Title page

1) Title: Recent trends in opioid consumption in South Korea from 2002 to 2015, based on the Korean NHIS-NSC cohort

2) Running Title: Opioid consumption trends in Korea

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Abstract

Objectives: Opioids are prescribed to treat moderate-to-severe pain. We aimed to investigate the recent trends in opioid (morphine, oxycodone, fentanyl, and hydromorphone) consumption using data from the Korean National Health Insurance Service-National Sample Cohort between 2002 and 2015.

Methods: Morphine milligram equivalent (MME) was calculated to standardize the relative potency of the opioids. The number (cases) or amount (MME) of annual opioid prescription per 10,000 registrants was computed to analyze trends of consumption of opioids after age standardization. Joinpoint regression analysis was conducted to calculate the annual percentage change and average annual percentage change (AAPC).

Results: The number (cases) of prescriptions per 10,000 registrants increased from 0.07 in 2002 to 41.23 in 2015 (AAPC [95% CIs], 76.0% [61.6–91.7%]). The MME per 10,000 registrants increased from 15.06 in 2002 to 40,727.80 in 2015 (AAPC [95% CIs], 103.0% [78.2–131.3%]). The highest AAPC of prescriptions and MME per 10,000 registrants were observed in the elderly (60–69 years) and at general hospitals. Fentanyl prescription increased most rapidly among four opioids.

Conclusions: Consumption of opioids greatly increased in South Korea over 14 years.

Keywords: analgesics, opioid; fentanyl; hydromorphone; morphine; pain; oxycodone

Introduction

Pain is defined by the International Association for the Study of Pain as an unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage [1]. Pain, also known as the fifth vital sign, has a significant impact on poor prognosis and patient quality of life [2]. According to a systematic review in 2016 [3], approximately 30 – 50% of patients suffered from moderate-to-severe pain, and the proportion of patients with pain increased in those with more advanced diseases. In particular, the prevalence of moderate-to-severe pain among all cancer patients was more than 80%, and approximately 60% of patients felt that their pain was adequately managed [4]. The prevalence of chronic non-cancer pain varies by country, with the US reporting 30% and European countries 19% [5, 6].

According to the three-step analgesic ladder to relieve cancer pain by the World Health Organization (WHO), opioids are very important drugs to treat moderate-to-severe pain [7]. Recent pain management guidelines recommend that doctors prescribe analgesics such as opioids depending on patient symptom severity [8]. The consumption of opioids has markedly increased in many Asian countries including Taiwan, Malaysia, and Singapore in addition to Western countries such as US, Canada, and European countries [9-12]. However, there is lack of studies to demonstrate the trends in prescribed strong opioids in South Korea (hereinafter, Korea).

Therefore, the purpose of this descriptive study is to provide the recent trends in opioid prescriptions in terms of cases (prescription numbers) and amounts (morphine milligram equivalent [MME]) in Korea over 14 years (from 2002 to 2015) using data from the Korean National Health Insurance Service (NHIS)-National Sample Cohort (NSC).

Methods

Study population and total prescriptions

This study was conducted on adults older than 20 years in the National Health Insurance Service-National Sample Cohort (NHIS-NSC) between 2002 and 2015. Most Koreans subscribe to obligatory universal national health insurance provided by the Korean NHIS. The sample size of the NHIS-NSC database is approximately one million, comprising 2% of randomly selected Koreans who had maintained the qualifications for at least 1 year as of December 2006. To secure representation of the Korean population, stratified sampling was performed considering sex, age, income level, and region. The registered subjects were followed from January 1, 2002 to December 31, 2015. The NHIS-NSC data provide subject medical history records, such as diagnosis codes, prescription details, and health screening results between 2002 and 2015. In addition, the cohort data include socio-demographic information, such as age, sex, death, past medical history (e.g., malignant neoplasm, hypertension, and diabetes), health behaviors (e.g., physical activity, cigarette smoking, and alcohol intake), monthly household income, and information from the healthcare unit that patients visited. The detailed explanation of the NHIS-NCS was published previously [13]. Because the year of qualification was 2006, no death was observed until 2006. To maintain the age structure over time, approximately 9,000 newborns had been added to the dataset every year since 2006.

