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Current use of analgesics and the risk of falls in people with knee osteoarthritis: A population-based cohort study using primary care and hospital records

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ABSTRACT

Objective: To examine the association between the current use of analgesics and the risk of falls in people with knee osteoarthritis (KOA).

Methods: A retrospective cohort study using data from the UK Clinical Practice Research Datalink, with linkage to Hospital Episode Statistics data. People diagnosed with KOA in England between 2000 and 2014 were included. The studied analgesic classes were antidepressants, antiepileptic drugs (AEDs), opioids, non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol. Cox Proportional Hazards model was used to estimate the risk of fall with current use of analgesics within one year of KOA diagnosis, reported as Hazard Ratio (HR) with 95% Confidence Intervals (CI).

Results: This study included 57,383 patients (mean age [SD] 67.0 [12.8] years, 59.3% were female); 44,010 (76.7%) were prescribed analgesics at least once within one year of KOA diagnosis. Within the first six months of KOA diagnosis, the reported HR (95%CI) were 1.46 (1.20, 1.78), 1.40 (0.91, 2.16), 2.40 (2.01, 2.85), 1.72 (1.43, 2.07), 1.98 (1.68, 2.33), while between 6 and 12 months after KOA diagnosis, the HR (95%CI) were 2.68 (2.14, 3.36), 2.22 (1.70, 2.91), 1.96 (1.70, 2.26), 1.47 (1.21, 1.78), 1.92 (1.63, 2.26) for antidepressants, AEDs, opioids, NSAIDs and paracetamol, respectively and adjusted for important potential confounders.

Conclusion: The current use of analgesics was associated with an increased risk of falls within one year of KOA diagnosis. These findings identify people with KOA who use analgesics as a priority for fall prevention programs/interventions, in an effort to optimise safety of analgesics in this population.

1. Introduction

Osteoarthritis (OA) is the most common chronic progressive musculoskeletal condition that affected 303 million people globally in 2017 [1]. It can affect any joint, however, knees are most commonly involved with 18.2% of people aged over 45 years in England being affected by knee osteoarthritis (KOA) and the prevalence increases with age [2]. It was reported that OA of the knee accounts for 83% of the total OA burden [3].

Treatment focuses on relieving pain and improving joint function, as currently, no curative therapy exists. Management includes prescribing analgesics such as paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids [4] or antidepressants [5]. Although not recommended by many international guidelines, anti-epileptic drugs (AEDs) are still prescribed for chronic non-cancer pain (CNCP) conditions including OA, as an off-label use [6]. Antidepressants and AEDs are centrally acting drug classes that are used in clinical practice for neuropathic pain management [7]. The use of analgesics is common among people with OA and ranges from 50% to 64% in community dwelling patients with OA [8–10]. Moreover, evidence suggests that people with OA have different patterns of analgesic use, including switching to an alternative analgesic class, augmentation with another analgesic or discontinuation of prescribed analgesics [8].

In common with older people, patients with OA might be at risk for drug-related adverse events caused by age related physiological changes,

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comorbidities and poly pharmacy [11]. In fact, evidence suggests that patients with KOA are at a greater risk for certain adverse events such as falls, due to joint instability and severe pain [12]. Falls are a major public health concern in the UK and many countries around the world, particularly those with ageing populations [13]. Whilst the use of analgesics particularly those with Central Nervous System (CNS) effects including opioids and antidepressants, has been identified as a risk factor for falls among older patients (aged ≥60 years) [14–17], this association is less well described in patients with KOA.

Studies were limited with the inclusion of only two analgesic classes [18], or the exposure was measured after establishment of long term analgesic (opioids) use [19]. In another study, exposure data (prescriptions taken in the previous month) collected at an annual interview while the outcome event was self-reported [20]. Hence, it is unclear whether fall risk varies during periods of analgesic use compared to periods of no-analgesic use in patients with KOA. Moreover, the relative safety of analgesic classes in relation to risk of fall is understudied.

The present study aimed to examine the association between current exposure to individual analgesic classes and the risk of fall for the following classes – antidepressants, AEDs, opioids, NSAIDs and paracetamol – compared to no-current exposure.

2. Methods

2.1. Study design

This was a retrospective cohort study.

