The Lancet Regional Health - Western Pacific 16 (2021) 100255

Contents lists available at ScienceDirect

The Lancet Regional Health - Western Pacific

journal homepage: www.elsevier.com/locate/lanwpc

Research paper

Impact of expanded strong opioid availability on opioid prescription patterns in patients with cancer: A population-wide cohort study in Taiwan ☆

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ARTICLE INFO

Article history:
Received 7 May 2021
Revised 7 July 2021
Accepted 3 August 2021
Available online 26 August 2021

Keywords:
Cancer pain
Opioids
Transdermal fentanyl
Hydromorphone
Oxycodone

ABSTRACT

Background One of the major barriers to adequate cancer pain management in Taiwan is the limited prescription options regarding strong opioids. Internationally recommended strong opioids, including oxycodone and hydromorphone, were not introduced in Taiwan until late 2014. We analysed the patterns in opioid prescription for cancer pain management, after the introduction of new opioid options.

Methods All inpatient and outpatient clinical visits from January 1, 2012, to December 31, 2017, with the diagnosis of cancer and the analgesic prescriptions were collected from the database of National Health Insurance, Taiwan, and analysed. Opioids were grouped into strong opioids, weak opioids, and guideline non-recommended opioids.

Findings A total of 1, 292, 905 patients with cancers were included. Approximately 50% of patients used analgesics, 50% of which were opioids; the proportions were stable during the study period. The annual cumulative opioid use per patient (defined daily dose, DDD) significantly decreased from 36•41±102•59 (Mean±SD) in 2012 to 32•42±100•99 in 2017 ($p < •001$). The annual cumulative strong opioid use per patient increased significantly from 17•54±89•23 in 2012 to 19•28±94•97 in 2017 (+9•90%, $p < •001$). In parallel, the annual cumulative weak opioids use per patient decreased from 18•64±40•81 in 2012 to 13•04±26•79 in 2017 (−30•04%, $p < •001$). Among extended-release strong opioids, the use of transdermal fentanyl significantly decreased after oxycodone and hydromorphone were introduced ($p < •001$).

Interpretation Increased therapeutic options in strong opioid prescriptions led opioid prescription patterns to evolve towards international cancer pain management guidelines. In addition, increased accessibility to a wider range of different strong opioids may facilitate more efficient opioid titration and rotation - and thus decrease, not increase, the opioid usage.

Funding This study was supported by Ministry of Science and Technology, Taiwan (MOST-106-2314-B-002-213 and MOST-108-2314-B-002-072-MY3), Ministry of Health and Welfare, Taiwan (MOHW109-TDU-B-211-114002), National Taiwan University Hospital, Taipei, Taiwan (NTUH-103-002314 and NTUH. 105-S2954), and National Center of Excellence for Clinical Trial & Research, National Taiwan University Hospital, Taipei, Taiwan (NCTRC201208 and NCTRC201603).

☆ Short title: Expanded opioid options improve opioid prescription pattern in Taiwan

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https://doi.org/10.1016/j.lanwpc.2021.100255

Research in context

Evidence before this study

We published a previous national cohort study of opioid prescriptions for cancer patients in Taiwan from 2003 to 2011. Several features of prescription patterns were identified, including prevalent and increasing use of weak opioids, use of non-recommended opioids, and dominant use of transdermal fentanyl among extended-release strong opioids. These findings conflicted with suggestions from international guidelines for cancer pain management.

During the previous study period, there were only two available extended-release strong opioids morphine and transdermal fentanyl in Taiwan, a country with strict control on opioid use. Limited opioid options may implicate in the deviation of opioid prescription patterns from international guidelines.

Added value of this study

In our current national cohort study from 2012 to 2017, use of strong opioids significantly increased while use of weak opioids significantly decreased. Despite shift to strong opioids, the total opioid dose significantly decreased. In addition, among extended-release strong opioids, the use of previously dominant transdermal fentanyl significantly decreased and use of new available options- hydromorphone and oxycodone of significantly increased. The turning point of above changes to more guideline-concordant prescription patterns was along with the timing of availability of hydromorphone and oxycodone.

Implications of all the available evidence

This study implies increased strong opioid options direct to more guideline-concordant prescription patterns. Furthermore, decreased total opioid dose may indicate better management of cancer pain. Above findings may inspire policy makers in designing nudges for individual countries and reflection on the universal opioid curbing strategy in the fear of opioid misuse.