The Institutional Review Board (IRB) of Chungbuk National University Hospital approved this study (CBNUH-2019-12-034) and waived the requirement of informed consent from study participants due to anonymity of the data obtained from the NHIS database. All research procedures followed the 1964 Declaration of Helsinki and were conducted in accordance with the relevant guidelines and regulations.

Definition and Variables

The opioids considered in our analysis were morphine, oxycodone, fentanyl, and hydromorphone. The primary interests were trends in number (or amount) of annual opioid prescriptions during the study period as follows: (1) number of annual opioid prescriptions (cases) per 10,000 people and (2) amount of annual opioid prescriptions per 10,000 registrants expressed as morphine milligram equivalent (MME). The MME of each opioid reflects its analgesic potency relative to morphine. Based on the prescription information of NHIS-NSC data, MME was computed as “strength per unit $\times$ (daily dose count $\times$ one dose) $\times$ MME conversion factor” to standardize the potency across opioids or dose formulations (e.g., tablet or patch). MME conversion factors were obtained from the literature [14]. In addition, the annual trends of opioid were investigated in subgroups of age, type of medical institute, and opioid type. Medical institute type was categorized into three groups as follows: a) general hospital, a medical institution with more than 100 beds and several specialized departments as designated by law; b) hospital, a medical institution with 30 to 99 beds; and c) clinic, a medical institution with less than 30 beds.

Statistical Analysis

The annual number (or amount) of opioids per 10,000 registrants was calculated by dividing the total number (or amount) of opioid prescriptions in a year by the number of registered people at the beginning of the study year and multiplying by 10,000. To account for the age changing structure of data, we applied age-standardization in each year to the standard population, which was the 2002 Korean population structure. Furthermore, the joinpoint regression analysis was performed to detect significant change [15]. The overall trend from 2002 to 2015 was calculated as average annual percentage change (AAPC). When

the trend changed significantly, the trends of shorter time segments were calculated at an annual percentage change (APC). APC and AAPC were marked with 95% confidence intervals (CIs). All p-values were two-tailed, and statistical significance was set at $p < 0.05$. The statistical package SAS enterprise guide version 7.1 (SAS Inc., Gary, NC), R Studio version 3.3.3, and Joinpoint version 4.7.0.0 (National Cancer Institute) were used to perform the analyses in this study.

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Results

Baseline characteristics of the study population

Table 1 shows the baseline characteristics of the study population. The median age of subjects increased from 40.0 years in 2002 to 47.0 years in 2015. During the study period, the number of individuals newly prescribed opioids increased over time from 3 to 941 individuals. In particular, the number of new opioid users abruptly increased from 58 to 247 individuals between 2008 and 2009.

Trends in opioid consumption

Table 2 presents the age-standardized annual opioid prescription number (cases) per 10,000 registrants. The cases per 10,000 registrants increased from 0.07 (0.03 in men and 0.10 in women) in 2002 to 41.23 (40.96 in men and 41.15 in women) in 2015. The cases per 10,000 registrants tended to increase continuously in the elderly. Table 3 demonstrates the age-standardized amount of annual opioid prescriptions as MME per 10,000 registrants. The overall MME per 10,000 registrants increased from 15.06 (0.85 in men and 28.89 in women) in 2002 to 40,727.80 (45,263.38 in men and 35603.54 in women) in 2015. Similar to the results presented in Table 2, increasing trends were observed in all subgroups.