2.2. Data source

Data were obtained from the Clinical Practice Datalink (CPRD GOLD) and linked Hospital Episode Statistics (HES). CPRD is a large primary care database that contains records of patients from practices across the UK since 1987 [21]. Data are collected as part of the normal clinical care when patients consult their general practitioners GPs, in participating practices. Within CPRD, therapy variables include drug name, strength, product code, numeric daily dose (NDD) and quantity. As of July 2013, 674 practices contributed data to CPRD GOLD and records of more than 4.4 million active patients were included [22]. The HES database contains information on all admissions to NHS trusts in England and data are collected during a patient's stay at hospital [23].

2.3. Study population

The study included adults with a recorded KOA diagnosis between January 1, 2000 and December 31, 2014 and had a record in the CPRD linked to HES data. Cases were defined using Read codes for KOA (Supplementary materials). Read codes are a hierarchical clinical coding system of over 80,000 terms that are used to record clinical data in general practice in the UK [24]. Each patient's study entry date was the date of the first recorded diagnosis of KOA in CPRD (index diagnosis date) until the earliest date of: first fall, death, transfer out (date the patient transferred out of the practice) or end of follow-up period (December 31, 2015). Patients were eligible for inclusion if their KOA diagnosis occurred at least 12 months after registration with the GP practice.

2.4. Exposure

Details of all analgesic prescriptions for the study cohort were obtained from CPRD (therapy file) following their index diagnosis. Analgesics were grouped into five exposure groups according to the prescribed analgesic class including: antidepressants, AEDs, opioids, NSAIDs and paracetamol (supplementary materials). The duration of each prescription was calculated by dividing the total quantity prescribed by the NDD, and the number of treatment episodes per patient for each analgesic class was then determined. A treatment episode (exposure period) was defined as a period of continuous analgesic use without gaps of more than 60 days between the end of a prescription (prescription's supply) and the start of the next prescription. A prescription after more than 60 days was counted as the start of a new treatment episode. Within general practice, prescriptions for an individual patient are generated at regular intervals of about a month up to two months' duration. This reflects a pattern of prescribing when a patient requires a repeat prescription at regular intervals because they have used up their previous supply of medication. A gap of >60 days would therefore, most likely indicate a period on no-analgesic use [25].

2.5. Outcome

Information on the first recorded fall within one year of KOA diagnosis was extracted using Read and ICD-10 codes (supplementary materials). The period of 12 months after diagnosis was selected as the majority of primary care patients with a diagnosis of KOA switch, augment or discontinue their analgesic treatments 2–6 months after initiation [8]. Hence a period of 12 months after KOA was selected to incorporate more periods of treatment (analgesic use) and more events (falls) than a shorter follow-up (e.g. 2- or 6-months), thus avoiding any concerns over under-powering the study.

2.6. Potential confounding variables

Age at the index diagnosis, gender, patient-level deprivation score (defined by the index of multiple deprivation [IMD] quintiles, a measure of relative deprivation/disadvantage) [26,27], previous falls, comorbidities and the use of fall risk increasing drugs (FRIDs) were included [28]. These were captured within 12 months prior to the index diagnosis date and were treated as binary variables. Comorbidities included: depression, seizure disorders, coronary heart disease (CHD), diabetes, hypertension, stroke and chronic obstructive pulmonary disease (COPD) and were identified using Read code lists available from the Quality and Outcome Framework (QOF) business rules [29]. Additionally, the prior use of other analgesic classes (other than the class analysed) at baseline was captured.

2.7. Statistical analysis

Cox proportional hazards model was used to estimate the associations between current use of analgesic drugs and the risk of falls, while treating analgesic exposure as a time-varying exposure. Applying time-varying analysis accounts for treatments changing during follow-up and changing from treatment to no treatment. Furthermore, such analysis addresses the immortal time bias (ITB) that is potentially present in crude time-fixed analysis. ITB occurs when there is variation in the timing of treatment initiation from cohort entry and time to treatment is ignored [30].

The entry date in the analysis was the date of KOA diagnosis and the date of the first fall after KOA diagnosis was marked as the event date. The period of 12 months after the diagnosis of KOA was split into two 6-month periods from the time of index KOA diagnosis (i.e., 0–6 months, and from 6 to 12 months). This was done because there was some evidence of non-proportional hazards over one, three and five years of follow-up, seen as crossing log-log curves on at least one point. The split of the follow-up period was also done to investigate changes in hazard ratios over time since KOA diagnosis. Patients who did not experience any fall were censored at the earliest date of: death, transfer out, study end or the end of the first year of follow-up.

