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► To cite this version:

Anne-Christine Rat, Mohammed Aqlan, Gilles Loggia, Elpidio Attoh-Mensah, Chantal Chavoix, et al.. Antihypertensive, Anticholinergic, and Opioid Drugs Impact Fall Events Differently in Patients with Knee And/Or Hip Osteoarthritis: A Five-Year Follow-Up of the Khoala Cohort. SSRN: Social Science Research Network, 2023, 10.2139/ssrn.4529286 . hal-04351241

HAL Id: hal-04351241

<https://hal.science/hal-04351241>

Submitted on 18 Dec 2023

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Antihypertensive, anticholinergic, and opioid drugs impact fall events differently in patients with knee and/or hip osteoarthritis: a five-year follow-up of the KHOALA cohort

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Background and Objectives

The risk of falling is increased in persons with knee osteoarthritis (OA), but the risk factors may not be the same as in the general population. It is of interest to know whether the use of medication, particularly anticholinergic drugs, has an impact on falls independently of functional impairment or pain, since drug prescriptions are modifiable factors.

The main objective of the study was to identify factors, particularly drug-related, associated with the occurrence and number of falls in patients with symptomatic knee and/or hip OA in a longitudinal study.

Patients and methods

This study was based on data from the Knee and Hip OsteoArthritis long-term Assessment (KHOALA) cohort, consisting of 878 patients aged 40 to 75 years with symptomatic knee and/or hip OA, recruited from the general population. Patients were followed up annually for 10 years. This study is a longitudinal analysis using data from years 5 to 10. The primary endpoints were the occurrence and the number of falls in the previous 12 months collected from the fifth year of cohort follow-up. The potential risk factors studied were drugs, demographic, clinical (comorbidities), perceived health (WOMAC-pain, WOMAC-function, quality of life (QoL) by the SF-36), and radiological (Kellgren stage) data. Statistical analyses used generalized linear mixed models.

Results

661 patients were included in the analyses. The majority of the sample was female (69%); the mean age was 62 years at year 5, and 153 patients (23.15%) had reported one or more falls in the previous 12 months.

In multivariate analyses, and thus independent of pain and functional abilities, at least one fall occurred, more often among patients using fewer antihypertensive drugs [OR=0.57; 95% CI (0.39–0.83)], using more opioid analgesics [OR=1.44 95% CI (1.05–1.96)], and using medication with a high anticholinergic burden [OR=1.31, 95% CI (1.00-1.73)]. Females, patients living alone and retired persons had increased risk. Being a woman, living alone, having several comorbidities [OR=1.10, 95% CI 1.01–1.21]], and using fewer antihypertensive drugs [OR 0.61, 95% CI (0.42–0.90)] or more opioid analgesics [OR 1.40, 95% CI (1.02–1.90)] were associated with an increased number of fall events. Impaired physical functioning was the only QoL dimension independently associated with an increased risk of falls.

Conclusions

Using opioid analgesics and drugs with high anticholinergic burden was associated with increased risk of falls, whereas antihypertensive treatments were a protective factor in patients followed for knee and/or hip OA. This new finding is crucial for drug management in this population and for improving fall prevention.

Keywords: osteoarthritis, falls, risk factor, cohort, drugs

Background

Falls are a major cause of morbidity and mortality and drive a substantial portion of healthcare costs in the elderly population. Having knee osteoarthritis (OA) puts individuals at particular risk of falling, 40 to 50% reporting having a fall every year compared to 30% in the elderly population [1,2]. The etiology of falls is multifactorial and can result from complex interactions between risk factors. Several studies have reported different risk factors that include age, comorbidities, drugs, muscle weakness, sedentary lifestyle, and psychiatric diseases [3].

