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Original article

Clinical comorbidities, treatment patterns, and direct medical costs of patients with osteoarthritis in usual care: a retrospective claims database analysis

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Abstract

Objective:
Comorbidities and resource utilization among patients with osteoarthritis (OA) in clinical practice have been infrequently characterized. The purpose of this study was to examine comorbidities, pain-related pharmacotherapy, and direct medical costs of patients with OA in clinical practice.

Method:
This retrospective cohort analysis used medical and pharmacy claims data from the LifeLink™ Database. OA patients (ICD-9-CM codes 715.XX) were matched (age, gender, and region) with individuals without OA. Comorbidities, pain-related pharmacotherapy, and direct medical costs (pharmacy, outpatient, inpatient, total) were examined for the calendar year 2008.

Results:
The sample consisted of 112,951 OA patients and 112,951 controls (mean age: 56.9 [SD = 9.5] years; 62% female). Relative to controls, OA patients were significantly more likely ($p < 0.0001$) to have comorbidities, including musculoskeletal (84.3 vs. 37.1%) and neuropathic pain (22.0 vs. 6.1%) conditions, depression (12.4 vs. 6.4%), anxiety (6.6 vs. 3.5%), and sleep disorders (11.9 vs. 4.2%). OA patients were significantly more likely ($p < 0.0001$) to receive pain-related medications, including opioids (40.7 vs. 17.1%), NSAIDs (37.1 vs. 11.5%), tramadol (9.8 vs. 1.8%), and adjunctive medications for treating depression, anxiety, and insomnia. Mean [SD] total direct medical costs were more than two times higher among OA patients ($12,905 [$21,884] vs. $5099 [$13,855]; $p < 0.001$) and median costs were more than three times higher ($6188 vs. $1879; $p < 0.0001$). Study limitations include potential errors in coding and recording; overestimation of the comorbidity burden; inability to link condition of interest, OA, with prescribed medications; and possible underestimation of the true costs of OA, because indirect costs were not considered and the direct costs were from a third party payer (commercial insurance) perspective.

Conclusion:
The patient burden of OA was characterized by a high prevalence of comorbidities. The payer burden was also substantial, with significantly greater use of pain-related and adjunctive medications, and higher direct medical costs.

Introduction

Osteoarthritis (OA), which has been estimated to occur in 27 million individuals in the United States (US)[1] and in 40.2 million individuals in Europe (WHO)[2], is ranked among the top three causes of disability in the US and is

among the top ten causes of disability worldwide[3,4]. There is limited information on the incidence rates of OA; with rates of knee OA reported between 0.19% and 0.25% in Europe and the US, respectively[5,6]. OA is also a costly disease, and indirect costs, most of which are derived from loss of work productivity and leisure time, have been reported to be the primary driver of total costs[7–9]. However, excess healthcare resource utilization relative to individuals without OA is responsible for a substantial proportion of the economic burden of OA[7–11]. These resources include not only pharmacologic and other therapies related to the OA diagnosis, but also management of treatment-related complications and surgery/rehabilitation.

Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) including the COX-2-specific NSAIDs are the mainstays of OA analgesic therapy and are considered first line agents[12,13], even though pain relief offered by these agents is often sub-optimal[13,14]. There is also a well-recognized risk of cardiovascular and gastrointestinal events associated with selective and nonselective NSAIDs[15–17], limiting their use in patients who may already have risk factors for these events. Furthermore, the use of adjunctive medications such as gastroprotective agents (e.g., proton pump inhibitors) are currently recommended as part of OA treatment guidelines to reduce the risk of NSAID-related side-effects[12,13]. Gastroprotective agents, which have been reported to be used in approximately one-third of OA patients taking NSAIDs, add to the pill burden of patients and substantially increase the cost of treatment; proton pump inhibitors account for up to 23% of pharmacy charges in patients treated for OA[11].

Although opioids have demonstrated efficacy in reducing OA pain, side-effects including somnolence, confusion, and constipation often cause patients to discontinue treatment[18]. Opioid-induced hyperalgesia has been suggested with long-term use, but this remains controversial[19]. The regulatory burden associated with opioid prescribing may also be intimidating from the prescribers' perspective, potentially presenting a barrier to adequate pain management[20–22]. Additionally, patient and physician concerns about opioid dependence, tolerance, and occasional addiction may limit opioid utility[23–27] with negative patient attitudes adding to the overall burden[28].