A separate Cox proportional-hazards regression model was applied for each analgesic class. Assumptions for performing Cox models were examined and were upheld. The analysis calculated Hazard Ratio (HR) and 95% Confidence Intervals (CI) for the current use of each analgesic class compared with no-current use. Statistical significance was reported as Pvalues of <0.05% using Chi-squared test.

The reference group was the no-current use category (for each analgesic class) and this included periods of non-exposure in patients treated with analgesics as well as periods of non-exposure from patients who were not prescribed any analgesics over the follow-up period.

CPRD data files were downloaded in a zipped text format from the CPRD Gold interface, while HES data were provided by the CPRD staff. Data cleaning involved data inspection for missing information or outliers. Patient records with missing year of birth (yob) were excluded.

Incomplete prescription data for prescribed quantity were excluded (n = 150, 0.03% of total prescriptions). Prescriptions with missing NDD were imputed with doses published in the British National Formulary [31], while outliers included non-plausible values of NDD (i.e. values ≥ 10 times the maximum) and were treated as missing data (total prescriptions with missing NDD ranged between 8% (n = 2134) and 27% (n = 47,736), for AEDs and opioids respectively).

Analyses were carried out using Stata 15.1 (StataCorp. 2017). This research was approved by the Independent Scientific Advisory Committee (ISAC) (protocol number 18_170R).

Table 1
Characteristics of the study population.

Number of patients	57,383
Gender	
Males	23,352 (40.7%)
Females	34,031 (59.3%)
Age in years[a]	
Mean (SD)	67.04 (12.82)
Range	(18.03–104.72)
Age ranks, years (% from total)	
<40	1157 (2.0%)
40–64	23,766 (41.4%)
65–80	22,790 (39.7%)
>80	9670 (16.9%)
IMD score (% from total)	
1 (least deprived)	12,100 (21.9%)
2	13,425 (23.4%)
3	12,153 (21.2%)
4	11,062 (19.2%)
5 (most deprived)	8620 (15.0%)

[a] Age at KOA diagnosis IMD: index of multiple deprivation.

3. Results

This study included 57,383 patients diagnosed with KOA between January 2000 and December 2014 and had HES-linked records (Figure S1 supplementary materials); 44,010 (76.7%) were prescribed analgesics at least once within one year of KOA diagnosis and 13,373 (23.3%) were not prescribed any. The sociodemographic and clinical characteristics of the study population are summarised in Tables 1 and 2. Across the studied analgesic classes, the majority of users were females (between 60.0% and 73.3%). The mean age of paracetamol users was higher compared to users of the other analgesic classes (Table 2). In total, 465,536 analgesic prescriptions were prescribed within the first year of KOA diagnosis (Table 3).

3.1. Number and proportion of patients who experienced a fall

A total 2384 patients experienced a fall within one year of KOA diagnosis, (4.1% of the study population N = 57,383) (Table 4). Among them, nine patients had a fall on the day of index diagnosis of KOA and were excluded in further analyses, leaving a total of 57,374 patients, and 2375 of them experienced a fall.

3.2. Association between analgesic use and the risk of falls

The unadjusted and adjusted HRs (95% CI) showed a significant association between analgesic use and the risk of falls for all analgesic classes and over both six-month follow-up periods, apart from AEDs in 0–6 months (Table 5). The log rank test was used to test the equality of survivor function for both intervals (0–6 and 6–12 months of KOA diagnosis) and P value were statistically significant for all classes (P< 0.001).

Across analgesic classes within 6 months of KOA diagnosis, the current use of opioids was associated with the greatest risk of fall versus no

Table 2
Characteristics of study cohort (n = 57,383) stratified by drug class. values are numbers of patients (%) unless stated otherwise.