Introduction

Pain is a common symptom among patients with cancers, regardless of the cancer stage.[1] Cancer pain has a huge effect on life quality, tolerance and compliance with cancer treatment, and survival outcomes.[2] Cancer pain is usually long term and combines somatic, visceral, and neuropathic pain; furthermore, cancer pain is generally more intense than non-cancer pain.[3] Therefore, non-opioids alone are usually inadequate to achieve satisfactory pain control and strong opioids are the mainstay of effective cancer pain management.

Although international guidelines for cancer pain management have been established for decades,[4–6] inappropriate care for cancer pain remains common and is reported in approximately 40% of patients.[7–9] Inappropriate cancer pain management is multifactorial.[10,11] The average consumption of opioids is extremely low in Asia compared with Europe and North America because the availability of appropriate opioids has been limited by regulatory problems and import difficulties, which is a major barrier to adequate cancer pain management.[10,12]

For example, the only guideline recommended strong opioids available in Taiwan before late 2014 were morphine and transdermal fentanyl. Although international guidelines on cancer pain management recognize the use of low-dose strong opioids for moderate to severe cancer pain, the limited options of strong opioids caused "nonconformities" in prescription patterns. In a nationwide study in Taiwan, we reported increasing use of weak opioids from 2003 to 2011. More than 50% of strong opioid prescriptions in patients with cancer were transdermal fentanyl.[13] These findings did not align with international guidelines for cancer pain management.[3,14,15]

Hydromorphone and oxycodone were introduced in Taiwan in 2014 to broaden the options of strong opioid prescriptions for patients with cancer. We analysed the patterns in opioid prescription for cancer pain management, after the introduction of new opioid options.

Methods

2.1. Study design and patient population

This is a national cohort study in Taiwan. The National Health Insurance (NHI) program in Taiwan is a mandatory single-payer system covering 97%–98% of the population.[16] We retrieved NHI data from the Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan. All inpatient and outpatient clinical visits from January 1, 2012, to December 31, 2017, with the diagnosis of cancer (ICD-9-CM: 140–208; ICD-10-CM: C00–C97) and age $\geq$ 20 years were included. Deidentified data sets that included diagnosis, demographic characteristics, medication claims, and costs were retrieved. For individual patients with visits in different calendar years, the records in each year were considered independent.

Definition and quantification for use of analgesics

Analgesics were classified as opioids and non-opioids. Opioids were further grouped into 3 categories: strong opioids, namely morphine, fentanyl, oxycodone, and hydromorphone; weak opioids, namely tramadol, buprenorphine (0•2mg sublingual tablet only; transdermal buprenorphine was not available during the study period and suboxone was only approved for heroin replacement therapy), and codeine; and non-recommended opioids, namely nalbuphine and meperidine.

A user of each category of opioids was defined as having one or more prescriptions of the specific opioid or category. Quantification was performed based on the defined daily dose (DDD), which is recommended by the World Health Organization for comparison between opioids. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.[17] For example, the DDD of morphine is 100 mg; therefore, a patient with daily use of 30 mg morphine is deemed to be 0•3 DDD. The cumulative opioid use was determined by summing the DDD of total prescribed opioids per individual year.

2.3. Statistical analysis

Descriptive statistics were used to report the distribution of opioid usage patterns. For continuous variables, mean and standard deviation were applied, whereas frequency distribution and percentage were applied for categorical variables. The change of cumulative opioid dose per patient from 2012 to 2017 was examined using simple linear regression with log link and year as continuous independent variable ranging from 1 to 6. For inferential statistics, type I error was set at α = •05. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all data analyses.

2.4. Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All corresponding authors had full access to all the data in the study

Table 1
Characteristics of patients with cancer from 2012 to 2017

		N	(%)
Total		1 292 905	(100)
Sex	Male	642 491	(49•7)
	Female	643 072	(49•7)
	missing	7342	(0•6)
Age	Mean (SD)	60•5	(15•8)
	Median (Q1, Q3)	61	(50,73)
Cancer site	Colon, rectum, and anus	181 823	(14•1)
	Breast	164 850	(12•8)
	Liver and intrahepatic bile ducts	131 534	(10•2)
	Trachea, bronchus, and lung	112 273	(8•7)
	Oral cavity, oropharynx, and hypopharynx	72 970	(5•6)
	Prostate gland	70 716	(5•5)
	Renal pelvis and bladder	52 205	(4•0)
	Thyroid gland	46 111	(3•6)
	Nasopharynx	37 871	(2•9)
	Stomach	36 748	(2•8)
	Cervix uteri	32 568	(2•5)
	Skin	26 265	(2•0)
	Corpus uteri	25 098	(1•9)
	Ovary, fallopian tube, and broad ligament	23 201	(1•8)
	Oesophagus	18 336	(1•4)
	Others	260 336	(20•1)

and had final responsibility for the decision to submit for publication.

