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Original article

Drug utilization in patients with OA: a population-based study

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Abstract

Objective. Patients with OA use different drugs in their search for relief. We aimed to study the prevalence of use and combinations of different medications for OA in a population-based cohort of OA patients in Catalonia, Spain, while characterizing users of each of the drugs available, with a particular focus on cardiovascular risk factors.

Methods. Data were obtained from the Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària (SIDIAP) database, which includes electronic medical records and pharmacy invoice data for >5 million people from Catalonia. Study participants were those with a clinical diagnosis of OA in 2006–10. Drugs studied included oral and topical NSAIDs, analgesics (paracetamol, metamizole), opioids (tramadol, fentanyl), cyclooxygenase 2 (COX-2) inhibitors and symptomatic slow-acting drugs in OA. Drug utilization was described using medication possession ratios (MPRs), equivalent to the proportion of days covered with the drug of interest. The annual incidence of new users in the first year after OA diagnosis from 2006 to 2010 was estimated for all studied drugs among newly diagnosed OA patients using Poisson regression.

Results. We identified 238 536 study participants. The most common regimen of treatment consisted of at least three drugs (53.9% of patients). The drugs most frequently used regularly (MPR ⩾50%) were chondroitin (21.2%), glucosamine (15.8%) and oral NSAIDs (14.4%). The incidence of the use of opioids, COX-2 inhibitors and chondroitin increased over the 5 year period, whereas all others decreased.

Conclusion. Drug combinations are common in the treatment of OA patients, who are thus exposed to potential drug interactions, with unknown impacts on their health. The increasing use of opioids and COX-2 inhibitors is noteworthy because of the potential impact on safety and costs.

Key words: osteoarthritis, pharmaceutical therapy, population-based cohort, Catalonia, pharmacoepidemiology, drug utilization, electronic health records.

CLINICAL SCIENCE

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Introduction

OA has a great impact on patients' quality of life and productivity, as well as on health care costs, with current predictions suggesting that OA will be the fourth leading cause of disability by the year 2020 [1]. A recent epidemiological study on the health burden of 291 different conditions places OA among the top 25 causes with the greatest impact on health worldwide [2].

It has also been shown that OA leads to increased morbidity, with strong associations with metabolic syndrome, diabetes and walking disability [3], and a recent study showed an increased risk of death (mainly of cardiovascular causes) among OA patients [4]. Joint replacement

surgery for OA represents a large economic burden: according to data from the UK National Joint Registry, 90–95% of the total number of knee/hip arthroplasties carried out nationally are due to OA [5].

Several medication therapies are available to reduce OA-associated symptoms, but consensus on therapeutic strategies is inadequate and guidance on first-line therapies is poorly implemented. This leads to great variability in the use of different drugs for OA, with unknown consequences for health care costs and patient safety [6]. A number of these drugs are associated with increased cardiovascular events in a population that is likely to have a high cardiovascular risk profile [4].

We aimed to study the prevalence of use of different medications (and drug combinations) for OA in a population-based cohort of OA patients in Catalonia, Spain, and to characterize users of each of the drugs available, with a particular focus on cardiovascular risk factors. Finally, we estimated the incidence of the use of each of these drugs among newly diagnosed OA patients in the first year following the date of their diagnosis.

Methods

Source of data

Data for this study were obtained from the Sistema d'Informació per al Desenvolupament de l'Investigació en Atenció Primària (SIDIAP) database. SIDIAP comprises electronic medical records of patients registered in any of the 274 participating primary health care practices in Catalonia, covering a population of ~5 million patients (70% of the Catalonian population in 2006) and with a total of 3414 participating general practitioners. SIDIAP encompasses the clinical and referral events registered in primary care medical records, comprehensive demographic information, prescriptions, referrals and laboratory test results and has recently been validated for OA [7, 8]. Health professionals gather this information using International Statistical Classification of Diseases and Related Health Problems (ICD) 10 codes for symptoms and co-morbidities and structured spreadsheets designed for the collection of clinical and administrative variables, including country of origin, gender, age, BMI, smoking status and drinking status. Encoding personal and clinic identifiers ensures the confidentiality of the information in the SIDIAP database. SIDIAP is fully linked to the official pharmacy invoice database (Facturació CatSalut – Institut Català de la Salut), which was the source of data on drug utilization for the current study.

