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CLINICAL SCIENCE

Trends and characteristics of pethidine use in Taiwan: a six-year-long survey

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OBJECTIVES: To investigate the trends and characteristics of pethidine prescriptions and users in Taiwan from 2002 to 2007.

METHOD: All pethidine users (n = 3,301,136) in Taiwan from 2002 to 2007 were linked to National Health Insurance claims to identify pethidine prescriptions. We examined the trends in pethidine user prevalence and the proportion of pethidine prescriptions according to health care characteristics. A logistic regression model was used to compare patient demographics and health care characteristics associated with pethidine prescriptions between 2002 and 2007.

RESULTS: Despite the decline in the number of pethidine users and prescriptions over the six-year period, more than half a million people were prescribed pethidine annually. In fact, an increasing proportion of pethidine prescriptions were observed in clinics, outpatient settings, and patients who had both operations and cancer diagnoses. Pethidine prescriptions were mostly associated with a non-operation status without a cancer diagnosis (>60%). However, approximately 10% of the total pethidine prescriptions were found in patients with a cancer diagnosis but no operation. Compared to those in 2002, pethidine prescriptions in 2007 were more likely to be found in people 80 years or older, rural residents, patients from clinics, outpatient settings and operation patients with cancer diagnoses.

CONCLUSIONS: A population-based survey in Taiwan demonstrated decreasing consumption of pethidine from 2002 to 2007; however, an increased proportion of prescriptions in certain health care settings was observed. In addition, 10% of the pethidine prescriptions were for cancer patients without operations. These cases need further evaluation for the determination of appropriate pethidine use.

KEYWORDS: Pethidine; Prescription; Consumption; Defined Daily Dose; Population-Based.

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INTRODUCTION

Pethidine (meperidine), which has a short duration of action, has been widely and routinely prescribed for moderate-to-severe pain in medical and surgical patients (1,2). Pethidine is a synthetic opioid that was introduced in 1939 for clinical use as an anticholinergic when its analgesic properties were discovered. It has an active metabolite, normeperidine (3), which accumulates in the organism causing stimulation (anxiety, hyperreflexia, myoclonus and mood changes) and even seizures, and interacts with monoamine oxidase inhibitor (MAOI) drugs causing complications such as serotonergic crisis (3-6). These adverse effects become evident if multiple doses are given over a period of time (3-5). In addition, adverse reactions to normeperidine can occur in patients with normal renal function if the administered doses are sufficiently high (4). In addition, the once-purported theoretical advantages of pethidine over morphine for patients with cholecystitis or pancreatitis have also been challenged (7). Consequently, as awareness of pethidine's adverse effects has increased, updated pain management protocols have called for its cautious use (3). The Agency for Health Care Policy and Research's recommendation suggests that oral pethidine should not be used for pain management and strongly recommends that parenteral pethidine be restricted to patients who have a true allergy or intolerance to other

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opioids, in which case it should only be used in acute pain situations for brief courses (8).

Despite the clinical guidelines that have been issued against pethidine use in many nations (9), it continues to be used in many parts of the world, including Taiwan (10-13). One of the arguments supporting the use of pethidine is that concurrent analgesics given with pethidine can achieve adequate analgesia without causing adverse effects in patients with renal failure (14). Moreover, pethidine was found to produce fewer side effects than morphine when used for short-term periods (15). Therefore, pethidine is still a frequently ordered opioid analgesic, especially for patients who receive shorter courses of narcotics (2,6).

Due to its habit-forming potential, serotonergic crisis risk and normeperidine toxicity, the consumption of pethidine is decreasing worldwide. A population-based study was conducted in Taiwan to describe the trends in the consumption of opioid analgesics from 2002 to 2007, and the report indicated that the consumption of transdermal fentanyl and oral morphine increased markedly over the study period (16). Although pethidine use decreased gradually, it was predominantly prescribed to patients without cancer diagnoses (16). Taiwan recently launched the ''Physician Guidelines on Clinical Use of Pethidine'' in September 2011 (17) to limit the clinical use of pethidine; however, there is no population-based evidence of pethidine prescriptions available for Taiwan and other nations. In addition, pethidine is currently the only available strong opioid in Taiwan for those with intolerable side effects from morphine or fentanyl. We therefore conducted this population-based study using data from National Health Insurance (NHI) claims to investigate the trends and characteristics of pethidine prescriptions and users in Taiwan from 2002 to 2007.