Results

A total of 1, 292, 905 patients with cancer were retrieved from the registry for the years 2012 to 2017. The median age was 61 years, the sex distribution was roughly equal, and the leading primary sites of malignancy were colorectal (14•1%), breast (12•8%), liver (10•2%), lung (8•7%), and head and neck (5•6%) (Table 1). The proportion of patients with cancer who used analgesics was relatively stable (approximately 50%) during the study period (figure 1A). The percentage of opioid users among patients with cancer was consistently approximately 25% (figure 1B). Therefore, approximately 50% of patients with cancer who used analgesics used opioids (figure 1C).

The annual cumulative opioid use per patient (DDD) significantly decreased from 36•41±102•59 (Mean±SD) in 2012 to 32•42±100•99 in 2017 (−10•96%, p < •001, figure 2A; table S1). The annual cumulative strong opioids consumption per patient (DDD) increased significantly from 17•54±89•23 in 2012 to 19•28±94•97) in 2017 (+9•90%, p < •001, figure 2B; table S1), whereas the annual cumulative weak opioid consumption per patient (DDD) decreased significantly from 18•64±40•81 in 2012 to 13•04±26•79 in 2017 (−30•04%, p < •001, figure 2B; table S1). The use of non-recommended opioids among patients with cancer remained at a negligible level. Because the annual opioid consumption varied, we adjusted the annual cumulative consumption per patient of every opioid category according to the annual total opioid consumption. The changes remained similar (Figure 2C). The ratio of strong opioid increased from 0•482 in 2012 to 0•595 in 2017, and the ratio of weak opioids decreased from 0•512 in 2012 to 0•402 in 2017.

Extended-release forms of hydromorphone and oxycodone were introduced to Taiwan in late 2014 and early 2015. Among extended-release strong opioids, the use of transdermal fentanyl (DDD) significantly decreased from 2015 (−21•08%, p < •001, figure 3A; table S2), with the introduction of hydromorphone and oxycodone (figure 3A; table S2). The use of oral extended-release morphine (DDD) was steady during the study period (−5•14%, p = •485, figure 3A, table S2). Among immediate-release strong opioids, the use of morphine (DDD) decreased significantly (−20•49%, p < •001, figure 3B, table S3). The use of 2 new immediate-release strong opioids (rapid onset, transmucosal fentanyl and immediate-release oxycodone) increased significantly from 2014 and 2015, respectively (both p < •001, figure 3B; table S3). Among weak opioids, the uses of tramadol (−5•86%), buprenorphine (−43•48%), and especially codeine (−100•0%) all decreased significantly from 2012 to 2017 (all p < •001, figure 3C; table S4).

Discussion

The present study revealed dramatic changes in opioid prescription patterns for patients with cancer following the expansion of more strong opioid options. A similar proportion of patients with cancer required analgesics and opioids for pain management throughout the study period and also from 2003 to 2011.[13] The use of strong opioids increased and the use of weak opioids decreased. The change is not as a result of an increase in disease severity, because the cumulative use of all opioids decreased.

The opioid prescription pattern for patients with cancers in Taiwan from 2003 to 2011 revealed several alarming problems,[13] including the increasing use of weak opioids for patients with cancer. These practices were in disagreement with recent cancer pain management consensus guidelines that favour upfront low-dose strong opioids for moderate to severe cancer pain.[3,14,15] Clinical trials have shown that low-dose strong opioids have superior pain relief efficacy and comparable or better tolerability compared with weak opioids.[18,19] Tramadol and codeine, the main weak opioids used in Taiwan, also exhibit ceiling effects in pain relief and high variations in drug metabolism. [3,14,20,21] We demonstrated that after introduction of multiple choices of strong opioids, the use of all weak opioids among patients with cancer declined. The decline was substituted by increased strong opioids without an increase of total opioid use.