However, risk factors for falls could affect differently people with or without OA. Indeed, some risk factors may not be independent of the manifestation of OA symptoms. A recent systematic review of studies on falls in patients with knee OA has identified the following risk factors: impaired balance, muscle weakness, presence of comorbidities, and an increasing number of symptomatic joints. Unfortunately, the level of evidence for the associations between the different risk factors and fall events in OA is moderate as a result of the small number of studies investigating each factors [4]. Hence, it is difficult to identify the factors that will be strongly associated with falls, regardless of OA symptoms. More recently, the Osteoarthritis Initiative (OAI) dataset has been used to identify risk factors for falls among persons with OA or at high risk of developing OA. This was done using the International Classification of Functioning, Disability and Health (ICF) framework. Interestingly, it appeared that personal factors (particularly self-reported history of falls and female gender) were stronger predictors of falls than OA symptoms (e.g., pain and stiffness), environmental factors, activity limitations, and participation restrictions [5].

The role of drug consumption in fall events is of particular interest as they are modifiable factors. Several drugs have been associated with an increased risk of falling in the

older adult population through meta-analysis studies [6–8]. Drugs with anticholinergic properties were among the most harmful, through their association with both impaired cognition and mobility [9]. In addition, several side effects of anticholinergic drugs, such as muscle weakness, drowsiness, sedation, and blurry vision can severely increase fall risks [10]. Of note, many frequently prescribed drugs (e.g. beta-blockers, calcium-channel blockers, opioids, benzodiazepines, and antihistamines) have mild anticholinergic properties [9]. The cumulative effects of the use of multiple drugs with such mild anticholinergic properties could significantly increase fall risks. In the OA population, there is no study, to our knowledge, that has investigated whether the use of medication, particularly anticholinergics, has an impact on falls independent of functional impairment or pain.

The main objective of the study was to identify factors, particularly drug-related, associated with the occurrence and number of falls in patients with symptomatic knee and/or hip OA in a longitudinal study.

The results of this study will provide a better understanding of modifiable risk factors in order to develop and implement fall prevention interventions tailored to this patient population.

Patients and methods

Population study

The patients studied were enrolled in the Knee and Hip Osteo Arthritis Long-term Assessment (KHOALA) cohort, between 2007 and 2009. This is a multiregional population-based cohort of 878 patients with symptomatic uni or bilateral symptomatic hip and/or knee OA. The inclusion criteria were age from 40 to 75 years, symptomatic OA of at least one hip or knee, satisfaction of the American College of Rheumatology criteria for knee and/or hip OA (ACR), and Kellgren–

Lawrence (KL) stage of grade 2 or higher)[11]. The exclusion criteria were joint replacement of the target joint, previous osteotomy, severe comorbidities severe enough to significantly affect quality of life or likely to induce high healthcare consumption, a history of rheumatic diseases other than OA, or patello-femoral OA without tibio-femoral OA.

All participants provided written informed consent. The study was approved by the regional ethics board (Le Comité de Protection des Personnes Est-III) and registered at www.ClinicalTrials.gov (registration number NCT00481338).

Data collection

Patients were followed up annually for 10 years. They completed self-reporting questionnaires every year and underwent a medical examination and X-rays at baseline and at years 3, 5, and 7.

This study is a longitudinal analysis using data from years 5 through 10, with falls data collected from year 5.

Outcome criteria

Falls

The main outcome criteria were the occurrence of at least one fall and the number of falls during the past year reported by the patient.

Compared to the occurrence of at least one fall, the number of falls may be more clinically meaningful since multiple falls may signal physical and cognitive deficits, as well as increased risk for subsequent falls and mobility decline in older adults [12,13].

Risk factors studied

Sociodemographic characteristics (age, sex, education, marital status [single or with a partner], retirement status), clinical data (date of first symptoms, joint of inclusion [hip or knee]), and radiological data (Kellgren & Lawrence [K/L] stage of the inclusion joint) were collected at baseline for the cohort.

Data collected annually included, comorbidities, drugs, and patients' reported outcome measures (PROMs).

To assess drug use, patients were asked to list their prescription medications. The drugs were grouped according to Anatomic Therapeutic Chemical (ATC) Classification System codes. The following variables were used in the analyses: taking or not taking antihypertensive, cardiovascular, nervous system, and analgesic drugs. These drugs have been associated with an increased risk of falls in meta-analyses [6–8].