Numerous studies have explored the economic and comorbidity burden of OA[9,29–31], but the characterization of comorbidities and resource utilization in usual US clinical practice, especially related to pain-related pharmacotherapy prescribing patterns, have only recently begun to be explored[32]. Therefore, the purpose of this study was to determine the prevalence of comorbidities in patients with OA, and to evaluate how these patients are being treated in usual care settings relative to individuals without OA, including medications generally prescribed for the treatment of pain, overall healthcare resource utilization, and direct medical costs.

Methods

Data source

Data for the study were obtained from the LifeLink™ Health Plan Claims Database (IMS Incorporated, Watertown, MA, USA). The LifeLink database is comprised of adjudicated medical and pharmaceutical claims data from a systematic sample of over 98 commercial managed-care health plans throughout the United States (Midwest 34%, Northeast 22%, South 29%, West 15%) covering more than 61 million individuals and approximately 16 million covered lives per year. The data are nationally representative of the US population, quality controlled and HIPAA (Health Insurance Portability and Accountability Act of 1996) compliant. The database includes patient demographic and enrollment information; inpatient and outpatient diagnoses; surgeries and procedures; and retail and mail order prescription records (National Drug Code numbers, days supply, and quantity dispensed). Charges, allowed and paid amounts are available for all services rendered (inpatient and outpatient services as well as prescriptions), and dates of service are recorded for all claims. All records for each patient can be linked with a unique encrypted patient identifier (thereby maintaining patient confidentiality) to create a longitudinal record of the individual's medical and pharmacy claims during the period of evaluation.

Sample selection

All patients with at least one healthcare claim with an associated diagnosis of OA (ICD-9-CM code 715.XX) during each of calendar years (CY) 2007 and 2008 were identified. OA patients who were continuously enrolled during CY2008 were then selected. The continuous enrollment requirement was imposed to ensure that all healthcare claims for the study patients during the entire study period (January through December 2008) were represented. Patients were excluded if they were less than 18 years old, had missing data for age or gender, or were $\geq$65 years old and not enrolled in a Medicare supplemental or capitated plan since claims histories of these patients may be incomplete. The control group consisted of randomly selected individuals from the complete database without any healthcare claims for OA during their entire tenure in the database. Controls were matched 1:1 to OA patients based on age (exact year-to-year match), gender, and region. All inclusion and exclusion criteria used to select the OA study population were applied to the control group.

Measures evaluated

Demographic and clinical characteristics of OA patients and controls were examined, including age, gender and co-prevalence of selected chronic conditions including cardiovascular disorders, neuropsychiatric disorders, sleep disorders, and musculoskeletal pain conditions. The prevalence of comorbidities was determined based on the presence of one or more healthcare claims with an associated diagnosis code for the specific comorbidity during the study period. ICD-9-CM diagnoses codes used to define comorbidities examined in this study are described in Table 1.

Pain-related medication exposure was determined in terms of proportions of subjects who had one or more prescription claims for the various medication classes recommended for the treatment of OA[13,33]. Medications potentially used to treat sequelae of chronic pain such as anxiety/depression and sleep disorders were evaluated as was the use of combinations of various medication classes. The average numbers of prescriptions for each of the medication classes among users of these medications was also determined. The medication classes examined in this study included: opioids, non-selective NSAIDs, COX-2 inhibitors, salicylates, tramadol, acetaminophen, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), tetracyclic and miscellaneous antidepressants, benzodiazepines, sedatives and hypnotics, miscellaneous agents (e.g., butorphanol, nalbuphine, pentazocine), topical agents, and intramuscular botox.

Use of healthcare resources including intraarticular injections of corticosteroids or hyaluronic acid,

Table 1. Diagnostic codes used to identify relevant comorbidities.