Another problem identified in the previous study was the extremely high use of transdermal fentanyl, which contributed to over half of the use of strong opioids.[13] Although transdermal patches are convenient, they should be reserved for patients with stable opioid requirements.[14,22] End-of-dose failure is common because warm and humid climates can reduce the adherence of transdermal patches.[23] We observed a significant decrease in the use of transdermal fentanyl after the introduction of other extended-release strong opioids. The increased options of strong opioids facilitated the possibilities of opioid rotation, which may lead to the decrease of total opioid use.[24] In the future, stud-

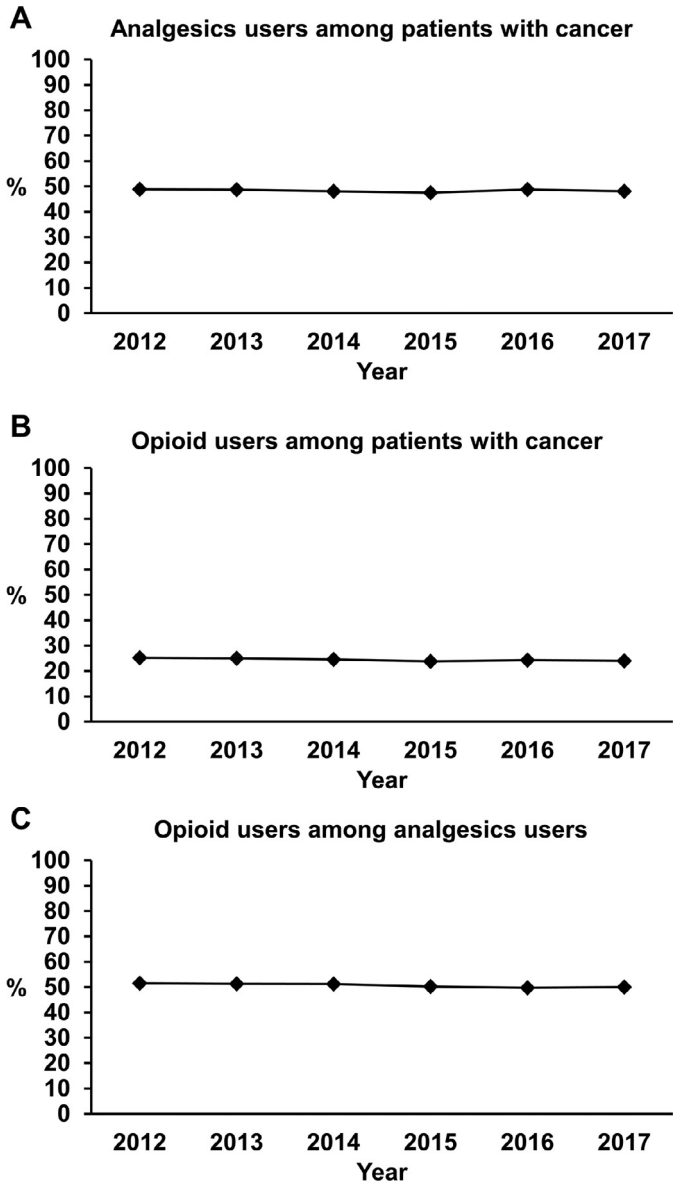

Figure 1. (A) Percentage of patients with prescriptions of analgesics among all patients with cancer from 2012 to 2017. Percentage of patients with prescriptions of opioids among all (B) patients with cancer and (C) analgesic users from 2012 to 2017.