Study population

All participants registered in SIDIAP and aged $\geqslant$40 years on 1 January 2006 were eligible ($n = 3\,266\,826$). Participants with a prevalent or incident diagnosis of OA (ICD codes M15 for polyarticular OA, M18 and M15.2–15.2 for hand OA, M16 for hip OA, M17 for knee OA, M47.8–47.9 for spine OA and M19 for unspecific OA) in the study period (2006–10) constituted the study population. Patients with a history of any inflammatory arthritis were excluded.

Variables of interest

Patient characteristics

Study participants were characterized at baseline (date of OA diagnosis) according to age, gender, BMI, joints affected, common co-morbidities and cardiovascular risk factors (chronic obstructive pulmonary disease, hypertension, type 2 diabetes and history of ischaemic heart disease and/or cerebrovascular disease).

Medications used

Information on drug utilization was retrieved from the official pharmacy invoice database and classified using the Anatomical Therapeutic Chemical (ATC) system (World Health Organization Collaborating Centre for Drug Statistics Methodology [9]). The list of ATC codes used is presented in supplementary Table S1, available at *Rheumatology* Online, and covers all the drugs with an indication for OA (according to current guidelines [10–14]) subsidized by the Spanish national health system in the study period. This includes oral NSAIDs, topical NSAIDs, paracetamol (alone and in combination with other drugs), cyclooxygenase 2 (COX-2) inhibitors, the three symptomatic slow-acting drugs in OA (SYSADOA) subsidized by the Spanish health system (chondroitin sulphate, glucosamine sulphate and diacerein), other common non-narcotic analgesics (metamizole) and the most commonly used narcotic analgesics in the data (tramadol and fentanyl).

Prevalence of use

Drug utilization was described in terms of prevalence of use (any number of doses at any time during follow-up), incidence of new use (only among patients with a new diagnosis of OA in the study period) and quantitative use. Drug combinations were defined as the concomitant use of different drugs in the same calendar year. For the study of prevalence, a patient was defined as a prevalent user of a particular drug if he/she filled at least one prescription for that drug at any time during the observation period. The denominator of prevalence estimates included both prevalent and incident OA patients. Quantitative use of each different medication (except topical NSAIDs) was described using medication possession ratios (MPRs). The MPR is a standard measurement that is defined as the number of days for which medication is available (number of daily defined doses as defined by the ATC classification) divided by the number of days of treatment (time from first to last prescription) [15]. Regular use of a certain medication was defined as an MPR of $\geqslant$50% and occasional use as an MPR of $\geqslant$25%.

Trends in drug use among newly diagnosed OA patients

For the study of the annual incidence of use of a particular drug in 2006–10, a participant was defined as a new (incident) user of that drug if he/she started using the drug of interest (any number of doses) in the first year after he/she was diagnosed with OA, having filled no prescriptions for

that same drug in the previous year. Thus the denominator of incidence estimates included only patients with an incident diagnosis of OA in the index year.

Statistical analyses

Number and prevalence (99% CI) of users of each of the drugs of interest and drug combinations were estimated in the entire study population (both prevalent and incident OA patients). The most commonly used drug combinations (in chronological order of prescription following incident OA diagnosis) were established. Patient baseline characteristics for each drug user group (based on prevalence of use) were described using descriptive statistics.

A Poisson distribution was assumed to estimate the incidence of new drug users and corresponding 99% CIs for each of the drugs of interest in annual intervals (2006, 2007, 2008, 2009 and 2010) only among newly diagnosed OA patients in each index year.

This study follows the national and international ethics principles stated in the Declarations of Helsinki and Tokyo. This study was approved by the SIDIAP Scientific Committee and the local ethics committee (CEIC IDIAP JordiGol). Confidentiality of data is ensured by coding individuals, as required by the Spanish Law for Data Protection and Confidentiality (15/1999, 13 December, Protección de Datos de Carácter Personal).

Results

Over the 5 year observation period, a total of 238 536 individuals were diagnosed with OA and included in these analyses. The cohort had a mean age of 67.0 years (S.D. 12) and 80 340 (33.7%) were male. A total of 72 887 (40.8% of those with a BMI available) were defined as overweight (BMI 25 to $<30\,kg/m^2$) and 77 119 (43.1%) were obese (BMI $\geqslant 30\,kg/m^2$) at the time of OA diagnosis. Of those with a diagnosis of OA, the most common joints affected were the knee [$n = 96\,222$ (40.3%)], followed by multiple joints/polyarticular OA [$n = 40\,016$ (16.8%)], hand [$n = 37\,590$ (15.7%)] and spine [$n = 33\,403$ (14%)]. Patient characteristics are displayed in Table 1.

