**Analgesic Use and Risk of Recurrent Falls in Participants With or At Risk of Knee Osteoarthritis: Data from the Osteoarthritis Initiative**

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**ABSTRACT**

**Objective:** Few studies have compared the risk of recurrent falls across different types of analgesic use, and were limited to adjust for potential confounders (e.g., pain/depression severity). We aimed to assess analgesic use and the subsequent risk of recurrent falls, among participants with or at risk of knee osteoarthritis (OA).

**Methods:** A longitudinal analysis included 4,231 participants aged 45-79 years at baseline with 4-year follow-up from the Osteoarthritis Initiative (OAI) cohort study. We grouped participants into six mutually exclusive subgroups based on annually assessed analgesic use in the following hierarchical order of analgesic/central nervous system potency: use of (1)opioids, (2)antidepressants, (3)other prescription pain medications, (4)over-the-counter pain medications, (5)nutraceuticals, and (6)no analgesics. We used multivariable modified Poisson regression models with a robust error variance to estimate the effect of analgesic use on the risk of recurrent falls(≥2) in the following year, adjusted for demographics and health status/behavior factors.

**Results:** Opioid use increased from 2.7% at baseline to 3.6% at the 36-month visit (>80% using other analgesics/nutraceuticals), while other prescription pain medication use decreased from 16.7% to 11.9% over this time period. Approximately 15% of participants reported recurrent falls. Compared to those not using analgesics, participants used opioids and/or antidepressants had a 22-25% increased risk of recurrent falls (opioids: $RR_{adjusted}$=1.22, 95%CI=1.04-1.45; antidepressants: $RR_{adjusted}$=1.25, 95%CI=1.10-1.41).

**Conclusion:** Participants with or at risk of knee OA who were on opioids and antidepressants with/without other analgesics/nutraceuticals may have an increased risk of recurrent falls after adjusting for potential confounders. Use of opioids and antidepressants warrants caution.

**Keywords**: analgesics, opioids, antidepressants, non-steroidal anti-inflammatory drugs, falls, knee osteoarthritis

## INTRODUCTION

Symptomatic knee osteoarthritis (OA) affects more than 9.3 million adults and is the leading cause of disability and lost workdays in the United States[1]. Persons with OA of the lower extremities report lower quality of life[2] and utilize more healthcare resources[3]. Treatment for knee OA focuses on relieving symptoms and improving function, and includes both non-pharmacological (e.g., exercise) and pharmacological approaches [4-6]. Because therapy is not curative, analgesics used to control pain are a mainstay of the management of OA [4].

Current guidelines for pain management of OA[4-6] recommend first-line use of acetaminophen, with nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, and opioids as second- or third-line options. Analgesic choice can be challenging, however, due to the varied benefit and risk profiles of analgesics and patient characteristics[4-6]. OA patients sometimes use nutraceuticals (e.g., glucosamine), defined as 'foodstuffs' with purported health benefits in addition to their basic nutritional value, though not recommended by current guidelines[4-6].

Low-extremity OA is a known risk factor for falls.[7] Although some studies and guidelines suggest that opioid and antidepressant use may increase the risk of falls and fractures[8-14], evidence surrounding analgesic use and falls is conflicting[8, 9, 13, 15, 16]. Few studies have comprehensively evaluated the use of different types of analgesics and risk of recurrent falls[13, 17-19]. Recurrent falls may be more clinically meaningful than a single fall, since multiple falls may signal physical and cognitive deficits, as well as increased risk for subsequent falls and mobility decline in older adults[20]. Pain severity, depressive symptoms, history of falls/fractures, body mass index [BMI]), and concurrent use of medications (e.g., anticholinergics) may have confounded the association between analgesic use and fall risk previously reported[15, 16, 21]. Therefore, the objective of this longitudinal study was to examine the association between

different types of analgesic use and risk of recurrent falls in the subsequent year among participants with or at risk of knee OA, controlling for the relevant confounders (e.g., pain severity).

## METHODS

### Data Source, Study Design, and Sample

The Osteoarthritis Initiative (OAI), a multi-center, longitudinal cohort study, was designed to identify biomarkers for the development and progression of knee OA. The data and additional study details are publicly available at http://oai.epi-ucsf.org. Briefly, the OAI recruited 4,796 persons aged 45 to 79 years with or at high risk for knee OA at four study sites (Pittsburgh, Pennsylvania; Columbus, Ohio; Pawtucket, Rhode Island; Baltimore, Maryland) between 2004 and 2006. Participants provided written informed consent and the protocol was approved by the participating institutions' review boards. Participants either had symptomatic OA in at least one knee or risk factors for developing knee OA, including being overweight or obese, knee symptoms, history of knee injury, surgery or repetitive knee bending, family history of knee replacement, or the presence of Heberden's nodes.

The sample for the current longitudinal analysis included 4,231 participants with complete information on medication use at baseline and fall data at the following annual visit, in order to establish a temporal association between analgesic use and fall outcome (i.e., baseline medication data and 12-month fall outcome; 12-month medication data and 24-month fall outcome, etc.). Participants (n = 525) were excluded due to missing data on medications and/or fall outcomes at baseline (**Supplemental eFigure 1**). Participants were followed through 36 months for analgesic and nutraceutical use and 48 months for recurrent falls.

### Data Collection and Management

Participants were assessed annually at clinic visits, and detailed self-reported questionnaires (e.g., demographics, health status/behaviors), clinical and physiological measurements, and measures of progression of knee OA were collected. Detailed medication data were collected by trained research personnel in the clinic including prescriptions taken in

the previous 30 days (Participants were instructed to bring all prescriptions used during the past month: i.e., the “brown bag method” of assessment.)[22] A similar data collection approach was used during telephone interviews if participants could not be seen in person. The “brown bag” method and telephone interviews have been established as highly accurate and concordant with information about dispensed prescription drugs in claims data[23, 24]. A trained interviewer recorded the name, dosage form, and frequency of use for each prescription. Each medication was then recorded using the Iowa Drug Information System (IDIS)[22], a hierarchical coding system for specific drug ingredients, and chemical and therapeutic categories. Prescription data were collected at baseline and annually up through the 72-month visit, and then every other year afterwards. The use of over-the-counter (OTC) analgesics and nutraceuticals such as glucosamine, chondroitin, methylsulfonyl-methane (MSM), or S-adenosylmethionine (SAMe) was self-reported on questionnaires that specifically asked about the use of these agents for joint pain or arthritis for more than half the days of the previous month.

**Primary Outcome: Recurrent Falls**

The number of falls in which the participant had landed on the floor or ground in the past 12 months was self-reported by participants and assessed at baseline and annually up through the 48-month visit, and then every other year afterwards. Our primary outcome was recurrent falls, defined as two or more falls in the ensuing 12 months following report of analgesic use (e.g., baseline medication data and 12-month fall outcome)[13]. Self-reported history of falls in the past year has been shown to be highly specific (91%-95%) compared with results using more frequent assessment[25].

**Primary Independent Variable: Analgesic Use**

Patients commonly take more than one analgesic/ nutraceutical agent for pain[26], therefore we categorized participants into six mutually exclusive subgroups in the following

hierarchical order of analgesic potency and central nervous system (CNS) effects: any use of (1) opioids (i.e., any oral or transdermal prescription opioids); (2) antidepressants (i.e., no opioids, but any selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants [TCA], or other antidepressants); (3) other prescription pain medications other than opioids (i.e., no opioids/antidepressants, but any NSAIDs (>95%), salicylates [<3%] or triptans [<1%]); (4) over-the-counter (OTC) pain medications (i.e., no opioids/antidepressants/other prescription pain medications, but OTC NSAIDs or acetaminophen); (5) nutraceuticals including chondroitin, glucosamine, methylsulfonylmethane (MSM), or S-adenosyl-L-methionine (SAMe); and (6) no pain medication use. (See **Appendix eTable 1** for a complete list of analgesics and **eTable 2** for concurrent utilization patterns of analgesic and nutraceutical use at baseline.)

**Covariates**

We first described demographic, health status/behavior, and access-to-care characteristics to address potential confounding based on prior literatures[10, 13, 19, 27]. Demographic factors included baseline age, sex, race (white vs. non-white), marital status (married vs. not married), and education (less than high school or high school graduate vs. some college/postsecondary).

We created a series of time-varying variables for health status and behavior factors including a self-reported version of Charlson's comorbidity index[28], Kellgren–Lawrence (K/L) grade category of the worst knee (0-1, 2-3, or 4), self-reported history of knee surgery, history of falls in the previous year, bisphosphonate use for osteoporosis, and body mass index (BMI). Physical and mental component summary scores (range 0-100, higher scores indicating better health status) from the 12-item Short-Form (SF-12) health survey, measures of general health status[29], were created. The Physical Activity Scale for the Elderly (PASE) measures the extent of purposeful activity (e.g., housework) and was used to control for healthy user effects[30-32].

Additionally, we adjusted for the Knee Injury and Osteoarthritis Outcome Score (KOOS)[33] self-reported global knee pain severity (NRS, 0 indicating no pain and 10 indicating pain as bad as you can imagine) during the past 30 days on the worst knee. The KOOS, an extension of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[34], assesses the level of pain, symptoms, limitations with activities of daily living, function in sport/recreation, and knee-related quality of life. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) was calculated for each subscale.