Joinpoint regression analysis for trends in opioid consumption

Figure 1 demonstrates the trends of age-standardized amount of annual opioid prescription as number (cases) per 10,000 registrants from the joinpoint analysis. The AAPC (95% CI) of the cases per 10,000 registrants in total, in men, and in women was 76.0% (61.6 – 91.7%), 79.3% (53.6 – 109.4%), and 69.7% (55.5 – 85.2%), respectively. In men, a single joinpoint was estimated in 2011. The APCs (95% CIs) were significant (106.4 [79.3–

137.6%]) between 2002 and 2011 but not between 2011 and 2015.

Figure 2 presents the age-standardized trends in the amount of annual opioid prescription as MME per 10,000 registrants. The overall trends represented as AAPC (95% CIs) were 103.0% (78.2 – 131.3%), 121.2% (80.5 – 171.0%), and 94.5% (66.7 – 126.8%) in total, in men, and in women, respectively. Similar to the results from Figure 1, joinpoint was identified only for men in 2010. The APCs (95% CIs) were significant (198.4% [136.0 – 277.2%]) between 2002 and 2010 but not between 2010 and 2015.

Further joinpoint regression analyses were performed by age group, medical institute, and opioid type (Supplementary Tables 1 & 2 and Supplementary Figures 1 & 2). Based on the annual number (cases) of opioid prescription per 10,000 registrants, 30-39 years, 60-69 years, and 70-79 years had a single joinpoint at 2006, 2005, and 2004, respectively. By opioid type, fentanyl had a joinpoint in 2008, while hydromorphone had two joinpoints in 2007 and 2010. In terms of the annual amount (MME) of opioid prescription per 10,000 registrants, 60-69 years and ≥ 70 years had a single joinpoint in 2005 and 2004, respectively. By opioid type, fentanyl had a joinpoint in 2005, while hydromorphone had two joinpoints in 2007 and 2010.

Discussion

The number and amount of annual opioid prescriptions have increased over the studied 14 years in Korea. AAPCs were dominant in the elderly population, patients in general hospitals, and patients receiving potent opioid such as fentanyl and hydromorphone.

Use of morphine is known as an indicator for cancer pain treatment by the WHO [16, 17]. Morphine consumption has not increased in several countries since 2000, while increased use of other opioids, such as fentanyl and oxycodone, has been reported in many countries [18-22]. Although the quantity of morphine prescriptions has not increased greatly, there continue to gradually increase many prescriptions for morphine. Other Korean study is consistent with this study. Oh et al. reported that chronic opioid use has increased since 2002 in this study [23]. The study demonstrated that chronic use of strong opioid was associated positively with a 5-year mortality while weak opioid use was inversely related to mortality in South Korea [23]. Although opioid use is a good indicator of pain control for cancer patients, it should be used with caution.

Several factors appear to contribute to the increasing trends in overall consumption of opioids. First, the number of patients in the elderly population increased. Age is closely associated with increasing opioid consumption [24]. Studies from European countries between 2000 and 2010 reported that consumption of strong opioids was highest among patients aged 66–80 years [21, 25]. One study from Malaysia showed that opioid prescriptions increased with patient age (11% in the 40s, 19% in the 50s, and 47.28% in the 60–80s) [25]. Elderly people consume more opioids due to pain from multiple comorbidities. Second, the prevalence of diseases that cause pain, such as cancer and musculoskeletal diseases, increased [26]. Opioids are the most used drugs to control cancer pain [2, 27]. In