The Anticholinergic Drug Scale (ADS) was used to identify the anticholinergic medications and calculate the cumulative anticholinergic burden (ADS score) for each participant [14]. The ADS score classifies drugs into four levels according to their affinity for muscarinic receptors (from zero for “no anticholinergic activity” to three for “strong anticholinergic activity”). For ease of reading, drugs with anticholinergic (antimuscarinic) properties are henceforth referred to as “anticholinergic drugs.”

Comorbidities were measured by the index developed by Groll et al and analyzed as the sum of the 18 following comorbidities: arthritis, osteoporosis, asthma, chronic obstructive pulmonary disease, acute respiratory distress syndrome, angina, heart disease, myocardial infarction, neurological disease, stroke, peripheral vascular disease, diabetes, upper gastrointestinal disease, depression, anxiety, visual impairment, hearing impairment, degenerative disc disease, obesity [15].

Patients Reported Outcome Measures (PROMs) included 2 subscales of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), measuring the level of pain and function (0=best, 100=worst) [16] and 3 dimensions of the Medical Outcomes Study Short Form36 (SF-36), measuring Physical functioning, mental health, and vitality, (0=worst,100=best) [17].

Physical activity participation was assessed by the average of Metabolic Equivalent of Task (MET) of physical activity declared measured by the validated French version, Modifiable Activity Questionnaire (MAQ) [18].

Statistical analysis

Descriptive statistics and frequency data were performed separately for persons who reported and did not report a fall at year 5. The quantitative variables were presented as mean \pm standard deviation (SD) and as frequency and percentage for categorical variables.

To estimate associations between each risk factor and fall outcomes (fall status (YES/NO), and number of falls), two univariate and multivariate analyses were carried out. The skewed distribution of the number of falls justified the categorization of the sample into 3 groups: no fall, one fall, and more than one fall (recurrence of falls).

We used a generalized linear mixed model (SAS PROC GLIMMIX). Mixed linear regression models are recommended when outcomes are measured repeatedly over time and are likely to be correlated within each patient. This model is also appropriate for its ability to incorporate both fixed and random effects, and to accommodate unbalanced data patterns, even when missing values are not completely random.

Factors with a moderate association ($p \leq 0.10$) with the outcome on bivariate analysis were entered into a multivariate model.

Because of the multicollinearity between the variable "number of Groll Index comorbidities" and the different comorbidities, as well as between drugs and the ADS score of drugs, two separate generalized linear mixed models were fitted for each analysis.

For the analysis with comorbidity and drugs by categories, the predictor included demographic variables, clinical variables, drugs, and comorbidity by categories (yes/no), and PROMs variables, were combined in blocks and entered to build the final generalized linear mixed model (Model Ia: demographics only; Model IIa: demographics, clinical variables, comorbidities, drugs; Model IIIa, demographics, clinical variables, comorbidities, drugs, PROMs variables)

For the analysis with the number of comorbidities and ADS score, we entered the variables into the model as follows: Model IIb, demographics, clinical variables, comorbidities, drugs; Model IIIb, demographics, clinical variables, comorbidities, medications, PROM variables).

To avoid collinearity, highly correlated predictors were identified by their content (e.g., different measures of pain) or by the variance inflation factor (VIF). The variable with the highest R^2 on univariate analysis was retained for entry into the multivariate model. Odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated through analysis.

All analyses were based on a significance level $p < 0.05$. All analyses used SAS 9.4 software (SAS Inst., Cary, NC).

Results

878 patients were included in the KHOALA cohort at baseline, 675 were followed at year 5 and 14 had missing data on falls. A total of 661 patients were included in the analyses. The majority of the sample was female (69%) with a mean age of 61.4 (8.4).

At year 5, 153 patients (23.15%) reported one or more falls in the preceding 12 months. Of the 153 patients with a history of falls, 67 (43.8 %) reported a single fall, and 86 (54.9 %) reported more than one fall. Among those with multiple histories of falling, the number of falls ranged from three to twelve.

