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# Drug prescription patterns in osteoarthris patients in a tertiary care hospital in China

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**Abstract**: The study was conducted to evaluate the prescription patterns of various agents for OA in a population specific cohort in Shandong Province, China. Data obtained from the Hospital Databases, which consisted of electronic medical records and prescription information. All the enrolled study subjects (n=212546) were having a clinically detected osteoarthritis (OA) during 2010-2015. Medicines prescription pattern was demonstrated using medication possession ratio (MPR), corresponding number of days administered with that particular medicine. The drugs examined comprised of analgesics (metamizole and paracetamol), oral and topical NSAIDs, cyclooxygenase 2 (COX-2) inhibitors, opioids (fentanyl and tramadol) and symptomatic slow-acting drugs in osteoarthris (SYSADOA). The most generally employed regimen for the treatment OA was consisted of mainly three agents (53.5% OA patients). Most regularly used medicines (MPR ≥50%) were chondroitin (21%), glucosamine (16%) and oral NSAIDs (14%). Use of chondroitin, COX-2 inhibitors and opioids was increased beyond five years of tenure. However, frequency of all the other drugs was decreased. The combination-regimens could cause potential drug interactions, may impact the health of OA patients. In this study, the increment in the use of COX-2 inhibitors and opioids is substantial due to the effect on safety and prices of the medication.

**Keywords**: Osteoarthritis, drug utilization pattern, chondroitin, glucosamine, NSAIDs.

## INTRODUCTION

Osteoarthritis can significantly influence the patient's quality of life and daily functioning, which in turn affects the productivity. Moreover, it may impact on the healthcare costs too, with present forecasting OA could be a fourth largest reason for the disability by the year 2020 (Woolf *et al*., 2003). A latest epidemiological report regarding the healthcare burden of 291 different health anomalies, keeps OA among major 25 reasons with the highest influence on health worldwide (Murray *et al*., 2012). Further, OA was proved to cause raised morbidity, with a robust link with metabolic syndrome, diabetes and walking anomaly (Yoshimura *et al*., 2012). A latest study demonstrated an amplified risk of mortality (especially of cardiovascular anomalies) in the OA patients (Nuesch *et al*., 2011). In addition, surgery in OA patients for joint replacement shows a great economic burden. Indeed, according to the UK based Registry, among all hip / knee joint related surgeries; among them around 90-95% cases were ascribable to OA (National Joint Registry for England and Wales, 2012).

Presently there are ample of gaps in the current literature to address the drug utilization practices among the Chinese patients, who are suffering from osteoarthritis. Numerous therapeutic options are there in the market to deal with OA-linked symptoms, however presently there is no unique practicing strategy. There is a need to have a consensus on the various therapeutic modalities to afford better healthcare for OA patients, with usage of first-line drugs. The diversity in treatment of OA with various medications led to new consequences for safety and healthcare cost concerns (Jordan *et al*., 2004). Among these medicines, several were linked with augmented cardiovascular incidents in OA population. Several other factors such as limitations of the current medications and need for the expedite recuperation current studies are required.

In this study, the objective was to ascertain the utility patterns of various drugs and their combinations for OA, in a geographically chosen population-based group of OA patients' pool in Wendeng, Shandong Province, China. Moreover, one of the emphases was on cardiovascular risk factors among OA patients. Lastly, in this study the utility of each therapeutic agent among freshly detected OA patients in the initial year was examined.