Antidepressants may be used for a variety of conditions. In order to control for potential confounding by indication, we created a time-varying dichotomous variable for significant depressive symptoms (20-item Center for Epidemiologic Studies-Depression Scale ≥16)[35]. We also created several time-varying dichotomous variables for exposure to any anticholinergics and individual anticholinergic class (i.e., benzodiazapines, muscle relaxants, gastrourinary antimuscarinics/gastrointestinal antispasmodics, and others [i.e., anti-vertigos, anti-histamines, anti-Parkinsons, antipsychotics, disopyramide and digoxin]) and other drugs shown to increase the risk of falls (i.e., diuretics, anticonvulsants including pregabalin and gabapentin). The total number of prescription medications (excluding analgesics and other medications that increase falls) was created as a time-varying proxy factors for comorbidity and medication burden[36]. All time-varying covariates were assessed at baseline, 12-month, 24-month and 36-month visits. Charlson's comorbidity index was measured twice during the study period, and we carried the last observation forward to obtain a time-varying variable for this covariate. Lastly, we examined health insurance coverage at baseline as an indicator of access-to-care.

**Statistical Analysis**

Participant characteristics were summarized overall and by analgesic group with appropriate descriptive statistics (mean, standard deviation, frequency and percentage).

Exposure to different analgesic groups was characterized according to use in the year preceding ascertainment of fall measures. 'Modified Poisson regression' models developed by Zou et al.[37] were used to estimate relative risks (RRs) with generalized estimating equations (GEE) to account for repeated assessments within an individual (using the SAS® GENMOD procedure). The modified Poisson Regression uses sandwich error estimation to obtain a robust error variance to avoid error misspecification and variance underestimation in correlated data analysis.[37] The modified Poisson Regression has shown to estimate RRs consistently and efficiently and is considered particularly appropriate when the outcome is common (e.g., incidence ≥10%)[37, 38]. We used multivariable models to examine the association between type of analgesic use (using no analgesic/ nutraceutical use as reference group) and risk of recurrent falls, adjusted for important confounders. We used the variable of any anticholinergic use (instead of individual anticholinergic classes), and excluded 2 covariates (i.e., use of anticonvulsants, and no health insurance coverage) from multivariable adjusted models because their low counts or prevalence (<5%) had little impact on the adjusted results. Three multivariable models were performed in stages to examine the impact of covariates including (1) adjusted model with major confounders based on the literature including demographics (baseline age, sex, race, marital status, education), time-varying health status/behavior (Charlson's comorbidity index, history of falls, any anticholinergic use), and time-varying pain and depression severity covariates (i.e., KOOS pain subscale, KOOS symptom subscale, pain numerical rating scale, and having significant depressive symptoms); (2) adjusted model with major confounders and time-varying physical and mental component scores from the Short Form-12 health survey and PASE score; (3) full adjusted model included major confounders, time-varying physical and mental component scores from the Short Form-12 health survey and PASE score, and other time-varying health status/behavior covariates [i.e., K/L grade, history of knee surgery, taking bisphosphonate for osteoporosis, BMI, KOOS quality of life subscale, and

total number of other prescriptions used]. We presented both unadjusted and adjusted RRs and 95% confidence intervals (CI). Statistical significance was determined based on 2-tailed tests (0.05). All predicted probabilities of any fall and recurrent falls fell within the range between 0 and 1 satisfying the assumption of Poisson models.

To evaluate robustness of the results, we conducted three sensitivity analyses. First, we used presence of any falls as an alternative outcome. Second, although over three-quarters (77%) of the participants had complete information on covariates, we used multiple imputation (MI) with an assumption of missing completely at random (MCAR) for missing covariate data (PROC MI procedures in SAS)[39]. The MI models simultaneously predicted missing values of variables using existing values of variables by modeling the joint distribution of all covariates. For each participant, conditional on the non-missing values, the missing values have a distribution from which several joint random samples are drawn. We analyzed each of five imputation datasets separately as if there were no missing values, then combined the results using Rubin's rules from these five imputation datasets to obtain risk estimates reflecting the uncertainty due to missing values[39]. Finally, given that the effect of analgesic utilization may differ by age, sex, race, and pain scores, we tested for interactions of the analgesic group with these factors, but none of the interaction terms were significant ($p > 0.05$). However, given the magnitude of analgesic use and risk of falls might be different among those who developed knee OA vs. those who did not, we examined the association by K/L grade (<2 vs. ≥2). The results from these sensitivity analyses were qualitatively similar to our primary analysis; therefore, we presented only the main results here and the results from the sensitivity analyses were included in the online supplement. All analyses were performed using SAS® version 9.4 (SAS Institute Inc. Cary, NC).

## RESULTS

Among 4,231 participants, 38.8% were aged 65 years and older (mean age: 61.3 [SD=9.2]), 58.4% were women, and 80.8% were non-Hispanic white at baseline (**Table 1**). In addition, 22.3% had a history of knee surgery, 12.3% used bisphosphonate for osteoporosis, 12.1% had serious depressive symptoms, and the average pain NRS severity was 3.3 out of a 0-10 scale for the worst knee.

Baseline characteristics by analgesic group are shown in **Table 1**. There were several differences ($p$ <0.001) among the analgesic groups. For example, compared to other analgesic groups, participants in the opioid and antidepressant groups were more often female (opioids: 71.9%, antidepressants: 74.4% vs. 52.9%-59.5%), less frequently married (opioids: 55.3%, antidepressants: 63.3% vs. 65.3%-70.6%), with significant depressive symptoms (opioids: 28.4%, antidepressants: 23.2% vs. 7.4%-10.5%), and more concurrent use of anticholinergic agents. While opioid users were more likely to be non-white (27.2% vs. 11.8%-24.8%) and have more severe pain, participants in the antidepressant and nutraceutical groups were more likely to be white (antidepressants: 87.8%, nutraceuticals: 88.3% vs. others: 72.8%-79.0%).

**Table 2** shows the prevalence of analgesic use over time. At baseline, 2.7% used any opioids, 13.2% used antidepressants, 16.7% used other prescription pain medications, and 16.8% used OTC pain medications, while 15.8% used nutraceuticals only, and 34.8% did not use any analgesics or nutraceuticals. By the 36-month visit, the prevalence of opioid use had increased to 3.6%, other prescription pain medication use had decreased to 11.9%, and participants without any analgesic or nutraceutical use had increased to 40.7%. Moreover, over 80% of participants who used opioids also used other prescription pain medications (83.3%) or antidepressants (38.6%; **eTable 2**). **Table 3** shows the prevalence of falls over time. Thirty percent (n= 1,276) of the participants reported having at least one fall in the previous year, and

14% (n=594) reported having ≥2 falls (i.e., recurrent falls). These proportions remained stable over time (recurrent falls: 13.5%-14.9%). Participants in the opioid and antidepressant groups had higher rates of recurrent falls than those in other analgesic groups across different time periods (opioids and antidepressants: 19.7%-28.1% vs. other groups: 10.3%-16.2%).

The effect size of relative risks for opioids, antidepressants and OTC pain medications attenuated considerably after adjustment for potential confounders, but that increased risk of recurrent falls was statistically significant for opioid and antidepressant groups after adjustment (**Table 4**). Participants who used any opioids (with or without using other analgesics) had a 22% increased risk of recurrent falls in the following year ($RR_{adj}$= 1.22, 95% CI=1.04-1.45, p=0.02) compared to those who used no pain medications. Likewise, participants in the antidepressant group had a 22% increased risk of recurrent falls in the following year ($RR_{adj}$= 1.25, 95% CI=1.10-1.40, p=<0.0001) compared to individuals using no pain medications. Similar results were found using any falls (i.e., having fallen at least once) as the outcome measure (**eTable 3**), and using multiple imputations for missing data (**eTable 4**). Among participants had K/L grade ≥ grade, any use of opioids (with or without other analgesic) and antidepressants had an increased risk of recurrent falls (opioids: $RR_{adj}$= 1.31, 95% CI=1.07-1.59, p=0.008; antidepressants: $RR_{adj}$= 1.23, 95% CI=1.05-1.45, p=0.01). However, among participants with K/L grade <2, only antidepressant use had an 28% increased risk (95% CI=1.06-1.54, p=0.009), but not any opioid use ($RR_{adj}$= 1.06, 95% CI=0.76-1.48, p=0.72; **eTable 5**),

## DISCUSSION

Our study yielded three key findings regarding the patterns of analgesic use and the association between types of analgesic used and recurrent falls in the subsequent year. First, almost two-thirds of participants used at least one analgesic or nutraceutical agent for their pain. The most commonly used analgesic agents were OTC and prescription NSAIDs and acetaminophen. Notably, one-third of participants used at least one nutraceutical agent for pain despite the lack of guideline recommendations supporting nutraceutical use. Secondly, although any use of opioids increased by 33% over the 4-year study period, overall, opioids were used infrequently (<5%). In contrast, the use of other prescription pain medications decreased by 29% over the same period. Thirdly, participants who used opioids and/or antidepressants had a 22%-24% increased risk of recurrent falls in the following year, after adjustment for relevant confounders such as pain severity and depression.