Characteristics of patients with and without a history of falls at year 5 are presented in Table 1. On bivariate analysis, the results showed that, compared to patients who did not report a fall, patients with a fall history were more likely to be older, female, single and retired. They also more frequently reported a history of psychological disorders or degenerative disk disease and osteoporosis. Their number of comorbidities and ADS scores were higher, and they used nervous system medications more often. Finally, PROMs were more impaired among fallers.

Table 1: Characteristics of patients with and without a history of falls at year 5

	Missing data	Without falls	With falls	p
		N=508 (76.9%)	N=153 (23.2%)	
		N (%)	N (%)	
Age, mean (SD)	0	60.7 (8.2)	62.9 (8.7)	0.005
Sex	0			0.006
Women		332 (65.4)	118 (77.1)	
Education	4			0.51
Primary		103 (20.3)	36 (23.5)	
Secondary		261 (51.4)	75 (49.0)	
University		141 (27.8)	41 (26.8)	
Marital status	2			0.04
Single		145 (28.5)	57 (37.3)	
Retirement status	2			0.002

Retired		285 (56.1)	107 (69.9)	
Joint at inclusion	0			0.65
Hip		131 (25.8)	39 (25.5)	
Knee		353 (69.5)	104 (68.0)	
Hip and knee		24 (4.7)	10 (6.5)	
Total Physical activity MET.min/wk		130.4 (49.6)	122.5 (54.1)	0.50
Comorbidity				
Comorbidities, n (mean (SD))	0	2.83 (1.7)	3.39 (1.9)	0.0006
Osteoporosis		32 (6.3)	18 (11.8)	0.02
Cardiovascular disease		63 (12.4)	19 (12.4)	0.99
Neurological disorders		30 (5.9)	13 (8.5)	0.25
Psychological disorders		92 (18.1)	46 (33.1)	0.001
Degenerative disk disease		182 (35.8)	70 (45.8)	0.02
Obesity (BMI > 30)		160 (31.5)	59 (38.6)	0.10
Medication use,	0			
Antihypertensives		244 (48.3)	77 (50.3)	0.67
Cardiovascular drugs		26 (5.1)	13 (8.5)	0.19
Nervous system medications		85 (16.7)	41 (26.8)	0.02
Non opioid analgesics		132 (26.0)	49 (32.0)	0.36
Opioid analgesics		53 (11.2)	20 (13.1)	0.57
Anticholinergic medications		68 (13.4)	32 (20.9)	0.06
Anticholinergic score (mean (SD))		0.21 (0.5)	0.33 (0.7)	0.04
WOMAC [0–100] (mean (SD))				
Pain	6	30.2 (18.1)	39.5 (19.7)	<.0001
Function	7	28.8 (18.6)	39.2 (21.2)	<.0001
SF36 [0–100] (mean (SD))				
Physical functioning	4	64.4 (23.4)	54.6 (25.1)	<.0001
Mental health	4	65.7 (17.7)	59.4 (22.9)	<.0001
Vitality	4	52.7 (17.2)	46.8 (17.4)	0.0003

M: mean, SD: standard deviation, BMI: body mass index, MET: metabolic equivalent task, WOMAC: Western Ontario and McMaster Universities questionnaire 0 (best state) to 100 (worst state); SF36 questionnaire 0 (worst state) to 100 (best state)

Table 2 provides results of multivariate analyses of the factors associated with the occurrence of at least one fall.

In the multivariate analysis with comorbidities and drugs analyzed by categories, the proportion of patients who fell was significantly higher among patients living alone, retired, and those using fewer antihypertensive drugs OR 0.57, 95% CI (0.39–0.83), more opioid analgesics OR 1.44, 95% CI (1.05–1.96), and having more impaired functional abilities. The

association between psychological disorders and obesity with falls disappeared after adjustment for PROM, particularly the physical function level.

