**Clinical Consumption of Compound Opioid Analgesics in China: A Retrospective Analysis of National Data 2015–2018**

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Compound opioid analgesics (COA) are widely used for cancer pain relief, but few studies investigated the use of that. We aimed to report the characteristics and trend of COA consumption in different regions and health facilities in China. The procurement data of two types of COA, compound codeine phosphate (CCP) and oxycodone and acetaminophen (OAA), in all medical institutions of 20 provinces from 2015 to 2018 were used. Data were presented as defined daily dose for statistical purpose (SDDD) and expenditures per million inhabitants per day. The annual consumption of COA and ratio of two combinations were compared among regions and institutions. We found, during 2015–2018, COA consumption increased at an average rate of 7.32% in SDDD and 19.19% in expenditures, while OAA accounted for most of the consumption. Highest COA consumption appeared in Northern China, with 121.72 SDDD and 1689.87 RMB (2015), whereas the lowest COA consumption was only 11.28 SDDD appearing in Southern China. The ratio of OAA and CCP (in SDDD) was highest in Southern China (53.14 in 2018), whereas lowest in West North (0.37 in 2018). In terms of institutions, tertiary had the highest COA consumption, with 16.74 SDDD and 292.73 RMB (2018). The SDDD of OAA was 27.44 times of that of CCP in tertiary, while it was only 0.11 in primary. Overall, COA consumption is on an upward trend and different among regions and health institutions in either amount or types of COA. These findings call for establishment of COA management regulations.

Key words compound opioid analgesics; cancer pain; consumption; region; health institution

**INTRODUCTION**

Cancer is a major public health problem globally. It is the leading cause of death among non-communicable diseases (NCDs) which are responsible for the majority of global deaths.1,2 The incidence and mortality of cancer keep rising all over the world. In 2018, there are 18.1 million new cases and 9.6 million cancer deaths.3 For patients with cancer, pain is an essential health care problem. A meta-analysis shows that 80% of cancer patients would experience moderate to severe pain in their final stage of life.4 As a vital component of fulfilling the right to health, adequate relief of pain for cancer patients is indispensable and necessary, especially for those in advanced stages of cancer.4–6

As a country with large population, China has plenty of patients suffered from cancer. About 4292000 new cancer cases occurred in 2015 in China, corresponding to over 11000 cancer occurrence on average per day.7 However, the pain management in China is very poor. A national investigation of cancer pain treatment, which was carried out in 175 health facilities across 17 provinces of China during 2012–2015, showed that the pain control of cancer patients received was very limited.8 More specifically, only about 10.8–11.8% of patients with cancer received pain treatment, and about 61.6% of cancer patients suffered from cancer pain.9 A recent retrospective study compared the consumption with the estimated need of morphine for pain treatment, and generated the result of inadequate consumption of opioid analgesic for pain treatment in mainland China.9 Some previous studies also generated similar results.10

In all the above studies, the level of the pain management is evaluated by the consumption of single formulation of opioid analgesics, which are commonly recommended for pain relief. Whereas the compound opioid analgesics (COA), which are also widely used for pain relief in China, were neglected. COA are composed of non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics. These two kinds of medicine have different mechanisms of action. The combination of these two components lead to different combined action mechanisms, onset time, metabolic pathways, which also can achieve synergistic analgesia and prolong the action time.11,12 In the latest version of guideline for diagnosis and treatment of cancer pain in China, two kinds of combinations are recommended.13 Both of them have been used in China for more than 20 years while the earliest single-agent opioids which were used for pain relief for at least 50 years in China.14–16

As far as we knew, there were few studies addressing the use of COA in China. To fill this research gap, this study aims to report the characteristics and trend of consumption of COA in different regions and different levels of health facilities in China and identify possible reasons.

**MATERIALS AND METHODS**

**Study Setting** Twenty out of thirty-one provinces in mainland China were selected, with total resident population...
of 999.51 million and GDP of 65540.73 billion RMB in 2018, accounting for 71.63% of population and 72.80% of GDP of China. These provinces were purposely selected to cover diverse characteristics of geographical location (seven regions: Northern, West North, North East, Eastern, South West, Central, and Southern) and socioeconomic status (underdeveloped, moderately developed and developed). The detailed information of 20 provinces was in Supplementary Table 1.

