</tr>
<tr>
<td>Unrecommended</td>
<td>2.6 (100)</td>
<td>3.8 (100)</td>
<td>5.5 (100)</td>
<td>6.3 (100)</td>
<td>7.1 (100)</td>
<td>7.6 (100)</td>
<td>7.9 (100)</td>
<td>6.6 (100)</td>
<td>1.5 (100)</td>
</tr>
<tr>
<td>Meperidine</td>
<td>0.9 (34)</td>
<td>0.8 (20)</td>
<td>0.7 (12)</td>
<td>0.6 (10)</td>
<td>0.6 (8)</td>
<td>0.5 (7)</td>
<td>0.5 (7)</td>
<td>0.5 (7)</td>
<td>0.5 (32)</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>0.0 (0)</td>
<td>0.1 (3)</td>
<td>0.2 (4)</td>
<td>0.2 (3)</td>
<td>0.2 (3)</td>
<td>0.3 (4)</td>
<td>0.3 (4)</td>
<td>0.4 (5)</td>
<td>0.4 (28)</td>
</tr>
<tr>
<td>Propoxyphene-containing medication</td>
<td>1.7 (66)</td>
<td>2.9 (77)</td>
<td>4.0 (84)</td>
<td>5.5 (88)</td>
<td>6.4 (89)</td>
<td>6.8 (89)</td>
<td>7.1 (89)</td>
<td>5.8 (88)</td>
<td>0.6 (39)</td>
</tr>
</tbody>
</table>

Figure 2. (A) Annual cumulative defined daily dose (DDD) per patient of the specific opioid categories for patients who used opioids; (B–D) annual cumulative DDD of specific opioids among (B) strong opioids; (C) weak opioids; (D) unrecommended opioids, for patients who used the specific opioid categories.
Continued education about pain management, both for physicians and patients, should be advocated to improve the understanding of reasonable opioid use.

Although many guidelines acknowledge transdermal opioids as an alternative to oral opioids,\textsuperscript{8-10} it is still surprising to find that transdermal fentanyl was the most commonly used strong opioid. Its use was approximately three- to four-fold higher than that of long-acting oral morphine. The oral route was generally considered to be the most common approach for providing long-term pain control, and the transdermal route was suggested to be reserved for patients with stable opioid requirements.\textsuperscript{9,10} The high use of transdermal fentanyl may be associated with the unavailability of hydromorphone and oxycodone during the study, which significantly limited the choice of oral strong opioids. However, a previous report of nine West European countries also reported the high use of transdermal fentanyl.\textsuperscript{19} Other potential reasons, such as an inadequate knowledge of pain management, should be further explored.

Weak opioids played a substantial role in cancer pain management in Taiwan. The use of weak opioids contributed to \textasciitilde 40\% of all opioid use. Although the WHO guidelines suggest a step-by-step analgesic use from non-opioids to weak opioids, then to strong opioids,\textsuperscript{21} recent guidelines have emphasized the importance of opioids, particularly strong opioids, in patients with cancer.\textsuperscript{8-10} The National Comprehensive Cancer Network guideline does not clearly categorize opioids into strong and weak opioids, and the guidelines from European Society of Medical Oncology and European Association of Palliative Care considers the direct use of strong opioids in opioid-naïve patients a reasonable choice.\textsuperscript{8-10} These suggestions were attributed to the lack of evidence showing the superior efficacy of weak opioids to non-opioids for cancer pain management.\textsuperscript{22} Moreover, most patients with cancer who received these weak opioids eventually opted for strong opioids.\textsuperscript{23} Whether the use of weak opioids increased because of their efficacy or the reluctance of physicians in using strong opioids warrants investigation.

Figure 3. (A) Annual costs of all expenditures and all medications; (B) annual opioid costs compared with all expenditures and medication costs; (C) annual costs of opioids summarized in opioid categories; (D) annual costs of specific strong opioids; (E) annual costs of specific weak opioids; (F) annual costs of specific unrecommended opioids.
Although the increased use of transdermal fentanyl and weak opioids may be a deviation from the guideline suggestions, the use of unrecommended opioids was minimal in this study. Many patients had been exposed occasionally to these medications; however, the actual use of these opioids was extremely low. After propoxyphene was withdrawn from the market, these unrecommended opioids only contributed to 2% of all opioid use in 2011.

This study has some limitations. First, we did not have data on the tumor stages. We could not determine whether changes in opioid use resulted from the differences in stage distribution. We did not have access to pain records; therefore, the choice of opioids could not be analyzed in detail. No information was available about the actual indication of prescriptions; consequently, the use of certain drugs on pain may be overestimated. For instance, codeine may serve as an antitussive for severe cough, and meperidine may be used as a substitute for morphine, but this information is unknown. We could not determine whether changes in opioid use resulted from the differences in stage distribution. We did not have access to pain records; therefore, the choice of opioids could not be analyzed in detail.

In conclusion, we observed several concerns regarding opioid prescription to Taiwanese patients with cancer. The use of short-acting strong opioids increased compared with that of long-acting opioids. Transdermal fentanyl was the most commonly used strong opioid for Taiwanese patients with cancer. The use of weak opioids, particularly tramadol, was high. These factors should be considered in pain management education.

Acknowledgments

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