To our knowledge, this is the first study to assess the effect of different types of analgesics on the subsequent risk of recurrent falls. Previous studies did not examine recurrent falls and have been limited in their ability to adjust for pain and depression severity and concurrent CNS medication use. Most of the prior studies obtained odds ratios and may overestimate the relative risk of falls, which are not rare events[38]. Our findings were generally consistent with prior reports that suggest opioids and antidepressants increase risk for falls in older adults[8, 10, 13, 15]. Even though only 38.8% of the participants were aged 65 years or older at baseline in the current study, given the mean age of 61.5 years, the majority of subjects were 65 years or older at the end of the four-year follow-up period. Our results are biologically plausible, as the blood brain barrier that prevents harmful chemicals from entering the brain becomes more permeable with age, allowing for easier passage of certain medications. The similar results between any fall and recurrent falls in our study ensure the robustness of our findings, but also could indicate our study cohort having less cognitive status problems. Opioids have

psychotropic effects and can cause drowsiness, dizziness and cognitive impairment[40]. The underlying causes of falls associated with antidepressants are unclear, but possible mechanisms include impaired level of alertness and neuromuscular function, sedation, insomnia, and confusion[13]. Notably, participants in the opioids and antidepressants groups had higher proportions of concurrent use of other psychotropic medications (e.g., benzodiazepines), exposing them to cumulatively higher risk of falls. Solomon et al. demonstrated that the relative risk of adverse outcomes varied by opioids and treatment duration,[9] but we did not have a sufficient sample size to examine specific opioids or antidepressants, combinations of medications, or duration effects of opioid use.

Half of the participants in the study took at least one OTC acetaminophen/ NSAID or prescription NSAID, the recommended initial analgesic for OA pain[4, 6]. The decreased trend in the use of non-opioid prescription agents over the study period may reflect increased awareness of adverse gastrointestinal, renal and cardiovascular effects of NSAIDs during this period[41]. The decreased prescription trend may also be related to withdrawal of rofecoxib in 2004 and valdecoxib in 2005 from the US market due to serious adverse events including myocardial infarction and stroke. As expected, the use of opioids and higher number of pain medications in combination were associated with severe pain. However, the prevalence of opioid use was low (<5%) in this cohort. Opioids have been reported as the most commonly used medications (58%) in OA patients prior to total hip or total knee replacement[42]. Our study cohort had similar mean age and proportion of females to the Berger's study, but only 6.4% of our study cohort had a K/L grade of 4 at baseline. A recent study also showed a significant increase in opioid prescribing between 2003 and 2009, with 31% of the Medicare patients with knee OA receiving opioids in 2003[43]. The low opioid use observed may be partly related to younger study cohort and different data sources compared to those in the Wright study[43] and

lack of clarity or consensus of long-term safety and effectiveness among guidelines on the use of opioids for the management of knee OA[4, 6].

Moreover, consistent with previous studies, some observed differences in baseline characteristics between participants receiving different types of analgesics have noteworthy implications for further research and patient care. Women participants received more opioids and/or antidepressants than men[43, 44]. Patients taking any opioids had higher comorbidity burden, more significant depression symptoms, and poor self-reported health. In addition, previous studies found racial disparities in OA treatment with analgesics[45-47]. For example, Albert et al. found older African Americans were significantly less likely to have prescription NSAIDs and more likely to use OTC pain medications, compared to older white Americans[45]. Dominick et al. reported black and Hispanic veterans with OA were prescribed NSAIDs with COX-2 selectivity and shorter duration than whites[46]. While non-white participants received more opioids in our study, white participants used more antidepressants and nutraceuticals. This finding may suggest that non-white older Americans may have less access to providers who use non-opioid analgesics or alternative/complementary therapies for pain management.

Given that there is no curative pharmacological treatment for OA, the decisions about analgesic selection should be driven by balancing the appropriate level of pain control and adverse drug effects. Our study found increased recurrent falls during the subsequent year following opioid or antidepressant use. Thus, before an opioid or antidepressant is prescribed, clinicians should consider assessing individual patient risk of falls. If an opioid or antidepressant is warranted, its use should be restricted to the lowest effective dose, and the need for continuation should be assessed regularly. In addition, individuals using opioids or antidepressants who concurrently use other medications associated with increased fall risk (e.g., anticholinergics) should be closely monitored, especially the elderly and those with a

history of falls or fractures[48, 49]. Further comparative effectiveness research is needed to determine the risk of falls among different opioid and antidepressant agents, however.

Strengths of the current study include the prospective design, the large sample of an adult population with or at risk of knee OA, incorporation of numerous patient-based factors (e.g., BMI, physical activity), and adjustment for relevant confounders such as pain severity and depression. Falls and medication use were monitored for 4 years, allowing for time-varying analyses. Medication use was captured carefully using eye-witness recording of information from prescription labels, demonstrated as the most reliable method of ascertaining medication use among community-dwelling participants[50].

Several potential limitations need to considered when interpreting our findings. First, the main outcome of recurrent falls was self-reported and collected retrospectively. The true rate may be underestimated compared with rates ascertained by more frequent prospective monitoring, although highly specific compared with self-reporting of falls via diary[25]. Second, the medication data were collected at fixed annual assessments, so medication changes, switches or discontinuation occurring between the assessments were not captured. The information on dosage was not collected, limiting our ability to examine dose-dependent relationships between analgesic use and recurrent falls. Third, other safety outcomes such as adverse effects from analgesics were not included. Fourth, as expected, over 80% of the participants in the opioid group used multiple pain medications. Given the overall infrequent opioid use (<5%) in our sample, we do not have sufficient power to stratify our analyses by those on opioid monotherapy vs. on opioids with other analgesics. Fifth, limitations inherent to observational studies and data collected in the OAI study, unmeasured confounders or residual confounding effects such as indications for antidepressants or other pain conditions for using analgesics, and medication nonadherence cannot be ruled out. Participants who dropped out of the study could have led to attrition bias, although sensitivity analyses employing imputation yielded similar

results. Lastly, the study sample was drawn from four US cities and may not be generalizable to other populations.

In conclusion, our findings suggest that among participants with or at risk of knee OA, subsequent recurrent falls occur more frequently among those taking opioids or antidepressants, even after adjusting for important confounders. Clinical management of OA pain with opioids or antidepressants in older patients at risk of falls warrants caution. Future comparative effectiveness research is needed to investigate relative safety of specific opioid and antidepressant agents used for OA pain.

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**Author contributions:**

All authors contributed to the conception and design of the study, analysis and interpretation of data, and drafting and critical revision of the article for important intellectual content. All approved the final version submitted. Dr. Lo-Ciganic takes responsibility for the integrity of the work as whole, from inception to finished article. Authors Lo-Ciganic, Floden, Lee, Ashbeck, Zhou and Kwoh had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: Lo-Ciganic, Floden, Ashbeck, Zhou and Kwoh. *Acquisition of data*: Lo-Ciganic and Kwoh. *Analysis and interpretation of data*: Lo-Ciganic, Floden, Lee, Ashbeck, Zhou and Kwoh. *Drafting of the manuscript*: Lo-Ciganic, Floden, Lee, Ashbeck, Zhou and Kwoh. *Critical revision of the manuscript for important intellectual content*: Lo-Ciganic, Floden, Lee, Ashbeck, Zhou, Purdy, and Kwoh. *Statistical analysis*: Floden. *Administrative, technical and material support*: Lo-Ciganic and Kwoh. *Study supervision*: Lo-Ciganic and Kwoh.

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**REFERENCES**


1. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo R, et al. Estimates of the prevalence of musculoskeletal disorders in the United States: part II. 2008; In press.
2. Salaffi F, Carotti M, Stancati A, Grassi W. Health-related quality of life in older adults with symptomatic hip and knee osteoarthritis: a comparison with matched healthy controls. Aging Clin Exp Res 2005; 17: 255-263.
3. Gupta S, Hawker GA, Laporte A, Croxford R, Coyte PC. The economic burden of disabling hip and knee osteoarthritis (OA) from the perspective of individuals living with this condition. Rheumatology (Oxford) 2005; 44: 1531-1537.
4. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken) 2012; 64: 465-474.
5. Conaghan PG, Dickson J, Grant RL, Guideline Development G. Care and management of osteoarthritis in adults: summary of NICE guidance. BMJ 2008; 336: 502-503.
6. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014; 22: 363-388.
7. Dore AL, Golightly YM, Mercer VS, Shi XA, Renner JB, Jordan JM, et al. Lower-extremity osteoarthritis and the risk of falls in a community-based longitudinal study of adults with and without osteoarthritis. Arthritis Care Res (Hoboken) 2015; 67: 633-639.
8. By the American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc 2015; 63: 2227-2246.

9. Solomon DH, Rassen JA, Glynn RJ, Garneau K, Levin R, Lee J, et al. The comparative safety of opioids for nonmalignant pain in older adults. Arch Intern Med 2010; 170: 1979-1986.
10. O'Neil CK, Hanlon JT, Marcum ZA. Adverse effects of analgesics commonly used by older adults with osteoarthritis: focus on non-opioid and opioid analgesics. Am J Geriatr Pharmacother 2012; 10: 331-342.
11. Hanlon JT, Semla TP, Schmader KE. Alternative Medications for Medications in the Use of High-Risk Medications in the Elderly and Potentially Harmful Drug-Disease Interactions in the Elderly Quality Measures. J Am Geriatr Soc 2015; 63: e8-e18.
12. Huang AR, Mallet L, Rochefort CM, Eguale T, Buckeridge DL, Tamblyn R. Medication-related falls in the elderly: causative factors and preventive strategies. Drugs Aging 2012; 29: 359-376.
13. Marcum ZA, Perera S, Thorpe JM, Switzer GE, Castle NG, Strotmeyer ES, et al. Antidepressant Use and Recurrent Falls in Community-Dwelling Older Adults: Findings From the Health ABC Study. Ann Pharmacother 2016; 50: 525-533.
14. Hartikainen S, Lonnroos E, Louhivuori K. Medication as a risk factor for falls: critical systematic review. J Gerontol A Biol Sci Med Sci 2007; 62: 1172-1181.
15. Ensrud KE, Blackwell TL, Mangione CM, Bowman PJ, Whooley MA, Bauer DC, et al. Central nervous system-active medications and risk for falls in older women. J Am Geriatr Soc 2002; 50: 1629-1637.
16. Quach L, Yang FM, Berry SD, Newton E, Jones RN, Burr JA, et al. Depression, antidepressants, and falls among community-dwelling elderly people: the MOBILIZE Boston study. J Gerontol A Biol Sci Med Sci 2013; 68: 1575-1581.
17. Tinetti ME, Williams CS. Falls, injuries due to falls, and the risk of admission to a nursing home. N Engl J Med 1997; 337: 1279-1284.

