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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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SUMMARY

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

Methods: A longitudinal analysis included 4231 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 (CNS) potency: use of (1) opioids, (2) antidepressants, (3) other prescription pain medications, (4) over-the-counter (OTC) 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 who 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 used 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.

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Introduction

Symptomatic knee osteoarthritis (OA) affects more than 9.3 million adults and is the leading cause of disability and lost work-days 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

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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 4796 persons aged 45–79 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 4231 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 (e.g., 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 eFig. 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) OTC pain medications (i.e., no opioids/antidepressants/other prescription pain medications, but OTC NSAIDs or acetaminophen); (5) nutraceuticals including chondroitin, glucosamine, MSM, or S-adenosyl-L-methionine (SAMe); and (6) no pain medication use (see Supplemental 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 literature[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