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Evaluation of opioid consumption trends for pain in Taiwan and comparison with neighboring Asian countries

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Abstract

Opioids are effective analgesics for pain relief, however, inappropriate use may cause risks. The aims of the study were to evaluate trends of opioid consumption for pain management in Taiwan and compare them among neighboring Asian countries. Opioid consumption data, including fentanyl, morphine, oxycodone, hydromorphone, codeine, and pethidine, were collected from the Controlled Drugs Management Information System of Taiwan Food and Drug Administration from 2008 to 2018. Data of different continents and neighboring Asian countries were retrieved from the WHO website. The major findings include: (1) In Taiwan, the total annual opioid consumption has gradually increased from 2008 to 2018, with fentanyl being the most frequently consumed opioid analgesic, followed by morphine. Codeine and pethidine consumption dropped significantly over the years. (2) In neighboring Asian countries, the opioid consumption in order from highest to lowest consumption were South Korea, Japan, Taiwan, Singapore, Hong Kong (China), and China. We concluded that, from 2008 to 2018, the total opioid consumption trend for pain management in Taiwan has slowly increased, with fentanyl and morphine being the most commonly used opioids. When compared with neighboring Asian countries, level of opioid consumption in Taiwan was between Japan and Singapore. The research results may provide a reference for healthcare professionals worldwide.

Keywords: Consumption trend, Opioid, Pain

1. Introduction

There are several strategies for pain management, however, in the field of pharmacologic management, opioids are considered the most effective analgesics for acute, chronic, and cancer pain management when moderate to severe pain present [1–4]. Although opioids relieve pain, inappropriate use may cause risks, e.g., addiction, respiratory depression, and/or even death [1–4]. WHO was also concerned about the safety use of opioid around the world and encouraged member

countries to report opioid consumption annually [5,6]. Since Taiwan is not a WHO member, its opioid consumption data were not collected and analyzed by the WHO [7]. Most opioids in Taiwan are controlled drugs/substances and regulated by the Taiwan Food and Drug Administration (TFDA) [7]. Based on the Taiwan Controlled Substances Act, TFDA developed a Controlled Drug Management Information System (CDMIS). All companies and institutions involved in import, export, manufacture, purchase, or sale of controlled drugs are required to report using the CDMIS on-line reporting system

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[7]. The CDMIS collects all information of opioid consumption in Taiwan, it is a suitable database for research on opioid consumption. The purpose of the study were to investigate the trends of opioid consumption for pain management in Taiwan and make comparison among neighboring Asian countries.

2. Material and method

Data on opioid consumption for pain from 2008 to 2018 in Taiwan were collected from the CDMIS of TFDA. In Taiwan, all controlled drugs are classified into four schedules based on their potential risks on habitual use, dependency, abuse, and danger to the public [8]. The schedule I drugs have the highest risks and the schedule IV have the least. All opioid analgesics are grouped into schedules I to III [8,9]. This study investigated the commonly used opioids, including fentanyl, morphine, oxycodone, hydromorphone, codeine, and pethidine. All formulations of these opioids were reviewed. On the basis of international comparison, data of morphine powder for research and codeine powder for cough were also collected. Tramadol was excluded because it is a schedule IV drug in Taiwan and not a pure opioid agonist but with actions on inhibition of serotonin and norepinephrine reuptake [9,10]. Buprenorphine and methadone were also excluded because they are commonly used in maintenance therapy for opioid use disorder in Taiwan [11–13]. Hydrocodone was not taken into account because it was not available in Taiwan.

Data were presented as defined daily doses for statistical purposes per million inhabitants per day (S-DDD/m/d) [5–7,14]. The number of Taiwan's inhabitants was derived from the Taiwan Ministry of Interior population statistics database. The S-DDD values (mg) for each opioid, obtained from the International Narcotics Control Board (INCB) 2017, were 0.6 for fentanyl, 100 for morphine, 75 for oxycodone, 20 for hydromorphone, 240 for codeine, and 400 for pethidine [5,6,14]. The S-DDD (m/d) for each opioid of years was derived by the following formula [5,6,14]: annual consumption of each opioid (mg)/[S-DDD value (mg) for each opioid \times inhabitants (million) \times 365 (days)].