MATERIALS AND METHODS

Source of data

The data analyzed in this study were retrieved from the National Health Insurance Research Database (NHIRD) provided by the Bureau of National Health Insurance (BNHI) (18). Taiwan reformed its insurance programs into the universal National Health Insurance (NHI) system in 1995, and more than 99% of residents in Taiwan were enrolled in the NHI program in 2007 (18). This NHI research database contains registration files and original claim data for reimbursements and offers information on each patient's characteristics, diagnosis, treatments, prescriptions, and associated ambulatory and inpatient medical benefit claims. The database also protects the privacy and confidentiality of all beneficiaries and only transfers health insurance data to health researchers after ethical approval has been obtained.

For the current analysis, we used all pethidine prescriptions issued in outpatient and inpatient claims from 2002 to 2007. All NHI datasets can be interlinked with each individual's personal identification number (PIN). The research protocol for this analysis was ethically approved by the Review Committee of the National Health Research Institutes.

Study subjects and measurements

This is a descriptive study that depicts secular trends and characteristics of pethidine prescriptions and users in Taiwan from 2002 to 2007. During the study period, a total of 3,380,884 prescriptions, of which 99.1% and 0.9% were injections (drug code: A005874209) and tablets (drug code: A005858100), respectively, were written for 3,301,136 patients. From each prescription claim, we retrieved information on the patient's date of birth, gender, the urbanization level of the patient's residential area, the medical institution's accreditation level (clinic, local, regional hospital, or medical center), the setting (hospital, outpatient, or emergency department), and the patient's operation status and cancer diagnosis status. The age of each patient was calculated as the difference between the date of the prescription and the date of birth. The urbanization level for each of the 365 townships in Taiwan was categorized (i.e., urban, suburban, or rural) according to the National Statistics of Regional Standard Classification (19). Outpatient claims provided one procedure code and up to three diagnostic codes for each ambulatory care visit. Inpatient claims included up to five codes for procedures and diagnoses separately. All codes are based on the International Classification of Diseases codes, 9th version Clinical Modification (ICD-9-CM). Operation status was determined by the entry of any procedure code of ICD-9-CM except for obstetrical procedures [72-75], miscellaneous diagnostic and therapeutic procedures [87-99], and diagnostic procedures (Appendix). Any claims accompanied by primary or secondary diagnoses of malignancy (140-209, 230-239) were classified as a cancer diagnosis.

The amount of pethidine prescriptions was expressed as the defined daily dose (DDD) per 1,000 inhabitants per day (20). The DDD is a technical unit of measurement, established by an expert panel as the assumed average maintenance dose when the drug is used for its main indication by an adult, and it is based on the Anatomical Therapeutic Chemical (ATC) classification index (20). The following formula was used in this analysis:

Number of DDD/1,000 inhabitants/day = (number of packages dispensed × number of doses per package × number of mg per dose) / (DDD in mg × number of 1,000 inhabitants in the mid-year population × 365 days).

The DDD value of pethidine is 400 milligrams (20). The mid-year population for each year of the study period was obtained from the Ministry of the Interior of Taiwan (21).

Data analysis

We first described the secular trends for the annual numbers of pethidine users, total prescriptions, total amounts, and DDD/1,000 inhabitants/day according to the forms of pethidine (i.e., injections or tablets). We then calculated the prevalence rate of pethidine users for each year. We also calculated the proportion of total pethidine prescriptions each year according to selected health care characteristics. To further compare patient demographics and health care characteristics for all pethidine prescriptions between 2002 and 2007, we performed simple and multiple logistic regression models, with a generalized estimation equation accounting for clustering of prescriptions administered to the same patient. The odds ratio (OR) of receiving a pethidine prescription in 2007 in relation to the selected patient demographics and health care characteristics was estimated. In addition, we calculated the distribution of the proportion of pethidine prescriptions across primary diagnoses based on ICD-9-CM diagnostic codes in non-operation patients over the six-year period. All statistical analyses were performed with SAS (version

Table 1 - Numbers of pethidine users, total prescriptions, total amounts, and defined daily dose, 2002-2007.

