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Brief Communication

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Proportion of Non-Medical Opioid Use of Prescription Opioids among Cancer Patients in Korea

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Purpose: Limited research has been conducted on the prevalence of non-medical opioid use (NMOU) in Korean cancer patients who have received prescription opioids (PO). This study aimed to identify the potential proportion of NMOU in cancer patients who had been prescribed opioids in Korea. **Methods:** A retrospective cohort analysis was conducted on 14,728 patients who underwent cancer-related treatment between January 2009 and December 2019, using electronically collected data from a tertiary hospital in Korea. Information regarding the type and duration of opioid use was gathered. A detailed review of medical charts was carried out, focusing on patients who had been prescribed opioids for over 60 days beyond a 12-month period following the completion of their cancer treatment (long-term PO users). **Results:** Out of the 5,587 patients who were prescribed PO and followed up for at least 12 months, 13 cases of NMOU were identified, representing 0.23% of the patient population. Among the 204 long-term PO users, the rate was 6.37% (13/204). The most commonly misused opioids were oxycodone and fentanyl. For the group confirmed to have NMOU, the median duration of prescription was 1,327 days in total. Of the 13 patients diagnosed with NMOU, 9 reported withdrawal symptoms, 3 exhibited craving behavior for opioids, and 1 experienced both symptoms. **Conclusion:** This study found that 0.23% of cancer patients who had been prescribed opioids in Korea demonstrated NMOU. Despite this relatively low rate, careful monitoring is necessary to minimize the risk of NMOU in this population, especially among long-term PO users.

Key Words: Prescription drug misuse, Opioid-related disorders, Epidemiology

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INTRODUCTION

The number of opioid overdose deaths in the United States (US) has increased fivefold since 1999 [1]. The incidence of prescription opioid (PO) overdose deaths began to rise in 1999, with a particularly notable surge in opioid-related deaths from synthetic drugs, primarily fentanyl, since 2013.

While substance use disorder is a specific clinical diagnosis

made based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, non-medical opioid use (NMOU) is a broader term that includes a variety of behaviors related to opioid use. These behaviors range from normal opioid adherence to clear substance use disorder [2,3]. NMOU behaviors may involve unscheduled clinic visits, self-increased opioid dosage, reports of lost or stolen prescriptions, seeking opioids for their euphoric effects, using opioids to alleviate symptoms such as anxiety or insomnia, and experiencing impaired functioning in daily activities due to opioid use. Physical dependence on opioids manifests through withdrawal symptoms, including a runny nose, yawning, and myalgia. Despite the distinctions between substance use disorder, physical dependence, and NMOU, clinicians often use these terms interchangeably [2,4].

Epidemiological studies examining the proportion of NMOU resulting from prescription opioids (PO) are vital, considering that roughly two-thirds of illegal opioid users begin their use with prescription drugs. Despite the significance of this issue, most studies have been conducted in patients with non-cancer pain, with minimal research focusing on the proportion of NMOU in cancer patients who have been prescribed opioids [5,6]. Moreover, studies on the proportion of NMOU resulting from PO have yielded conflicting results. A paper arguing the rarity of addiction to PO was published 40 years ago, which has since served as the foundation for the universal use of PO in patients with pain. However, this study has recently come under intense scrutiny for potentially downplaying the risk of NMOU [7,8]. Yennurajalingam and colleagues reported that approximately 19% of cancer patients referred to the supportive care center developed NMOU behavior, with a median duration of 8 weeks [9].

The risk of NMOU is contingent upon the availability of opioids [10]. The prevalence of NMOU, which can serve as a parameter for opioid accessibility, varies significantly across different countries. The highest estimated prevalence is observed in the US, while Korea is among the countries with the lowest prevalence [11]. Since most epidemiological studies on NMOU resulting from PO have been conducted in the US, and half of adult heroin users develop NMOU due to PO, it is crucial to conduct research in countries with lower opioid accessibility. Specifically, the proportion of NMOU resulting from PO might be overestimated in countries where NMOU is prevalent among the general population and where opioids are easily accessible. The purpose of this study was to determine the proportion of NMOU in cancer patients who have been prescribed opioids in Korea, with the aim of better understanding the actual proportion of NMOU in Korea.