In the WHO data [5,6], the world is divided into 6 continents. In order to investigate the opioid consumption internationally, data on 6 continents (North America, South America, Europe, Oceania, Asia and Africa) from 2015 to 2017 were collected [5,6]. An

analysis of the neighboring Asian countries, including Japan, South Korea, Singapore, China and Hong Kong (China), was also performed [5,6]. Linear regression analysis was used to estimate consumption trends of each opioid in Taiwan. A p value < 0.05 was considered significant. In international comparison, the absolute value of opioid consumption (S-DDD/m/d) for each opioid or total opioids was used for the ranking.

3. Results

3.1. Opioid consumption in Taiwan

Figure 1A shows the trends of opioid consumption in Taiwan, including fentanyl, morphine, oxycodone, hydromorphone, codeine, and pethidine, from 2008 to 2018. The total annual consumption of opioids (S-DDD/m/d) was 575 in 2008 and 1107 in 2018 (an increase of 1.9 fold), among which fentanyl was the top-ranked, followed by morphine while other opioids only accounted for a small proportion. The use of fentanyl, morphine, oxycodone, and hydromorphone increased annually, and that of codeine and pethidine presented a decreasing trend. Figure 1B shows that the transdermal patch was the most commonly used form of fentanyl, followed by injection form while buccal form (film or tablet) accounted for only a small percentage. Among the dosage forms, injection showed an upward trend over the years. Figure 1C shows that the short-acting form of morphine was most commonly used, followed by long-acting form (tablet or capsule), injection, and oral solution. Powder that is commonly used for research was the least consumed form. There was a yearly upward trend in consumption of all above dosage forms.

Figure 2A shows that the commonly used form of oxycodone was the short-acting capsule, followed by long-acting tablet. Both forms showed an upward trend during this period. For hydromorphone, as shown in Fig. 2B, only extended-release tablet was available in Taiwan and the consumption has increased since 2014. The most commonly used dosage form of codeine (see Fig. 2C) was tablet, while injection and powder forms were seldom used. There was a significant decline in consumption of tablet and powder forms and the injection form showed an upward trend. Figure 2D indicates that the most commonly used form of pethidine was injection and tablet was rarely used. Total pethidine consumption dropped from 25.72 in 2008 to 9.42 (S-DDD/m/d) in