	Calendar year						Percent change 2002 *vs.* 2007
	2002	2003	2004	2005	2006	2007	
Injections							
No. of users	553,364	527,054	560,044	550,979	546,515	533,776	-3.5
Total prescriptions	568,389	543,070	571,415	563,129	559,779	545,581	-4.0
Total amount ($mg \times 10^6$)	79	77	77	76	74	69	-12.7
DDD/1,000/day	0.024	0.023	0.023	0.023	0.022	0.021	-12.5
Tablets							
No. of users	6,283	6,106	6,461	4,772	2,870	2,912	-53.7
Total prescriptions	6,317	6,141	6,479	4,781	2,883	2,920	-53.8
Total amount ($mg \times 10^6$)	8	9	7	3	3	4	-50.0
DDD/1,000/day	0.003	0.003	0.002	0.001	0.001	0.001	-66.7
Total							
No. of users	559,647	533,160	566,505	555,751	549,385	536,688	-4.1
Total prescriptions	574,706	549,211	577,894	567,910	562,662	548,501	-4.6
Total amount ($mg \times 10^6$)	87	86	84	79	77	73	-16.1
DDD/1,000/day	0.027	0.026	0.025	0.024	0.023	0.022	-18.5

DDD/1,000/day = defined daily dose (DDD) per 1,000 inhabitants per day.

9.2; SAS Institute, Cary, NC). *P* values <0.05 were considered statistically significant.

RESULTS

Pethidine was prescribed to more than 500,000 people annually for pain relief from 2002 to 2007 (Table 1); the numbers of pethidine users and total prescriptions decreased slightly, by 4.1% and 4.6%, respectively. The DDD/1,000 inhabitants/day decreased from 0.027 to 0.022, representing a reduction of 18.5%; this decreasing trend was more obvious for tablets than for injections.

Table 2 shows the prevalence rate of pethidine users during the study period. The overall prevalence rate of pethidine users was 24.9 per 1,000 people in 2002; it increased slightly in 2004, and then declined gradually in 2007, representing a 6.4% decrease over the study period. However, pethidine use increased with age, especially in those over 80 years old. Males had a higher prevalence than females. Additionally, there was an apparent geographic variation in the prevalence of pethidine use; people living in rural areas had a higher prevalence rate of pethidine use than in urban areas. We also noted that the subgroups with higher prevalence rates of pethidine users tended to have a smaller percentage of reduction in the prevalence over the study period. People over 80 years old, males and those from rural areas all experienced small reductions in prevalence at 2.9%, 2.1% and 1.3%, respectively. However, the largest reduction in the prevalence of pethidine users was among people under 40 years old (15.0%-16.0%); the corresponding figures for females and urban residents were 8.0% and 9.6%, respectively.

Table 3 illustrates the distributions of pethidine prescriptions across various health care characteristics. Medical centers accounted for the largest proportion of prescriptions; however, these prescriptions decreased by 9.6% from

Table 2 - Prevalence rate of pethidine users, 2002-2007.

Variables	2002 (n = 559,647)	2003 (n = 533,160)	2004 (n = 566,505)	2005 (n = 555,751)	2006 (n = 549,385)	2007 (n = 536,688)	Percent change 2002 *vs.* 2007
Age							
<18	5.6	4.9	5.3	5.2	5.0	4.7	-16.0
18-40	22.7	22.1	23.3	21.3	20.3	19.3	-15.0
41-64	33.3	31.3	33.4	32.0	31.3	30.0	-9.9
65-79	58.5	54.9	58.9	56.4	55.7	53.8	-8.1
≥80	66.3	64.4	68.3	65.9	66.4	64.4	**-2.9**
Gender							
Male	26.2	26.0	28.0	26.9	26.5	25.6	**-2.1**
Female	22.9	21.0	23.2	22.2	21.7	21.1	-8.0
Urbanization							
Urban	22.7	21.5	23.4	21.8	21.4	20.5	-9.6
Satellite	24.2	22.6	24.2	23.0	22.7	21.8	-9.9
Rural	30.0	29.0	31.3	30.6	30.1	29.7	**-1.3**
Total	24.9	23.9	25.8	24.5	24.1	23.3	**-6.4**

Incidence density: Per 1,000 people.