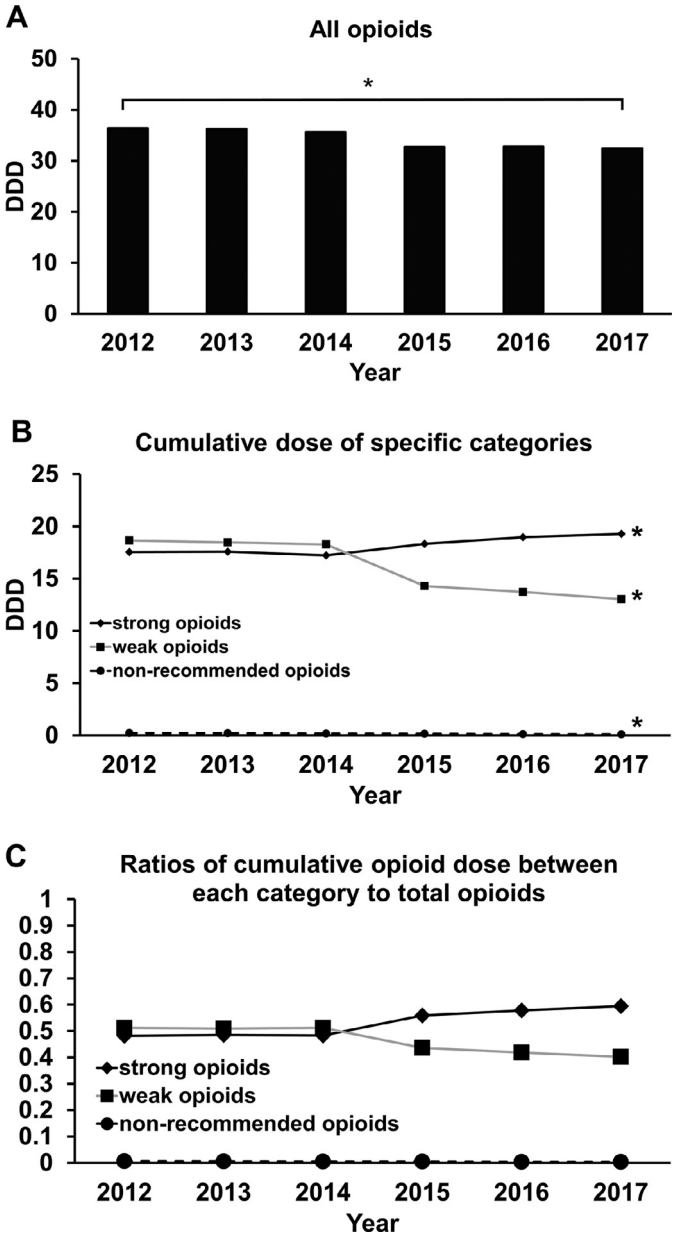

Figure 2. (A) Annual cumulative dose per patient of all opioids calculated by the defined daily dose (DDD). (B) Annual cumulative dose per patient (DDD) of specific categories (strong opioids, weak opioids, and non-recommended opioids). (*: statistically significant trend with $p < \cdot 05$) (C) Ratios of cumulative opioid dose between each category to total opioids.

ies on patient outcomes such as patient satisfaction and quality of life may be addressed to investigate whether more guideline-concordant practice leads to better patient outcomes.

There are more stringent regulations on opioid use in Taiwan compared with in North American and European countries. For example, opioids are mostly reserved for patients with cancer in Taiwan. It had been reported that only three hundred non-cancer patients using opioids in 2010 in Taiwan, a country with a population of 23 million.[25] Contrary to the opioid misuse problem in the United States,[26] the underuse and stigmata toward opioids in Asian countries are major problems in cancer pain management.[9] For instance, the opioid epidemic and crisis in North America did not seem to interfere the opioid prescription pattern among Korean practitioners.[27] Furthermore, multiple workforces are combating opioid abuse in the United States,[28,29] which may affect or compromise patients who require opioids for cancer pain management.[30] In addition, the excessive restrain on opioid prescription may lead to suboptimal cancer pain control, which may be associated with non-medical opioid use (NMOU) and may paradoxically worsen the opioid crisis.[31] In this study, we demonstrated that the increased options of strong opioids did not necessarily lead to more misuse under adequate management. The decrease in the consumption of all opioids indicated that more efficacious cancer pain management may reduce opioid use. Future analysis to estimate the adequacy of opioids consumption for cancer patients in Taiwan may further delineate the relationship between needs and actual consumption, as notions from previous studies estimating opioid adequacy in the country level.[32,33]

There were several limitations to our study. Detailed cancer severity data or pain scores could not be obtained. Therefore, the increased strong opioid use may reflect increased cancer severity or cancer pain over the study period. However, the decrease in overall consumption indicated that an overall increase in can-