	Antidepressant	AED	Opioids	NSAIDs	Paracetamol
	n = 11,569	n = 2635	n = 26,997	n = 20, 473	n = 16,007
Females (%)	8488 (73.3)	1704 (64.6)	17,227 (63.8)	12,297(60.0)	10,635 (66.4)
Mean age, years (SD)	67.0 (13.6)	65.8 (12.9)	68.2 (12.5)	66.6 (11.6)	73.8 (11.6)
Age groups[a], years (% from total prescribed respective drug class)					
>40	239 (2.1)	41 (1.6)	342 (1.3)	398(1.9)	105(0.7)
40–64	5228 (45.2)	1175 (44.6)	10,542(39.0)	9372(45.8)	3797(23.7)
65–80	4113 (35.5)	1015 (38.5)	11,317(41.9)	8201 (40.1)	7481(46.7)
>80	1989 (17.2)	404 (15.3)	4796 (17.8)	2511(12.2)	4624(28.9)
IMDs score					
1(least deprived)	2099 (18.1)	428 (16.2)	4836 (17.9)	4124 (20.1)	2767 (17.3)
2	2472 (21.4)	576 (21.9)	5962 (22.1)	4666 (22.8)	3582 (22.4)
3	2411 (20.8)	515 (19.5)	5523 (20.5)	4428 (21.6)	3498 (21.8)
4	2402 (20.8)	558 (21.2)	5613 (20.8)	3997 (19.5)	3331 (20.8)
5	2177 (18.8)	556 (21.1)	5050 (18.7)	3249 (15.9)	2825 (17.6)
Not recorded	8 (0.1)	2 (0.1)	13 (0.05)	9 (0.1)	4 (0.1)
Comorbidities at baseline					
Cardiovascular disease	930 (8.0)	179 (6.8)	2286 (8.5)	1464 (7.1)	1508 (9.4)
Diabetes	463 (4.0)	106 (4.0)	1074 (3.9)	649 (3.1)	692 (4.3)
COPD	262 (2.3)	67 (2.5)	529 (1.9)	228 (1.1)	307 (1.9)
Epilepsy	115 (1.0)	443 (16.8)	252 (0.9)	160 (0.7)	191 (1.1)
Stroke	124 (1.1)	44 (1.7)	212 (0.7)	100 (0.4)	171 (1.0)
Depression	1790 (15.4)	187 (7.1)	1424 (5.2)	965 (4.7)	752 (4.6)
Other characteristics at baseline					
Using FRID	7812 (67.5)	1883 (71.5)	17,712 (65.6)	11,306 (55.2)	11,300 (70.5)
Using analgesics[b]	9948 (86.0)	2402 (91.2)	19,417 (71.9)	14,532 (70.9)	12,471(77.9)
Previous fall	1432 (12.4)	379 (14.4)	2790 (10.3)	1392 (6.7)	2020 (12.6)

[a] Age at KOA diagnosis.

[b] Analgesics other than the studied class FRID: fall risk increasing drugs; IMD: index of multiple deprivation; AEDs: Antiepileptic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; COPD: Chronic Obstructive Pulmonary Disease; SD: standard deviation.

Table 3
Number of patients and prescriptions by analgesic class.

Analgesic class	Number of patients	Proportion of population (%)* N = 57,383	Number of prescriptions	Proportion of prescriptions (%) N = 465,536
Antidepressants	11,569	20.1	97,545	21.0
AEDs	2635	4.5	26,687	5.7
Opioids	26,997	47.0	176,802	38.0
NSAIDs	20,473	35.6	82,347	17.7
Paracetamol	16,007	27.8	82,155	17.6

AEDs: Antiepileptic drugs NSAIDs: non-steroidal anti-inflammatory drugs *exceeds 100% as some patients were prescribed > 1 class.

Table 4
Number (%) of patients who experienced a fall[a].

	Patients who experienced a fall	Patients who did not experience a fall	Total	P Value
Analgesic Users	2125 (4.8%)	41,885 (95.2%)	44,010 (100%)	<0.001
Analgesic Non-users	250 (1.8%)	13,114 (98.2%)	13,364 (100%)	<0.001

[a] This is a crude analysis.

use (HR-adjusted [95% CI] 2.40 [2.01, 2.85]) compared to the current use of paracetamol, NSAIDs and antidepressants (HR-adjusted [95%CI]) of (1.98 [1.68, 2.33], 1.72 [1.43, 2.07], 1.46 [1.20, 1.78] respectively) (Table 5). An example of survival curves for current use versus no-use for paracetamol are presented in supplementary materials.