Table 3 - Proportion of total pethidine prescriptions according to health care characteristics, 2002-2007.

Variables	2002 (n = 574,706)	2003 (n = 549,211)	2004 (n = 577,894)	2005 (n = 567,910)	2006 (n = 562,662)	2007 (n = 548,501)	Percent change 2002 *vs.* 2007
Accreditation level							
Medical center	47.4	45.6	45.3	43.9	45.0	42.8	-9.7
Regional hospital	36.0	36.6	36.8	38.4	38.5	41.4	**15.1**
Local hospital	15.7	16.7	16.3	15.9	15.2	14.7	-6.6
Clinic	1.0	1.1	1.6	1.8	1.4	1.2	**19.7**
Patient setting							
Inpatient	73.6	71.8	73.2	71.7	71.0	70.6	-4.1
Outpatient	10.9	11.8	12.6	13.5	13.1	13.1	**20.1**
Emergency department	15.5	16.4	14.2	14.8	15.9	16.3	**5.1**
Operation/Cancer status							
Operation							
With cancer diagnosis	4.4	4.7	5.0	5.2	5.4	5.4	**22.7**
Without cancer diagnosis	22.0	21.6	22.6	23.0	22.7	22.4	**2.2**
Non-operation							
With cancer diagnosis	10.2	10.5	10.2	9.8	10.0	9.7	-5.4
Without cancer diagnosis	63.4	63.3	62.3	62.0	61.9	62.5	-1.5

2002 to 2007. Although the proportion of pethidine prescriptions for clinics was small (<2%), it showed a substantial increase (19.7%). More than 70% of pethidine prescriptions were given in inpatient settings; and 61.9% to 63.4% of pethidine was prescribed to non-operation patients without cancer diagnoses. Despite that, the proportion of prescriptions for inpatient settings and for those non-operation patients without cancer diagnoses decreased by 4.1% and 1.5%, respectively. However, pethidine prescriptions from outpatient settings that were administrated to operation patients with cancer diagnoses demonstrated notable increases in proportion, at 20.1% and 22.7%, respectively.

The patient demographics and health care characteristics for pethidine prescriptions between 2002 and 2007 are shown in Table 4. Pethidine prescriptions tended to be administered more to older people in 2007. Compared to those prescribed in 2002, the pethidine prescribed in 2007 was 1.27 times and 1.77 times more likely to be administered to patients aged 65 to 79 years and greater than 80 years, respectively. Additionally, pethidine was more likely to be prescribed to patients living in rural areas (OR = 1.09, 95% confidence interval (CI) = 1.08-1.10) in 2007. With respect to the health care characteristics, compared to the 2002 prescriptions, the prescriptions in 2007 were more likely to be obtained in clinics (OR = 1.48, 95% CI = 1.43-1.54) and outpatient settings (OR = 1.27, 95% CI = 1.26-1.29), as well as in operation patients with a cancer diagnosis (OR = 1.24, 95% CI = 1.22-1.27).

Because non-operation patients without cancer diagnoses accounted for more than 60% of the total prescriptions, we further examined the leading diagnosis associated with these prescriptions. We noted that the top five leading diagnoses of disease included kidney and ureter calculus and other symptoms involving the abdomen and pelvis, such as abdominal pain, pancreatic diseases, hemorrhoids, and acute appendicitis; these causes accounted for 23.48% of all prescriptions (Table 5). In addition, we also noted that approximately 10% of pethidine prescriptions were administered to non-operation cancer patients, which is usually considered to be inappropriate. The top five cancer diagnoses with non-operation status included malignant neoplasm of the liver and intrahepatic bile ducts, malignant neoplasm of the colon, malignant neoplasm of the trachea, bronchus and lung, malignant neoplasm of the rectum, recto sigmoid junction, and anus, and malignant neoplasm of the female breast (Table 5).

