ACR Open Rheumatology
Vol. 1, No. 6, August 2019, pp 359–364
DOI 10.1002/acr2.11058

American College of Rheumatology
Empowering Rheumatology Professionals

BRIEF REPORT

Adults With Incident Accelerated Knee Osteoarthritis Are More Likely to Use Pharmacological Treatment Options and Receive Arthroscopic Knee Surgery: Data From the Osteoarthritis Initiative

Julie E. Davis,[1] Matthew S. Harkey,[2] Shao-Hsien Liu,[3] Kate Lapane,[3] Lori Lyn Price,[4] Bing Lu,[5] Grace H. Lo,[6] Charles B. Eaton,[7] Mary F. Barbe,[8] Timothy E. McAlindon,[9] and Jeffrey B. Driban[9]

Objective. To determine if people with incident accelerated knee osteoarthritis (AKOA) were more likely to receive a pharmacological treatment or arthroscopic knee surgery than those with typical knee osteoarthritis (KOA) or no KOA.

Methods. We conducted a nested cohort study using data from baseline and the first 8 years of the Osteoarthritis Initiative. Eligible participants had no radiographic KOA at baseline (Kellgren-Lawrence [KL] < 2). We classified three groups using KL grades: 1) AKOA: knee progressed to advanced-stage KOA (KL 3/4) in 4 years or less, 2) typical KOA: knee increased in KL grade by 8 years (excluding AKOA), and 3) No KOA: no change in KL grade by 8 years. The outcome was self-reported arthroscopic knee surgery or a pharmacological treatment option: nonsteroidal anti-inflammatory drugs (NSAIDs), hyaluronic acid injections, intra-articular corticosteroid injections, or prescription analgesics. Between-group differences in therapeutic use were evaluated with Chi-square tests.

Results. Adults who developed AKOA (n = 92) were more likely to report arthroscopic knee surgery (AKOA: 32%, KOA [n = 380]: 8%, no KOA [n = 875]: 3%; $P < 0.001$), hyaluronic acid injections (AKOA: 10%, KOA: 4%, no KOA: 1%; $P < 0.001$), intra-articular corticosteroid injections (AKOA: 30%, KOA: 7%, no KOA: 4%; $P < 0.001$), and NSAID use (over the counter: AKOA: 65%, KOA: 48%, and no KOA: 46%; $P = 0.003$; prescription: AKOA: 61%, KOA: 43%, no KOA: 41%; $P = 0.002$).

Conclusion. Adults with AKOA are more likely to receive pharmacological treatment or arthroscopic knee surgery than their peers. Adults with AKOA are an important patient population that is understudied in clinical research despite their use of greater health care resources.

The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs. The following was prepared using an Osteoarthritis Initiative public use data set and does not necessarily reflect the opinions or views of the Osteoarthritis Initiative investigators, the NIH, or the private funding partners.

These analyses were financially supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the NIH under Award R01 AR065977. The Osteoarthritis Initiative is a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the NIH, a branch of the Department of Health and Human Services, and conducted by the Osteoarthritis Initiative Study Investigators. Private funding partners include Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc. Private sector funding for the Osteoarthritis Initiative is managed by the Foundation for the National Institutes of Health. Dr. Lo is supported by K23 AR062127, an NIH/NIAMS-funded mentored award, providing support for design and conduct of the study, analysis, and interpretation of the data. This work is supported in part with resources at the VA Health Services Research and Development Center for Innovations in Quality, Effectiveness and Safety (CIN 13-413) at the Michael E. DeBakey VA Medical Center (Houston, TX). Dr. Harkey was supported by the NIH (grant TL1 TR001454).

[1]Julie E. Davis, BS: George Washington University, Washington, DC; [2]Matthew S. Harkey, PhD, ATC: Tufts Medical Center, Boston, Massachusetts, and University of Massachusetts Medical School Worcester, Massachusetts; [3]Shao-Hsien Liu, PhD, Kate Lapane, PhD: University of Massachusetts Medical School, Worcester, Massachusetts; [4]Lori Lyn Price, MAS, MLA: Tufts Medical Center, Boston, Massachusetts and Tufts University, Boston, Massachusetts; [5]Bing Lu, MD, DrPH: Brigham & Women's Hospital and Harvard Medical School, Boston, Massachusetts; [6]Grace H. Lo, MD, MSc: Houston Health Services Research and Development (HSR&D) Center of Excellence, Houston, Texas and Baylor College of Medicine, Houston, Texas; [7]Charles B. Eaton, MD, MS: Alpert Medical School of Brown University, Pawtucket, Rhode Island; [8]Mary F. Barbe, PhD: Temple University School of Medicine, Philadelphia, Pennsylvania; [9]Timothy E. McAlindon, MD, MPH, Jeffrey B. Driban, PhD, ATC, CSCS: Tufts Medical Center, Boston, Massachusetts.