METHODS

A retrospective cohort analysis was conducted using electronic data collected from a tertiary hospital institution between January 2009 and December 2019. We applied two criteria. The first criterion was that 12 months had passed since the last cancer-related treatments (surgery, radiotherapy, and chemotherapy) were administered to patients who were being followed up, in order to identify those who may no longer require PO for pain management. The second criterion was whether weak and strong opioids were prescribed for a duration exceeding 60 days, regardless of the frequency of prescriptions or hospital visits, beyond a 12-month period after completing cancer treatment. This was to identify potential NMOU, as patients with NMOU typically take opioids for more than 12 months (Figure 1A) [4]. An in-depth medical chart review was performed for this cohort. We expanded the diagnostic criteria for NMOU to address the inherent limitations of retrospective diagnosis. Although physical dependence and substance use disorder are conceptually distinct from NMOU, these terms are sometimes used interchangeably, particularly in Korea. Therefore, a case was classified as NMOU if the patient requested opioids due to any of the following physical dependence symptoms: sweating, restlessness, bone or joint aches, rhinorrhea, yawning, anxiety, palpitations, or goose flesh. A diagnosis of NMOU was also made if two or more items were met according to the DSM-5 criteria for substance use disorder [12]. Information on the type and duration of opioid use was also collected. This study was approved by the Institutional Review Board of Gyeongsang National University Hospital (IRB No. GNUH 2021-06-004-002). Informed consent was waived due to the retrospective nature of the study design.

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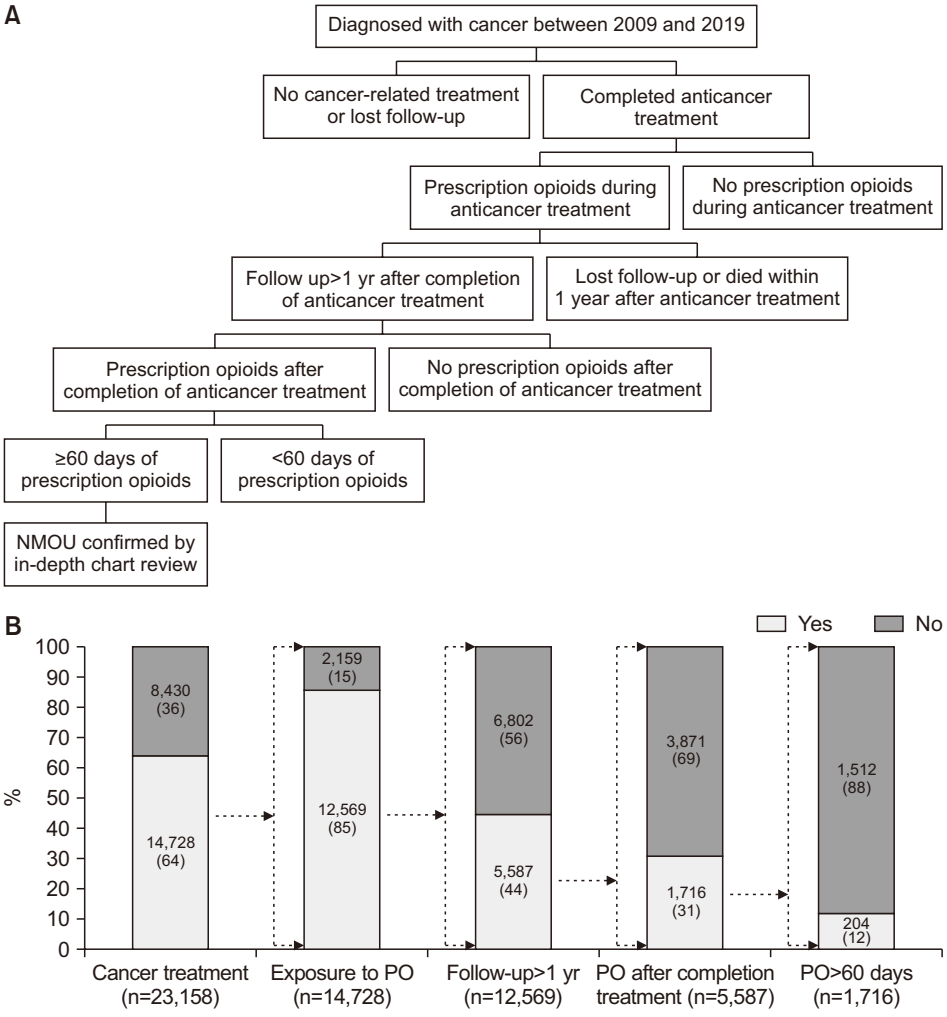

Figure 1. Patterns of prescription opioid use in cancer patients. (A) Algorithmic flow diagram for screening, (B) Proportion by classification criteria.
NMOU: non-medical opioid use, PO: prescription opioids.