DISCUSSION

This is the first national study to analyze the trends and characteristics of pethidine use in Taiwan. Although there were declining trends in the prevalence of pethidine users, total prescriptions and DDD/1,000 inhabitants/day in Taiwan over the study years, there were still more than 500,000 people who received pethidine prescriptions for pain each year, representing 2.4% of the total population of Taiwan. Additionally, older people, males and people living in rural areas showed a smaller reduction in the prevalence rate of pethidine users than the national average (6.4%). Moreover, there was an increasing proportion of pethidine prescriptions from clinics, outpatient settings and operation patients with cancer diagnoses. We noted that pethidine prescriptions were mostly found in non-cancer patients (85%). However, 10% of the total pethidine prescriptions were found in non-operation patients with a cancer diagnosis, and these prescriptions should be evaluated for their appropriateness.

The decreasing trend in pethidine use noted in Taiwan is consistent with previous reports from other nations (11,12,22-24). Joranson et al. (23) retrospectively surveyed the U.S. medical record database, which revealed a 35% decrease (5.2 to 3.4 million grams) in the medical use of pethidine from 1990 to 1996. Gilson et al. (22) also used the same database to demonstrate that there was a further decline in medical use of pethidine by over 6% (5.8 to 5.4 million grams) from 1997 through 2002. Additionally, in Israel from 2000 to 2008, pethidine consumption fell by 65%, from 0.07 to 0.02 DDD/1,000 inhabitants/day (12). However, two population-based surveys found that pethidine consumption was less than 0.01 DDD/1,000 inhabitants/day and remained constant in both Spain between 1992 and 2006 (11) and in the Slovak Republic between 1998 and 2002 (24). The fall in pethidine consumption in recent years may reflect the campaign by major authorities towards a decrease in regular and long-term use of pethidine. This decrease may also signify the growing awareness of pethidine's shortcomings, including its short duration of action and conversion to a long-lasting toxic metabolite (4). Moreover, multifaceted

Table 4 - Comparisons of the demographics and health care characteristics of patients who received pethidine prescriptions between 2002 and 2007.

Variables	Pethidine prescriptions		Crude estimate		Adjusted estimate	
	in 2002 (Controls)	in 2007 (Cases)				
	n	*n*	OR	95% CI	OR	95% CI
Demographics						
Age (years)						
<18	30,849	23,685	reference		reference	
18-40	209,079	169,413	1.06	1.04-1.08	1.04	1.02-1.06
41-64	206,909	217,571	1.37	1.35-1.39	1.32	1.29-1.34
65-79	102,193	102,205	1.30	1.28-1.33	1.27	1.24-1.29
≥80	25,676	35,627	1.81	1.77-1.85	1.77	1.73-1.81
Gender						
Male	307,001	299,759	1.02	1.01-1.03	1.00	0.99-1.01
Female	259,357	248,741	reference		reference	
Urbanization						
Urban	228,234	211,054	reference		reference	
Satellite	161,113	151,828	1.02	1.01-1.03	1.02	1.01-1.03
Rural	185,359	185,619	1.08	1.07-1.09	1.09	1.08-1.10
Health care characteristics						
Accreditation level						
Medical center	272,180	234,568	reference		reference	
Regional hospital	206,631	227,008	1.28	1.26-1.29	1.28	1.27-1.29
Local	90,224	80,448	1.03	1.02-1.05	1.05	1.03-1.06
Clinic	5,671	6,477	1.33	1.28-1.37	1.48	1.43-1.54
Patient setting						
Inpatient	422,710	387,078	reference		reference	
Outpatient	62,727	71,907	1.25	1.24-1.27	1.27	1.26-1.29
Emergency department	89,269	89,516	1.10	1.08-1.11	1.12	1.11-1.13
Operation/Cancer status						
Operation						
With cancer diagnosis	25,322	29,647	1.25	1.22-1.27	1.24	1.22-1.27
Without cancer diagnosis	126,202	123,102	1.04	1.03-1.05	1.08	1.07-1.09
Non-operation						
With cancer diagnosis	58,706	53,020	0.96	0.95-0.97	0.90	0.89-0.91
Without cancer diagnosis	364,476	342,732	reference		reference	
Total	574,706	548,501				

education, combining a pethidine formulary restriction and a computerized provider order entry regulation initiative, has also minimized pethidine prescriptions (25-27). Furthermore, restricting the use of pethidine to patients who are allergic to or unable to tolerate all other opioids has been advocated in Taiwan as well as in many other countries worldwide (3,12).

