Drug Prescription Patterns in Osteoarthris Patients in a Tertiary Care Hospital in China

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Wang *et al.*: Drug Utilization Patterns for Osteoarthritis in a Chinese Province

The study was conducted to evaluate the prescription patterns of various agents for osteoarthritis 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=212 546) are with a clinically detected osteoarthritis during 2010-2015. Medicine prescription pattern was demonstrated using medication possession ratio, corresponding number of days administered with that particular medicine. The drugs examined comprised of analgesics (metamizole and paracetamol), oral and topical non-steroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors, opioids (fentanyl and tramadol) and symptomatic slow-acting drugs in osteoarthritis. The most generally employed regimen for

the treatment osteoarthritis was consisted of mainly three agents (53.5 % osteoarthritis patients). Most regularly used medicines (medication possession ratio ≥50 %) were chondroitin (21 %), glucosamine (16 %) and oral non-steroidal antiinflammatory drugs (14 %). Use of chondroitin, cyclooxygenase 2 inhibitors and opioids was increased beyond 5 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 osteoarthritis patients. In this study, increase in the use of cyclooxygenase 2 inhibitors and opioids is substantial due to the effect on safety and prices of the medication. Findings of this study should alert clinicians to the potential unnecessary costs and iatrogenic effects in the management of patients with osteoarthritis.

Key words: Osteoarthritis, drug utilization pattern, chondroitin, glucosamine, NSAIDs

Osteoarthritis (OA) can significantly influence a 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 the fourth largest reason for the disability by the year 2020[1]. 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[2]. China is a large country, with a population of 1.3 billion. In 2010, 25.3 % of the population comprised of age group ≥50 y, who are very much prone to get affected with OA. To date, data regarding the precise estimates of prevalence of OA in Chinese population is lacking. However, a recent study from China comprising of 17 128 individuals, reported 8.1 % symptomatic knee OA[3].

OA was proved to be the cause of raised morbidity, with a robust link with metabolic syndrome, diabetes and walking anomaly[4]. A latest study demonstrated an amplified risk of mortality (especially of cardiovascular anomalies) in the OA patients[5]. 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 around 90-95 % cases were ascribable to OA[6].

Presently there are ample gaps in the current literature to address the drug utilization practices among the Chinese OA patients. Numerous therapeutic options are available 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[7]. Among these medicines, several were linked with augmented cardiovascular incidents in OA population[5]. 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 patient 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.

The data are acquired from Wendeng, Shandong Province, electronic database. It consists of health records of OA patients who were registered in one of the 212 health care centers, which participated in this study. The database covers a population of two million OA patients and an overall 2801 participating general practitioners. The electronic database comprised of the clinical and referral incidents recorded in the primary health centers[8,9]. 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[8,9]. Encryption of personal and clinical information guarantees the concealment of the data in the electronic database. The data is completely

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Accepted 21 March 2019
Revised 14 November 2018
Received 17 August 2018
Indian J Pharm Sci 2019;81(3):555-561

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.

This study considered subjects aged above 40 y as of 1 January 2010 (n=212 546). In the study tenure (2010-15), subjects of various types of OA, such as polyarticular, hand, hip, knee, spine and unspecific OA. Subjects with a previous history of inflammatory allied arthritis were not included.

All the study subjects were segregated at baseline (date diagnosing OA) age, sex, joints affected and BMI. Drug utilization data were acquired from the authorized dispensary invoices sources database further segregated by employing Anatomical Therapeutic Chemical (ATC) system[10]. The types of agents utilized were oral nonsteroidal antiinflammatory drugs (NSAIDs), topical NSAIDs, paracetamol alone or in combination, cyclooxygenase (COX)-2 enzyme inhibitors, the 3-symptomatic slow-acting drugs (SSADs) in OA, other generally employed non-narcotic analgesics (metamizole) and the most generally utilized narcotic analgesics (tramadol and fentanyl).

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 one 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 one 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 a drug was taken divided by the total number of days of treatment[11]. Frequent utility of a certain medication was termed as an MPR=50 % and occasional use as an MPR=25 %.

The annual occurrence of employing a particular drug during 2010-15, a patient was termed as a new user of a medication if that patient started employing the drug in the first year after OA diagnosis, having filled no prescriptions for the 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.

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.