The most common class of medication used at any time during follow-up was oral NSAIDs [$n = 184\,690$ (77.4%)], followed by paracetamol (alone or in combination) [$n = 176\,309$ (73.9%)], chondroitin sulphate [$n = 41\,684$ (17.5%)], diacerein/glucosamine sulphate [$n = 34\,930$ (14.6%)], tramadol [$n = 30\,811$ (12.9%)] and COX-2 inhibitors [$n = 28\,075$ (11.8%)]. Patient characteristics separated by use of each drug class can be found in supplementary Table S2, available at *Rheumatology* Online. Users of SYSADOAs were youngest, while those using tramadol were oldest. SYSADOA users showed a higher prevalence of knee and hand OA, while tramadol users had the highest prevalence of hip and polyarticular OA. Tramadol users were those most commonly affected by all the comorbid conditions studied. Interestingly, cardiovascular risk factors were frequent among users of COX-2 inhibitors and NSAIDs, with prevalence of >50% and 17% for hypertension and type 2 diabetes, respectively.

Table 1 Patient characteristics at the time of OA diagnosis

Characteristic	Value
Population, *n*	238 536
Sex (male), *n* (%)	80 340 (33.68)
Age, mean (S.D.), years	66.95 (12)
BMI, mean (S.D.), kg/m^2	
Underweight	480 (0.1)
Normal	28 167 (11.8)
Overweight	72 887 (30.6)
Obese	77 199 (32.4)
Missing	59 803 (25.1)
Joint(s) affected, *n* (%)	
Knee	96 222 (40.34)
Polyarticular	40 061 (16.79)
Hand	37 590 (15.76)
Spine	33 403 (14)
Hip	30 350 (12.72)

Underweight (BMI $<18.5\,kg/m^2$), normal (BMI 18.5 to $<25\,kg/m^2$), overweight (BMI 25 to $<30\,kg/m^2$) and obese (BMI $\geqslant 30\,kg/m^2$).

The prevalence of use of each of the drugs studied and the most common drug combinations are displayed in Table 2. More than half of the patients had at least three drugs in a single year [$n = 128\,655$ (53.9%)], while only a few patients were exposed to either one [$n = 34\,766$ (14.6%)] or none [$n = 14\,339$ (6.0%)] of the drugs studied. The most common two-medication drug regimens were (in order) oral NSAIDs + analgesics, topical NSAIDs + analgesics and SYSADOAs + oral NSAIDs.

In chronological order, 50.4% ($n = 120\,271$) of the patients started analgesics, 32.4% ($n = 77\,270$) oral NSAIDs and 9.1% ($n = 21\,819$) topical NSAIDs as first-line treatments after an OA diagnosis. Among those who started analgesics first, oral NSAIDs in second place followed by opioids in third place constituted the most common drug chronology. Similarly, analgesics and oral NSAIDs were the most commonly prescribed second-line medication groups following initial oral NSAIDs and analgesics, respectively, and opioids were the most prescribed third-line medication in both groups. Detailed results on drug chronologies are described in Table 3.

Quantitative drug utilization is illustrated in Table 4, where the percentages of individuals defined as regular users (MPR $\geqslant$50%) and occasional users (MPR $\geqslant$25%) for each drug group are presented. The highest prevalence of regular users was for chondroitin sulphate (21.2%), followed by glucosamine sulphate (15.8%) and oral NSAIDs (14.4%). Conversely, the lowest percentages of regular users were seen for metamizole (0.68%), paracetamol in combination (0.75% with tramadol, 0.41% with other drugs) and fentanyl (0.22%).

The annual incidence of use for the different medications among newly diagnosed OA patients is displayed in Figs. 1 and 2. Fig. 1 shows the incidence of all analgesic

Table 2 Prevalence of use of different drugs and combinations from participants with an incident diagnosis of OA between 2006 and 2010 ($n = 238\,536$)

	Drug/combination	*n*	%	99% CI
⩾3	Three or more drugs	128 655	53.94	53.67, 54.20
2	Oral NSAIDs + analgesics	34 257	14.36	14.18, 14.55
	Topical NSAIDs + analgesics	7186	3.01	2.92, 3.10
	SYSADOA + oral NSAIDs	5175	2.17	2.09, 2.25
	Oral + topical NSAIDs	5047	2.12	2.04, 2.19
	SYSADOA + analgesics	2621	1.10	1.04, 1.15
1	Oral NSAIDs	15 011	6.29	6.16, 6.42
	Other analgesics	13 473	5.65	5.53, 5.77
	SYSADOA	3389	1.42	1.36, 1.48
	Topical NSAIDs	1794	0.75	0.71, 0.80
	Opioids	652	0.27	0.25, 0.30
	COX-2 inhibitors	483	0.20	0.18, 0.23
0	No drugs	14 339	6.01	5.89, 6.14

COX-2: cyclooxygenase 2; SYSADOA: symptomatic slow-acting drug in OA.