Dr. Driban reports personal fees from Pfizer Inc., outside the submitted work for provided lectures.

Address all correspondence to Jeffrey Driban, PhD, ATC, CSCS, Division of Rheumatology, Allergy, & Immunology, Tufts Medical Center, 800 Washington Street, Box 406, Boston, MA 02111. E-mail: Jeffrey.Driban@tufts.edu.

Submitted for publication January 29, 2019; accepted in revised form June 28, 2019.

INTRODUCTION

Knee osteoarthritis (KOA) is typically a slowly progressive disorder. However, accelerated KOA (AKOA) is a subset of KOA that is characterized by a rapid onset and progression of disease within 4 years (from preradiographic disease to advanced-stage disease) and often in as little as 12 months (1–3). Adults with AKOA report greater pain and functional limitations up to 3 years prior to the onset of radiographic disease compared with those with a more common, gradual onset of KOA (typical KOA) (2,4). Additionally, individuals who developed AKOA were ~25 times more likely to receive a knee replacement than those who developed incident typical KOA (5). Given that adults with AKOA experience more severe and early symptoms, they may be more likely to seek other surgical or pharmacological interventions as treatment options, even prior to the onset of disease.

Unfortunately, it remains unclear how adults who develop AKOA use pharmacological treatments (eg, over the counter or prescription nonsteroidal anti-inflammatory drugs [NSAID], intra-articular injections) or arthroscopic knee surgery before, during, and after disease onset compared with those who develop typical KOA or no KOA. Because adults with AKOA report greater pain and dysfunction even prior to the onset of disease, we hypothesized that adults with AKOA were more likely to receive a pharmacological treatment or arthroscopic knee surgery than those who develop typical KOA or no KOA, even prior to disease onset. Therefore, our primary purpose was to determine if those with incident AKOA were more likely to receive pharmacological or surgical treatment than those with incident typical KOA or no KOA. Secondarily, we sought to determine if individuals who developed AKOA received more pharmacological or surgical treatments prior to the onset of disease than their peers who developed typical KOA.

METHODS

We conducted a nested cohort study using data from baseline and the first 8 years of the Osteoarthritis Initiative (OAI). The OAI is a multicenter cohort study of 4796 adults with or at risk for symptomatic KOA. Staff at four clinical sites (Memorial Hospital of Rhode Island, The Ohio State University, University of Maryland and Johns Hopkins University, and the University of Pittsburgh) recruited participants between 2004 and 2006. OAI data, images, and protocols are publicly available (6). Institutional review boards at all OAI clinical sites and coordinating center (University of California, San Francisco) approved the study. The OAI has been approved and the study protocol is in compliance with the ethical guidelines of the 1975 Declaration of Helsinki. Institutional review boards at each OAI clinical site and the OAI coordinating center (University of California, San Francisco) approved the OAI study. All participants provided informed consent prior to participation.

For our primary analysis, we considered any pharmacological or surgical treatment option during the first 8 years of the OAI, regardless of timing of disease onset. We performed one secondary analysis by examining the pharmacological or surgical treatment options prior to disease onset among those with incident AKOA or typical KOA.

Participants. For our primary analysis, we included participants with no radiographic KOA (Kellgren-Lawrence [KL] less than 2) and no knee replacement at baseline (n = 1935) to assess whether adults who developed AKOA received pharmacological or surgical treatment more than those who developed typical KOA or remained with no KOA. We classified three groups using KL grades from the first 8 years of the OAI: 1) AKOA: at least one knee progressed to advanced-stage KOA (KL 3 or 4) in 4 years or less, 2) typical KOA: at least one knee with any increase in KL grade (excluding those with AKOA), and 3) No KOA: no change in KL grade by 8 years (3,5).

Index Visit. For individuals who developed accelerated or typical KOA, the index visit was defined as the visit when a person met the definition for accelerated or typical KOA (12-, 24-, 36-, or 48-, 72-, or 96-month OAI visit).