Comorbidities	ICD-9-CM codes
Cardiovascular disorders	
Myocardial infarction	410.X, 412.X
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428.X
Peripheral vascular disease	093.0, 437.3, 440.X, 441.X, 443.1–443.9, 447.1, 557.1, 557.9, V43.4
Cerebrovascular disease	362.34, 430.X–438.X
Coronary heart disease	410.XX-414.XX
Hypertension	401.X
Hyperlipidemia	272.0, 272.1, 272.2, 272.4
Neuropsychiatric disorders	
Depression	296.2X, 296.3X, 300.4, 311
Bipolar disorder	296.4X, 296.5X, 296.6X, 296.7
Anxiety	300.00, 300.5, 300.09, 300.20, 300.22, 300.23, 300.29, 300.3, 308.3
Generalized anxiety disorder	300.02
Panic disorder	300.01, 300.21
Post-traumatic stress disorder	309.81
Psychosis	296.9X, 298.X
Sleep disorders	
Insomnia/sleep disorders	780.5X, 307.4X, 347.0X, 347.1X, V69.4
Sleep apnea	780.51, 780.53, 780.57
Diseases of the digestive system	
Irritable bowel syndrome	564.1
Gastroesophageal reflux disease	530.11, 530.81
Gastritis	535.00 – 535.5X
Duodenitis	535.6X
Other	520.5–530.10, 530.19–530.7, 530.82–530.9, 536.0–537.X, 540.0–543.X, 550.00–553.XX, 555.0–558.X, 560.XX, 562.00–562.01, 562.10–562.11, 564.2–569.2, 569.41–569.81, 569.84–577.9, 579.X
Musculoskeletal pain conditions	
Lupus	710
Diffuse diseases of connective tissue	710.1, 710.2, 710.3, 710.4, 710.5, 710.8, 710.9
Arthritis and other arthropathies	711.XX, 712.XX, 713.X, 714.4X, 714.8X, 714.9X, 716.XX, 717.XX, 718.XX, 719.XX
Rheumatoid arthritis	714.0, 714.1, 714.2
Low back pain	720.0, 720.1, 720.2, 721.3, 722.10, 722.32, 722.5, 722.83, 722.93, 724.00, 724.02, 724.2, 724.5, 724.6, 724.70, 724.71, 724.79, 738.4, 739.3, 739.4, 756.11, 756.12, 805.4, 805.6, 846.0, 846.1, 846.2, 846.3, 846.8, 846.9, 847.2, 847.3, 847.4
Back and neck pain, other than low back pain	720.81, 720.89, 720.9, 721.0, 721.2, 721.5, 721.6, 721.7, 721.8, 721.90, 722.11, 722.30, 722.31, 722.39, 722.4, 722.6, 722.80, 722.81, 722.82, 722.90, 722.91, 722.92, 723.X (except 723.4), 724.01, 724.1, 724.8, 724.9, 737.10, 737.11, 737.12, 737.19, 737.20, 737.21, 737.22, 737.29, 737.30, 756.10, 756.13, 756.14, 756.15, 756.16, 756.17, 756.19, 805.8, 847.9
Rheumatism, excluding the back	725–728.9, 729.3–729.9
Other	730.00–739.X

acupuncture, OA-related surgeries (knee and hip replacements and arthroscopies), assistive devices (e.g., walker, crutches, orthotics, wheel chair), physician office visits by specialty type (primary care, internal medicine, orthopedists, rheumatologists, anesthesiologists, and occupational/physical therapists), emergency room (ER) visits, hospitalizations, and use of other outpatient services (e.g., labs, radiology, imaging), and the direct medical costs of these healthcare resources (in US dollars) were examined for the OA and the control groups. Direct costs included amounts reimbursed by payers as well as patient co-pays. All study measures were evaluated for the calendar year 2008 for the OA and control groups.