18. Hanlon JT, Boudreau RM, Roumani YF, Newman AB, Ruby CM, Wright RM, et al. Number and dosage of central nervous system medications on recurrent falls in community elders: the Health, Aging and Body Composition study. J Gerontol A Biol Sci Med Sci 2009; 64: 492-498.
19. Marcum ZA, Perera S, Thorpe JM, Switzer GE, Gray SL, Castle NG, et al. Anticholinergic Use and Recurrent Falls in Community-Dwelling Older Adults: Findings From the Health ABC Study. Ann Pharmacother 2015; 49: 1214-1221.
20. Cumming RG, Kelsey JL, Nevitt MC. Methodologic issues in the study of frequent and recurrent health problems. Falls in the elderly. Ann Epidemiol 1990; 1: 49-56.
21. Kerse N, Flicker L, Pfaff JJ, Draper B, Lautenschlager NT, Sim M, et al. Falls, depression and antidepressants in later life: a large primary care appraisal. PLoS One 2008; 3: e2423.
22. Pahor M, Chrischilles EA, Guralnik JM, Brown SL, Wallace RB, Carbonin P. Drug data coding and analysis in epidemiologic studies. Eur J Epidemiol 1994; 10: 405-411.
23. Pit SW, Byles JE, Cockburn J. Accuracy of telephone self-report of drug use in older people and agreement with pharmaceutical claims data. Drugs Aging 2008; 25: 71-80.
24. Caskie GI, Willis SL, Warner Schaie K, Zanjani FA. Congruence of medication information from a brown bag data collection and pharmacy records: findings from the Seattle longitudinal study. Exp Aging Res 2006; 32: 79-103.
25. Ganz DA, Higashi T, Rubenstein LZ. Monitoring falls in cohort studies of community-dwelling older people: effect of the recall interval. J Am Geriatr Soc 2005; 53: 2190-2194.
26. Kingsbury SR, Hensor EM, Walsh CA, Hochberg MC, Conaghan PG. How do people with knee osteoarthritis use osteoarthritis pain medications and does this change over time? Data from the Osteoarthritis Initiative. Arthritis Res Ther 2013; 15: R106.

27. Marcum ZA, Perera S, Donohue JM, Boudreau RM, Newman AB, Ruby CM, et al. Analgesic use for knee and hip osteoarthritis in community-dwelling elders. Pain Med 2011; 12: 1628-1636.

28. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994; 47: 1245-1251.

29. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996; 34: 220-233.

30. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol 1993; 46: 153-162.

31. Martin KA, Rejeski WJ, Miller ME, James MK, Ettinger WH, Jr., Messier SP. Validation of the PASE in older adults with knee pain and physical disability. Med Sci Sports Exerc 1999; 31: 627-633.

32. Shrank WH, Patrick AR, Brookhart MA. Healthy user and related biases in observational studies of preventive interventions: a primer for physicians. J Gen Intern Med 2011; 26: 546-550.

33. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS) - Development of a self-administered outcome measure. Journal of Orthopaedic & Sports Physical Therapy 1998; 78: 88-96.

34. Bellamy N, Buchanan W, Goldsmith C, Campbell J, Stitt L. Validation study of WOMAC: A health status instrument for measuring clinically-important patient-relevant outcomes following total hip or knee arthroplasty in osteoarthritis. J Orthop Rheum 1988; 1: 95-108.

35. Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. Appl Psych Measur. 1977; 1: 385-401.

36. Schneeweiss S, Wang PS, Avorn J, Glynn RJ. Improved comorbidity adjustment for predicting mortality in Medicare populations. Health Serv Res 2003; 38: 1103-1120.

37. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004; 159: 702-706.

38. McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. Am J Epidemiol 2003; 157: 940-943.

39. Rubin DB. Multiple Imputation for Nonresponse in Surveys. John Wiley and Sons, New Yok 1987.

40. Ping F, Wang Y, Wang J, Chen J, Zhang W, Zhi H, et al. Opioids increase hip fracture risk: a meta-analysis. J Bone Miner Metab 2016.

41. Marcum ZA, Hanlon JT. Recognizing the Risks of Chronic Nonsteroidal Anti-Inflammatory Drug Use in Older Adults. Ann Longterm Care 2010; 18: 24-27.

42. Berger A, Bozic K, Stacey B, Edelsberg J, Sadosky A, Oster G. Patterns of pharmacotherapy and health care utilization and costs prior to total hip or total knee replacement in patients with osteoarthritis. Arthritis Rheum 2011; 63: 2268-2275.

43. Wright EA, Katz JN, Abrams S, Solomon DH, Losina E. Trends in prescription of opioids from 2003-2009 in persons with knee osteoarthritis. Arthritis Care Res (Hoboken) 2014; 66: 1489-1495.

44. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. JAMA 2002; 287: 337-344.

45. Albert SM, Musa D, Kwoh CK, Hanlon JT, Silverman M. Self-care and professionally guided care in osteoarthritis: racial differences in a population-based sample. J Aging Health 2008; 20: 198-216.

46. Dominick KL, Bosworth HB, Jeffreys AS, Grambow SC, Oddone EZ, Horner RD. Racial/ethnic variations in non-steroidal anti-inflammatory drug (NSAID) use among patients with osteoarthritis. Pharmacoepidemiol Drug Saf 2004; 13: 683-694.

47. Pahor M, Guralnik JM, Wan JY, Ferrucci L, Penninx BW, Lyles A, et al. Lower body osteoarticular pain and dose of analgesic medications in older disabled women: the Women's Health and Aging Study. Am J Public Health 1999; 89: 930-934.

48. Tinetti ME. Clinical practice. Preventing falls in elderly persons. N Engl J Med 2003; 348: 42-49.

49. Berry SD, Kiel DP. Medication Review After a Fracture-Absolutely Essential. JAMA Intern Med 2016; 176: 1539-1540.

50. Psaty BM, Lee M, Savage PJ, Rutan GH, German PS, Lyles M. Assessing the use of medications in the elderly: methods and initial experience in the Cardiovascular Health Study. The Cardiovascular Health Study Collaborative Research Group. J Clin Epidemiol 1992; 45: 683-692.