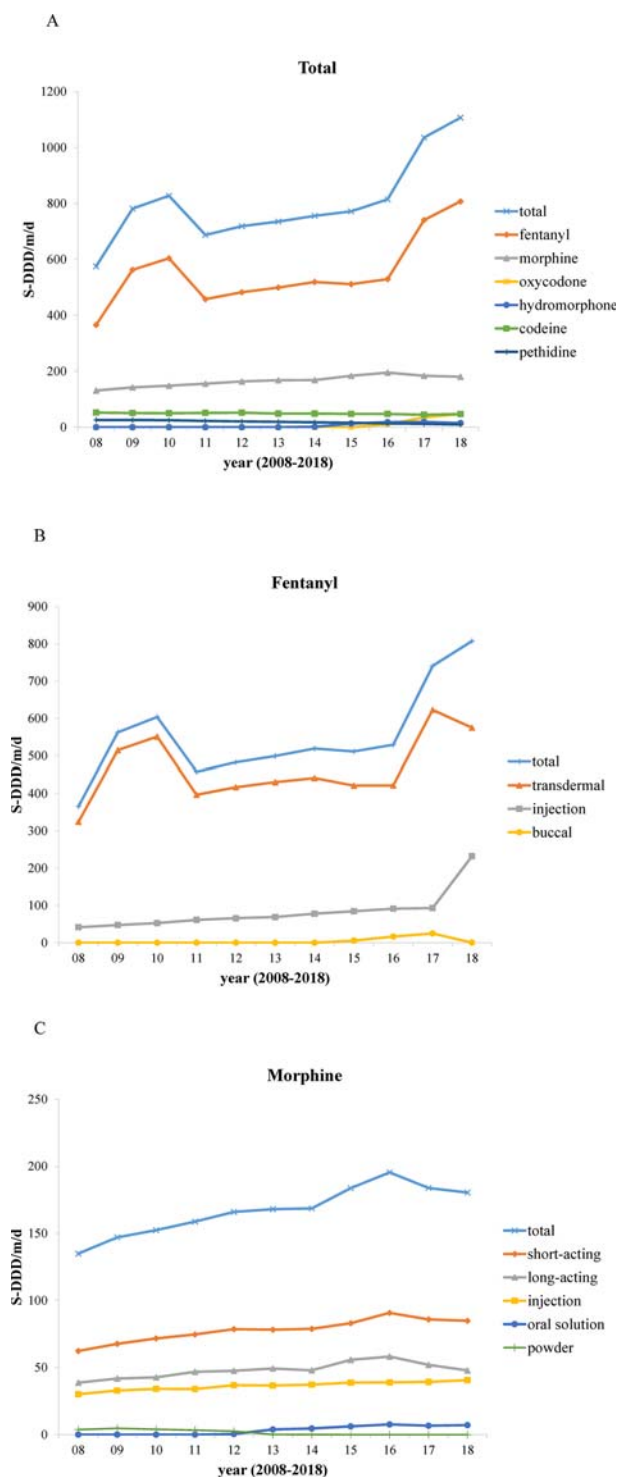


Fig. 1. The trend of opioid consumption in S-DDD per million inhabitants per day (S-DDD/m/d) from 2008 to 2018. (A) Total opioid consumption. Trend test: total, $p = 0.006$; fentanyl, $p = 0.021$; morphine, $p < 0.001$; oxycodone, $p = 0.013$; hydromorphone, $p = 0.032$; codeine, $p < 0.001$; pethidine, $p < 0.001$. (B) Fentanyl consumption. Trend test: total, $p = 0.021$; transdermal, $p = 0.151$; injection, $p = 0.007$; buccal, $p = 0.638$. (C) Morphine consumption. Trend test: total, $p < 0.001$; short-acting, $p < 0.001$; long-acting, $p = 0.004$; injection, $p < 0.001$; oral solution, $p = 0.001$; powder, $p = 0.001$.

2018, showing a remarkable decline (63%) over the years.

3.2. International comparison of opioid consumption

Dividing the world into 6 continents, North America had the highest opioid consumption, with Oceania, Europe, South America, Asia and Africa following behind (Table 1). In North America, fentanyl and oxycodone were the two most consumed opioids followed by morphine, hydromorphone, codeine, and pethidine. In the 6 continents, fentanyl and oxycodone were still the two opioids most consumed, while pethidine was the least consumed. The data comparison among neighboring Asian countries was made and found that South Korea had the highest opioid consumption, followed in order by Japan, Taiwan, Singapore, Hong Kong (China) and China (Table 2) with fentanyl being the most consumed, followed in order by oxycodone, morphine, hydromorphone, codeine and pethidine.

4. Discussion

The major findings of the study are: (1) The total annual consumption of opioids in Taiwan increased gradually from 2008 to 2018 (1.9 fold), with fentanyl being the most consumed opioid, followed by morphine. (2) Among fentanyl dosage forms, the transdermal patch was the most used, followed by the injection. (3) For morphine, the short-acting form was the most used, followed by long acting form. (4) Pethidine consumption has declined sharply over the years, with injection being the main form. (5) Among the 6 continents, North America had the highest opioid consumption, with Oceania, Europe, South America, Asia, and Africa following behind. (6) A comparison among neighboring Asian countries showed that South Korea had the highest opioid consumption, followed in order by Japan, Taiwan, Singapore, Hong Kong (China) and China.