During the 5-y tenure of the study, around 212 546 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 y and 74 391 (34.9 %) were males. Among these subjects, around 62 764 (38.7 %; BMI presented) were overweight and 67 091 (41.5 %) were obese during the time of OA detection. In this study, frequently affected joints in subjects diagnosed OA were the knee (n=86 018, 40.4 %), followed by polyarticular/multiple joints (n=37 266, 17.5 %), hand (n=32 381, 15.2 %) and spine (n=29 756, 13.9 %). Patient characteristic features are shown in Table 1.

Frequently prescribed agents among different types of medications were NSAIDs (n=164 566, 77.4 %), paracetamol (alone or in combination, (n=154 421, 72.6 %), chondroitin (n=37 142, 17.4 %), glucosamine (n=24 283, 11.4 %), tramadol (n=31 954, 15.0 %) and COX-2 enzyme inhibitors (n=25 016, 11.7 %). Younger people frequently used SSADs in OA, whereas in elderly people, tramadol was most frequently used. SSADs 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 OA patients who were suffering with all the comorbidities. Incidentally, cardiovascular risk factors were very frequent (30 % had hypertension and >10 % had type 2 diabetes in our observations) 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 in this study are described in Table 2. Among the patients, about half of the patients used at least 3 agents per year (n=113 675, 53.5 %), whereas only a limited patients used one of the agents (n=34 766, 14.6 %) or

TABLE 1: DEMOGRAPHIC FEATURES OF PATIENTS AT THE TIME OF OSTEOARTHRITIS DETECTION

Demographic feature	Frequency
Sample size, n	212 546
Age (mean±SD) years	65.48±8.10
Gender (males), n (%)	74 391 (34.9)
BMI (kg/m^2)	
Underweight (mean±SD)	870±0.4
Normal (mean±SD)	30 881±14.5
Overweight (mean±SD)	62 764±29.5
Obese (mean±SD)	67 091±31.5
No data (mean±SD)	50 940±23.9; with data 161 606
Joint(s) affected, n (%)	
Knee	86 018 (40.4)
Polyarticular	37 266 (17.5)
Hand	32 381 (15.2)
Spine	29 756 (13.9)
Hip	27 125 (12.7)

SD: Standard deviation; BMI: body mass index; underweight: BMI <18.5 kg/m^2; normal weight: BMI 18.5 to <25 kg/m^2; overweight: BMI 25 to <30 kg/m^2; and obesity: BMI ≥30 kg/m^2

no agent (n=14 487, 6.8 %) of the total drugs studied. Frequently used combined drug regimens are topical NSAIDs+analgesics, oral NSAIDs+analgesics and SSADs + oral NSAIDs.

The magnitude of medications usage is displayed in Table 3. The medication consumers are defined as regular (MPR=50 %) and irregular type (MPR= 25 %). Frequent medication consumers were observed with chondroitin (21.0 %), after that glucosamine (16.0 %) and NSAIDs (14.0 %). On the contrary, very low numbers 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 %).

This study showed that among the several agents, NSAIDs (~80 %) and paracetamol (~75 %) were frequently employed in the population of this study. Opioid drugs such as fentanyl and tramadol were

TABLE 2: PRESCRIBING PATTERN OF VARIOUS DRUGS AND COMBINATIONS IN PATIENTS DIAGNOSED WITH OSTEOARTHRIS

Drug/combination		n	%	99 % CI (LL, UL)
More than three (≥3)	Three or more drugs	113 675	53.5	43.6, 44.2
	Oral NSAIDs+analgesics	29 456	13.9	13.1, 12.5
	Topical NSAIDs+analgesics	6276	3.0	3.8, 2.1
Two (2)	SSADs+oral NSAIDs	4250	2.0	3.0, 3.2
	Oral+topical NSAIDs	6776	3.2	2.2, 2.5
	SSADs+analgesics	2125	1.0	0.9, 1.7
	Oral NSAIDs	15 640	7.4	7.1, 6.4
	Other analgesics	13 177	6.2	6.5, 6.7
One (1)	SSADs	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	14 487	6.8	6.8, 5.2

NSAIDs: Non-steroidal anti-inflammatory drugs; SSADs: symptomatic slow-acting drug in OA, (n=212 546)