2017, there was a total of 232,255 new cancer cases in Korea [28]. Furthermore, the number of cancer survivors has been increasing due to high incidence rate of cancers and improved survival rates [28]. In addition, the Korean Ministry of Health and Welfare has supported more hospice and palliative care services since 2009 [29]. Because cancer is recorded with a special code, patients with cancer pay five percent of their total hospital costs and the remaining hospital costs are paid by the NHIS. Thus, low out-of-pocket payment of cancer patients might result in more active pain management and increased prescriptions of pain medications such as opioids. In addition to the increased number of cancer patients as one factor influencing the upward trend in opioid consumption in Korea, opioid consumption has been gradually rising among non-cancer diseases, including diseases that cause musculoskeletal pain [27]. Third, some new opioids were launched after 2000. Oxycodone was launched in the Korean market in 2001 and have taken, together with fentanyl, part of the market share of morphine. Hydromorphone was introduced to Korea in 2006, and since 2009, Korean national insurance covered its use in treatment for cancer pain, which might have contributed to the dramatically increased consumption of hydromorphone. A sharp increase in use of fentanyl, oxycodone, and hydromorphone was identified. Higher growth rates for fentanyl, oxycodone, and hydromorphone use have been observed in other countries [18, 20, 21]. Fourth, awareness of active pain management has improved. The Korean Ministry of Health and Welfare launched pilot research for hospice and palliative care in 2005 and piloted a new payment system in 2009 [29]. The introduction and stabilization of hospice and palliative care improved awareness and policy, such as insurance coverage, which supported more active management of pain.

This study has several limitations. First, the data contained no clinical information on compliance with opioid medication. Second, only strong opioids (morphine, fentanyl,

oxycodone, and hydromorphone) were included in the analyses. Weak opioids, such as codeine and tramadol, are more commonly used but are not finely controlled by the Korean health authorities. Thus, it is difficult to know and estimate how many prescriptions of weak opioids were issued. On the contrary, because the Korean health authorities tightly regulate prescription of strong opioids, we can estimate relatively accurate usage trends. Third, the cohort from the Korean NHIS-NSC database was operated as a partly closed system. Only newborn infants were newly enrolled during the study period after baseline. Thus, accumulation of double-counted people in each year might have contributed to the increasing pattern of opioid consumption. To minimize these errors, we calculated total MME per year per 10,000 registrants after age-standardization. In addition, the number of patients who were newly prescribed opioids increased from 3 individuals in 2002 to 941 individuals in 2015. Fourth, since the clinical outcomes were not evaluated (e.g., whether patient symptoms such as pain were improved after administration of opioids), it was not possible to determine whether consumption of opioids directly indicated an improvement in pain control. Fifth, we could not compare the increasing trends of opioid prescriptions with other pain killers such as acetaminophen or non-steroidal anti-inflammatory drugs as a control. Because these drugs are available without a prescription in south Korea, the exact amount of usage is infeasible. If a comparison between opioids and painkillers was possible, a more accurate trend would have been known. As an alternative method, we investigated age-standardized trends of opioid use. Changes in the age structure of the study population have a great impact on such epidemiologic studies.

There are several strengths in the present study. First, trends in both the number and amount of prescribed opioids over a period of 14 years were investigated using a nationally representative cohort. Second, trends in both the number and amount of annual opioid

prescriptions per 10,000 registrants were estimated. There are a few reports that used a national patient sample of Health Insurance Review and Assessment (HIRA) claims data in Korea, and the study analyzed the pattern of opioid prescription [30]. Third, long-term and short trends were examined. After AAPCs for the entire study period were estimated, we calculated segmental short-term trends. This approach allows us to infer factors influencing the increasing trends.

In summary, opioid use disorder and overdose deaths currently pose a great threat to public health in the US [31], while Europe does not appear to be facing an opioid crisis [32]. On the contrary, underuse was more of a problem in South Korea, as Korean culture forbids opioid use and the Korean government strictly regulates strong opioids. However, this study reported that opioid consumption, which is calculated as the total prescription cases (numbers) and amount (MME), markedly increased over 14 years from 2002 to 2015 in South Korea. These increasing patterns are prominent in the elderly population, general hospitals, and potent opioids (fentanyl and hydromorphone). These findings that the legal use of opioids has increased support an improved awareness of the importance of pain control over time. These increasing trends in opioid prescriptions and use in Korea will be very helpful in relieving and managing pain for patients suffering from severe pain. However, policy-making to prevent misuse, dependence, addiction, and death from overuse is required.