In the multivariate analysis with comorbidities and drugs analyzed by number of comorbidities and ADS score, the proportion of patients who fell was significantly higher among women, individuals living alone, and patients having a higher ADS score OR 1.31 95% CI (1.00-1.73) and having more impaired functional abilities. The association between the number of comorbidities and fall disappeared after adjustment for PROM, particularly the physical function level.

Table 3 provides results of multivariate analyses of the factors associated with the number of falls (no fall, one fall, two or more than two falls).

In the multivariate analysis with comorbidities and drugs analyzed by categories, the number of falls decreased in patients living in a couple or using antihypertensive medication OR 0.61, 95% CI (0.42–0.90). The number of falls increased with the use of opioid analgesics OR 1.40, 95% CI (1.02–1.90) and in patients having more impaired functional abilities.

In the multivariate analysis with comorbidities and drugs analyzed by number of comorbidities and ADS score, the number of falls was higher in women and in patients living in a couple, with more comorbidities (OR 1.10, 95% CI 1.01–1.21), or having more impaired functional abilities. Level of education, joint at inclusion, participation in physical activity, cardiovascular disease, and KL grade were not associated with falls.

Table 2: Factors associated with the occurrence of at least one fall (yes/no): results from multivariate analyses

	Multivariate analysis with comorbidities and medications analyzed by categories			Multivariate analysis with no. of comorbidities and score of medications	
	Model 1a OR (95% CI)	Model 2a OR (95% CI)	Model 3a OR (95% CI)	Model 2b OR (95% CI)	Model 3b OR (95% CI)
Age	1.02 (0.98-1.05)	1.00 (0.97-1.04)	1.00 (0.97-1.04)	1.01 (0.97-1.04)	0.99 (0.96-1.03)
Sex (women vs men)	2.26 (1.50-3.32)*	1.57 (0.98-2.27)	1.44 (0.93-2.37)	1.87 (1.24-2.83)*	1.63 (1.08-2.46)*
Marital status (in a couple /alone)	0.76 (0.55-1.04)	0.68 (0.47-0.98)*	0.65 (0.47-0.95)*	0.68 (0.48-0.97)*	0.64 (0.45-0.92)*
Retirement status	1.67 (1.00-2.78)*	2.00 (1.14-2.51)*	1.92 (1.09-3.37)*	1.54 (0.89-2.68)	1.60 (0.93-2.74)
Comorbidity					
No. of comorbidities				1.13 (1.04-1.23)*	1.07 (0.98-1.16)
Osteoporosis		1.37 (0.82-2.29)	1.45(0.86,2.45)		
Neurological disorders		1.67(0.94-2.97)	1.38 (0.76,2.53)		
Psychological disorders		1.52(1.06-2.19)*	1.31 (0.89,1.93)		
Degenerative disk disease		0.98 (0.73-1.33)	0.9 6(0.70,1.31)		
Obesity (BMI > 30)		1.44(1.03-2.03)*	1.31 (0.92,1.87)		
Drugs					
Antihypertensives		0.57 (0.40-0.82) *	0.57 (0.39-0.83)*		
Cardiovascular drugs		1.64 (0.88-3.06)	1.36 (0.72-2.59)		
Nervous system medications		1.31 (0.88-1.96)	1.29 (0.85-1.96)		
Non opioid analgesics		1.34 (0.89-2.02)	1.30 (0.85-1.99)		
Opioid analgésique		1.50 (1.11-2.03)*	1.44 (1.05-1.96)*		
Anticholinergic medications		1.22 (0.80-1.87)	1.18 (0.76-1.82)		
Anticholinergic score				1.36 (1.04- 1.79)*	1.31 (1.003-1.73)*
PROM					
WOMAC pain (0–100)			0.93 (0.86-1.08)		0.95 (0.82-1.09)
WOMAC function (0–100)			1.25 (1.05-1.50)*		1.25 (1.05-1.48)*
SF36 physical functioning (0–100)			1.01 (0.91-1.12)		1.01 (0.91-1.11)
SF36 mental health (0–100)			0.92 (0.81-1.05)		0.93 (0.82-1.05)