RESULTS

A total of 23,158 patients were screened, of whom 14,728 (61.0%) received cancer-related treatment (Figure 1B). Out of this cohort of 14,728 patients who underwent cancer treatment, 12,569 patients (85.3%) were prescribed opioids, and 44.5% (5,587 out of 12,569) of these patients were followed for more than 12 months. Approximately one-third of the patients (30.7%, N=1,716) from this followed cohort received PO for at least one day after completing their cancer treatment. The median prescription duration was two days. Among these 1,716 patients, 204 (11.9%) were identified as long-term PO users and were evaluated for potential NMOU (Table 1). The median prescription duration for these patients was 198 days (interquartile range, 91~444 days). The primary reasons for administration were pain, cough, and NMOU, in that order. Thirteen patients were identified with NMOU after a comprehensive chart review. In the fully followed patient cohort, 13 out of 5,587 patients developed NMOU, representing 0.23% of the total. However, when considering only the 204 long-term PO users, the proportion increased to 6.37%. If the diagnostic criteria for NMOU were restricted to include only patients exhibiting craving behavior, the proportion dropped significantly to 0.07% (4 out of 5,587 patients). Of the 13 patients diagnosed with NMOU, nine reported withdrawal symptoms, three exhibited craving behavior for opioids, and one experienced both symptoms. Notably, the proportion of head and neck cancer was 7% in the potential NMOU group (5 out of 204 patients), but it rose to 38% in the NMOU-confirmed group (5 out of 13 patients). Upon analyzing the opioid prescription duration for the NMOU-confirmed group, the median prescription duration was found to be 1,327 days in total. Regarding the opioids involved, immediate-release and extended-release forms of oxycodone led to NMOU in four

Table 1. Epidemiology of Long-Term Users of Prescription Opioids (N=204).

Category	N (%)
Sex	
Female	83 (41)
Male	121 (59)
Median age, yr (Q1~Q3)	74 (65.5~80.5)
Median period of PO use (Q1~Q3)	
Total time	939 days (590~1527 days)
Time since completion of cancer treatment	198 days (91~444 days)
Caregiver (spouse)	
Yes	166 (81)
No	38 (19)
Alcohol drinking	
Yes	69 (34)
No	135 (66)
Smoking	
Yes	55 (27)
No	149 (73)
Primary cancer	
Hepato-pancreato-biliary cancer	52 (25)
Lung cancer	46 (22)
Gastric cancer	23 (11)
Hematologic malignancy	22 (11)
Genitourinary cancer	19 (9)
Head and neck cancer	15 (7)
Others	27 (13)
Reasons for PO	
Benign pain	121 (59)
Cough	22 (11)
Stage IV without treatment	48 (24)
Non-medical opioid use	13 (6)

PO: prescription opioids.

patients, while fentanyl transdermal patches and rapid-onset buccal tablets were implicated in two patients, respectively. All 13 patients had stopped taking PO at the time of analysis.

CONCLUSION

Our study differs from previous literature on NMOU in two significant ways. Firstly, it focuses on a patient cohort with cancer, and secondly, it utilizes data not from the US, but from a country with generally lower opioid accessibility in the general population. Our results indicated that the proportion of NMOU among cancer patients in Korea who were prescribed opioids was relatively low (0.23%). When applying strict criteria for NMOU diagnosis to exclude mere physical dependence, the proportion of NMOU from PO was even lower (0.07%, 4/5,587). We surmise that this outcome can be attributed to the distinctive characteristics of the cancer population and the limited opioid accessibility in Korea.

Despite the strengths of our research, it had a few limitations. First, the retrospective diagnosis of NMOU, which is dependent on medical records, is inherently limited, as the potential for underestimation cannot be dismissed. Second, the study was carried out at a single institution, which limits the generalizability of our findings to a broader context. Third, among the cancer patients who received PO, 56% were monitored for less than 12 months, and the proportion of NMOU was not evaluated in this group. This could have potentially led to either an underestimation or an overestimation of the overall prevalence of NMOU.

In conclusion, our study indicates that the proportion of NMOU resulting from PO among cancer patients in Korea is 0.23%. Therefore, societal stigmas towards PO should not prevent cancer patients from receiving effective pain management. However, it is important not to underestimate the risk of NMOU associated with PO, especially in long-term users. Our results highlight the necessity for extensive, prospective studies to delve deeper into this issue. Future research should incorporate more detailed analyses, such as investigating the impact of demographic factors, the types of healthcare professionals involved, patients' history of psychological disorders, and the specific opioids prescribed, on the incidence of NMOU in cancer patients.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR'S CONTRIBUTIONS

Conception or design of the work: JH Kang, EB. Data collection: SIG, SWP, JH Kang. Data analysis and interpretation: SIG, JH Kwon, GWL, JH Kang. Drafting the article: SIG, JH Kang, EB. Critical revision of the article: all authors. Final approval of the version to be published: all authors.

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