## MATERIALS AND METHODS

### *Methods*

The present exploration is a population-based, nested case-control study, in which data are acquired from

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Wendeng, Shandong Province, electronic database. It consists of health records of OA patients who were registered in one of the 212 health care centers and participated in this study. The database covers a population of two million OA patients and an overall 2801 participating general practitioners. The electronic database comprises of the clinical and referral incidents recorded in the primary health centers (Garcia-Gil Mdel *et al*., 2011; Prieto-Alhambra *et al*., 2014). Healthcare community collects the data (comprehensive demographic features, prescription documents, and diagnostic laboratory test findings) using ICD 10 codes for various symptoms and comorbidities and properly prepared sheets for collecting the clinical and administrative data, such as country of birth, sex, age, height, weight, smoking and drinking habits (Garcia-Gil Mdel *et al*., 2011; Prieto-Alhambra *et al*., 2014). Encryption of personal and clinical information guarantees the concealment of the data in the electronic database. The data is completely interconnected to authorized dispensary (Pharmacy, Wendeng Hospital of Traditional Chinese Orthopedics and Traumatology of Shandong Province) which is the source for the current study data.

***Study participants***

This study considered the subjects aged above 40 years as of on 1 January 2010 (n = 212546). In the study tenure (2010-15), subjects of various types of osteoarthritis, such as polyarticular, hand, hip, knee, spine and unspecific osteoarthritis. Subjects with a previous history of inflammatory allied arthritis were not included.

***Data points of interest for this study***

*Demographical characteristics*

All the study subjects were segregated at baseline (date diagnosing OA) age, sex, joints affected, BMI, general comorbidities and cardiovascular risk factors.

***Medications***

The drug utilization data were acquired from the authorized dispensary invoices sources database further segregated by employing Anatomical Therapeutic Chemical (ATC) system (http://www.whocc.no/). The types of agents utilized were oral NSAIDs, topical NSAIDs, paracetamol (alone or in combination), COX-2 enzyme inhibitors, the 3-symptomatic slow-acting drugs in OA, other generally employed non-narcotic analgesics (metamizole) and the most generally utilized narcotic analgesics (tramadol and fentanyl).

***Prevailing patterns of medications usage***

The medications usage pattern was demonstrated in the data points such as present incidence of use, incidences in the new cases use and overall amount of utility. A combination of medications was defined as the concurrent utility of more than once in the same calendar year. Prevalent case was defined, a patient who was frequent user of a specific drug if the patient filled at least 1-prescription for that drug at any point of time during the tenure. The denominator of prevalence values was considered both prevalent and incident OA patients.

Overall extent of utilization of each medication was showed in as medication possession ratios (MPRs). The MPR is a standard measure, which can be termed as the total number of days for which drug is divided by the total number of days of treatment (Sikka *et al*. 2005). Frequent utility of a certain medication was termed as an MPR of =50% and occasional use as an MPR of =25%.

***Drug prescribing patterns in the freshly diagnosed patients of OA***

The annual occurrence of employing a particular drug during 2010-15, a patient was termed as a new user of that medication if that patient started employing the drug in the first year after OA diagnosis, having filled no prescriptions for that same medication in the previous year. Therefore, the denominator of occurrence measured included only subjects with an incident diagnosis of OA in the index year.

## STATISTICAL ANALYSIS

The quantity and the rate of using each drug and their combinations were investigated in this study (in both already existing and freshly diagnosed OA cases). During the initial days, features of each drug user groups were captured employing descriptive statistical methods. The work was done in line with the highest ethical principles specified in the Declarations of Helsinki. Present study was permitted by Ethics Committee of Wendeng Hospital of Traditional Chinese Orthopedics and Traumatology of Shandong Province. Coding of individuals was done to warrant the confidentiality of data.

## RESULTS

During the 5-year tenure of the study, around 212546 subjects were diagnosed with OA and encompassed in the analyses of this study. The study population was having an average age of 65.48+8.10 years and 74391 (34.9%) were males. Among these subjects, around 62764 (38.7%; BMI presented) were overweight and 67091 (41.5%) were obese during the time of OA detection. In this study, frequently affected joints in subjects diagnosed OA were the knee [n = 86018 (40.4%)], followed by polyarticular / multiple joints [n = 37266 (17.5%)], hand [n = 32381 (15.2%)] and spine [n = 29756 (13.9%)]. Patient characteristic features are showed in the table 1.