Index Knee. For analyses with arthroscopic knee surgery or injections, the index knee was defined as the first knee to develop AKOA or typical KOA. For individuals with no KOA, we considered surgery or injections to either knee.

Knee Radiographs. Bilateral weight-bearing, fixed-flexion posteroanterior knee radiographs were obtained at baseline and the first four annual follow-up visits as well as at the 6- and 8-year follow-up visits. Blinded central readers recorded KL grades (0 to 4). The interrater agreement for the KL grades was good (weighted kappa = 0.70-0.80) (6). For baseline and the first four annual readings, we primarily used KL readings in the OAI read project 15 (files: kXR_SQ_BU##_SAS [versions 0.8, 1.8, 3.7, 5.7, 6.5]). Because the 6- and 8-year follow-up images were read separately from the initial readings (read projects: 37/42; files: kXR_SQ_BU##_SAS [versions 8.2 and 10.2]), we used 13 criteria to harmonize KL readings across read projects (see Supplementary Material for criteria).

Self-Reported Arthroscopic Knee Surgery. Arthroscopic knee surgery was self-reported at each follow-up visit in response to a question for the right and left knee: “Since your last annual visit to the OAI clinic, did you have arthroscopy (where they put a scope) in your right knee?”. A similar question was asked for the left knee. We defined arthroscopic knee surgery as an affirmative response to an arthroscopy for the index knee during the observation period.

Self-Reported Pharmacological Treatment. *NSAIDS and injections.* At baseline and each follow-up visit, participants reported the use of nonprescription NSAIDs or knee injection (eg, hyaluronic acid [HA], intra-articular corticosteroid [IACS]). For nonprescription NSAID use, study staff asked: "During the past 30 days, have you used any of the following medications for joint pain or arthritis on most days? By most days, we mean more than half the days of the month….Non-steroidal anti-inflammatory drugs, also called NSAIDs, that you can get without a prescription, such as Aspirin, Ibuprofen (Advil, Nuprin, Motrin), or Naproxen (Aleve)?" They then checked: "yes," "no," "don't know," or "refused." (6) For knee injections, study staff asked at each follow-up visit: "During the past 6 months, have you had any injections in either of your knees for treatment of arthritis?" If the participant responded "yes", then they were asked two follow-up questions: 1) "During the past 6 months, have you had an injection of hyaluronic acid (ie, HA; Synvisic or Hyalgan) in either knee of your knees for treatment of your arthritis? These injections are given in a series of 3 to 5 weekly injections" and 2) "During the past 6 months, have you had an injection of steroids (cortisone, corticosteroids) in either of your knees for treatment of your arthritis?" If the participant responded "yes" to either question, then they were asked "In which knee?" and the participant could reply: "right", "left", "both knees," or "don't know".

Nutraceuticals. At baseline and each follow-up visit, participants recorded the use of nutraceuticals (ie, chondroitin sulfate, glucosamine). Study staff asked: "During the past 6 months, did you use the following health supplements for joint pain or arthritis?" Chondroitin sulfate and glucosamine were the most common among users in the OAI and were combined because of the small percentage of users taking only one. For each chondroitin sulfate and glucosamine, they then checked: "yes," "no," "don't know," "or "refused."

Medication Inventory Form–Based Pharmacological Treatment. To assess use of prescription NSAIDs (eg, ibuprofen, naproxen), narcotics (eg, hydrocodone, codeine), and other analgesics (eg, acetaminophen, celecoxib, aspirin), we used the publicly available OAI Medication Inventory Forms, which have been described in detail elsewhere (6,7). At each visit, participants were advised to bring all prescription medications used in the 30 days prior to the visit. An examiner recorded all the prescription medications. In the medication inventory form data files, the medications are coded based on the Iowa Drug Information Service (IDIS) database developed at the University of Iowa (8,9). We used OAI-provided indicator variables that noted when a person brought in a relevant class of medication. Specifically, we considered prescription NSAIDs (IDIS number: 28080400-28080540), prescription narcotics (IDIS number: 28080800-28080898, 48000063, 48000071, 48000072), and other prescription analgesics (IDIS number: 28081200-28081320). We also included in our analyses an overall prescription analgesic category that grouped together the prescription NSAIDs, narcotics, and other analgesics.

Other Clinical Variables. We extracted participant characteristics from the public OAI data files: age, sex, and body mass index (BMI) (Files: enrollees, v.23; allclinical00, v.0.2.2). All variables were collected based on standardized procedures, which are defined in the OAI protocols and available on the OAI website (6).