Table 3 Chronology of drugs

First drug dispensed			Second drug dispensed			Third drug dispensed		
Drug group	*n*	% of total	Drug group	*n*	% of group	Drug group	*n*	% of group
Analgesics	120 271	50.4	1. Oral NSAIDs	87 237	72.5	1. Opioids	58 855	67.5
						2. SYSADOA	17 397	19.9
						3. COX-2 inhibitor	7005	8.0
			2. Topical NSAIDs	21 721	18.1	1. SYSADOA	12 840	59.1
						2. COX-2 inhibitor	3974	18.3
						3. Oral NSAIDs	3496	16.1
			3. SYSADOA	6192	5.1	1. Opioids	4161	67.2
						2. COX-2 inhibitor	992	16.0
						3. Topical NSAIDs	529	8.5
Oral NSAIDs	77 270	32.4	1. Analgesics	52 856	68.4	1. Opioids	27 085	51.2
						2. Topical NSAIDs	16 337	30.9
						3. SYSADOA	7589	14.4
			2. Topical NSAIDs	11 803	15.3	1. Analgesics	7595	64.3
						2. Opioids	2397	20.3
						3. SYSADOA	1499	12.7
			3. SYSADOA	8048	10.4	1. Opioids	6053	75.2
						2. Topical NSAIDs	842	10.5
						3. COX-2 inhibitor	738	9.2
Topical NSAIDs	21 819	9.1	1. Oral NSAIDs	12 418	56.9	1. Opioids	8279	66.7
						2. SYSADOA	2438	19.6
						3. COX-2 inhibitor	1093	8.8
			2. Analgesics	8126	37.2	1. Opioids	5577	68.6
						2. SYSADOA	1709	21.0
						3. COX-2 inhibitor	550	6.8
			3. SYSADOA	876	4.0	1. Opioids	635	72.5
						2. COX-2 inhibitor	136	15.5
						3. Analgesics	16	1.8

COX-2: cyclooxygenase 2; SYSADOA: symptomatic slow-acting drug in OA.

and anti-inflammatory medications studied: incident users of opioids significantly increased by 26%, from 15.3/100 person-years (99% CI 14.5, 16.1) in 2006 to 19.3 (99% CI 18.3, 20.5) in 2010. In contrast, new users of oral NSAIDs, topical NSAIDs and paracetamol decreased by 5.5%, 11.9% and 7.0%, respectively. The annual incidence of new users of COX-2 inhibitors increased rapidly by 11-fold in the years 2006 [0.64/100 (99% CI 0.56, 0.74)] to

Table 4 Description of individuals with MPR who are defined as regular and occasional users

Medication	Any use *N*	Regular users (MPR ⩾50%)			Occasional users (MPR ⩾25%)		
		n	%	95% CI	*n*	%	95% CI
Oral NSAID	184 690	26 605	14.41	14.2, 14.62	52 902	28.64	28.37, 28.91
Paracetamol	173 304	17 679	10.23	10.01, 10.39	40 619	23.44	23.18, 23.7
Metamizole	58 417	400	0.68	0.6, 0.77	1181	2.02	1.87, 2.17
Chondroitin	41 684	8834	21.19	20.68, 21.71	16 462	39.49	38.88, 40.11
Tramadol + paracetamol	35 862	268	0.75	0.63, 0.86	838	2.34	2.13, 2.54
Tramadol	30 811	1779	5.77	5.43, 6.12	4014	13.03	12.53, 13.52
COX-2 inhibitor	28 075	3253	11.59	11.09, 12.08	6257	22.29	21.65, 22.93
Glucosamine	27 253	4318	15.84	15.27, 16.41	8405	30.84	30.12, 31.56
Paracetamol combinations	22 060	91	0.41	0.3, 0.52	214	0.97	0.8, 1.14
Diacerein	9913	953	9.61	8.85, 10.38	2026	20.44	19.39, 21.48
Fentanyl	9822	22	0.22	0.1, 0.35	45	0.46	0.28, 0.63

Percentages do not sum to 100 by column or row. Percentages are in relation to the whole sample for each treatment. COX-2: cyclooxygenase 2; MPR: medication possession ratio.