When dividing the world into 6 continents (Table 1), North America had the highest opioid consumption. In general, Asia countries consumed less opioid than in other continents except Africa. According to the WHO's 2020 report [5,6], in the past 10 years, there has been a marked increase in opioid consumption in North America and some European countries. In United States, the opioid epidemic has broken out, especially from 2015 to 2017 (also known as opioid crisis) [15–17]. The safety of opioid use thus became a primary concern [13–15]. Our study shows that the total opioid consumption in Taiwan has increased gradually in small amplitude in the

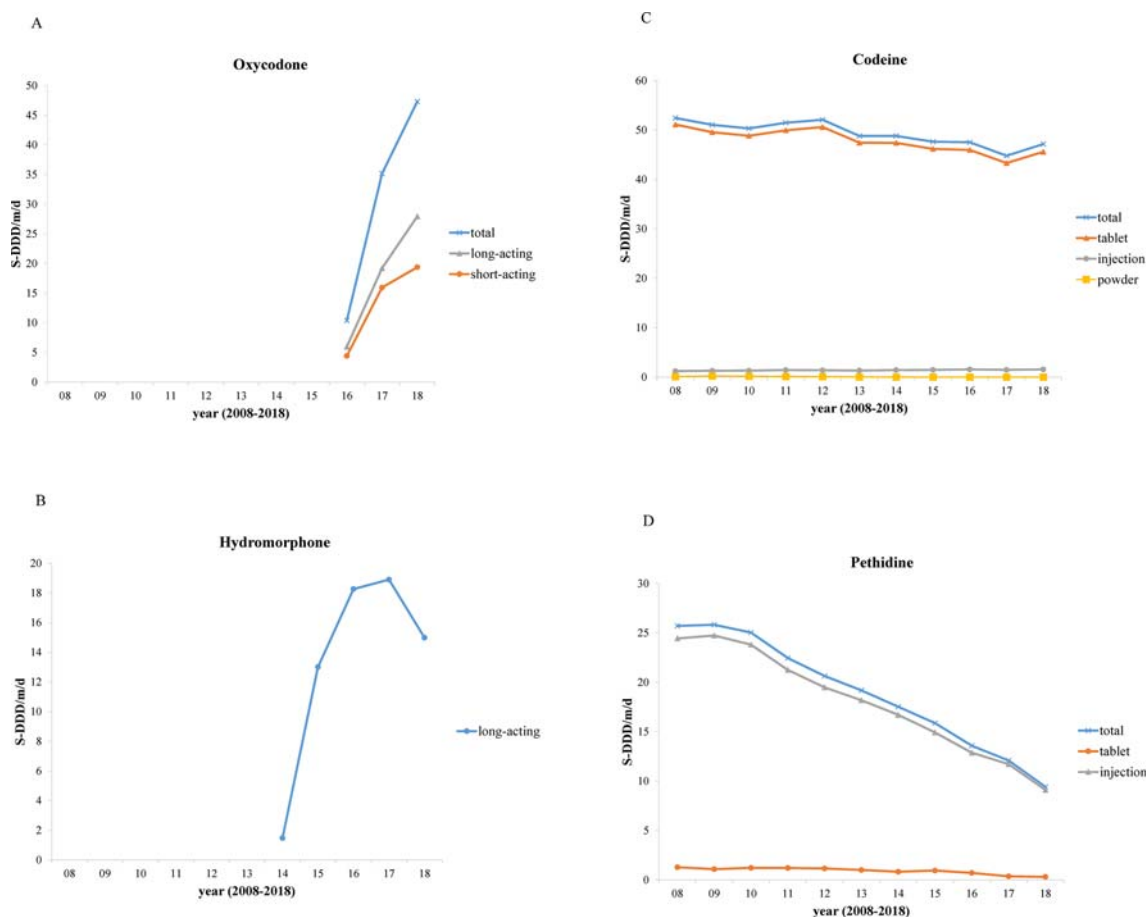


Fig. 2. The trend of opioid consumption in S-DDD per million inhabitants per day (S-DDD/m/d) from 2008 to 2018. (A) Oxycodone consumption. Trend test: total, $p = 0.013$; long-acting, $p = 0.009$; short-acting, $p = 0.024$. (B) Hydromorphone consumption. Trend test: long-acting, $p = 0.032$. (C) Codeine consumption. Trend test: total, $p < 0.001$; tablet, $p < 0.001$; injection, $p < 0.001$; powder, $p = 0.002$; (D) Pethidine consumption. Trend test: total, $p < 0.001$; tablet, $p < 0.001$; injection, $p < 0.001$.

past decade. This phenomenon was also seen in neighboring Asian countries, and may be due to the differences between Eastern and Western cultures and concerns about the safety use of opioids [18].

According to the WHO data [5,6], fentanyl was the top one opioid consumed, followed in order by oxycodone, morphine, hydromorphone, codeine and pethidine. Global opioid consumption ranking from 2015 to 2017 after population adjustment (S-

DDD/m/d) was headed by the United States, followed by Germany, Canada, Austria, Belgium and other North American and European countries. In the United States, hydrocodone was most commonly used, with oxycodone and fentanyl being the second and third in the ranking, respectively. In Germany, fentanyl topped the list of the most commonly consumed opioid, far exceeding other opioids; in Canada, fentanyl, hydromorphone and