Statistical analysis

Descriptive statistics (numbers and percents for categorical variables; means with standard deviations [SD] and medians with interquartile ranges [IQR] for continuous variables) were used to evaluate the different variables as appropriate. Fisher's exact tests were used to evaluate the differences between OA patients and controls in the prevalence of comorbidities and percent exposure to pain-related medications. Analysis of covariance models with age and gender as covariates were used to calculate the statistical significance of differences between the OA and control groups in the magnitude of prescription and healthcare resource use. Because cost data are highly skewed, the non-parametric Kruskal–Wallis test was used to compare cost differences between the OA and control groups. Odds ratios (OR) with 95% confidence intervals (95% CI) provided an estimate of relative risk. Because matching the OA and control groups violated the assumption of independence of samples, bootstrapping with 2000 repetitions was used to generate bias-corrected 95% CIs around the point estimates as well as providing *p*-values using the bootstrapped *t*-tests. A *p*-value <0.05 was considered statistically significant. All analyses were performed using the SAS software system, PC version 8.0 (SAS Institute Inc., Cary, NC, USA).

Results

Demographic and clinical characteristics

A total of 112,951 patients with OA satisfied all the study entry criteria and were included in the analyses. The control group comprised a 1:1 age, gender and region match to the OA group. In both cohorts, 62% of patients were female and the mean age was 56.9 ± 9.5 years; more than half (53%) were between 55 and 64 years of age, and 10% were $\geq$65 years. In the OA cohort, nearly half (47.6%) of the patients had OA of the lower leg, 11.9% had OA of the pelvic/thigh region and 46.8% had other types of OA; summation to >100% indicates that some patients had OA in more than one body region.

The prevalence of all the examined comorbidities was significantly higher ($p<0.0001$) in patients with OA compared to controls (Table 2), with ORs that ranged from 1.55 (95% CI 1.55, 1.56) for posttraumatic stress disorder to 11.65 (95% CI 11.64, 11.65) for arthritis and arthropathies other than OA. The most prevalent comorbidities in the OA group were arthritis and arthropathies other than OA (62%), hypertension (54.4%), hyperlipidemia (52.1%), rheumatism (49.3%), and low back pain (32.5%). The prevalence rates of common sequelae of chronic pain were, depression (12.4%), anxiety (6.6%) and sleep disorders (11.9%) with OA patients having a 2.1-, 1.7- and 3.1-fold higher likelihood of these comorbidities, respectively, than controls.

Pain-related treatment patterns

Exposure to pain-related treatments and adjunctive medications among OA patients and controls is described in Table 3 and results suggest that OA patients were characterized by a high burden of medications generally prescribed for the treatment of pain. Except for intramuscular botox (not statistically significant), significantly higher proportions of OA patients ($p<0.0001$) received the evaluated pain-related medications compared to controls during the study period. These medications included any opioids (40.7 vs. 17.1%; $p<0.0001$), any NSAIDs (37.1 vs. 11.5%; $p<0.0001$), prescription acetaminophen (1.3 vs. 0.8%; $p<0.0001$) and tramadol (9.8 vs. 1.8%; $p<0.0001$). Relative to the control cohort, the likelihood of an OA patient receiving a pain-related medication ranged from 1.7-fold higher for acetaminophen to 7.8-fold higher for long-acting opioids. Many OA patients were also prescribed 'adjunctive' medications often used to treat conditions associated with pain such as depression, anxiety, and insomnia.

Nearly two-thirds of OA patients (62%) compared to a little over one-third (37.4%) of controls were prescribed at least one of the evaluated pain-related or adjunctive medications, whereas 26.7% vs. 7.9% received $\geq$3 of the evaluated pain-related or adjunctive medications ($p<0.0001$). Combination therapy was consistently higher ($p<0.0001$) in OA patients compared to controls, with prescription combinations of pain and adjunctive medications reported for more than one-third (38%) of patients in the OA group and 12.6% of individuals in the control group. The most frequent combinations in the OA group were NSAIDS + opioids (19.1%), followed by opioids + antidepressants (14.3%).

Except for antidepressants, OA patients received a significantly greater number of prescriptions (mean [SD; median, IQR]) for a majority of the evaluated medications

Table 2. Prevalence of specific chronic comorbidities in osteoarthritis (OA) patients and controls.