**Table 1. Baseline Characteristics Overall and by Analgesic Group from the Osteoarthritis Initiatives (OAI)[a]**

| | All (n= 4,231) | Opioids (n=114) | Anti-depressants (n= 559) | Prescription pain medications (n= 706) | OTC pain medications (n= 712) | Nutraceuticals (n= 667) | No pain medications (n= 1,473) | P value |
|---|---|---|---|---|---|---|---|---|
| **Demographics** | | | | | | | | |
| Age, mean (SD) | 61.3 (9.2) | 60.1 (9.2) | 59.3 (8.7) | 62.8 (9.1) | 61.8 (9.1) | 61.3 (9.0) | 61.2 (9.3) | <0.0001 |
| Female, n (%) | 2,471 (58.4) | 82 (71.9) | 416 (74.4) | 420 (59.5) | 408 (57.3) | 353 (52.9) | 792 (53.8) | <0.0001 |
| Race, n (%) | | | | | | | | <0.0001 |
| White | 3,419 (80.8) | 83 (72.8) | 491 (87.8) | 556 (78.8) | 536 (75.3) | 589 (88.3) | 1,164 (79.0) | |
| Non-white | 812 (19.2) | 31 (27.2) | 68 (12.1) | 150 (21.2) | 176 (24.8) | 78 (11.8) | 309 (21.0) | |
| Marital status[b], n (%) | | | | | | | | 0.0009 |
| Married | 2,861 (67.6) | 63 (55.3) | 353 (63.3) | 480 (68.0) | 465 (65.3) | 471 (70.6) | 1,029 (69.9) | |
| Not married | 1,369 (32.4) | 51 (44.7) | 205 (36.7) | 226 (32.0) | 247 (34.7) | 196 (29.4) | 444 (30.1) | |
| Education, n (%) | | | | | | | | <0.0001 |
| <high school or high school graduate | 640 (15.1) | 23 (20.2) | 71 (12.7) | 121 (17.1) | 139 (19.5) | 69 (10.3) | 217 (14.7) | |
| Some college/postsecondary | 3,591 (84.9) | 91 (79.8) | 488 (87.3) | 585 (82.9) | 573 (80.5) | 598 (89.7) | 1,256 (85.3) | |
| **Health status/behavior factors** | | | | | | | | |
| Charlson's comorbidity index, mean (SD) | 0.4 (0.8) | 0.8 (1.1) | 0.5 (1.0) | 0.5 (0.9) | 0.4 (0.8) | 0.2 (0.6) | 0.3 (0.8) | <0.0001 |
| Cardiovascular disease, n (%) | 73 (1.9) | 0 (0) | 4 (0.8) | 11 (2.2) | 17 (2.8) | 12 (1.8) | 29 (0.8) | 0.1595 |
| Heart failure, n (%) | 74 (1.9) | 4 (3.8) | 7 (1.4) | 12 (2.3) | 14 (2.3) | 5 (0.7) | 32 (2.2) | 0.1061 |
| Diabetes, n (%) | 270 (7.0) | 9 (8.5) | 37 (7.6) | 50 (9.7) | 51 (8.4) | 29 (4.4) | 94 (6.5) | 0.0082 |
| Cerebrovascular disease, n (%) | 110 (3.1) | 5 (4.7) | 14 (3.0) | 21 (3.9) | 17 (2.8) | 8 (1.2) | 45 (3.1) | 0.0685 |
| Peripheral vascular disease, n (%) | 38 (1.0) | 3 (2.9) | 1 (0.2) | 7 (1.3) | 12 (1.9) | 1 (0.2) | 14 (1.0) | 0.0026 |
| K/L grade (worst knee)[b], n (%) | | | | | | | | <0.0001 |
| 0-1 | 1,813 (43.4) | 42 (37.5) | 251 (45.1) | 241 (34.7) | 279 (39.7) | 286 (43.5) | 714 (49.1) | |
| 2-3 | 2,093 (50.1) | 62 (55.4) | 288 (51.7) | 377 (54.3) | 361 (51.4) | 321 (48.9) | 684 (47.1) | |
| 4 | 269 (6.4) | 8 (7.1) | 18 (3.2) | 76 (11.0) | 62 (8.8) | 50 (7.6) | 55 (3.8) | |
| History of knee surgery, n (%) | 941 (22.3) | 30 (26.3) | 123 (22.1) | 178 (25.3) | 169 (23.8) | 161 (24.1) | 280 (19.0) | 0.0067 |
| History of falls in the previous year, n (%) | 652 (15.4) | 30 (26.3) | 142 (25.4) | 104 (14.7) | 108 (15.2) | 99 (14.8) | 169 (11.5) | <0.0001 |
| Taken bisphosphonate for osteoporosis, n (%) | 519 (12.3) | 14 (12.3) | 74 (13.2) | 98 (13.9) | 79 (11.1) | 86 (12.9) | 168 (11.4) | 0.5027 |
| BMI, mean (SD) | 28.5 (4.8) | 30.8 (5.2) | 29.1 (5.3) | 29.3 (4.8) | 28.9 (4.9) | 27.5 (4.4) | 28.0 (4.6) | <0.0001 |
| Depression (CES-D ≥16), n (%) | 440 (10.4) | 31 (28.4) | 122 (23.2) | 65 (10.5) | 85 (13.7) | 47 (8.3) | 90 (7.4) | <0.0001 |

**Table 1 (Continued).**

| | All (n= 4,231) | Opioids (n=114) | Anti-depressants (n= 559) | Prescription pain medications (n= 706) | OTC pain medications (n= 712) | Nutraceuticals (n= 667) | No pain medications (n= 1,473) | P value |
|---|---|---|---|---|---|---|---|---|
| Short Form-12 health survey score, mean (SD) | | | | | | | | |
| Physical health | 49.2 (8.9) | 39.6 (9.9) | 48.4 (9.6) | 46.5 (9.2) | 47.0 (9.1) | 51.4 (7.6) | 51.7 (7.5) | <0.0001 |
| Mental health | 53.8 (7.9) | 50.6 (10.4) | 49.2 (9.8) | 55.2 (7.4) | 54.0 (8.1) | 54.8 (7.0) | 54.5 (6.7) | <0.0001 |
| PASE, mean (SD) | 161.4 (81.7) | 146.2 (78.9) | 156.7 (82.8) | 152.5 (84.4) | 165.8 (84.3) | 169.2 (79.6) | 163.0 (79.4) | 0.0003 |
| KOOS score, mean (SD) | | | | | | | | |
| Quality of Life | 67.8 (22.1) | 54.1 (23.7) | 64.4 (22.5) | 63.6 (22.3) | 60.0 (22.2) | 69.9 (19.2) | 75.0 (20.5) | <0.0001 |
| Pain | 91.3 (12.8) | 81.3 (19.6) | 89.9 (13.2) | 89.9 (13.8) | 87.4 (15.3) | 94.0 (9.1) | 94.0 (10.4) | <0.0001 |
| Symptoms | 92.0 (10.6) | 85.0 (15.4) | 89.9 (11.8) | 90.9 (11.4) | 89.5 (11.9) | 93.7 (8.2) | 94.4 (8.6) | <0.0001 |
| Pain NRS severity on the worst knee (range 1-10), mean (SD) | 3.3 (2.7) | 5.0 (2.9) | 3.6 (2.7) | 3.8 (2.7) | 4.2 (2.7) | 2.8 (2.3) | 2.6 (2.5) | <0.0001 |
| Any anticholinergic use, n (%) | 417 (10.7) | 35 (33.0) | 108 (21.8) | 75 (14.3) | 70 (11.3) | 35 (5.2) | 94 (6.4) | <0.0001 |
| Benzodiazepines | 209 (4.9) | 15 (13.2) | 80 (14.3) | 40 (5.7) | 32 (4.5) | 12 (1.8) | 30 (2.0) | <0.0001 |
| GI and urinary antispasmodics | 159 (3.8) | 12 (10.5) | 42 (7.5) | 39 (5.5) | 19 (2.7) | 12 (1.8) | 35 (2.4) | <0.0001 |
| Muscle relaxants | 64 (1.5) | 9 (7.9) | 15 (2.7) | 23 (3.3) | 9 (1.3) | 5 (0.8) | 3 (0.2) | <0.0001 |
| Others | 90 (2.1) | 9 (7.9) | 24 (4.3) | 16 (2.3) | 9 (1.3) | 9 (1.4) | 23 (1.6) | <0.0001 |
| Diuretics, n (%) | 861 (20.4) | 26 (22.8) | 109 (19.5) | 189 (26.8) | 16 0 (22.5) | 106 (15.9) | 271 (18.4) | <0.0001 |
| Anticonvulsants, n (%) | 59 (1.4) | 8 (7.0) | 12 (2.2) | 15 (2.1) | 9 (1.3) | 3 (0.5) | 12 (0.8) | <0.0001 |
| Number of other prescriptions, mean (SD) | 2.4 (2.3) | 3.9 (3.4) | 3.3 (2.5) | 3.1 (2.4) | 2.1 (2.1) | 1.8 (1.9) | 2.0 (2.1) | <0.0001 |
| **Access-to-care factor** | | | | | | | | |
| Health insurance coverage, n (%) | 4,107 (97.2) | 105 (92.1) | 547 (98.0) | 686 (97.2) | 680 (95.6) | 655 (98.4) | 1,434 (97.5) | 0.0005 |

**Abbreviations**: **BMI**: body mass index; **KOOS:** Knee Injury and Osteoarthritis Outcome Score; **NRS**, numerical rating scale; **NSAIDs**: non-steroidal anti-inflammatory drugs; **PASE**: Physical activity scale for the elderly; **SD**: standard deviation; **OTC**: over the counter.

[a]Patients were grouped into 6 exclusive subgroups in the following hierarchical order of analgesic potency and central nervous system (CNS) effects: any use of (1) opioids (i.e., any oral or transdermal prescription opioids), (2) antidepressants (i.e., no opioids, but with any antidepressants), (3) prescription pain medications (i.e., no opioids/antidepressants, but with any NSAIDs, triptans and salicylates) (4) OTC pain medications (i.e., no opioids/antidepressants/prescription pain medications, but with OTC NSAIDs and acetaminophen), (5) nutraceuticals

including chondroitin, glucosamine, methylsulfonylmethane (MSM), S-adenosyl-L-methionine (SAMe), and (6) no pain medications use.
[b]Numbers did not sum up to total due to missing value

**Table 2: Analgesic Use Over time**

| Analgesic group[a] | Baseline (n=4,231), n (%) | 12-month visit (n=3,891), n (%) | 24-month visit (n=3,764), n (%) | 36-month visit (n=3,762), n (%) |
|---|---|---|---|---|
| Opioids | 114 (2.7) | 106 (2.7) | 109 (2.9) | 137 (3.6) |
| Antidepressants | 559 (13.2) | 496 (12.8) | 497 (13.2) | 484 (12.9) |
| Prescription pain medications | 706 (16.7) | 526 (13.5) | 468 (12.4) | 449 (11.9) |
| OTC pain medications | 712 (16.8) | 620 (15.9) | 557 (14.8) | 584 (15.5) |
| Nutraceuticals | 667(15.8) | 676 (17.4) | 624 (16.6) | 576 (15.3) |
| No pain medications | 1,473 (34.8) | 1,467 (37.7) | 1,509 (40.1) | 1,532 (40.7) |

**Abbreviations**: **NSAIDs**: non-steroidal anti-inflammatory drugs; **OTC**: over the counter.
[a]Patients were grouped into 6 exclusive subgroups in the following hierarchical order of analgesic potency and central nervous system (CNS) effects: any use of (1) opioids (i.e., any oral or transdermal prescription opioids), (2) antidepressants (i.e., no opioids, but with any antidepressants), (3) prescription pain medications (i.e., no opioids/antidepressants, but with any NSAIDs, triptans and salicylates) (4) OTC pain medications (i.e., no opioids/antidepressants/prescription pain medications, but with OTC NSAIDs and acetaminophen), (5) nutraceuticals including chondroitin, glucosamine, methylsulfonylmethane (MSM), S-adenosyl-L-methionine (SAMe), and (6) no pain medications use.