**Data Source** Centralized Drug Procurement Service Center in each province was responsible for the centralized transactions and medical products procurement in medical institutions. We extracted compound opioid analgesics procurement data from 2015 to 2018 in 20 Centralized Drug Procurement Service Centers and analyzed the total and individual consumption of COA.

The data obtained included all compound opioid analgesics procurement records in all levels of medical institutions in these 20 provinces. More specifically, it included generic name, chemical substance name, dosage form, strength, quantity purchased, expenditure, etc.

And the population information was obtained through the statistical yearbook of the corresponding province in specific year.

**Data Analysis** Five compound opioid analgesics are used in China for treatment of moderate to severe pain: ibuprofen and codeine phosphate, compound codeine phosphate, hydrocodone bitartrate and acetaminophen, oxycodone and acetaminophen, tramadol and paracetamol. But only compound codeine phosphate (CCP) and oxycodone and acetaminophen (OAA) are included in our study according to the recommendations of cancer pain medications in the 2018 edition of Diagnosis and Treatment Guidelines for Cancer Pain. CCP is composed of paracetamol and codeine, and OAA is composed of paracetamol and oxycodone. Each of these two combinations has two strengths. The specific information of the combinations is listed in Table 1. However, one specification consisting of 5 mg oxycodone and 500 mg acetaminophen was excluded in the study as only few provinces (no more than 5) used it during the study period.

Two indicators were used for analysis: defined daily dose for statistical purpose (SDDD) per million inhabitants per day (referred to as SDDD) and expenditures on COA per million inhabitants per day (referred to as expenditures). Defined daily dose (DDD) is a technical unit of measurement, not a recommended prescription dose. The DDD of all the three specifications included in this study was not available in WHO Collaborating Centre (WHOCC) for Drug Statistics Methodology. But WHOCC has specific regulations for establishing DDD for combinations, and they require that all analgesics should be taken into account when calculating DDD for combination products. In the 2018 edition of Diagnosis and Treatment Guidelines for Cancer Pain, the use of paracetamol should not exceed 1.5 g per day. According to these rules, the DDD for the three formulations were generated and listed in Table 1. The first indicator, SDDD per million inhabitants per day, was calculated as follows: annual use of each formulation was divided by its DDD, divided by the population in millions of the provinces during the year, divided by 365 d. The second indicator, the expenditures on each combination were calculated as: annual expenditures divided by the inhabitant in millions of the provinces during the year, divided by 365 d. The number of inhabitant used here were the annual average resident population.

The total consumption of two combinations (amount and expenditure) was reported nationally. Then the consumption of each combination was compared among different regions and different levels of health institutions. The COA consumed at rural and urban community health centers or unrated health institutions were all included in the consumption in primary medical institutions. In the comparison part, to make the data clear and visible, we used the total consumption of COA and the ratio of consumption of the two combinations.

**RESULTS**

**Total Consumption** The total consumption of COA in 20 provinces of China increased year by year, as shown in the Fig. 1. The SDDD raised from 36.59 in 2015 to 44.63 in 2018, with an average growth rate of 7.32%. The expenditure was 369.98 RMB in 2015, and reached 582.95 RMB in 2018, increasing by 19.19% per year.

For the two medicines, OAA was more commonly consumed than CCP. Among the total consumptions, the SDDD of OAA accounted for 50.59% in 2015, and this ratio increased to 72.42% in 2018. Similar result was found in the expenditures. The cost of COA per million inhabitants per day was 369.98 RMB in 2015 and OAA contributed 94.10% of the total cost. Moreover, the ratio of expenditure on OAA increased to 96.50% in 2018.

**Regional Consumption** The consumption of COA in different regions was presented in Tables 2 and 3. The consumption of COA in northern China was higher than other regions, as the SDDD in this area was exceeding 120 and expenditures was over 1500 RMB during the four years. While Southern China had the lowest consumption of COA, with only 11.28 SDDD and 100.14 RMB in 2015, less than one-tenth of the consumption in northern China.