List of abbreviations

AAPC: average annual percentage change; APC: annual percentage change; HIRA: health insurance reivew and assessment; IRB: institutional review board; MME: morphine milligram equivalent; NHIS: national health insurance service; NSC: national sample cohort; WHO: world health organization

Authors' contributions

Conceptualization, GY, HSK, JWL, JK, and HTK.; methodology, SJS, HSK, JK, and HTK.; statistical analysis, SJS, HSK, JWL, and JK; interpretation, GY, JK, JWL, YSK, HSY, and HTK; writing—original draft preparation, GY, HSK, JWL, JK, and HTK.; funding acquisition, HTK. All authors have read and agreed to the published version of the manuscript.

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Competing interest:

None declared.

Availability of data and materials

Korean National Health Insurance Sharing Service (NHIS) provides this cohort data (URL: <https://nhiss.nhis.or.kr/>).

References

1. Treede RD. The International Association for the Study of Pain definition of pain: as valid in 2018 as in 1979, but in need of regularly updated footnotes. *Pain Rep* 2018; 3(2): e643.
2. Wiffen PJ, Wee B, Derry S, Bell RF, Moore RA. Opioids for cancer pain - an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2017;7(7): Cd012592.
3. van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, Tjan-Heijnen VC, Janssen DJ. Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. *J Pain Symptom Manage* 2016;51(6):1070-1090.
4. Ho KY, Ahn JS, Calimag MM, Chao TC, Kim YC, Moon H, et al. Inadequate treatment practices for pain relief and adverse event management in cancer patients across 10 countries/regions in Asia: a call for greater efforts to improve standards for patient care. *Asia Pac J Clin Oncol* 2018;14(3):159-166.
5. Johannes CB, Le TK, Zhou X, Johnston JA, Dworkin RH. The prevalence of chronic pain in United States adults: results of an Internet-based survey. *J Pain* 2010;11(11): 1230-1239.
6. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain* 2006;10(4):287-333.
7. Ventafridda V, Saita L, Ripamonti C, De Conno F. WHO guidelines for the use of analgesics in cancer pain. *Int J Tissue React* 1985;7(1):93-96.
8. Swarm RA, Paice JA, Anghelescu DL, Are M, Bruce JY, Buga S, et al. Adult Cancer Pain, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2019;17(8): 977-1007.

9. 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.
10. Bosetti C, Santucci C, Radrezza S, Erthal J, Berterame S, Corli O. Trends in the consumption of opioids for the treatment of severe pain in Europe, 1990-2016. *Eur J Pain* 2019;23(4):697-707.
11. Kang KH, Kuo LF, Cheng IC, Chang CS, Tsay WI. Trends in major opioid analgesic consumption in Taiwan, 2002-2014. *J Formos Med Assoc* 2017;116(7):529-535.
12. Zin CS. Ten Years of Strong Opioid Analgesics Consumption in Malaysia and Other Southeast Asian Countries. *J Pharm Bioallied Sci* 2020;12(Suppl 2):S846-s851.
13. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort Profile: The National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. *Int J Epidemiol* 2017;46(2):e15.
14. Centers for Medicare & Medicaid Services. Opioid oral morphine milligram equivalent (MME) conversion factors. [cited 2021 Nov 1]. Available from: <https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-April-2017.pdf>.
15. National Cancer Institute., Joinpoint trend analysis software. [cited 2021 Nov 1]. Available from: <https://surveillance.cancer.gov/joinpoint/>
16. Zin CS, Chen LC, Knaggs RD. Changes in trends and pattern of strong opioid prescribing in primary care. *Eur J Pain* 2014;18(9):1343-1351.
17. World Health Organization. Cancer Pain Relief with a guide to opioid availability. 1986. [cited 2021 Nov 1]. Available from:

<https://apps.who.int/iris/bitstream/handle/10665/37896/9241544821.pdf;jsessionid=8FDC926A6865AE6B820DF1E6A4D787AD?sequence=1>