Comorbid diagnosis*	*n* (%)		Odds ratio (95% CI)	*p*-value†
	OA (*n* = 112,951)	Control (*n* = 112,951)		
Cardiovascular disorders				
Myocardial infarction	1,619 (1.4)	970 (0.9)	1.68 (1.68, 1.68)	<0.0001
Congestive heart failure	4,286 (3.8)	1,945 (1.7)	2.25 (2.25, 2.25)	<0.0001
Peripheral vascular disease	5,927 (5.2)	2,602 (2.3)	2.35 (2.35, 2.35)	<0.0001
Cerebrovascular disease	5,588 (4.9)	3,098 (2.7)	1.85 (1.84, 1.85)	<0.0001
Coronary heart disease	11,998 (10.6)	6,489 (5.7)	1.95 (1.95, 1.95)	<0.0001
Hypertension	61,458 (54.4)	35,263 (31.2)	2.63 (2.63, 2.63)	<0.0001
Hyperlipidemia	58,891 (52.1)	37,549 (33.2)	2.19 (2.19, 2.19)	<0.0001
Neuropsychiatric disorders				
Depression	14,051 (12.4)	7,267 (6.4)	2.07 (2.06, 2.07)	<0.0001
Bipolar disorder	766 (0.7)	394 (0.3)	1.95 (1.95, 1.96)	<0.0001
Anxiety	7,431 (6.6)	3,939 (3.5)	1.95 (1.95, 1.95)	<0.0001
Generalized anxiety disorder	2,228 (2.0)	1,306 (1.2)	1.72 (1.72, 1.72)	<0.0001
Panic disorder	931 (0.8)	501 (0.4)	1.87 (1.87, 2.00)	<0.0001
Posttraumatic stress disorder	482 (0.4)	310 (0.3)	1.55 (1.55, 1.56)	<0.0001
Psychosis	865 (0.8)	490 (0.4)	1.77 (1.77, 1.77)	<0.0001
Sleep disorders				
Insomnia/sleep disorders	13,409 (11.9)	4,735 (4.2)	3.08 (3.08, 3.08)	<0.0001
Sleep apnea	7,381 (6.5)	2,024 (1.8)	3.83 (3.82, 3.84)	<0.0001
Diseases of the digestive system				
Irritable bowel syndrome	2,708 (2.4)	980 (0.9)	2.80 (2.80, 2.81)	<0.0001
Gastroesophageal reflux disease	20,432 (18.1)	7,392 (6.5)	3.15 (3.00, 3.16)	<0.0001
Gastritis	6,235 (5.5)	2,271 (2.0)	2.84 (2.84, 2.85)	<0.0001
Duodenitis	491 (0.4)	260 (0.2)	1.89 (1.89, 1.90)	<0.0001
Other	24,734 (21.9)	14,433 (12.8)	1.91 (1.91, 1.91)	<0.0001
Musculoskeletal pain conditions				
Lupus	1,121 (1.0)	165 (0.1)	6.85 (6.83, 6.87)	<0.0001
Diffuse diseases of connective tissue	826 (0.7)	115 (0.1)	7.22 (7.20, 7.26)	<0.0001
Arthritis and other arthropathies	69,992 (62.0)	13,858 (12.3)	11.65 (11.64, 11.66)	<0.0001
Rheumatoid arthritis	6,338 (5.6)	721 (0.6)	9.25 (9.24, 9.27)	<0.0001
Low back pain	36,658 (32.5)	13,740 (12.2)	3.47 (3.47, 3.47)	<0.0001
Back and neck pain, other than low back pain	23,020 (20.4)	7,986 (7.1)	3.36 (3.36, 3.37)	<0.0001
Rheumatism, excluding the back	55,667 (49.3)	17,842 (15.8)	5.18 (5.18, 5.18)	<0.0001
Other	32,059 (28.4)	14,878 (13.2)	2.61 (2.61, 2.61)	<0.0001

*Comorbidities defined as ≥1 claim(s) for each comorbidity during the study period.
†Fisher's exact tests.

during the study period compared to controls including (Table 4): any opioids (5.7 [6.9; 3, 1–7] among OA patients, 2.9 [4.6; 1, 1–2] among controls, $p < 0.0001$); any NSAIDs (3.9 [3.3; 3, 1.0–5.0] among OA patients, 2.3 [2.4; 1, 1.0–3.0] among controls, $p < 0.0001$); tramadol (3.5 [3.9; 2, 1–4] among OA patients, 2.8 [3.5; 1, 1–3] among controls, $p < 0.0001$); and benzodiazepines (4.9 [4.6; 3, 1–8] among OA patients, 4.4 [4.2; 2, 1–7] among controls, $p < 0.0001$).