During the study period, the trend of using COA varied across different regions. The consumption of COA in northern China increased year by year. In this area, SDDD was 121.72 in 2015 and this number reached 238 in 2018 with an increasing rate of 95.53%; the expenditures was 1689.89 RMB in 2015 and it reached 3796.30 RMB in 2018 with an increasing rate of 124.65%. Compared with 2015, the con-

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**Table 1. Basic Information of the Components and DDD of COA**

| Name of medicine                  | Components                                | DDD |
|----------------------------------|-------------------------------------------|-----|
| Compound codeine phosphate       | 8.4 mg codeine plus 500 mg acetaminophen  | 25.2|
|                                  | 15 mg codeine plus 300 mg acetaminophen  | 75  |
| Oxycodone and acetaminophen      | 5 mg oxycodone plus 325 mg acetaminophen | 20  |
|                                  | 5 mg oxycodone plus 500 mg acetaminophen | 15  |
The consumption (SDDD and expenditure) of COA in the West North and central China increased in 2018, while the consumption of that in northeast and eastern of China declined, especially in northeast, decreasing by 58.03% in SDDD and 55.58% in expenditures.

The difference in the use of COA was also reflected in the types of medications. CCP was more commonly used in west north and southwest of China than OAA during 2015–2018. In central China, CCP was more commonly used at the beginning. However, by 2017, the use of OAA exceeded the use of CCP. In the rest regions, OAA was more commonly used, especially in southern China, where the use of OAA was 30 to 50 times the use of CCP. However, the expenditure on OAA was higher than on CCP in all regions of China. Even in the west north region, where the SDDD of OAA was much lower than CCP, the expenditure on OAA was still higher than that on CCP.

### Health Institutions’ Consumption

The use of COA in different levels of medical institutions was presented in Tables 4 and 5. During the four years, the SDDD of COA was sorted in the order of tertiary, primary and secondary, while the expenditure on COA increased with the levels of medical institutions. Overall, the consumption of COA in tertiary medical institutions was higher than that in primary or secondary institutions.

Compared with 2015, in 2018, the SDDD of COA in pri-
DOSING OF COA AND THE RATIO OF TWO DRUGS IN VARIOUS LEVELS OF MEDICAL INSTITUTIONS DURING 2015–2018

| Level   | COA  | OAA/CCP | COA  | OAA/CCP | COA  | OAA/CCP | COA  | OAA/CCP | Growth rate for COA |
|---------|------|---------|------|---------|------|---------|------|---------|--------------------|
| Primary | 13.82| 0.02    | 12.02| 0.03    | 12.03| 0.07    | 9.83 | 0.11    | −28.91%            |
| Secondary| 6.03 | 0.86    | 7.00 | 1.48    | 8.35 | 1.61    | 7.81 | 2.14    | 29.54%             |
| Tertiary| 16.74| 12.51   | 21.25| 13.72   | 22.00| 19.33   | 26.99| 27.44   | 61.26%             |

COA refers to compound opioid analgesics; OAA/CCP refers to the ratio of SDDD of oxycodone and acetaminophen and compound codeine phosphate.

Table 5. Expenditures of COA and the Ratio of Two Drugs in Various Levels of Medical Institutions during 2015–2018

| Levels  | COA  | OAA/CCP | COA  | OAA/CCP | COA  | OAA/CCP | COA  | OAA/CCP | Growth rate for COA |
|---------|------|---------|------|---------|------|---------|------|---------|--------------------|
| Primary | 22.38| 0.25    | 25.80| 0.42    | 31.46| 0.86    | 32.63| 1.04    | 45.83%             |
| Secondary| 54.88| 20.03   | 80.55| 28.49   | 94.33| 28.60   | 95.33| 30.37   | 73.72%             |
| Tertiary| 292.73| 227.29  | 371.59| 224.46  | 373.95| 317.74  | 454.99| 339.80  | 55.43%             |

COA refers to compound opioid analgesics; OAA/CCP refers to the ratio of expenditures of oxycodone and acetaminophen and compound codeine phosphate.

primary medical institution decreased while the SDDD of COA in secondary and tertiary medical institutions increased. Specifically, the SDDD in primary medical institutions dropped from 13.82 in 2015 to 9.83 in 2018, with a decreasing rate of 28.91%. However, the SDDD in secondary and tertiary medical institution increased by 29.54% and 61.26%, respectively during the same period. And the expenditures on COA at all levels of medical institutions increased to varying degree.