TABLE 3: DESCRIPTION OF INDIVIDUALS WITH MPR DEFINED AS REGULAR AND OCCASIONAL USERS

Medication	Any use	Regular users (MPR≥50 %)			Occasional users (MPR≥25 %)		
	n	n	%	95 % CI (LL, UL)	n	%	95 % CI (LL, UL)
Oral NSAID	164 566	23 039	14	13.9, 13.64	46902	28.5	29.2, 28.8
Paracetamol	154 421	16 456	10.7	9.0, 11.1	40619	26.3	24.18, 24.5
Metamizole	52 052	480	0.9	0.7, 0.8	1181	2.3	2.7, 2.2
Chondroitin	37 142	7799	21	19.6,19.8	14462	38.9	37.2, 39.4
Tramadol+paracetamol	31 954	380	1.2	0.8, 0.7	818	2.6	2.4, 2.1
Tramadol	27 453	1647	6	6.1, 56.9	3814	13.9	11.9, 12.9
COX-2 inhibitor	25 016	3001	12	10.9, 11.8	5857	23.4	20.9, 22.8
Glucosamine	24 283	3885	16	16.2, 15.9	7405	30.5	29.1, 32.7
Paracetamol combinations	19 656	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: Cyclo-oxygenase 2; MPR: medication possession ratio

frequently prescribed drugs in poly-articular and hip OA patients. Whereas, SSADs utility was highly frequent in younger age group patients, mainly in the patients of knee and hand OA.

This study showed that prescription pattern and usage of various medicines in the subjects who were clinically detected with OA in a 5-y tenure in Wendeng, Shandong Province, China. This study witnessed about 80 % using 2 or more drugs and more than 50 % patients used at least 3 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 occupied second position after oral NSAIDS among the frequently prescribed medication of OA. Oral NSAIDS usage has been related with concerns of augmented cardiovascular risks (30 % had hypertension and >10 % had type 2 diabetes), although the usage was for short-term[12]. The recommended first-line therapy to treat OA symptoms is paracetamol[13,14]. Similarly, for the patients who are suffering from joint pain of modest to severe grade; oral NSAIDS are recommended[15]. The observations in this study are particularly relevant for OA patients, who were previously at risk for cardiovascular incidents (>30 % had hypertension and >10 % 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[16].

Various trends in the employment of drugs in treating OA were exhibited in this study. The most common medications (paracetamol and NSAIDS) reduced gradually with time and only 3 medications usage was increased during the study tenure, which were, opioids, chondroitin and COX-2 enzyme inhibitors. There were no particular straight forward explanations for these findings. However, probable reasons might be ageing and obesity, which were linked with augmented vulnerability towards cardiac arrest and bleeding might explain the findings[17]. Opioids prescriptions were more in OA patients who were having comorbid conditions, which might be due to decrease in 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 suffering from OA symptoms, comprised of all-cause hospitalization, cardiovascular incidents and a more than higher risk (4-fold) of fractures[18]. It is clinically sensible, as a latest multi-national study reported that OA patients exhibited augmented vulnerability to falls and fractures[19]. Moreover, the yearly occurrence of new drug users of COX-2 enzyme inhibitors was anticipated to reduce gradually, but rates continuously rose in the last two years of this study[20,21].

Findings of this study can demonstrate that only chondroitin and topical NSAIDS were frequently used (50 %) by a minimum 20 % of the users of these medications, while the proportions of regular users endured between 10 and 20 % for most of the general medications, including oral NSAIDS, paracetamol and COX-2 enzyme inhibitors. Usage of opioids has been particularly very low, including both tramadol (weaker) and fentanyl (stronger), which was 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 appeared much lower than in experimental clinical 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[20]. Moreover, it is suggested that non-tramadol opioids must rarely be used, even if OA pain is high[22]. Negligible use of metamizole indicated that this drug was used as a rescue medicine for flareup of symptoms. The present study, warrants a well-designed similar type of real-life setting studies with a large pool of patient population to derive valuable medical solutions. The present study, being with a large population it is first of its kind in this geography of China. Authors anticipate more of similar studies, addressing several other aspects of healthcare issues.

In summary, this study revealed that the use of various drugs for OA differed with the patient characteristic

features. Opioids, COX-2 enzyme inhibitors and NSAIDs were extensively prescribed in elderly OA patients, which in turn could cause adverse events such as cardiovascular and fractures. The usage was very low in terms of quantity; therefore it is hard to interpret these results from clinical studies into actual practice for imparting efficacy and safety. Moreover, combined therapies were very frequent in OA patients and further data required for understanding the potential drug interactions. Findings of this study created awareness among clinicians to the potential cost implications and drug-induced side effects (iatrogenic) in the treatment of OA patients.

Acknowledgements:

This project was funded by the Wendeng Hospital of Traditional Chinese Orthopedics and Traumatology of Shandong Province. The authors, therefore, acknowledge with thank the Institution for technical and financial support.

Conflicts of interest:

The authors declare that there is no conflict of interest.

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