18. Hamunen K, Paakkari P, Kalso E. Trends in opioid consumption in the Nordic countries 2002-2006. *Eur J Pain* 2009;13(9):954-962.
19. Kalkman GA, Kramers C, van Dongen RT, van den Brink W, Schellekens A. Trends in use and misuse of opioids in the Netherlands: a retrospective, multi-source database study. *Lancet Public Health* 2019;4(10):e498-e505.
20. Hider-Mlynarz K, CavaliP, Maison P. Trends in analgesic consumption in France over the last 10 years and comparison of patterns across Europe. *Br J Clin Pharmacol* 2018;84(6): 1324-1334.
21. Ruscitto A, Smith BH, Guthrie B. Changes in opioid and other analgesic use 1995-2010: repeated cross-sectional analysis of dispensed prescribing for a large geographical population in Scotland. *Eur J Pain* 2015;19(1):59-66.
22. Nissen SK, Pottegrd A, Ryg J. Trends of Opioid Utilisation in Denmark: A Nationwide Study. *Drugs Real World Outcomes* 2019;6(4):155-164.
23. Oh TK, Jeon YT, Choi JW. Trends in chronic opioid use and association with five-year survival in South Korea: a population-based cohort study. *Br J Anaesth* 2019;123(5):655-663.
24. Weesie YM, Hek K, Schermer TRJ, Schellevis FG, Leufkens HGM, Rook EJ, et al. Use of Opioids Increases With Age in Older Adults: An Observational Study (2005-2017). *Front Pharmacol* 2020;11:648.
25. Zin CS, Nazar NI, Rahman NS, Alias NE, Ahmad WR, Rani NS, et al. Trends and patterns of analgesic prescribing in Malaysian public hospitals from 2010 to 2016: tramadol predominately used. *J Pain Res* 2018;11:1959-1966.

26. Castañeda AM, Lee CS, Kim YC, Lee D, Moon JY. Addressing Opioid-Related Chemical Coping in Long-Term Opioid Therapy for Chronic Noncancer Pain: A Multicenter, Observational, Cross-Sectional Study. *J Clin Med* 2018;7(10):354.
27. Choi H, Lee E. Market analysis of narcotic analgesics in Korea using HIRA claims data. *J Korean Acad Manag Care Pharm* 2015;4(1):31-37.
28. Hong S, Won YJ, Park YR, Jung KW, Kong HJ, Lee ES, et al. Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2017. *Cancer Res Treat* 2020;52(2):335-350.
29. Kyung M-H, Jang Y-M, Han K-H, Yun Y-H. Current status and activation plan of hospice palliative care in Korea-based on hospice palliative care facilities survey. *The Korean J Hosp Palliat Care* 2010;13(3):143-152.
30. Cho NR, Chang YJ, Lee D, Kim JR, Ko DS, Choi JJ. Trends in opioid prescribing practices in South Korea, 2009-2019: Are we safe from an opioid epidemic? *PLoS One* 2021;16(5):e0250972.
31. Wilson N, Kariisa M, Seth P, Smith 4th H, Davis NL. Drug and opioid-involved overdose deaths – United States, 2017-2018. *MMWR Morb Mortal Wkly Rep* 2020;69(11):290-297.
32. Häuser W, Buchser E, Finn DP, Dom G, Fors E, Heiskanen T, et al. Is Europe also facing an opioid crisis? – A survey of European Pain Federation chapters. *Eur J Pain* 2021;25(8):1760-1769.