Considering the two medicines, the use of CCP in primary medical institutions was higher than that of OAA, while the opposite was observed in tertiary medical institutions. In 2015, the SDDD of CCP consumed at primary medical institutions was 50 times that of OAA. Although the ratio of OAA to CCP increased year by year, the use of OAA was still far lower than the use of CCP in primary medical institutions. On the contrary, the SDDD of OAA in tertiary medical institutions was much higher than that of CCP. Moreover, the ratio of OAA to CCP was increasing. In terms of SDDD, the ratio of OAA to CCP in tertiary medical institutions in 2018 was 27.44 (1601.6 times to that in primary medical institution in 2015). In secondary medical institutions, the SDDD of OAA was higher than CCP except in 2015. In terms of expenditures, during 2015–2018, the secondary and tertiary medical institutions spent more on OAA than CCP, while the primary medical institution spent more on CCP than OAA, except in 2018.

DISCUSSION

This study examined the COA consumption characteristics and trends in 20 provinces of China during 2015–2018. The results showed that: (1) COA consumption and the proportion of OAA increased from 2015 to 2018 in China, in terms of both SDDD and expenditure. (2) COA consumption varied across different regions and levels of facilities.

An increase in the COA consumption was observed during 2015–2018, consistent with the findings generated from previous studies on the consumption of opioid analgesics.

To be specific, a worldwide study estimating the use and barriers of opioid analgesics showed that the use of opioid analgesics in China increased from 29 defined daily dose for statistical purpose in 2001–2003 to 91 defined daily dose for statistical purpose in 2001–2003. Many factors including pharmacology, availability, marketing, reimbursement and prescription policies would have impact on the use of analgesics. The increase in the number of cancer patients could be one important possible reason, with a 20% rise in cancer new cases from 3586200 in 2012 to 4291600 in 2015. Moreover, it is estimated that cancer incidence would keep rising. More importantly, the increase in the use of analgesics in China may be attributed to the progress of improved pain management by Chinese government. Over the last decade, a series of expert consensus in pain management was released and clinical guideline for managing cancer-related pain was revised. In addition, during 2011–2013, the Ministry of Health carried out Good Pain Management (GPM) Ward Program, which improved the levels of standardized treatment of cancer pain, medical services and QOL of cancer patients. More specifically, after the implement of GPM Ward Program, the pain-reporting rate was elevated significantly. In terms of CCP consumption, it decreased year by year. One possible explanation is that CCP has serious adverse reactions. Though the evidence is not so sufficient, several literatures reported that inappropriate use of codeine, including overdose and combination with other drug, would lead to death. This may affect CCP prescription by doctor to some extent, leading to a reduction overall in turn. In general, it is necessary to carry out a large-scale study on the safety of CCP.

Although great progress has been made, compared with developed countries, pain management was still at a low stage in China. Specifically, a study conducted in 2016 showed the SDDD of opioid analgesics in China was 91, which was about 2% of that in the U.S.A. and less than half of that in east and southeast of Asia. Such poor pain management in China may be caused by insufficient ability for pain assessment, management, relief, and strict regulation of opioid. A study showed that over 80% of physicians were unable to choose the right dosing and conversion for opioid analgesics.

Another study showed that none of the participated nurses can recall any hospital policy regarding pain assessment and their knowledge on pain assessment was extremely poor. Patients’ insufficient awareness of pain was another barrier for pain management. According to a survey, hospitalized cancer
patients showed poor attitudes toward cancer pain management. The misconception of the use of opioid by physician and patients influenced the pain management to some degree. Moreover, strict regulation of opioid affected opioid accessibility, bringing indirect effects to pain management. In China, opioids were only available in hospital pharmacy and the accessibility to dispensing was limited. The prescription of opioid required registration and the prescribed amount of a single prescription had a 7-d-limit. All in all, the pain management in China needs be improved. Firstly, as a fundamental part, pain assessment needs to be popularized and standardized. Numerical rating scale (NRS), facial expression and verbal rating scale (VRS) were mainly used for current pain assessment, but none of them were objective. A study indicated that 84% of physician perceived that the pain assessed by clinicians was inconsistent with that experienced by patients. Secondly, health professionals played an important role in pain management. However, their knowledge for pain relief was not enough. Continuing education and training were essential for them. Finally, awareness of pain management by patients should be enhanced. Many measures can be taken to strengthen it, such as adding pain bulletin boards in hospital, handing pamphlets to patients, etc.