Between 6 and 12 months after KOA diagnosis, the greatest risk of fall was associated with the current use of antidepressants followed by AEDs with HR-adjusted (95% CI) of 2.68 (2.14, 3.36) and 2.22 (1.70, 2.91) respectively and was increased since first six months (Table 5). The association between current opioid use and the risk of fall was attenuated in the second 6-month period with HR-adjusted (95% CI) of 1.96 (1.70, 2.26), although remained statistically significant. Unlike opioids, NSAIDs and paracetamol, for which the HRs lowered in the second follow-up interval, the adjusted HRs for antidepressants and AEDs increased in the second interval compared to the first one.

The proportional hazard assumption was tested using Schoenfeld residuals and the Pvalue was found not significant (P= 0.38). This implied that the proportional hazards assumption was not violated.

4. Discussion

4.1. Main findings

The current use of analgesic medicines was associated with an increased risk of fall compared to periods of no use in people diagnosed with KOA. The risk ranged from more than 2-fold higher in those currently prescribed opioids, antidepressants, AEDs or paracetamol, and up to 72% higher in those currently using NSAIDs during the first year of KOA diagnosis. The risk of falls varied across follow-up intervals and showed a stronger association with the current use of opioids, NSAIDs and paracetamol in the first 6 months after KAO diagnosis. On the other hand, the current use of antidepressants and AEDs showed a stronger association with the risk of fall within 6–12 months after KOA diagnosis.

4.2. Comparison with other studies

The present study's findings were in agreement with those reported in a case-control study in UK primary care using data from The Health Improvement Network (THIN) database [17]. The study found that there was an increased risk of fall with the current prescribing of serotonin norepinephrine reuptake inhibitor antidepressants (SNRIs) (adjusted OR [95% CI] of 1.79 [1.42, 2.25]) compared to controls [17]. Similarly, a population-based cohort study using UK primary care data reported an increased risk of fall with current antidepressant use [16]. The reported HRs (95% CI) were 1.66 (1.58, 1.73) for SSRIs, 1.39 (1.28, 1.52) for other antidepressants and 1.30 (1.23, 1.38) for tricyclic antidepressants. Although both studies included patients aged 60 years or older who were diagnosed with depression, the estimated risks may be different in people with painful conditions such as KOA. The risk in the second 6-month interval within the present study was higher than that reported by Coupland et al. (2011). This could be explained by the shorter follow-up period compared to a follow-up of 5 years in Coupland et al.'s study, resulting in a smaller number of treatment and non-treatment periods, potentially leading to an over-estimation of the association.

The present study also found an association between current use of AEDs and the risk of falls within 6–12 months after KOA diagnosis. This was in agreement with findings of a recent study using the US Renal Data System [32]. The current use of gabapentin and pregabalin was associated with a significant increase in the risk of fall with HR (95% CI) of 1.35 (1.15, 1.57) and 1.68 (1.36, 2.08), respectively.

Consistent with previous research findings, this study found an association between current opioid use and the risk of fall. In a study of community-dwelling adults aged 60 years or over, opioid use was

Table 5
Association between analgesic use and the risk of fall.

	Unadjusted			**Adjusted**		
0–6 months						
	HR	95% CI	P value	HR	95% CI	P value
No current use	1.0	Reference	Reference	1.0	Reference	Reference
Antidepressants	2.52	2.17–2.89	<0.001	1.46	1.20–1.78	<0.001
AEDs	2.01	1.53–2.63	<0.001	1.40	0.91–2.16	0.122
Opioids	3.11	2.74–3.53	<0.001	2.40	2.01–2.85	<0.001
NSAIDs	1.70	1.45–2.00	<0.001	1.72	1.43–2.07	<0.001
Paracetamol	3.61	3.13–4.16	<0.001	1.98	1.68–2.33	<0.001
6–12 months						
No current use	1.0	Reference	Reference	1.0	Reference	Reference
Antidepressants	2.31	1.98–2.69	<0.001	2.68	2.14–3.36	<0.001
AEDs	2.02	1.55–1.65	<0.001	2.22	1.70–2.91	<0.001
Opioids	2.58	2.26–2.94	<0.001	1.96	1.70–2.26	<0.001
NSAIDs	1.51	1.27–1.79	<0.001	1.47	1.21–1.78	<0.001
Paracetamol	3.32	2.88–3.84	<0.001	1.92	1.63–2.26	<0.001