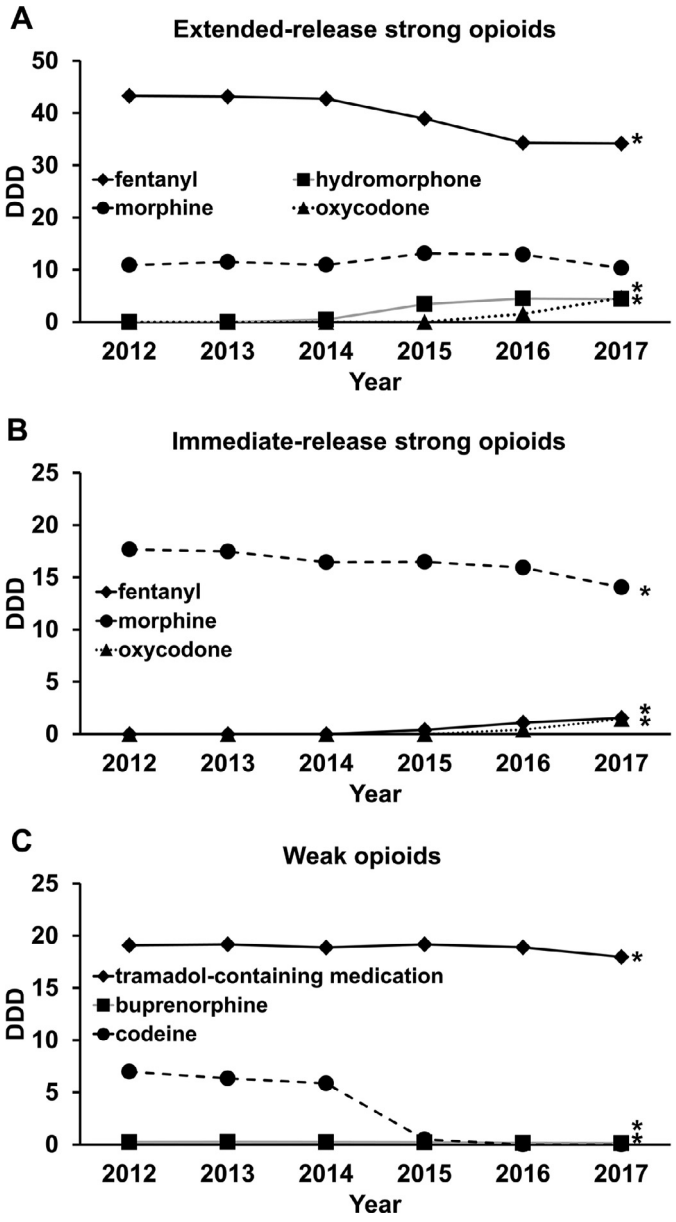

Figure 3. Annual cumulative dose of (A) extended-release strong opioids, (B) immediate-release strong opioids, and (C) weak opioids. (*: statistically significant trend with $p < \cdot 05$)

cer severity is highly unlikely. An analysis of cancer patients in Taiwan also showed that pain prevalence and patient satisfaction were better in 2014 than in 2008,[34] which could serve as an indirect evidence of no increased cancer pain severity in the period. This was a retrospective study based on Nation Health Insurance databases. The drastic prescription changes could be attributed to factors other than the increase in opioid varieties, such as improvements in pain management education.[35] However, no nationwide educational program on cancer pain management was conducted during the study period. The intention of prescription change was also unavailable. Increased strong opioid consumption could result from guideline-directed practice and also the "new is the better" attitude. Furthermore, a minority of weak opioids may be prescribed for other indications. For example, codeine could be prescribed as an antitussive. However, single doses of codeine of less than 15 mg were excluded from the analysis.

Another issue is that the calculation between weak and strong opioids using a single conversion factor may not be optimal. However, DDD is the WHO-defined basis for comparison between drugs and was used extensively in similar research and our previous analysis. In addition, we did not analyse or adjust for demographic factors in current study. Whether such demographic factors could influence our findings is worth exploring in the future.

In conclusion, through this nationwide cohort study we demonstrated that the expansion of strong opioid options in Taiwan altered the opioid prescription pattern and steered it more toward the guideline recommendations, with more strong opioids and fewer weak opioids prescribed. Better accessibility to a larger choice of strong opioids may facilitate more efficient cancer pain management thus decrease, not increase, the opioid usage.

Contributors

Dr. Tsung-Che Wu analysed and interpreted the data, wrote the first version of the manuscript, and revised and reviewed the manuscript.

Prof. Chih-Hung Hsu provided administrative support and revised and reviewed the manuscript.

Prof. Wei-Zen Sun provided administrative support and revised and reviewed the manuscript.

Ho-Min Chen analysed the data and provided statistical consulting.

Dr. Chih-Peng Lin coordinated data collection, analysed and interpreted the data, and reviewed and revised the manuscript.

Dr. Yu-Yun Shao conceptualised and designed the study, coordinated data collection, analysed and interpreted the data, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Data sharing statement

All available data were included in the manuscript and supplementary materials.

Editor note: The Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanwpc.2021.100255.

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