The COA consumption varied across regions of China. The use of COA in north region, including West north, North east, and Northern China, were higher than other regions. Two possible reasons could explain this regional disparity. Firstly, lack of evidence-based guideline to support the use of COA might be the main reason. A study showed that the advantages of COA have not been demonstrated by large-scale randomized controlled trial (RCT) experiments. Lots of studies indicated that COA had many advantages, compared with a single preparation, but many others indicated that these strengths lacked the support of laboratory evidences or the evidences were somewhat controversial. Inconsistent view about COA may affect its use. Moreover, some clinical trials indicated that the analgesics and adverse effects of these two combinations were not significantly different from other formulations. A double-blind, randomized clinical trial which compared the analgesics efficacy of acetaminophen and its combination with codeine showed that there was no difference between these two groups of medicines in analgesics and adverse effects. Similar conclusion can also be obtained from other studies. In other words, these two can be substituted by opioid and NSAID, which have clear adverse reaction, while the adverse reaction of COA was unclear. Secondly, the difference in unit costs might be another important reason. Generally, drug procurement in China is carried out at the provincial level, and some drugs are purchased through inter-regional alliance. Therefore, medicine prices varied across provinces. Comparing the two COAs, the unit price of CCP was lower than OAA, while some research indicated CCP could replace OAA in clinical use. Hence, CCP may be more preferred in economically underdeveloped regions (west of China, including West North and South West).

The COA consumption also varied across different levels of medical institutions. COA consumption in tertiary medical institutions was higher than primary and secondary medical institutions, which was determined by the characteristics and function of the medical institutions. Tertiary medical institution provided more medical services and served more people. In addition to limited service population, medical resources were deficient in the primary institutions, such as poor availability of medicines, even no opioid analgesics in some primary institutions. Moreover, the prescription of opioid analgesics required doctors to be qualified, while primary medical institutions may have no such qualified physicians. All these have led to the high use of COA in primary medical institutions, especially CCP, which were managed and used as ordinary medicine and required not special authorization. Thus, the secondary medical institutions, which have less service targets than tertiary institutions, but higher availability of opioid analgesics and more qualified physicians than primary institutions, had the lowest COA consumption. And the difference in the types of medicines used for pain relief may be caused by the characteristics and management strategy of these two combinations. The unit prices of these two are different, and cheaper one referring to CCP was preferred in primary medical institution. When referred to management policies, the government included OAA in the management of psychotropic drug in 2019, while CCP was treated as a general medicine. Moreover, OAA was managed as a psychoactive drug long before 2019 among many hospitals because of the risk of abuse. All in all, more evidence-based medical researches on COA need be conducted, and the government need to establish reliable regulations for COA. Besides, pharmacist, who is responsible for reporting adverse drug reaction in the health institutions, should report the adverse reaction events of COA in time to help form a national guideline of COA. More importantly, conducting evaluations on prescriptions with COA will achieve its reasonable use and finally eliminate the difference among regions and levels of medical institutions.

As far as we knew, this was the first study concentrating on the use of COA, and the characteristics of COA consumption among regions and levels of health institutions were presented. However, our work had some limitations. Firstly, not all the provinces were included due to data availability. However, the 20 provinces in the study were representative, covering all levels of economic development and geographic locations. Secondly, since the medicines were selected according to the latest version of Diagnosis and Treatment Guidelines for Cancer Pain in China, only 2 kinds and 3 specifications of combinations were studied. In fact, many combinations can be used for pain relief. Finally, DDD was used as the measurement unit in this study, but it cannot reflect the relative clinical potencies in daily use.

**CONCLUSION**

The COA consumption is on an upward trend though CCP decreased year by year. Regional difference in COA consumption was observed. Considering the amount consumed, COA consumption in north regions was higher than other regions; while in terms of the types, the difference was mainly existed between west and other regions. These differences may be caused by lack of evidence-based support for the use of COA and regional economic difference. Similar result can also be found in different levels of health institutions. The COA consumption in tertiary medical institution was highest and OAA accounted for most of the consumption; while in primary medical institution, CCP were more consumed. The difference
of unit price and management policies are the main reasons for the difference among levels of health institutions. Overall, more efforts were needed for COA evidence-based researches, and the guideline and management of COA also need to be established urgently.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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