The frequently prescribed agents among the different types of medications were NSAIDs [n = 164566 (77.4%)], paracetamol (alone or in combination) [n = 154421 (72.6%)], chondroitin [n = 37142 (17.4%)], glucosamine [n = 24283 (11.4%)], tramadol [n = 31954 (15.0%)] and COX-2 enzyme inhibitors [n = 25016 (11.7%)].

**Table 1**: Demographic features patients at the time of osteoarthritis detection

| Demographic Feature | Frequency |
|---|---|
| Sample size, n | 212546 |
| Age (mean±S.D) years | 65.48+8.10 |
| Gender (males), n (%) | 74391 (34.9) |
| BMI (kg/m$^2$) | |
| Underweight (mean±S.D) | 870±0.4 |
| Normal (mean±S.D) | 30881±14.5 |
| Overweight (mean±S.D) | 62764±29.5 |
| Obese (mean±S.D) | 67091±31.5 |
| No data (mean±S.D) | 50940±23.9; with data 161606 |
| Joint(s) affected, n (%) | |
| Knee | 86018±40.4 |
| Polyarticular | 37266±17.5 |
| Hand | 32381±15.2 |
| Spine | 29756±13.9 |
| Hip | 27125±12.7 |

SD: Standard Deviation; BMI: Body Mass Index; Underweight: BMI <18.5 kg/m$^2$; normal weight: BMI 18.5 to <24.9 kg/m$^2$; overweight: BMI 25 to <30 kg/m$^2$; and obesity: BMI ≥30 kg/m$^2$)

**Table 2**: Prescribing pattern of various drugs and their combinations in the patients diagnosed with osteoarthritis. (n=212546)

| Drug/combination | | n | % | 99% CI (LL, UL) |
|---|---|---|---|---|
| More than three (≥3) | Three or more drugs | 113675 | 53.5 | 43.6, 44.2 |
| Two (2) | Oral NSAIDs + analgesics | 29456 | 13.9 | 13.1, 12.5 |
| | Topical NSAIDs + analgesics | 6276 | 3.0 | 3.8, 2.1 |
| | SYSADOA + oral NSAIDs | 4250 | 2.0 | 3.0, 3.2 |
| | Oral + topical NSAIDs | 6776 | 3.2 | 2.2, 2.5 |
| | SYSADOA + analgesics | 2125 | 1.0 | 0.9, 1.7 |
| One (1) | Oral NSAIDs | 15640 | 7.4 | 7.1, 6.4 |
| | Other analgesics | 13177 | 6.2 | 6.5, 6.7 |
| | SYSADOA | 3081 | 1.4 | 1.2, 1.5 |
| | Topical NSAIDs | 1702 | 0.8 | 0.7, 0.9 |
| | Opioids | 1062 | 0.5 | 0.3, 0.5 |
| | Cyclooxygenase- 2 inhibitors | 839 | 0.4 | 0.1, 0.3 |
| 0 | No drugs | 14487 | 6.8 | 6.8, 5.2 |

NSAIDs: Non-steroidal Anti-inflammatory Drugs; SYSADOA: symptomatic slow-acting drug in osteoarthritis.