Statistical Analyses. After calculating basic descriptive statistics for the groups, we conducted a series of Chi-square tests to determine if use of pharmacological treatment or arthroscopic knee surgery differed among the three groups. When we conducted our secondary analysis, we performed Chi-square tests to determine if use of pharmacological treatment or arthroscopic knee surgery differed between adults who developed AKOA and typical KOA prior to the onset of disease (prior to index visit). For all analyses, we considered a *P* value less than 0.006 to be statistically significant (for eight comparisons). We performed all analyses in SAS Enterprise Guide 7.15.

RESULTS

Among 1935 participants without radiographic KOA at OAI baseline, we had sufficient longitudinal KL data to classify 1347 participants (69.6%). We identified 92 individuals with AKOA (63% female, 60.9 ± 8.8 years, BMI: 29.3 ± 4.8 kg/m^2), 380 with typical KOA (67% female, 58.7 ± 8.4 years, BMI: 27.8 ± 4.5 kg/m^2), and 875 with no KOA (52% female, 58.4 ± 8.6 years, BMI: 26.8 ± 4.4 kg/m^2). The most commonly used analgesic ingredients taken within the AKOA group were celecoxib, acetaminophen, and oxycodone. The typical KOA group used mainly naproxen, ibuprofen, and acetaminophen. Among those with no KOA, acetaminophen, celecoxib, and hydrocodone were the most commonly used analgesics.

Overall, those with AKOA were more likely to undergo an arthroscopic knee surgery (AKOA: 32% versus typical KOA: 8% or no KOA: 3%), receive HA injections (10% versus 4% or 1%) or IACS injections (30% versus 7% or 4%), or take nonprescription NSAIDs (65% versus 48% or 46%) or prescription analgesics (61% versus 43% or 41%), than those with typical KOA or no KOA, respectively (Table 1). Adults with AKOA were slightly more likely to take nutraceuticals than those with typical KOA or no KOA (68% versus 52% or 49%).

Prior to the index visit, those who developed AKOA were more likely to use other prescription analgesics (eg, acetaminophen, celecoxib, aspirin: 7% versus 1%) than those who went on to develop typical KOA, as well as receive an arthroscopic knee

Table 1. Surgical or pharmacological treatments over 8 years among accelerated knee osteoarthritis (AKOA), typical knee osteoarthritis (KOA), and no KOA

Treatment	No KOA (n = 875) n (%)	KOA (n = 380) n (%)	AKOA (n = 92) n (%)	Chi-Square *P* value
Arthroscopic Knee Surgery	25 (3%)	32 (8%)	29 (32%)	<0.001[b]
HA Injection	11 (1%)	14 (4%)	9 (10%)	<0.001[b]
IACS Injection	38 (4%)	26 (7%)	28 (30%)	<0.001[b]
NSAIDs (nonprescription)	405 (46%)	182 (48%)	60 (65%)	0.003[b]
Rx Analgesic[a]	363 (41%)	162 (43%)	56 (61%)	0.002[b]
Rx NSAIDs	194 (22%)	98 (26%)	31 (34%)	0.030
Rx Narcotic	122 (14%)	53 (14%)	19 (21%)	0.209
Rx Other Analgesics	68 (8%)	24 (6%)	9 (10%)	0.460
Nutraceuticals	425 (49%)	198 (52%)	63 (68%)	0.001[b]

Abbreviation: HA = hyaluronic acid, IACS= intra-articular corticosteroid, Rx = prescription, NSAIDs = nonsteroidal anti-inflammatory drugs.
All participants had no KOA in either knee at baseline. Median number of visits with self-reported data (out of nine possible visits): No KOA nine visits (fifth percentile: eight visits), KOA nine visits (fifth percentile: eight visits), AKOA eight visits (fifth percentile: seven visits). Less than 3% of participants in each group had missing data at three or more visits (n = 4 to 6 adults).
[a] Sample sizes do not add up for overall Rx analgesic because of individuals receiving multiple Rx's.
[b] Statistical significance defined as $P < 0.006$.

surgery (11% versus 4%; Table 2). We observed no other differences prior to disease onset.