SF36 vitality (0–100)

1.03 (0.91-1.12)

0.97 (0.85-1.11)

PROM: Patient-reported outcome measures

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

*p< .05, Effects of continuous variables are assessed as 10 units of change from the mean except for age, McMaster Universities questionnaire 0 (best state) to 100 (worst state); SF36 questionnaire 0 (worst state) to 100 (best state)

Multivariate analysis with comorbidities and medications analyzed by categories: Model Ia: demographics only; Model IIa: demographics, clinical variables, comorbidities, drugs; Model IIIa, demographics, clinical variables, comorbidities, drugs, PROM variables)

Multivariate analysis with no. of comorbidities and score of medications: Model IIb, demographics, clinical variables, comorbidities, drugs; Model IIIb, demographics, clinical variables, comorbidities, medications, PROM variables)

Table 3: Factors associated with the number of falls: results from multivariate analyses

	Multivariate analysis with comorbidities and medications analyzed by categories			Multivariate analysis with no. of comorbidities and score of medications	
	Model 1a OR (95% CI)	Model 2a OR (95% CI)	Model 3a OR (95% CI)	Model 1b OR (95% CI)	Model 2b OR (95% CI)
Age	1.02 (0.93-1.05)	1.00 (0.97-1.04)	1.01 (0.97-1.05)	1.01 (0.98-1.05)	1.00 (0.97-1.04)
Sex (Women vs Men)	2.31 (1.57-3.40)*	1.63 (1.06-2.52)*	1.53 (0.98-2.39)	1.94 (1.28-2.95)*	1.73 (1.14-2.63)*
Marital status (in a couple / alone)	0.76 (0.55-1.05)	0.66 (0.46-0.95)*	0.67 (0.45-0.97)*	0.70 (0.49-1.00)	0.64 (0.45-0.93)*
Retirement status	1.53 (0.91-2.56)	1.85 (1.06-3.24)*	1.64 (0.93-2.89)	1.44 (0.82-2.50)	1.50 (0.87-2.60)
Comorbidity					
No. of comorbidities				1.15 (1.06-1.25)*	1.10 (1.01-1.21)*
Osteoporosis		1.44 (0.86-2.43)	1.40 (0.81-2.37)		
Cardiovascular disease		1.35 (0.86- 2.12)	1.20 (0.75-1.92)		
Neurological disorders		1.93 (1.06-3.51)*	1.63 (0.88-3.02)		
Psychological disorders		1.56 (1.09-2.24)*	1.40 (0.94-2.05)		
Degenerative disk disease (Yes vs No)		1.04 (0.77-1.40)	0.99 (0.73-1.35)		
Obesity (BMI > 30) (Yes vs No)		1.40 (0.93-2.10)	1.44 (0.95-2.20)		
Drugs					
Antihypertensives		0.59 (0.40-0.86)*	0.61 (0.42-0.90)*		
Cardiovascular drugs		1.45 (0.75-2.81)	1.39 (0.71-2.73)		
Nervous system medications		1.47 (0.98-2.22)	1.30 (0.85-1.96)		
Opioid analgesics		1.45 (1.08-1.95)*	1.40 (1.02-1.90)*		
Anticholinergic medications		1.00 (0.66- 1.53)	0.97 (0.63-1.50)		
Anticholinergic score				1.19 (0.91-1.56)	1.09 (0.83-1.43)
PROM					
WOMAC pain (0–100)			0.99 (0.86-1.14)		0.97 (0.85-1.12)
WOMAC function (0–100)			1.20 (1.01-1.43)*		1.22 (1.03-1.44)*
SF36 mental health score (0–100)			0.96 (0.84-1.09)		0.95 (0.84-1.07)
SF36 physical functioning (0–100)			0.99 (0.89-1.10)		0.98 (0.88-1.09)

SF36 vitality (0–100)

0.97 (0.85-1.12)

0.96 (0.84-1.10)