Table 1. The S-DDD per million inhabitants per day (S-DDD/m/d) of each opioid on each country. Data were extracted from the WHO website 2020 [5,6].

Continent	S-DDD/m/d (2015–2017)						
	fentanyl	morphine	oxycodone	hydromorphone	codeine	pethidine	total
North America	4978	1337	4846	1020	57	17	12255
Oceania	4274	672	2848	340	98	14	8246
Europe	5293	384	690	258	13	10	6648
South America	294	101	21	7	31	8	462
Asia	102	19	28	2	5	4	160
Africa	33	27	8	3	1	8	80
total	14974	2540	8441	1630	205	61	27851

Table 2. The S-DDD per million inhabitants per day (S-DDD/m/d) of each opioid on neighboring Asia countries. International data were extracted from the WHO website 2020 [5,6].

Country	S-DDD/m/d (2015–2017)						
	fentanyl	morphine	oxycodone	hydromorphone	codeine	pethidine	total
South Korea	1810	30	377	68	0	24	2309
Japan	1109	50	193	1	18	4	1375
Taiwan	580	183	15	16	46	14	854
Singapore	504	25	33	1	0	8	571
Hong Kong	76	94	33	0	1	14	218
China	21	35	24	0	2	3	85
total	4100	417	675	86	67	67	5412

oxycodone were the main opioids used. The most-consumed opioids in Austria were morphine and fentanyl; fentanyl consumption is the highest in Belgium, far leading other opioids. Globally, the most consumed opioid from 2015 to 2017 was fentanyl [5,6], with hydrocodone, oxycodone and morphine following behind. In line with international trends, our study indicates that the most and second most used opioids in Taiwan were fentanyl and morphine. Oxycodone was introduced in Taiwan in 2016 and therefore consumption was low (Table 2).

Comparing neighboring Asian countries (Table 2), South Korea had the highest opioid consumption, followed in order by Japan, Taiwan, Singapore, Hong Kong (China), and China. In these countries, fentanyl was the top consumed opioid, followed in order by oxycodone, morphine, hydromorphone, codeine and pethidine. According to a previous study [7] comparing opioid consumption in Taiwan and neighboring Asian countries from 2011 to 2013, the opioid use in Taiwan ranked between Japan and Hong Kong (China). Our study further included Singapore for comparison using data from 2015 to 2017, and the results showed that the ranking of opioid consumption in Taiwan was between Japan and Singapore.