**Table 3: Prevalence of Falls Over Time, Overall and by Analgesic Use**

| Analgesic group[a] | 12-month visit (n=4,231), n (%) | 24-month visit (n=3,891), n (%) | 36-month visit (n=3,764), n (%) | 48-month visit (n=3,762), n (%) |
|---|---|---|---|---|
| Overall any falls | 1,276 (30.2) | 1,210 (31.1) | 1,228 (32.6) | 1,166 (31.0) |
| Overall recurrent falls (i.e., ≥2 falls) | 594 (14.0) | 527 (13.5) | 546 (14.5) | 561 (14.9) |
| % of recurrent falls among each analgesic group | | | | |
| Opioids | 32 (28.1) | 26 (24.5) | 25 (22.9) | 27 (19.7) |
| Antidepressants | 123 (22.0) | 104 (21.0) | 114 (22.9) | 106 (21.9) |
| Prescription pain medications | 100 (14.2) | 69 (13.1) | 76 (16.2) | 70 (15.6) |
| OTC pain medications | 95 (13.3) | 98 (15.8) | 75 (13.5) | 100 (17.1) |
| Nutraceuticals | 92 (13.8) | 78 (11.5) | 93 (14.9) | 69 (12.0) |
| No pain medications | 152 (10.3) | 152 (10.4) | 163 (10.8) | 189 (12.3) |

**Abbreviations**: **NSAIDs**: non-steroidal anti-inflammatory drugs; **OTC**: over the counter.
[a]Patients were grouped into 6 exclusive subgroups in the following hierarchical order of analgesic potency and central nervous system (CNS) effects: any use of (1) opioids (i.e., any oral or transdermal prescription opioids), (2) antidepressants (i.e., no opioids, but with any antidepressants), (3) prescription pain medications (i.e., no opioids/antidepressants, but with any NSAIDs, triptans and salicylates) (4) OTC pain medications (i.e., no opioids/antidepressants/prescription pain medications, but with OTC NSAIDs and acetaminophen), (5) nutraceuticals including chondroitin, glucosamine, methylsulfonylmethane (MSM), S-adenosyl-L-methionine (SAMe), and (6) no pain medications use.

**Table 4: Association between Analgesic Use and Recurrent Falls: Overall**

| Analgesic groups[a] | Recurrent falls at 12-month visit, n (%) | Unadjusted model | | Adjusted model with major confounders[b] | | Adjusted model with major confounders and SF-12 health scores and PASE scores[c] | | Full adjusted model[d] | |
|---|---|---|---|---|---|---|---|---|---|
| | | $RR_{Unadj}$ (95% CI) | P value | $RR_{adj}$ (95% CI) | P value | $RR_{adj}$ (95% CI) | P value | $RR_{Adj}$ (95% CI) | P value |
| | | **N=4,231** | | **N=3,401[e]** | | **N=3,294[e]** | | **N=3,239[e]** | |
| Opioids | 32 (28.1) | 1.58 (1.28, 1.95) | <0.0001 | 1.37 (1.16, 1.59) | 0.0002 | 1.25 (1.06, 1.47) | 0.009 | 1.22 (1.04, 1.45) | 0.02 |
| Antidepressants | 123 (22.0) | 1.70 (1.49, 1.93) | <0.0001 | 1.32 (1.17, 1.48) | <0.0001 | 1.27 (1.12, 1.43) | <0.0001 | 1.25 (1.10, 1.41) | <0.0001 |
| Prescription pain medications | 100 (14.2) | 1.13 (0.99, 1.29) | 0.07 | 1.10 (0.97, 1.25) | 0.14 | 1.08 (0.95, 1.23) | 0.25 | 1.08 (0.95, 1.23) | 0.25 |
| OTC pain medications | 95 (13.3) | 1.24 (1.11, 1.39) | 0.0002 | 1.17 (1.04, 1.31) | 0.01 | 1.14 (1.01, 1.28) | 0.04 | 1.13 (1.00, 1.28) | 0.05 |
| Nutraceuticals | 92 (13.8) | 1.13 (1.00, 1.29) | 0.05 | 1.12 (0.99, 1.27) | 0.063 | 1.13 (0.99, 1.27) | 0.06 | 1.13 (0.99, 1.28) | 0.05 |
| No pain medications | 152 (10.3) | Reference | - | Reference | - | Reference | - | Reference | - |

**Abbreviations**: **CI**: confidence intervals; **RR**: relative risk; **OTC**: over-the-counter.

[a] Patients were grouped into 6 exclusive subgroups in the following hierarchical order of analgesic potency and central nervous system (CNS) effects: any use of (1) opioids (i.e., any oral or transdermal prescription opioids), (2) antidepressants (i.e., no opioids, but with any antidepressants), (3) prescription pain medications (i.e., no opioids/antidepressants, but with any NSAIDs, triptans and salicylates) (4) OTC pain medications (i.e., no opioids/antidepressants/prescription pain medications, but with OTC NSAIDs and acetaminophen), (5) nutraceuticals including chondroitin, glucosamine, methylsulfonylmethane (MSM), S-adenosyl-L-methionine (SAMe), and (6) no pain medications use.

[b] Adjusted model with major confounders included demographics (baseline age, sex, race, marital status, education), time-varying health status/behavior (Charlson's comorbidity index, history of falls, any anti-cholinergic use), and time-varying pain and depression severity covariates (i.e., KOOS pain subscale, KOOS symptom subscale, pain numerical rating scale, and having significant depressive symptoms).

[c] adjusted model with major confounders that were listed in the footnote b above and physical and mental component scores from the Short Form-12 health survey and Physical Activity Scale for the Elderly (PASE) score.

[d] Full adjusted model included confounders that were listed in the footnotes b and c above and other time-varying health status/behavior covariates (i.e., K/L grade, history of knee surgery, taking bisphosphonate for osteoporosis, BMI, KOOS quality of life subscale, and total number of other prescriptions used).

[e] Observations with any missing covariates were not included in multivariate analyses.

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**eTable 1. List of Opioids, Antidepressants, and Prescription Pain Medications**

| Analgesic groups | Medications included |
|---|---|
| Opioids | Fentanyl, Hydromorphone, Meperidine, Methadone, Morphine, Propoxyphene, Tramadol, Oxycodone, Oxymorphone, Pentazocine |
| Antidepressants | Amitriptyline, Atomoxetine, Bupropion, Citalopram, Clomipramine, Desipramine, Doxepin, Duloxetine, Escitalopram, Fluoxetine, Fluvoxamine, Imipramine, Maprotiline, Mirtazapine, Nefazodone, Nortriptyline, Paroxetine, Phenelzine, Sertraline, Sibutramine, Trazodone, Trimipramine, Venlafaxine |
| Prescription NSAIDs | Aspirin, Almotriptan, Celecoxib, Choline Salicylate, Diclofenac Sodium, Diflunisal, Eletriptan, Etodolac, Etoricoxib, Flurbiprofen, Frovatriptan, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Lumiracoxib, Magnesium Salicylate, Meloxicam, Nabumetone, Naproxen, Naratriptan, Oxaprozin, Phenacetin, Phenyl Salicylate, Piroxicam, Rizatriptan, Rofecoxib, Salsalate, Sulindac, Sumatriptan, Valdecoxib, Zolmitriptan, |

**eTable 2. Utilization Patterns of Analgesics and Nutraceuticals at Baseline by Exclusive Analgesic Group (n= 4,231)**

| | Opioids (n=114) | Anti-depressants (n= 559) | Prescription pain medications (n= 706) | OTC pain medications (n= 712) | Nutraceuticals (n= 667) | Total (N=4,231) |
|---|---|---|---|---|---|---|
| **Any opioids** | 114 (100) | - | - | - | - | 114 (2.7) |
| **Any antidepressants** | 44 (38.6) | 559 (100%) | - | - | - | 603 (14.3) |
| **TCAs** | 7 (0.1) | 78 (14.0) | - | - | - | - |
| **SSRIs/SNRIs** | 25 (21.9) | 346 (61.9) | - | - | - | - |
| **Others** | 26 (22.8) | 210 (37.6) | - | - | - | - |
| **Any prescription pain medications** | 95 (83.3) | 181 (32.4) | 706 (100%) | - | - | 982 (23.2) |
| **Any OTC pain medications** | 44 (38.6) | 180 (32.2) | 194 (27.5) | 712 (100%) | - | 1,130 (26.7) |
| **Any nutraceuticals** | 35 (30.7) | 199 (35.6) | 298 (42.2) | 281 (39.5) | 667 (100.0) | 1,480 (34.9) |
| **Total number of analgesic and nutraceutical class used, mean (SD)** | 2.9 (0.9) | 2.0 (0.9) | 1.7 (0.7) | 1.4 (0.5) | 1.0 (-) | 1.0 (1.0) |
| **Total number of pain medications used, mean (SD)** | 3.3 (1.6) | 2.6 (1.4) | 2.2 (1.3) | 1.9 (1.1) | 2.0 (0.5) | 1.4 (1.4) |

**Abbreviations**: **SD**: standard deviation; **OTC**: over the counter.

[a]Patients were grouped into 6 exclusive subgroups in the following hierarchical order of analgesic potency and central nervous system (CNS) effects: any use of (1) opioids (i.e., any oral or transdermal prescription opioids), (2) antidepressants (i.e., no opioids, but with any antidepressants), (3) prescription pain medications (i.e., no opioids/antidepressants, but with any NSAIDs , triptans and salicylates) (4) OTC pain medications (i.e., no opioids/antidepressants/prescription pain medications, but with OTC NSAIDs and acetaminophen), (5) nutraceuticals including chondroitin, glucosamine, methylsulfonylmethane (MSM), and S-adenosyl-L-methionine (SAMe), and (6) no pain medications use.