AEDs: Antiepileptic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; HR: hazard ratio; CI: confidence interval. Adjusted for age, gender, comorbidity, previous fall, use of other analgesics and use of FRIDs.

associated with an increased risk of fall OR (95% CI) 2.4 (1.5, 3.7) [33]. Additionally, in a population based nested case control study, using data from Scania's 245 healthcare database, the risk of fall associated with opioid use was reported separately for men and women as follows: OR (95% CI) 1.92 (1.68, 2.20) and 1.90 (1.49, 2.24) respectively [34].The present study showed a stronger association between current opioids use and the risk of fall, earlier in the follow-up period compared to the later 6–12 months. This was also consistent with previous research. Soderberg et al. (2013), in a population-based case-crossover study from Sweden, identified the period of the first 28 days after opioid initiation as a high-risk period for sustaining a fall-related injury, HR (95% CI) was 2.85 (2.74, 3.00) [35]. The risks were greater during the first week after the start of treatment than during the three consecutive weeks and the reported estimates were 5.14 (4.76, 5.55), 2.57 (2.35, 2.81) 1.46 (1.31, 1.62) and 1.23 (1.10, 1.38) for weeks 1–4 respectively [35]. It is possible that the greatest risk related to opioid treatment is after initiation and is due to sedation, dizziness and cognitive impairment, all of which are risk factors for falls [36].

In a recent study using CPRD a higher risk of fall was reported during episodes of long-term use of opioids: HR (95% CI) 1.23 (1.19, 1.28) compared to non-long-term use [19]. These estimates were lower than those from the present study for opioids in the first 6 months (HR 2.40 [95% CI 2.01, 2.85]), which may be explained by the fact that fall events were captured after long-term use was established (i.e. after 90 days of use) which meant that events which occurred after opioid initiation were not included.

The association between the use of NSAIDs and paracetamol and the risk of fall is less well studied compared to other analgesics. Moreover, the available studies have analysed their exposure as a time-fixed variable and therefore could not be compared to results from the present study [37]. Our results are biologically plausible, as the blood-brain barrier becomes more permeable with age letting easier passage of medications. Opioids have psychotropic effects and can cause drowsiness and dizziness [38], while for antidepressants and AEDs, possible underlying causes include sedation, insomnia and confusion [39]. Similarly, NSAIDs can cross the blood-brain barrier and cause adverse CNS effects [40], however, the exact mechanism by which paracetamol might put people at risk of fall is unclear.

4.3. Strengths and limitations

This study was population based rather than hospital-based, its size allowed the inclusion of sufficient numbers within each analgesic class, hence, its findings are generalisable to all patients with KOA. The study included several medicine classes, most of which are recommended by clinical guidelines [4,5] and are commonly prescribed by GPs.

Analgesic use was treated as a time-varying exposure and related the risk of fall to the analgesic drug class currently being used, rather than basing the results on other analgesic use patterns such as after long-term use [19]. The estimated risk of falls may vary with different definitions of long-term use (e.g. 3 months after the first prescription or 3 prescriptions within 90 days after first prescribing) and it implies missing events occurring before the long-term use was established. The time-varying analysis addressed a common and often overlooked source of bias in epidemiological studies, namely the ITB [41]. This type of bias can potentially overestimate the risk of the outcome, stemming from exposure misclassification (i.e. patients were classified as exposed when they are actually not).

The main limitations with the present study are indication and ascertainment bias. Indication bias is found when medications are prescribed for a condition that is itself associated with the outcome of interest [42]. KOA pain itself is associated with the adverse outcome of interest, fall; however, the TV analysis ensured that the same patient was a user at a period and a non-user of analgesics at the subsequent period.

Additionally, there may be other confounders that were not adjusted for, such as alcohol intake. Alcohol has long been considered as a risk factor for falls; however, a number of published studies have failed to confirm this assumption [43]. Nevertheless, this may have overestimated the risk of falls with analgesic use. It was assumed that that prescribed medicines were dispensed and actually taken by patients. This may overestimate exposure, as research has shown that up to 50% of patients do not comply with long-term therapies [44].

Although the prescription records were comprehensive, OTC drug utilisation is not recorded in the CPRD, which may have led to an underestimation of drug exposure as paracetamol and some NSAIDs (e.g. Ibuprofen 200 mg and 400 mg) are widely accessed as OTC products. However, most of the included patients were aged over 60 years old, thus qualifying for free prescriptions in the UK [45].