Our study found that the total consumption of opioid for pain in Taiwan has gradually increased. The reason for the increase may be explained as follows: 1. Nearly all opioid use is covered by the National Health Insurance in Taiwan, which has nearly 100% population coverage. Prescription opioids are easy to access and less costly [14]. 2. Since most Schedule Class I and II opioids are manufactured by the TFDA Pharmaceutical Plant of Controlled Drugs, with only a few being imported, the supply is sufficient to meet the demand [14]. 3. The priority of controlled drug management in Taiwan has been drug safety. The medical staff is encouraged to follow the international and Taiwan's recommendations on opioid use for pain management based on clinical presentation [19–21].

In Taiwan, fentanyl was the most consumed opioid, in line with international trends. The transdermal patch was the most used form, followed by the injection. Since fentanyl buccal forms (film and tablet) were available in Taiwan (since 2015) later than other forms, the consumption was low. Morphine was the second commonly use opioid; short-acting and long-acting dosage forms were commonly used than injection form and oral solution. The injection form is for use in hospital only while the oral solution is used in tube feeding patients with swallowing difficulties. The powder form used mostly for medical research was consumed the least.

Our study found that codeine consumption declined gradually during this period. The reasons for the decline may be due to the following reasons [14,22,23]. (1) Metabolism of codeine is genetically determined by the highly polymorphic enzyme p450 2D6 pathway. The use of codeine in known ultra-rapid metabolizers (1–2% population) or poor metabolizers (5–10% of population) is contraindicated. (2) The use of codeine in renal failure and dialysis is not recommended due to the accumulation of active metabolites (morphine and norcodeine). (3) Codeine is not recommended in patients under the age of 12 due to potential serious side effects and should be used with caution in adolescents under 18 years with obesity or pulmonary disease. Respiratory depression and death may occur in children with a high enzyme actions of cytochrome p450 2D6.

We also found that pethidine consumption dropped rapidly from 25.72 in 2008 to 9.42 (S-DDD/m/d) in 2018. Since prolonged use of pethidine may lead to norpethidine (metabolite of pethidine) accumulation and cause central nervous system side effects, such as seizure. There is an international consensus to reduce pethidine consumption and replace it with other opioids [24], and Taiwan also aligns with this global trend. For oxycodone and hydromorphone, the use of both drugs was low because they were relatively new in Taiwan. However, there was a

rapidly increase in oxycodone use, especially the short-acting form. Continuous observation of this trend is needed.

The limitations of the study are: (1) S-DDD/m/d, an internationally commonly method to measure opioid consumption, was not able to study the effect of different administration routes on the potency of each opioid [14]. (2) Also, they did not provide information to differentiate the clinical usage (e.g., cancer, non-cancer, the user's age) of opioids [14]. Further studies are warranted to elucidate these issues.

5. Conclusion

We collected and analyzed data on opioid consumption from the CDMIS of TFDA (2008–2018) including fentanyl, morphine, oxycodone, hydro-morphone, codeine, and pethidine. The results showed that the total opioid consumption has gradually increased in Taiwan. Fentanyl was the most used opioid, followed by morphine while pethidine consumption has declined rapidly over the years. A comparison among neighboring Asian countries showed that South Korea topped other countries in opioid consumption, followed in order by Japan, Taiwan, Singapore, Hong Kong (China), and China. Since Taiwan is not a member of the World Health Organization, the information on opioid consumption in Taiwan is limited. Additionally, the information on trends of opioid consumption for pain management by countries is also limited. The results of this study may serve as a reference to both Taiwanese and international scholars on the study of opioid consumption for pain.

Authorship

Jhi-Joung Wang, conceived and designed the study, acquired data, analyzed and interpreted data, and revised the manuscript; Yu-Roo Chu, helped design the study and drafted the manuscript; Shu-Fang Teng, reviewed the literature, acquired data and interpreted the results; Chin-Chen Chu, drafted the manuscript and interpreted the results; Chung-Han Ho and Li-Ling Chu, acquired data and did the statistical analyses.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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