PROM: Patient-reported outcome measures

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

*p < .05, Effects of continuous variables are assessed as 10 units of change from the mean except for age and BMI, McMaster Universities questionnaire 0 (best state) to 100 (worst state); SF36 questionnaire 0 (worst state) to 100 (best state)

Multivariate analysis with comorbidities and medications analyzed by categories; Model Ia: demographics only; Model IIa: demographics, clinical variables, comorbidities, drugs; Model IIIa, demographics, clinical variables, comorbidities, drugs, PROM variables)

Multivariate analysis with no. of comorbidities and score of medications: Model IIb, demographics, clinical variables, comorbidities, drugs; Model IIIb, demographics, clinical variables, comorbidities, medications, PROM variables)

Discussion

While opioid analgesics and the ADS score measuring drug-related cumulative anticholinergic burden increased the occurrence and the number of fall events, the use of antihypertensive treatments was protective, in our cohort of patients followed for knee or hip OA. The risk of falls was also increased in female, patients living alone, retired persons, and patients with a high number of comorbidities. All these associations were independent of OA symptoms such as pain and functional impairment.

The protective effect of antihypertensive drugs against falls found in this study, might seem surprising. Indeed, early studies found an increased risk of falls in older adults using antihypertensive agents, diuretics, and beta-blockers [19] and this belief tends to persist, although this has been contradicted by several later studies [20–23]. Thus, Wong and colleagues reported that the use of cardiovascular drugs in older adults did not increase the risk of falls and that using angiotensin system-blocking medications was even associated with a lower fall risk [20]. A 2019 meta-analysis found no evidence to suggest that antihypertensive treatment is associated with falls, even if an association was found with syncope but not all falls are caused by syncope [21]. In a prospective cohort study in women, the risk of falling was significantly reduced in women with controlled and uncontrolled hypertension compared with women without hypertension [22]. However, the risk of falls was increased in the first weeks following initiation or with more intensive antihypertensive therapy [24].

The increase in falls associated with opioid use has previously been reported in two studies of OA [1,25], but to our knowledge the present study is the first to examine the effects of drug-related anticholinergic burden on the risk of falls in OA patients. Our results show that drug-related anticholinergic burden increases the occurrence of falls. This risk factor is

important to know and to measure as many commonly used medications have mild anticholinergic properties and combining them puts individuals at particular risk of falling as much as the use of a single agent with strong anticholinergic properties. In elderly persons, cross-sectional data have also highlighted the risk of falls with the use of medications with anticholinergic properties, even those with potential or mild anticholinergic properties [10]. Interestingly, consequences may persist beyond 20 years after initial exposure to anticholinergic drugs [10].

In a 2019 systematic review, the risk factors for falls in individuals with knee OA included the presence of comorbidities such as fracture, diabetes, and visual impairment [4]. In a cross-sectional study, depression was also associated with an increased risk of falling in patients with knee OA or at risk for knee OA [1]. However, this association was not found during the follow-up of the same study [5]. In our study, the increased risk of falling associated with several specific comorbidities such as obesity, neurological, or psychological disorders disappeared after adjustment for PROM, particularly the level of physical function. This finding suggests that the increased risk of falling in patients with these comorbidities could be mediated by the level of impairment in physical function. However, the number of comorbidities was independently associated with the number of falls.

Among PROMs, only the WOMAC function score was significantly associated with falls in multivariate analyses. In a European study combining random samples of existing population-based cohorts, physical performance assessed using three tests of walking speed, repeated chair stands, and standing balance was not associated with falls [26]. Discrepancies with this study might reside in differences in objective measures of physical performance and perceived physical function.

The association between female sex and increased risk of fall has already been found in the OAI cohort [1,5] and in older persons [27,28]. Similarly, living alone was a significant environmental factor associated with falling in the studies of the OAI cohort, but the association disappeared after adjustment for personal factors [5]. In the present study, the association between living alone and fall risk was independent of age, physical activity, health status, and other fall risk factors. It can be assumed that being alone, decreases social or physical activities and thus favors physical functioning impairment. One's significant other may also be performing difficult tasks that could be a cause of a fall.