Fig. 1 Incidence and 99% CI by OA diagnostic year for all analgesic and anti-inflammatory medications

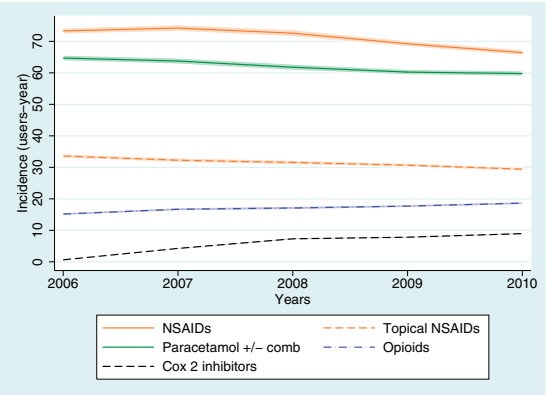
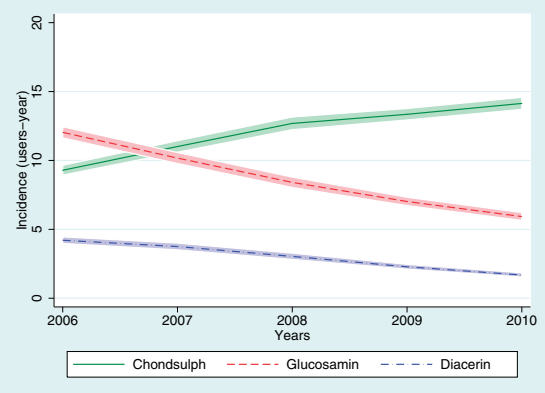


Fig. 2 Incidence and 99% CI by OA diagnostic year for symptomatic slow-acting drugs in OA



Chondsulph: chondroitin sulphate; Glucosamin: glucosamine sulphate.

2008 [7.3/100 (99% CI 7.0, 7.7)], with a slower but still significant increase of 24.7% after 2008, with a final estimate of incidence of new users of 9.1/100 (99% CI 8.6, 9.6) in 2010. Fig. 2 shows the incidence trends of new SYSADOA users, with chondroitin sulphate showing a steady increase of 58.7%, from 9.2 (99% CI 8.9, 9.6) in 2006 to 14.6 (99% CI 14.0, 15.2) in 2010, and glucosamine and diacerein declining over the 5 years, from 12.0 (99% CI 11.6, 12.4) to 6.1 (99% CI 5.7, 6.5) and from 4.2 (99% CI 4.0, 0.4) to 1.8 (99% CI 1.6, 2.0), respectively, in the same period.

Discussion

This study describes the use of various prescribed medications among patients with clinically diagnosed OA in a 5 year period in Catalonia, Spain. We show patterns of use of different groups of drugs commonly indicated for OA according to patient characteristics. Oral NSAIDs and paracetamol were the drugs most widely used in this population, with almost 80% and 75%, respectively, of individuals having used them at some point. Opioids were most used among the oldest patients with hip and polyarticular OA, while SYSADOA use was more prevalent in the younger groups, and particularly in patients with knee and hand OA. Drug combinations are very common in OA patients, with >80% using two or more of these drugs and more than half using at least three simultaneously. Analgesics, oral NSAIDs and topical NSAIDs (in that order) are the most commonly used first-line treatment, with oral NSAIDs and analgesics being the most commonly added second drug and opioids being the most frequent third-line therapy. Quantitative utilization appears to be poor for all these

drugs, with >98% of metamizole and opioid users (including combinations with paracetamol) having low drug use (<25% MPR). NSAIDs, paracetamol, chondroitin sulphate, glucosamine and COX-2 inhibitors were regularly used (MPR ⩾50%) by >10% of the total number of users of each of these drugs. This rose to >20% for chondroitin sulphate.

We also report trends of initiation of each of these therapies in the period 2006–10. The incidence of new indications of oral and topical NSAIDs and paracetamol have decreased by 6%, 12% and 7%, respectively, in this period. In contrast, we observed a continuously incremental initiation of opioids and COX-2 inhibitors. Opioid initiation increased steadily and reached a 26% increase overall, while the incidence of new COX-2 inhibitor therapy experienced a rapid rise of 11-fold in the first 3 years after commercialization, followed by a slower but still significant increase of 25% in the last 2 years. The three SYSADOA drugs we studied showed two different patterns: the number of new users of chondroitin sulphate increased by almost 60% in the 5 year period, while glucosamine and diacerein initiation rates both decreased by ~50%.