Despite a decrease in the prevalence of pethidine use, our study reveals an increased number and proportion of pethidine users aged 80 years and older. Similar increases in number and proportion were also noted in pethidine prescriptions in operation patients with cancer diagnoses, as well as in those from rural areas, regional hospitals, clinics,

Table 5 - Leading diagnoses associated with pethidine prescriptions for non-operation patients with and without cancer diagnoses, 2002-2007.

Rank	ICD-9-CM	Prescription for non-operation without cancer diagnosis (n = 2,115,366)	ICD-9-CM	Prescription for non-operation with cancer diagnosis (n = 339,816)
		%		%
1	592-Calculus of kidney and ureter	8.99	155-Malignant neoplasm of liver and intrahepatic bile ducts	16.37
2	789-Other symptoms involving abdomen and pelvis	4.26	153-Malignant neoplasm of colon	5.97
3	577-Diseases of pancreas	3.88	162-Malignant neoplasm of trachea, bronchus and lung	5.18
4	455-Hemorrhoids	3.28	154-Malignant neoplasm of rectum, rectosigmoid junction, and anus	4.70
5	540-Acute appendicitis	3.07	174- Malignant neoplasm of female breast	4.18
Total		23.48		36.40

ICD-9-CM: International Classification of Diseases codes, 9th version Clinical Modification.

outpatient settings and emergency departments. Elderly patients usually have higher risks of suffering from both acute and chronic pain (28). Valano et al. (29) conducted a cross-sectional study and reported that the majority of patients treated with opioids were aged 41 to 65 years, which is similar to our findings. A population-based study indicated that patients aged 80 years and older who received care in clinics tended to be prescribed potentially inappropriate medications (30). Previous studies also reported that pethidine was administered to only approximately one in eigth older surgical patients (10), mainly due to the greater likelihood that the elderly would experience side effects from pethidine, which may have affected physician prescribing behavior (31). The increased number and proportion of elderly pethidine users in recent years noted in our study warrants further intervention to effectively reduce the use of pethidine in this vulnerable population.

The geographic and medical institutional variations in pethidine use might be due to varying barriers of access to healthcare. Sadowski et al. (32) conducted a cross-sectional population-based study to describe accessibility and intensity of analgesic use among older Manitobans by region. The age- and sex-standardized accessibility and intensity measures revealed that the highest overall analgesic use occurred in the most rural/remote regions of the province. Valano et al. (29) used a cross-sectional study design to demonstrate that adherence to analgesic treatment guidelines was higher in large hospitals than in medium- and small-sized hospitals. A recent study also reported that pethidine was prescribed to 7.6% and 4.3% of all study patients at a large private tertiary care teaching hospital and a smaller academically affiliated Veteran's Affairs medical center, respectively, but the number of doses administered was similar at both sites (10). The variation in the number of pethidine doses prescribed to patients treated in hospitals with different accreditation levels may reflect the different severity of diseases that required different strategies to manage pain. Alternatively, ordering pethidine was also found to be associated with physician specialty, hospital location, patient race, insurance coverage, and physician gender (2), which might also account for the observed variations in pethidine use among geographic and medical institutions in Taiwan.

We were not surprised by the increased proportion of pethidine prescriptions in patients with cancer diagnoses together with operations, which is also consistent with previous findings (29). Previous studies reported that after surgery, patients with cancer were more frequently treated with analgesics than other patients (29). Furthermore, a cancer diagnosis was found to be associated with greater access to and use intensity of all analgesics classes (32). Physicians do not appear hesitant to prescribe higher amounts of opioid analgesics to individuals with cancer diagnoses (33). Jarlbaek et al. (34) analyzed the changes in opioid use from 1994 to 1998 in an entire cohort of cancer patients (n = 24,190) in a Danish county. The results indicated that the overall consumption of opioids increased from 20 kg to 37 kg oral morphine equivalents (omeq) per year, the average consumption increased from 7.6 to 10.7 g omeq/opioid user/year, the annual proportion of users increased from 17% to 20%, and the proportion of patients who were alive two years after their first opioid prescription increased from 38% to 55%. The results also indicate that 14% of the population's opioid users were cancer patients and that they consumed 23% of the total opioids from 1993 to 1997.