**eTable 3. Association between Analgesic Use and Any Falls**

| Analgesic groups[a] | Any falls at 12-month visit, n (%) | $RR_{Unadj}$ (95% CI)[b] | P value | $RR_{Adj}$ (95% CI)[b] | P value |
|---|---|---|---|---|---|
| | | **n=4,231** | | **N=3,239[c]** | |
| Opioids | 50 (43.9) | 1.41 (1.24, 1.60) | <0.0001 | 1.23 (1.04, 1.45) | 0.016 |
| Antidepressants | 220 (39.4) | 1.41 (1.30, 1.52) | <0.0001 | 1.25 (1.10, 1.41) | 0.0004 |
| Prescription pain medications | 225 (31.9) | 1.11 (1.02, 1.20) | 0.014 | 1.08 (0.95, 1.23) | 0.25 |
| OTC pain medications | 198 (27.8) | 1.13 (1.05, 1.21) | 0.001 | 1.13 (1.00, 1.28) | 0.04 |
| Nutraceuticals | 187 (28.0) | 1.05 (0.97, 1.14) | 0.188 | 1.13 (0.99, 1.28) | 0.05 |
| No pain medications | 396 (26.9) | Reference | - | Reference | - |

**Abbreviations**: **CI**: confidence intervals; **RR**: relative risk; **OTC**: over-the-counter.

[a] Patients were grouped into 6 exclusive subgroups in the following hierarchical order of analgesic potency and central nervous system (CNS) effects: any use of (1) opioids (i.e., any oral or transdermal prescription opioids), (2) antidepressants (i.e., no opioids, but with any antidepressants), (3) prescription pain medications (i.e., no opioids/antidepressants, but with any NSAIDs, triptans and salicylates) (4) OTC pain medications (i.e., no opioids/antidepressants/prescription pain medications, but with OTC NSAIDs and acetaminophen), (5) nutraceuticals including chondroitin, glucosamine, methylsulfonylmethane (MSM), and S-adenosyl-L-methionine (SAMe), and (6) no pain medications use.

[b] Multivariate models were adjusted for demographics (age, sex, race, marital status, education), and time-varying health status/behavior (Charlson's comorbidity index, K/L grade, history of knee surgery, history of falls in the previous year, taking bisphosphonate for osteoporosis, BMI, having severe depressive symptoms, physical and mental component scores from the Short Form-12 health survey, Physical Activity Scale for the Elderly (PASE) score, KOOS quality of life subscale, KOOS pain subscale, KOOS symptom subscale, pain numerical rating scale, use of anticholinergics, and diuretics).

[c] Observations with missing covariates were not included in multivariate analyses.

**eTable 4. Association between Analgesic Use and Recurrent Falls using Multiple Imputations (MI)[a]**

| Analgesic groups (Referent= no pain medications)[b] | Adjusted model (95% CI)[c] | Multiple imputation models[d] | | | | | |
|---|---|---|---|---|---|---|---|
| | | Model 1 $RR_{Adj}$ | Model 2 $RR_{Adj}$ | Model 3 $RR_{Adj}$ | Model 4 $RR_{Adj}$ | Model 5 $RR_{Adj}$ | Average results from MI models $RR_{Adj}$ |
| Opioids | 1.22 (1.04, 1.45) | 1.28 | 1.32 | 1.30 | 1.31 | 1.32 | 1.31 |
| Antidepressants | 1.25 (1.10, 1.41) | 1.44 | 1.45 | 1.45 | 1.44 | 1.45 | 1.45 |
| Prescription pain medications | 1.08 (0.95, 1.23) | 1.07 | 1.06 | 1.06 | 1.06 | 1.06 | 1.06 |
| OTC pain medications | 1.13 (1.00, 1.28) | 1.18 | 1.18 | 1.18 | 1.18 | 1.18 | 1.18 |
| Nutraceuticals | 1.13 (0.99, 1.28) | 1.13 | 1.14 | 1.13 | 1.13 | 1.14 | 1.14 |

**Abbreviations**: **CI**: confidence intervals; **RR**: relative risk; **OTC**: over-the-counter.

[a] We used PROC MI procedures in SAS to impute missing values for marital status, time-varying health status/behavior (Charlson's comorbidity index, history of falls, any anti-cholinergic use), and time-varying pain and depression severity covariates (i.e., KOOS pain subscale, KOOS symptom subscale, pain numerical rating scale, and having significant depressive symptoms, physical and mental component scores from the Short Form-12 health survey and Physical Activity Scale for the Elderly [PASE] score). The MI models simultaneously predicted missing values of variables using existing values of variables by modeling the joint distribution of all covariates. For each participant, conditional on the non-missing values, the missing values have a distribution from which several joint random samples are drawn. We analyzed each of five imputation datasets separately as if there were no missing values, then combined the results using Rubin's rules from these five imputation datasets to obtain risk estimates reflecting the uncertainty due to missing values.

[b] Patients were grouped into 6 exclusive subgroups in the following hierarchical order of analgesic potency and central nervous system (CNS) effects: any use of (1) opioids (i.e., any oral or transdermal prescription opioids), (2) antidepressants (i.e., no opioids, but with any antidepressants), (3) prescription pain medications (i.e., no opioids/antidepressants, but with any NSAIDs, triptans and salicylates) (4) OTC pain medications (i.e., no opioids/antidepressants/prescription pain medications, but with OTC NSAIDs and acetaminophen), (5) nutraceuticals including chondroitin, glucosamine, methylsulfonylmethane (MSM), S-adenosyl-L-methionine (SAMe), and (6) no pain medications use.

[c] Adjusted model with major confounders included demographics (baseline age, sex, race, marital status, education), time-varying health status/behavior (Charlson's comorbidity index, history of falls, any anti-cholinergic use), and time-varying pain and depression severity covariates (i.e., KOOS pain subscale, KOOS symptom subscale, pain numerical rating scale, and having significant depressive symptoms, physical and mental component scores from the Short Form-12 health survey and Physical Activity Scale for the Elderly (PASE) score).

[d] the 95% CIs were similar to the adjusted models without multiple imputations.

**eTable 5: Association between Analgesic Use and Recurrent Falls: by K/L grade**

| Analgesic groups[a] | Recurrent falls at 12-month visit, n (%) | Unadjusted model | | Adjusted model with major confounders[b] | | Adjusted model with major confounders and SF-12 health scores and PASE scores[c] | | Full adjusted model[d] | |
|---|---|---|---|---|---|---|---|---|---|
| | | $RR_{Unadj}$ (95% CI) | P value | $RR_{Adj}$ (95% CI) | P value | $RR_{Adj}$ (95% CI) | P value | $RR_{Adj}$ (95% CI) | P value |
| **K/L grade ≥2** | | | | | | | | | |
| | | **N=2,525[e]** | | **N=2,309[e]** | | **N=2,237[e]** | | **N=2,213[e]** | |
| Opioids | 22 (31.4) | 1.79 (1.37, 2.32) | <0.001 | 1.41 (1.16, 1.70) | 0.0004 | 1.32 (1.08, 1.60) | 0.006 | 1.31 (1.07, 1.59) | 0.008 |
| Antidepressants | 68 (22.2) | 1.74 (1.45, 2.10) | <0.001 | 1.31 (1.12, 1.54) | 0.001 | 1.25 (1.07, 1.47) | 0.007 | 1.23 (1.05, 1.45) | 0.01 |
| Prescription pain medications | 58 (12.8) | 1.11 (0.93, 1.33) | 0.26 | 1.07 (0.91, 1.26) | 0.41 | 1.06 (0.90, 1.25) | 0.50 | 1.05 (0.89, 1.24) | 0.56 |
| OTC pain medications | 61 (14.4) | 1.20 (1.03, 1.41) | 0.02 | 1.15 (0.98, 1.34) | 0.09 | 1.13 (0.96, 1.32) | 0.14 | 1.11 (0.95, 1.30) | 0.18 |
| Nutraceuticals | 51 (13.8) | 1.19 (1.00, 1.40) | 0.05 | 1.13 (0.96, 1.33) | 0.15 | 1.13 (0.96, 1.33) | 0.15 | 1.12 (0.95, 1.33) | 0.17 |
| No pain medications | 79 (10.7) | Reference | - | Reference | - | Reference | - | Reference | - |
| **K/L grade <2** | | | | | | | | | |
| | | **N=1,649** | | **N=1,516[e]** | | **N=1,474[e]** | | **N=1,460[e]** | |
| Opioids | 10 (22.7) | 1.50 (1.04, 2.18) | 0.03 | 1.21 (0.99, 1.64) | 0.23 | 1.07 (0.78, 1.46) | 0.69 | 1.06 (0.76, 1.48) | 0.72 |
| Antidepressants | 55 (21.7) | 1.78 (1.42, 2.08) | <0.001 | 1.35 (1.13, 1.61) | 0.001 | 1.29 (1.08, 1.55) | 0.006 | 1.28 (1.06, 1.54) | 0.009 |
| Prescription pain medications | 42 (16.6) | 1.27 (1.02, 1.58) | 0.03 | 1.17 (0.95, 1.44) | 0.14 | 1.12 (0.91, 1.38) | 0.29 | 1.12 (0.91, 1.39) | 0.30 |
| OTC pain medications | 34 (12.8) | 1.30 (1.07, 1.56) | 0.008 | 1.18 (0.98, 1.42) | 0.08 | 1.13 (0.93, 1.36) | 0.22 | 1.15 (0.95, 1.39) | 0.16 |
| Nutraceuticals | 41 (13.9) | 1.10 (0.90, 1.34) | 0.34 | 1.11 (0.93, 1.33) | 0.26 | 1.12 (0.93, 1.34) | 0.24 | 1.14 (0.95, 1.37) | 0.17 |
| No pain medications | 73 (10.0) | Reference | - | Reference | - | Reference | - | Reference | - |