DISCUSSION

Despite all participants starting with no radiographic KOA at baseline, adults that developed AKOA were more likely to receive pharmacological treatment or arthroscopic knee surgery over the subsequent 8 years than those with typical KOA or no KOA. Contrary to our hypothesis, differences in treatment use were typically not as apparent prior to disease onset, even though individuals with AKOA present with more severe symptoms prior to disease onset (2). This indicates that those with AKOA utilized treatment options and health care resources far more often than adults who developed typical KOA, likely because they quickly developed advanced-staged disease.

Table 2. Surgical or pharmacological treatments between baseline visit and disease onset

Treatment	KOA Prior to Progression (n = 338) n (%)	AKOA Prior to Progression (n = 92) n (%)	Chi-Square *P* value
Arthroscopic Knee Surgery[a]	10 (4%)	6 (11%)	0.041
HA Injection	7 (2%)	0 (0%)	0.181
IACS Injection	8 (2%)	7 (8%)	0.009
NSAIDs (nonprescription)	112 (33%)	34 (40%)	0.241
Rx Analgesic[b]	103 (30%)	33 (38%)	0.141
Rx NSAIDs	56 (17%)	17 (20%)	0.454
Rx Narcotic	24 (7%)	11 (13%)	0.081
Rx Other Analgesics[c]	5 (1%)	6 (7%)	0.004
Nutraceuticals	156 (46%)	40 (48%)	0.810

Abbreviation: AKOA, accelerated knee osteoarthritis; HA, hyaluronic acid; IACS, intra-articular corticosteroid; KOA, knee osteoarthritis; NSAIDs, nonsteroidal anti-inflammatory drugs; Rx, prescription.
Some participants had missing data that precluded an accurate assessment of the number of visits prior to progression. All participants had no KOA in either knee at baseline.
[a] Omits people who developed KOA or AKOA at 12-month follow-up.
[b] Sample sizes do not add up for overall Rx analgesic because of individuals receiving multiple Rx's.
[c] Statistical significance defined as $P < 0.006$.

Overall, adults with AKOA commonly received more treatments than their peers after disease onset, but not prior to disease onset. Previously, we observed that in the year before radiographic onset, individuals with AKOA experienced greater pain and dysfunction than adults who developed typical KOA (4). Although we observed no differences in most therapeutic options between groups prior to the onset of disease, prescription analgesic use was common in adults who developed typical KOA (30%) and AKOA (38%). This may support previous research showing that incident KOA, in general, is preceded by joint pain that may be sufficient enough to cause people to seek analgesic relief from a physician (4,10,11). The presence of prodromal symptoms and frequent use of prescription analgesics reinforce suggestions that researchers and clinicians need to develop and deploy more comprehensive treatment strategies that address the underlying risk factors and etiology rather than palliative care prior to disease onset.

Interestingly, individuals who developed AKOA were more likely to receive arthroscopic knee surgery, even prior to disease onset, compared with their peers, which may contribute to greater cost of health care for people who develop AKOA. The high rate of arthroscopic knee surgery may be related to knee injuries, especially injuries causing a destabilizing meniscal tear, that are a risk factor for AKOA (1,12,13). It may be prudent to more frequently examine patients during the first year or two after arthroscopic knee surgery for signs of AKOA.

A person with AKOA is more likely to receive a knee replacement than someone who develops typical KOA (5). This and the more frequent receipt of arthroscopic knee surgery reiterates previous findings that AKOA is a clinically significant and severe subset of KOA that increases the likelihood of seeking out surgical treatment options (2–5). Adults with AKOA may be an important patient population that is understudied in current clinical research and a particularly appealing population for early disease-modifying interventions that will slow, halt, or reverse the onset of radiographic KOA.

Although this study is an important step in characterizing the pharmacological and surgical treatments among adults with AKOA, we acknowledge there are limitations. First, it is unclear who provided the treatments and why the individual was treated with certain medications or received an arthroscopic knee surgery. Although this may lessen our ability to infer causation, we believe this indicates that people with AKOA are more likely to receive pharmacological or surgical treatment regardless of cause. Additionally, the OAI is not a population-based study and relies on self-reported surgery, injections, and nonprescription NSAID use. Despite this, the OAI provides a unique opportunity to explore how adults who develop AKOA, or other subsets of OA, may manage their joint symptoms. It also provided valuable insight into the use of pharmacological options prior to the onset of KOA.

Despite starting without radiographic KOA, adults with AKOA received more pharmacological or surgical treatments over 8 years than those who develop typical KOA or no KOA. Adults with AKOA are an important patient population that is understudied in clinical research despite their use of greater health care resources.