The diagnoses of KOA and fall were not validated in the present study; however, the validity of diagnoses in CPRD was examined in a systematic review including 183 different diagnoses. It reported an overall high estimate of validity as the median proportion of cases with a confirmed diagnosis was 89% [22]. Moreover, the diagnosis of hip OA recording in CPRD was validated in a study including a random sample of 170 cases, where the positive predictive value of hip OA codes was found to be 79% based on clinical criteria [46]. Data from UK primary care databases (CPRD, QResearch and THIN) have been previously used to examine the association between medication use and the risk of adverse events including falls [16,17]. Prescription data in CPRD are reliably recorded; however, analgesics received during hospitalisation episodes were not included. As the majority of people with KOA are managed in primary care, this should not have had much effect on the findings.

The model treated drug use as a time varying exposure, hence a separate cox model was run for each analgesic class. Classifying the use and non-use periods for a given analgesic, while taking into account the status of use of the remaining four classes would generate a complex model with potential instability. Therefore, analyses were not expanded to consider multiple medications, however the model adjusted for the use of other analgesics (other than the class being analysed). Finally, a generalised ascertainment bias may have arisen as patients attending primary care consultations are more likely to report falls, or recall them when asked, than those not attending such consultations. Clinicians treating patients who are prescribed medications may be more conscious with regard to enquiring about falls in compliance with national guidance [47]. On the other hand, patients are less likely to report or recall falls where they did not experience an injury, hence leading to a potential underestimation/under ascertainment of the outcome.

Several variables, which may potentially have influenced the risk of falling are not captured in CPRD, such as pain intensity, severity of comorbidities, and certain lifestyle measures (e.g. physical activity). However, the studied patients probably had similar levels of pain severity or physical function impairment, when labelled with a diagnosis of KOA [48].

Findings from the present study suggest optimised fall-prevention strategies during periods of medication use in patients with KOA. Firstly, risk of falls should be highlighted with starting and monitored during treatment. Prescribers as well as patients need to be aware of such information and follow appropriate measures, such as restricting (if appropriate) new prescriptions of any additional treatments which may increase the risk of falls. Keeping patients and practitioners informed (through offering oral and written information) of the heightened risk of fall during periods of medication use will optimise self-care, an important component of fall prevention programs. Taken together, these results convey a clear message on the need to prioritise patients with KOA taking analgesics for falls risk assessment, management and prevention strategies, in order to achieve optimal care and safety of prescribed analgesics within this group of patients.

The striking finding is that current paracetamol use was associated with an increased risk of falling among the studied patients, which forms an additional call for routine reviews to ensure the safety of patients who are prescribed any analgesic, even those regarded as safe (e.g. paracetamol). It is still possible that the results for paracetamol were driven by

the fact that users were older patients, who in general are more likely to fall and have serious falls, however, age was adjusted for in the analysis.

The study also identifies community dwelling people with KOA currently using analgesics as a high-risk group for falls which implies regarding them as a group with a priority for referral to fall clinics. Future work needs to examine the association between current exposure to higher compare to lower dosage ranges to explore any dose-response relationship between analgesics' use and falls. It will also be worth exploring the risk in a sample of KOA with and without comorbidities separately.

5. Conclusion

This study quantified the risk associated with the current use of analgesics within one year of KOA diagnosis. The association varied between the two 6-month intervals of the year; opioids, NSAIDs and paracetamol showed a stronger association within the first 6-month interval, while antidepressants and AEDs showed a stronger association within the second 6-month interval. These findings add to the body of knowledge on safety of analgesic medicines in people with KOA.

Declaration of competing interest

The authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2021.100165.

Contributions

AT initiated and developed the research questions, accessed the research data, conducted data management, data analysis and led on drafting the manuscript. RDK and SG advised on the study design and data analysis. All of the authors contributed to the interpretation of the data, critically revised the manuscript and approved the final version submitted for publication.

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AT was funded by a PhD scholarship from the Ministry of Higher Education, Sultanate of Oman. Funders had no role in study design, data collection, data analysis, interpretation of results and writing of this manuscript.

Data Availability Statement

CPRD data were provided under a licence that does not allow data sharing. Data can be, however, obtained from CPRD directly under their standard conditions.

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