**Abbreviations**: **CI**: confidence intervals; **RR**: relative risk; **OTC**: over-the-counter.

[a] Patients were grouped into 6 exclusive subgroups in the following hierarchical order of analgesic potency and central nervous system (CNS) effects: any use of (1) opioids (i.e., any oral or transdermal prescription opioids), (2) antidepressants (i.e., no opioids, but with any antidepressants), (3) prescription pain medications (i.e., no opioids/antidepressants, but with any NSAIDs, triptans and salicylates) (4) OTC pain medications (i.e., no opioids/antidepressants/prescription pain medications, but with OTC NSAIDs and acetaminophen), (5) nutraceuticals including chondroitin, glucosamine, methylsulfonylmethane (MSM), S-adenosyl-L-methionine (SAMe), and (6) no pain medications use.

[b] Adjusted model with major confounders included demographics (baseline age, sex, race, marital status, education), time-varying health status/behavior (Charlson's comorbidity index, history of falls, any anti-cholinergic use), and time-varying pain and depression severity covariates (i.e., KOOS pain subscale, KOOS symptom subscale, pain numerical rating scale, and having significant depressive symptoms).

[c] Adjusted model with major confounders that were listed in the footnote b above and physical and mental component scores from the Short Form-12 health survey and Physical Activity Scale for the Elderly (PASE) score.

[d] Full adjusted model included confounders that were listed in the footnotes b and c above and other time-varying health status/behavior covariates (i.e., K/L grade, history of knee surgery, taking bisphosphonate for osteoporosis, BMI, KOOS quality of life subscale, and total number of other prescriptions used).

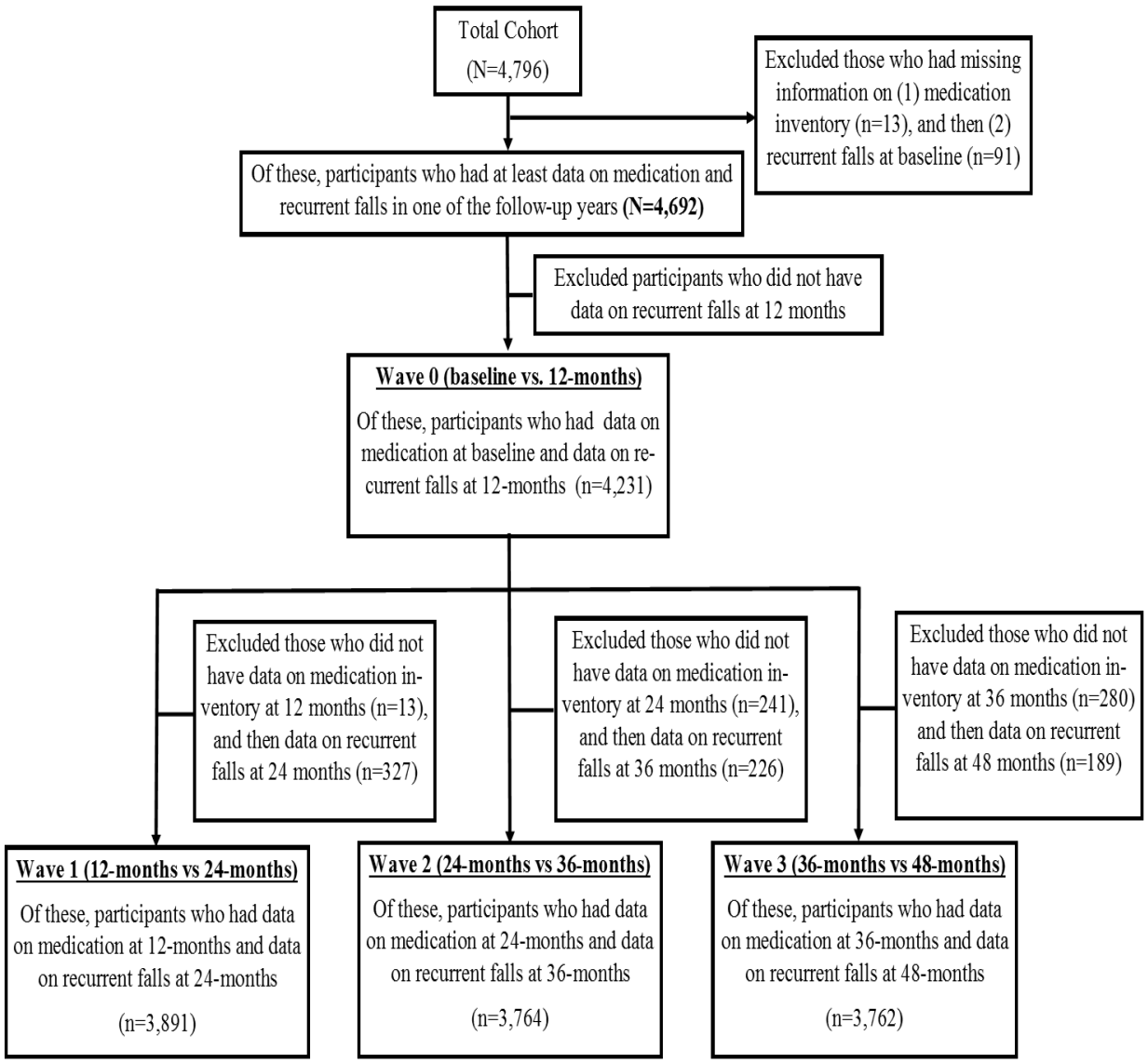
[e] Observations with any missing covariates were not included in multivariate analyses.

**eTable 6. Association between Analgesic Use and Recurrent Falls: Full Models with Other Covariates**

| Variable | $RR_{adj}$ (95% CI) | P value |
|---|---|---|
| **Analgesic groups (ref=no pain medications)** | **N=3,239[a]** | |
| Opioids | 1.22 (1.04, 1.45) | 0.02 |
| Antidepressants | 1.25 (1.10, 1.41) | <0.0001 |
| Prescription pain medications | 1.08 (0.95, 1.23) | 0.25 |
| OTC pain medications | 1.13 (1.00, 1.28) | 0.05 |
| Nutraceuticals | 1.13 (0.99, 1.28) | 0.05 |
| **Demographics** | | |
| Age, year (ever one unit) | 1.00 (0.99, 1.00) | 0.44 |
| Male (ref=female) | 1.03 (0.99, 1.08) | 0.19 |
| White (ref=non-white) | 1.08 (1.02, 1.15) | 0.007 |
| Married (ref=not married) | 0.95 (0.91, 0.99) | 0.02 |
| Having education Some college/postsecondary (ref=<high school or high school graduate) | 0.94 (0.88, 1.00) | 0.06 |
| **Health status/behavioral actors** | | |
| Charlson's comorbidity index (every one unit increase) | 1.05 (1.01, 1.09) | 0.007 |
| K/L grade (worst knee; reference: 0-1) | | |
| 2-3 | 1.02 (0.93, 1.11) | 0.67 |
| 4 | 1.03 (0.96, 1.11) | 0.39 |
| History of knee surgery | 1.00 (0.96, 1.05) | 0.88 |
| History of falls in the previous year | 2.14 (2.04, 2.24) | <0.0001 |
| Taken bisphosphonate for osteoporosis | 0.99 (0.94, 1.06) | 0.86 |
| BMI, $kg/m^2$ (every one unit) | 1.00 (1.00, 1.01) | 0.38 |
| Depression (CES-D ≥16) | 0.99 (0.93, 1.06) | 0.77 |
| Short Form-12 health survey score (every unit increase) | | |
| Physical health | 0.99 (0.98, 0.99) | <0.0001 |
| Mental health | 0.99 (0.98, 0.99) | <0.0001 |
| PASE (every unit increase) | 1.0008 (1.000, 1.001) | 0.001 |
| KOOS score (every unit increase) | | |
| Quality of Life | 1.00 (1.00, 1.00) | 0.91 |
| Pain | 1.00 (0.99, 1.00) | 0.50 |
| Symptoms | 1.00 (1.00, 1.00) | 0.61 |
| Pain NRS severity on the worst knee (every unit increase) | 1.00 (0.98, 1.03) | 0.78 |
| Any anticholinergic use | 1.07 (1.02, 1.13) | 0.01 |
| Any diuretics use | 0.94 (0.89, 0.99) | 0.02 |
| Number of other prescriptions, mean (SD) | 1.01 (0.99, 1.03) | 0.24 |

**Abbreviations**: **BMI**: body mass index; **KOOS:** Knee Injury and Osteoarthritis Outcome Score; **NRS**, numerical rating scale; **NSAIDs**: non-steroidal anti-inflammatory drugs; **PASE**: Physical activity scale for the elderly; **SD**: standard deviation; **OTC**: over the counter.

[a] Observations with any missing covariates were not included in multivariate analyses.




**eFigure 1. Sample Size Flow Chart**