Figure Legends

Figure 1. The age-standardized annual percentage change and average annual percentage of the amount of annual prescription as cases per 10.000 registrants during 2002–2015 by sex

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Figure 2. The age-standardized annual percentage change and average annual percentage of the amount of annual prescription as MME per 10.000 registrants during 2002–2015 by sex

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Table 1. Baseline characteristics of study population

Year	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	
Total	725,224	739,052	752,581	765,674	778,544	791,680	799,645	808,031	817,608	827,503	837,231	846,676	855,723	864,702	
Newly Prescribed	3	3	11	10	8	26	58	247	230	282	390	585	692	941	
Median age, years (S.D.)	40.0 (15.0)	41.0 (15.1)	41.0 (15.3)	42.0 (15.5)	43.0 (15.7)	43.0 (15.9)	44.0 (16.0)	44.0 (16.1)	45.0 (16.2)	45.0 (16.4)	46.0 (16.5)	46.0 (16.6)	47.0 (16.8)	47.0 (16.9)	
Age	20~29 years	165,637	161,551	158,814	156,018	152,643	150,780	146,573	142,452	139,584	137,866	137,332	138,385	139,370	140,703
	30~39 years	184,223	184,735	183,333	182,252	180,735	176,416	174,077	172,308	170,090	168,247	165,070	160,918	158,132	155,271
	40~49 years	166,981	171,396	173,766	175,918	177,274	180,362	181,371	180,627	181,090	181,079	183,053	183,367	181,843	180,646
	50~59 years	95,871	101,144	109,172	115,781	122,083	128,355	135,945	145,291	154,323	159,761	164,474	168,493	170,538	172,342
	60~69 years	72,178	74,481	75,714	77,646	81,088	84,059	85,649	87,367	87,840	89,832	92,789	97,431	104,790	110,826
	≥70 years	40,334	45,745	51,782	58,059	64,721	71,708	76,030	79,986	84,681	90,718	94,513	98,082	101,050	104,914

Table 2. The age-standardized number of annual opioid prescription as cases per 10,000 registrants during 2002-2015

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Prescription	0.07	0.04	0.22	0.32	0.18	0.64	1.33	7.15	9.99	11.05	16.01	26.81	30.78	41.23
Sex														
Male	0.03	0.03	0.19	0.19	0.16	0.63	1.16	5.47	9.54	13.98	18.97	26.52	32.36	40.96
Female	0.10	0.06	0.25	0.43	0.19	0.65	1.53	8.89	10.31	7.97	12.69	26.9	28.54	41.15
Age														
20~29 years	0.00	0.00	0.03	0.00	0.00	0.00	0.02	0.00	0.00	0.56	0.75	0.54	0.83	0.83
30~39 years	0.04	0.03	0.03	0.03	0.04	0.03	0.07	0.22	0.27	0.60	0.66	1.28	1.73	3.81
40~49 years	0.00	0.00	0.06	0.00	0.03	0.14	0.09	0.47	0.76	1.45	2.29	3.85	5.08	6.58
50~59 years	0.03	0.00	0.05	0.03	0.00	0.21	0.28	1.56	1.80	2.08	2.21	4.20	4.59	7.24
60~69 years	0.00	0.00	0.03	0.14	0.06	0.12	0.51	1.92	3.66	3.29	5.68	9.04	9.46	11.52
≥70 years	0.00	0.01	0.02	0.12	0.05	0.14	0.36	2.98	3.50	3.07	4.42	7.90	9.09	11.25
Institute type														
General hospital	0.00	0.00	0.01	0.01	0.03	0.00	0.04	3.18	7.48	8.80	12.37	22.53	25.18	34.75
Hospital	0.01	0.03	0.05	0.04	0.01	0.10	0.18	1.01	0.73	1.03	1.87	1.97	2.59	3.05
Clinic	0.06	0.00	0.15	0.26	0.14	0.52	1.10	2.92	1.75	1.25	1.77	2.27	2.85	3.42
Opioid type														
Fentanyl	0.00	0.00	0.01	0.05	0.01	0.10	0.95	4.31	4.13	4.13	4.95	7.70	8.26	10.51
Oxycodone	0.04	0.02	0.10	0.21	0.14	0.25	0.25	2.35	5.28	5.55	8.66	14.60	16.78	24.82
Hydromorphone	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.40	0.35	1.23	2.10	4.24	5.12	5.06