**Table 3**: Description of individuals with medication possession (MPR) who are defined as regular and occasional users

| Medication | Any use N | Regular users (MPR≥50%) | | | Occasional users (MPR≥25%) | | |
|---|---|---|---|---|---|---|---|
| | | n | % | 95% CI (LL, UL) | n | % | 95% CI (LL, UL) |
| Oral NSAID | 164566 | 23039 | 14.0 | 13.9, 13.64 | 46902 | 28.5 | 29.2, 28.8 |
| Paracetamol | 154421 | 16456 | 10.7 | 9.0, 11.1 | 40619 | 26.3 | 24.18, 24.5 |
| Metamizole | 52052 | 480 | 0.9 | 0.7, 0.8 | 1181 | 2.3 | 2.7, 2.2 |
| Chondroitin | 37142 | 7799 | 21.0 | 19.6,19.8 | 14462 | 38.9 | 37.2, 39.4 |
| Tramadol + paracetamol | 31954 | 380 | 1.2 | 0.8, 0.7 | 818 | 2.6 | 2.4, 2.1 |
| Tramadol | 27453 | 1647 | 6.0 | 6.1,56.9 | 3814 | 13.9 | 11.9, 12.9 |
| COX-2 inhibitor | 25016 | 3001 | 12.0 | 10.9, 11.8 | 5857 | 23.4 | 20.9, 22.8 |
| Glucosamine | 24283 | 3885 | 16.0 | 16.2, 15.9 | 7405 | 30.5 | 29.1, 32.7 |
| Paracetamol combinations | 19656 | 75 | 0.4 | 0.2, 0.4 | 184 | 0.9 | 0.8, 1.2 |
| Diacerein | 8832 | 983 | 11.1 | 10.8, 11.4 | 1816 | 20.6 | 18.9, 20.4 |
| Fentanyl | 8751 | 18 | 0.2 | 0.1, 0.35 | 35 | 0.4 | 0.29, 0.6 |

COX-2: Cyclooxygenase 2; MPR: Medication Possession Ratio.

The younger people frequently used SYSADOAs, whereas in elderly people tramadol was most frequently used. Symptomatic slow-acting drug in Osteoarthritis (SYSADOA) usage was very frequent in hand and knee OA; whereas tramadol usage was very frequent in polyarticular and hip OA. Overall, tramadol usage was most common in all the OA patients who were suffering with all the comorbidities. Incidentally, cardiovascular risk factors were very frequent in the OA patients who employed COX-2 enzyme inhibitors and NSAIDs, with an incidence of more than 50% and 17% for type 2-diabetes and hypertension, correspondently.

The frequencies of using various medications studied in this study are described in table 2. Among the patients, about half of the patients used at least three agents per year [n = 113675 (53.5%)], whereas only a limited patients used one of the agents [n = 34766 (14.6%)] or no agent [n = 14487 (6.8%)] of the total drugs studied. The frequently used combined drug regimens are topical NSAIDs + analgesics, oral NSAIDs + analgesics and SYSADOAs + oral NSAIDs.

The magnitude of medications usage is displayed in in Table 3. The medication consumers are defined as regular (MPR =50%) and irregular type (MPR =25%). The frequent medication consumers were observed with chondroitin (21.0%), after that glucosamine (16.0%) and NSAIDs (14.0%). On the contrary, very lower amounts of regular medication consumers were found with metamizole (0.9%), paracetamol [in combination with tramadol (1.2%) or other drugs (0.4%)] and fentanyl [0.2%)].

## DISCUSSION

This study shows that among the several agents, NSAIDs (~80%) and paracetamol (~75%) were frequently employed in the population of this study. Opioid drugs namely, fentanyl and tramadol were the frequently prescribed drugs in poly-articular and hip OA patients. Whereas, SYSADOA utility was highly frequent in younger age group patients, mainly in the patients of knee and hand OA.

This study shows prescription pattern and usage of various medicines in the subjects who were clinically detected with OA in a 5-year tenure in Wendeng, Shandong Province, China. This study witnessed about 80% using two or more drugs and more than 50% patients used at least three drugs concurrently. NSAIDs and analgesics were the frequently employed first line medications, with oral NSAIDs and analgesics being the generally used add on secondary medication and opioids being the frequently used third-level therapy. The degree of using these medications appears to be very low with all these agents, with more than 98% of metamizole and opioid users having low drug use (<25% MPR). NSAIDs, paracetamol, chondroitin sulphate, glucosamine and COX-2 enzyme inhibitors were generally employed (MPR =50%) by more than 10% of the total number of users of each of these agents. This increased to more than 20% for chondroitin. Therefore combination therapies are mainstay in the management of OA.