The number of falls may be more clinically significant than a single fall, as multiple falls may be associated with an increased risk of subsequent falls and decreased mobility in the elderly [12,13]. Thus, in the van Schoor et al. study, clinical knee OA was associated with the risk of becoming a recurrent faller, but not with the risk of becoming a faller [26]. However, the factors associated with the risk of falling at least once and the risk associated with the number of falls were almost the same. Only the number of comorbidities remained associated with the number of falls but not with the occurrence of at least one fall in the multivariate analysis. However, in most of the models, the association between falls and the number of comorbidities or several specific comorbidities such as psychological disorders disappeared after adjustment for PROM, particularly the physical function level.

This study has several limitations. The fall question ("Have you fallen in the last 12 months?") was self-reported and is thus dependent on the participants' recollections of a fall, which might have caused some measurement bias due to poor memory recall in some of the study participants. However, the self-reported history of falls in the past year is highly specific (91%–95%) but less sensitive (sensitivity 80–89%) compared with results using more frequent

assessment [29]. Another limitation is that the severity or consequences of falls were not studied. However, a fall or recurrence of the fall are risk factors for further falls with serious consequences.

The major strength of the present study is that we used data from a population-based cohort of patients with symptomatic hip and/or knee OA with a longitudinal design and a relatively long-term follow-up. The cohort allowed us to consider multiple potential confounders and examined the factors associated with the number of falls and not only the occurrence of at least one fall. Factors associated with falls have almost never been studied in hip OA. Furthermore, the present study goes beyond prior studies by investigating the role of drugs, especially the use of antihypertensive drugs and the cumulative effects of the use of multiple drugs with mild anticholinergic properties. Another strength is the association study of falls and hip OA, which has rarely been studied [26]. We did not find any difference between patients with hip and knee OA.

Conclusions

An increased ADS score measuring drug-related anticholinergic burden and opioid analgesics, increases the risk of occurrence or number of falls, whereas antihypertensive treatments decrease the risk during the follow-up of patients with knee and/or hip OA.

In order to improve fall prevention in patients with knee and/or hip OA, it is the cumulative effect of anticholinergic therapies, even those with weak anticholinergic activity that are commonly prescribed, that should be considered, and anticholinergic medications should be avoided whenever possible. Among other modifiable factors, improving physical functioning and managing comorbidities should be part of fall prevention strategies in patients with knee and/or hip OA.

Acknowledgements:

The authors thank Alfousseyn Coly and the Clinical Investigation Center (Clinical Epidemiology) for study coordination and monitoring, all investigators who recruited, and followed subjects, Claudine Gard for drug coding, and the members of the scientific committee (J Coste, Paris-Descartes; L Euller Ziegler and CH Roux, Nice; P Fardellone, Amiens; B Fautrel, Paris-Université Pierre-et-Marie-Curie; Jeremy Sellam Paris Sorbonne Université, A Saraux, Brest), Valérie Fong Constans for proof reading.

Authors' contributions

Conception of the study protocol: ACR, MLB, MA

Statistical analysis: MA

Interpretation of the data: ACR, MA, GL, EAM, CV, MLB

First draft of the manuscript: MA, ACR

Revision of the manuscript: GL, EAM, CV, MLB

Role of the funding source: Funding for the study cohort was obtained from public sources (INSERM, CHRU de Nancy, Conseil Régional de Lorraine, Société Française de Rhumatologie, Agence Nationale de la Recherche) and unrestricted grants from pharmaceutical companies (Expanscience, Genevrier, Genzyme, Negma, Almirall, Grünenthal, Merck & Co, Inc, Pfizer, Pierre Fabre Médicaments, Sanofi France) and groupe APICIL and groupe Pasteur mutualité. Opinions expressed in the present article are those of the authors and do not necessarily reflect those of the sponsors. The study sponsors did not take part in the study design,

collection, analysis and interpretation of data, writing of the report or the decision to submit the article for publication.

Conflicts of interest: None

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