Morphine

0.03

0.01

0.10

0.05

0.03

0.27

0.13

0.09

0.21

0.14

0.31

0.27

0.62

0.83

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Table 3. The age-standardized number of annual opioid prescription as MME per 10,000 registrants during 2002 – 2015

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Prescription	15.06	3.38	72.51	221.44	168.70	355.50	501.17	5727.09	10837.51	13793.05	16838.76	26243.82	34206.90	40727.80
Sex														
Male	0.85	4.22	62.07	35.70	210.66	373.86	402.55	4974.07	9090.91	18734.48	23341.95	28278.94	38256.23	45263.38
Female	28.89	2.60	83.48	411.01	128.66	345.85	603.53	6521.57	12603.26	8809.25	10014.66	23780.26	29163.46	35603.54
Age														
20~29 years	0.00	0.00	1.00	0.00	0.00	0.00	10.09	0.00	0.00	1406.94	3832.59	1066.72	916.83	874.94
30~39 years	5.37	2.47	12.93	5.01	20.02	22.67	16.26	477.24	221.50	497.18	621.75	1636.54	3489.28	4120.55
40~49 years	0.00	0.00	14.80	0.00	65.96	135.40	39.56	291.27	698.78	2787.19	2253.61	3101.23	6337.56	7355.27
50~59 years	9.69	0.00	34.73	4.51	0.00	35.67	68.12	1864.63	1750.89	2367.10	1964.12	4620.35	4801.05	7055.79
60~69 years	0.00	0.00	7.89	79.21	51.99	43.16	151.34	1553.22	5151.58	3271.36	4618.68	8572.50	10111.60	11733.29
≥70 years	0.00	0.91	1.16	132.71	30.73	118.60	215.80	1540.73	3014.76	3463.28	3548.01	7246.48	8550.58	9587.96
Institute type														
General hospital	0.00	0.00	1.07	3.35	21.36	0.00	8.12	3782.35	9705.51	12691.00	15066.66	24349.74	30267.67	38362.58
Hospital	0.41	2.47	34.73	1.77	0.86	68.13	72.84	514.83	331.91	567.10	1100.18	946.11	1390.79	1254.08
Clinic	14.65	0.00	36.62	216.33	146.47	287.36	412.90	1395.31	796.60	534.97	671.90	865.01	1232.51	1098.99
Opioid type														
Fentanyl	0.00	0.00	12.46	95.59	12.64	167.55	324.51	3239.75	4371.67	7190.50	7871.61	10207.31	14174.34	15580.43
Oxycodone	5.37	1.32	17.37	109.33	143.33	100.10	119.84	2123.48	5900.42	5460.25	7058.17	12447.28	14936.97	20158.60

Hydromorphone	0.00	0.00	0.00	0.00	0.00	0.00	0.00	303.84	391.83	1083.57	1814.88	3387.20	4516.84	4529.21
Morphine	9.69	2.06	42.68	16.51	12.72	87.84	56.83	60.01	173.60	58.74	94.06	202.01	578.77	459.56

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	Overall trend (2002-2015)	Trend 1		Trend 2	
	AAPC	Year	APC	Year	APC
Total	76.0* (61.6 – 91.7)	N.A	N.A	N.A	N.A
Male	79.3* (53.6 – 109.4)	2002-2011	106.4* (79.3 – 137.6)	2011-2015	30.7 (-19.7 – 112.9)
Female	69.7* (55.5 – 85.2)	N.A	N.A	N.A	N.A

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	Overall trend (2002-2015)	Trend 1		Trend 2	
	AAPC	Year	APC	Year	APC
Total	103.0* (78.2 – 131.3)	N.A.	N.A.	N.A.	N.A.
Male	121.2* (80.5 – 171.0)	2002-2010	198.4* (136.0 – 277.2)	2010-2015	36.9 (-15.3 – 121.4)
Female	94.5* (66.7 – 126.8)	N.A.	N.A.	N.A.	N.A.