Our findings demonstrate that a large proportion of pethidine was prescribed to non-operation patients without cancer diagnoses. The indications for pethidine use documented by emergency departments included abdominal pain, back pain, biliary pain, chest pain, migraine/headache, pancreatitis, renal colic, trauma/fracture, and morphine allergy (26), which were all non-cancer diagnoses. Nevertheless, our data showed that 10% of the total pethidine prescriptions were found in cancer diagnoses without operations. Therefore, there was a potential for improper use of pethidine in non-operation cancer patients in Taiwan, which affirms the need for further evaluation of the appropriateness of pethidine prescriptions in non-operation cancer patients to avoid adverse events from such use.

This study has the following strengths. First, it is population based and includes all eligible pethidine users in Taiwan during the study period. Therefore, the data are highly representative and less likely to have selection bias. Second, the study sample was collected from the NHI database, which makes it possible to cover all pethidine claims of individual patients with little likelihood of non-response from the study subjects. Finally, the advantage of using insurance claim datasets in clinical research is the ease of access to longitudinal records of pethidine use in a large sample of geographically dispersed patients (35).

Despite the above strengths, there are several limitations in our study. First, the data contain no information on compliance with prescription drugs in outpatient settings, which could entail a degree of pethidine use misclassification in this study. However, there is no evidence showing that medication compliance varies with secular years, which provides reassurance that the potential pethidine use misclassification should not have a great effect on the secular trends reported in this study. Second, although we used the ICD-9-CM procedure codes to determine whether a pethidine user had an operation, we were unable to differentiate between acute and chronic pain associated with the operation.

In conclusion, the prevalence of pethidine users and prescriptions steadily decreased from 2002 to 2007 and so did the DDD/1,000 inhabitants/day. Nevertheless, our data show that the number and proportion of pethidine prescriptions increased in certain subgroups, including elderly patients, rural residents, patients with cancer diagnoses who had operations and patients from regional hospitals/clinics and outpatient/emergency settings. We suggest further investigation of the appropriateness of prescribing pethidine to these patients.

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AUTHOR CONTRIBUTIONS

Pan HH, Li CY, Wang JO and Lin TC conceived and designed the study and were responsible for the data acquisition, analysis and interpretation. Ho ST and Wang KY contributed equally to this work and were

responsible for drafting the article and revising it critically for important intellectual content. All authors approved the final version of the manuscript.

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Appendix- ICD-9-CM codes of diagnosis procedures classifications.

Diagnosis procedures classifications	ICD-9-CM codes
Nervous system	01.1, 03.3, 05.1
Endocrine system	06.1, 07.1
Eye	08.1, 09.1, 10.2, 11.2, 12.2, 14.1,15.0, 16.2
Ear	18.1, 20.3
Nose, mouth, and pharynx	21.2, 22.1, 24.1, 25.0, 26.1, 27.2, 28.1, 29.1
Respiratory system	31.4, 33.2, 34.2
Cardiovascular system	37.2, 38.2
Hemic and lymphatic system	40.1, 41.3
Digestive system	42.2, 44.1, 45.1, 45.2, 48.2, 49.2, 50.1, 51.1, 52.1, 54.2
Urinary system	55.2, 56.3, 57.3, 58.2, 59.2
Male genital organs	60.1, 61.1, 62.1, 63.0, 64.1
Female genital organs	65.1, 66.1, 67.1,68.1,70.2,71.1
Musculoskeletal system	76.1, 78.8, 80.2, 80.3, 83.2
Integumentary system	85.1, 86.1

ICD-9-CM: International Classification of Diseases codes, 9th version Clinical Modification.