In the study, surprisingly paracetamol prescription took place 2$^{nd}$ position after oral NSAIDS in the frequently prescribed medications of OA. Oral NSAIDS usage has been related with concerns of augmented cardiovascular risks, although the usage was for short-term (McGettigan *et al*., 2011). The recommended first-line therapy to treat OA symptoms is paracetamol (Hochberg *et al*., 2012; Jordan *et al*., 2003). Similarly, for the patients who are suffering from joint pain of modest to severe grade; oral NSAIDS are recommended (Towheed *et al*., 2006). The observations in this study are particularly relevant for OA patients, who were previously at risk for cardiovascular incidents (>50% had hypertension and >17% had diabetes in the data). This study is analogous to a latest Canadian study of community-living persons aged more than 55 with knee/hip OA that exhibited those OA therapies diverse by age and gender, regardless of disease and medical and social background (Fisher *et al*., 2012)

Various trends in the usage of drugs in treating OA are exhibited in this study. The most common medications (paracetamol and NSAIDS) reducing gradually with the time and only three medications usage was raised during the study tenure comprises: opioids, chondroitin and COX-2 enzyme inhibitors. There are no particular straight forward explanations for these findings. However, probable reasons might be ageing and raised obesity, which are linked with augmented vulnerability of cardiac arrest and bleeding may explain the findings (Poirier *et al*., 2006). Opioids prescriptions are more in OA patients who are having comorbid conditions, which may be due to decrease the safety concerns. However, this practice could be a false belief, because opioids usage has been linked with an augmented risk of various adverse events as compared to oral NSAIDS in older patients who are suffering from OA symptoms, comprised of all-cause hospitalization, cardiovascular incidents and a more than higher risk (4-fold) of fractures (Solomon *et al*., 2010). It is clinically sensible, as a latest multi-national study reported that the OA patients exhibit an augmented vulnerability to for falls and fractures (Prieto-Alhambra *et al*., 2012). Moreover, the yearly occurrence of new drug users of COX-2 enzyme inhibitors was anticiated to reduce gradually, but rates continuously rose in the last two years of this study (Zhang *et al*., 2005; Zhang *et al*., 2008).

Findings of this study can demonstrate that only chondroitin and NSAIDS (topical) were frequently used

(=50%) by as a minimum 20% of the users of these medications, while the proportions of regular users endured between 10% and 20% for the most of the general medications, including oral NSAIDS, paracetamol and COX-2 enzyme inhibitors. Usage of opioids is particularly very low, including both week (tramadol) and strong (fentanyl) derivatives, which is in harmony with the recommendations. The efficacy and safety of therapeutic agents in randomized trials should be considered cautiously for medical interventions. Because usage in the actual practice conditions looks like much lesser than clinical experimental evidences. According to the ORSI (Osteoarthritis Research Society International) recommendations, opioids usage to be very restricted in time and surgical modality must be chosen for OA patients. Moreover, it is suggested that non-tramadol opioids must rarely be used, even if OA pain is high (Nu¨esch *et al*., 2009). The negligible use of metamizole shows that this is mainly used as a rescue medicine for flare symptoms. The present study warrants a well-designed similar type of real-life setting studies with a large pool of patients population to derive valuable medical solutions.

## CONCLUSION

In conclusion, present study demonstrated that usage of various drugs for OA depends upon the patient characteristic features. In this study, it was found that Opioids, COX-2 enzyme inhibitors and NSAIDs are extensively prescribed in elderly OA patients, which in turn could cause cardiovascular events adverse events and fractures. Moreover, combined therapies are very common in OA patients and further simultaneous usage multiple medications may pose potential drug interactions. Therefore, observations of this study suggest that clinicians need to be alert while prescribing medication, which could prevent with the potential unnecessary costs and iatrogenic effects in the management of patients with osteoarthritis.

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