Paracetamol is recommended as the first-line pharmaceutical therapy to treat OA symptoms, [10, 12] while oral NSAIDs are widely recommended for OA subjects with moderate to severe joint pain [16]. It is therefore surprising to find paracetamol in second position of the most prescribed drugs following oral NSAIDs. Oral NSAID use has been associated with increased risk of cardiovascular events, even in short-term therapy [17]. This is particularly relevant for OA patients, who are a population already at high risk for cardiovascular events (>50% had hypertension and >17% had type 2 diabetes in our data).

This study is comparable to a recent Canadian cohort of community-dwelling persons aged ⩾55 with hip or knee OA that reported that OA medication varied by age and gender, independent of disease and medical and social context [18].

Different trends in the use of medications in OA are reported here, with the use of the most common drugs (paracetamol, NSAIDs) decreasing with time and only three drugs increasing during the study period: opioids, chondroitin sulphate and COX-2 inhibitors. The reasons for an increase in the use of opioids in OA are not clear, but ageing and increasing obesity, which are associated with increased risk of cardiovascular disease and bleeding, [19] could explain this finding. Physicians are possibly prescribing opioids to patients with more co-morbidities aiming to minimize safety issues. However, this might be a false belief, as opioid use has been related to a higher risk of several serious side effects when compared with oral NSAIDs in elderly patients with OA, including all-cause hospitalization, cardiovascular events and a >4-fold higher risk of fractures [20]. This is clinically meaningful, as a recent multinational study proved that patients with OA have an increased risk of falls and fractures [21]. In addition, we expected the annual incidence of new users of COX-2 inhibitors to decrease after 2008, following the publication of results showing an increased risk of serious cardiovascular events related to these therapies [11, 13], but rates continued to increase in the last 2 years of our study (2009–10).

Any evidence on the safety and efficacy of these drugs in randomized clinical trials must be viewed with caution when applied to actual practice conditions, as drug utilization appears to be much lower than in experimental settings. From our data, only chondroitin sulphate and topical NSAIDs were used regularly (MPR ⩾50%) by at least 20% of the users of these drugs, while the proportion of regular users remained somewhere between 10% and 20% for the most common drugs, including oral NSAIDs, COX-2 inhibitors and paracetamol. Use of opioids is particularly low, including both weaker (tramadol) and stronger (fentanyl) derivatives, consistent with current recommendations. According to the Osteoarthritis Research Society International recommendations, opioids should be limited in time and surgical treatment should be considered for patients who need them [13]. Furthermore, it is recommended that non-tramadol opioids should rarely be used, even if OA pain is severe [22]. The very low use of metamizole might suggest that this is primarily used as a rescue medication for flare symptoms.

Strengths and limitations

This study is unique due to the population size, scope of medications and 5 year time span. One of the major strengths of this study is that diagnosis and severity of OA have been validated, as OA coding in SIDIAP has been shown to be highly specific in previous studies [8, 21]. Also, NSAIDs and some analgesics (such as paracetamol alone) can be acquired over the counter in Spain, likely explaining our findings on low drug utilization of these medications. However, all the drugs studied are subsidized in Spain, and patients aged ⩾65 years get them free of charge, which might minimize this issue. It is likely that there is a good proportion of individuals with mild to moderate OA in our cohort, since the patients were collected in primary care practice settings. However, this is representative of the overall OA population, and the fact that this information was gathered in actual practice conditions improves its generalizability.

Conclusions

We conclude that the use of different medications for OA varies with patient characteristics: oral NSAIDs, COX-2 inhibitors and opioids are widely used among elderly OA patients, which may lead to serious side effects, including cardiovascular events and fractures. However, the quantitative utilization of these therapies is low, making it difficult to translate findings from clinical trials into actual practice regarding safety and efficacy. In addition, drug combinations are very common among these patients, and more data on potential drug interactions are urgently needed. The incidence of new users of paracetamol and oral NSAIDs has decreased in the last 5 years, while the use of SYSADOAs has remained stable overall and the use of opioids and COX-2 inhibitors has increased. Our

findings should alert clinicians to the potential unnecessary costs and iatrogenic effects in the management of patients with OA.

Rheumatology key messages

- Oral NSAIDs and opioids are the most common medications among elderly OA patients.
- Drug combinations in treating OA are common and more data on potential drug interactions are needed.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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