Contrary to our hypothesis, differences between AKOA and typical KOA in treatment use were less apparent prior to disease onset, except for arthroscopic knee surgery. It may be beneficial to frequently evaluate patients after arthroscopic knee surgery for signs of possible AKOA. Finally, prior to disease onset almost 1 in 3 people with incident KOA used prescription analgesics, which supports calls for researchers and clinicians to develop and deploy more comprehensive treatment strategies that address the underlying risk factors and etiology prior to disease onset.

AUTHOR CONTRIBUTIONS

Davis, Harkey, and Driban drafted and revised the article. Liu, Lapane, Price, Lu, Lo, Eaton, Barbe, and McAlindon revised the article. All authors provided final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Study conception and design. Liu, Lapane, Lu, Eaton, Barbe, McAlindon, Driban.

Acquisition of data. Eaton, McAlindon.

Analysis and interpretation of data. Davis, Harkey, Liu, Lapane, Price, Lu, Lo, Eaton, McAlindon, Driban.

REFERENCES

1. Driban JB, Eaton CB, Lo GH, Ward RJ, Lu B, McAlindon TE. Association of knee injuries with accelerated knee osteoarthritis progression: data from the Osteoarthritis Initiative. Arthritis Care Res (Hoboken) 2014;66:1673–9.
2. Driban JB, Price LL, Eaton CB, Lu B, Lo GH, Lapane KL, et al. Individuals with incident accelerated knee osteoarthritis have greater pain than those with common knee osteoarthritis progression: data from the Osteoarthritis Initiative. Clin Rheumatol 2016;35:1565–71.
3. Driban JB, Stout AC, Lo GH, Eaton CB, Price LL, Lu B, et al. Best performing definition of accelerated knee osteoarthritis: data from the Osteoarthritis Initiative. Ther Adv Musculoskelet Dis 2016;8:165–71.
4. Davis J, Eaton CB, Lo GH, Lu B, Price LL, McAlindon TE, et al. Knee symptoms among adults at risk for accelerated knee osteoarthritis: data from the Osteoarthritis Initiative. Clin Rheumatol 2017;36:1083–9.
5. Davis JE, Liu SH, Lapane K, Harkey MS, Price LL, Lu B, et al. Adults with incident accelerated knee osteoarthritis are more likely to receive a knee replacement: data from the Osteoarthritis Initiative. Clin Rheumatol 2018;37:1115–8.
6. Eckstein F, Wirth W, Nevitt MC. Recent advances in osteoarthritis imaging–the osteoarthritis initiative. Nat Rev Rheumatol 2012;8:622–30.
7. Driban JB, Lo GH, Eaton CB, Lapane KL, Nevitt M, Harvey WF, et al. Exploratory analysis of osteoarthritis progression among medication users: data from the Osteoarthritis Initiative. Ther Adv Musculoskelet Dis 2016;8:207–19.
8. Pahor M, Chrischilles EA, Guralnik JM, Brown SL, Wallace RB, Carbonin P. Drug data coding and analysis in epidemiologic studies. Eur J Epidemiol 1994;10:405–11.
9. Iowa Drug Information Services. IDIS Drug Vocabulary and Thesaurus Description. 2012. URL: http://citeseerx.ist.psu.edu/viewdoc/download;jsessionxml:id=63F7C4551D35213274A7983C7E934392?doi=10.1.1.674.2511&rep=rep1&type=pdf

10. Case R, Thomas E, Clarke E, Peat G. Prodromal symptoms in knee osteoarthritis: a nested case-control study using data from the Osteoarthritis Initiative. Osteoarthritis Cartilage 2015;23: 1083–9.
11. Hensor EM, Dube B, Kingsbury SR, Tennant A, Conaghan PG. Toward a clinical definition of early osteoarthritis: onset of patient-reported knee pain begins on stairs. Data from the osteoarthritis initiative. Arthritis Care Res (Hoboken) 2015;67:40–7.
12. Davis JE, Price LL, Lo GH, Eaton CB, McAlindon TE, Lu B, et al. A single recent injury is a potent risk factor for the development of accelerated knee osteoarthritis: data from the osteoarthritis initiative. Rheumatol Int 2017;37:1759–64.
13. Driban JB, Davis JE, Lu B, Price LL, Ward RJ, MacKay JW, et al. Accelerated knee osteoarthritis is characterized by destabilizing meniscal tears and preradiographic structural disease burden. Arthritis Rheumatol 2019;71:1089–100.