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Research Paper

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.

1. Introduction

Pain is one of the most common symptoms of cancer.[1,2] For example, > 90% of patients with pancreatic or bone cancers have experienced pain.[1] Approximately one-third of patients who completed curative cancer treatment continue to experience pain.[2] Cancer pain can generally be controlled using adequate medications.[3] An efficient management of pain ensures patient comfort. Studies have reported that early and aggressive management of symptoms, including pain, may improve patient survival.[4,5]

Although opioid use for noncancer-related pain might be controversial, opioids are crucial in cancer pain management, taking into account their potency and safety.[6,7] 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.

Table 1
Opioids available for cancer pain management in Taiwan during the study period.

Categories	Medication
Recommended strong opioids	Long-acting morphine (interval ≥ 12 h)
	Short-acting morphine
	Transdermal fentanyl
Recommended weak opioids	Tramadol-containing medications
	Codeine
	Buprenorphine
Unrecommended opioids	Propoxyphene-containing medications
	Nalbuphine
	Meperidine

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