Healthcare resource utilization and direct medical costs

All patients in the OA group and 91% of controls had at least one outpatient visit during the study period; 99.4% of OA patients and 86.5% of controls had at least one physician office visit; 21.1% of OA patients and 11.0% of controls had at least one ER visit; and 16.8% of OA patients and 5.4% of controls had at least one hospitalization during the study period. Nearly half of OA patients (48.4%) and 36.6% of controls had at least one visit to a primary care physician; half of OA patients and 6.1% of controls had at least one visit to orthopedists; and 17.3% of OA patients and 4.3% of controls had visits to physical therapists during the study period. The average number of physician office visits during the study period (Table 5) among OA patients was 14.3 (SD 13.2; median 10.0, IQR 6.0–18.0), compared with 5.9 (SD 7.7; median 4.0, IQR 2.0–8.0) among controls ($p < 0.0001$). Among users of these services, the average number of ER visits among OA patients were 1.7 (SD 2.0; median 1), compared to 1.4 (SD 0.9; median 1), among controls ($p < 0.0001$); and the average number of hospitalizations during the study period among OA patients were 5.5 (SD 8.0; median 3), compared with 5.5 (SD 9.1; median 3), among controls (not statistically significant).

Approximately one-third of OA patients (34%) received intraarticular injections, less than one percent (0.7%) reported receiving acupuncture, 13.3% had an OA-related surgery, and 19.1% used some type of an

Table 3. Proportions of osteoarthritis (OA) patients and controls using various pain-related medications.

Medications	*n* (%)		Odds ratio (95% CI)	*p*-value*
	OA (*n* = 112,951)	Control (*n* = 112,951)		
Long-acting opioids	4,677 (4.1)	626 (0.6)	7.75 (7.74, 7.77)	<0.0001
Short-acting opioids	45,588 (40.4)	19,261 (17.1)	3.29 (3.29, 3.29)	<0.0001
Strong opioids	19,527 (17.3)	5,438 (4.8)	4.13 (4.13, 4.14)	<0.0001
Weak opioids	38,128 (33.8)	16,262 (14.4)	3.03 (3.03, 3.03)	<0.0001
Any opioids	45,924 (40.7)	19,342 (17.1)	3.31 (3.31, 3.32)	<0.0001
COX-2 inhibitors†	9,592 (8.5)	1,383 (1.2)	7.48 (7.48, 7.50)	<0.0001
Non-selective NSAIDs	35,339 (31.3)	11,855 (10.5)	3.88 (3.88, 3.88)	<0.0001
Any NSAIDs	41,925 (37.1)	12,944 (11.5)	4.56 (4.56, 4.56)	<0.0001
Salicylates	770 (0.7)	382 (0.3)	2.02 (2.02, 2.03)	<0.0001
Tramadol	11,105 (9.8)	2,052 (1.8)	5.89 (5.89, 5.90)	<0.0001
Acetaminophen	1,423 (1.3)	846 (0.7)	1.69 (1.69, 1.69)	<0.0001
SSRIs	14,403 (12.8)	11,684 (10.3)	1.26 (1.27, 1.27)	<0.0001
SNRIs	6,044 (5.4)	2,931 (2.6)	2.12 (2.12, 2.12)	<0.0001
Tricyclic antidepressants	3,726 (3.3)	2,041 (1.8)	1.85 (1.85, 1.86)	<0.0001
Tetracyclic and miscellaneous antidepressants	6,553 (5.8)	4,721 (4.2)	1.41 (1.41, 1.41)	<0.0001
Benzodiazepines	15,360 (13.6)	10,276 (9.1)	1.57 (1.57, 1.57)	<0.0001
Sedative and hypnotics	10,825 (9.6)	5,946 (5.3)	1.91 (1.91, 1.91)	<0.0001
Miscellaneous agents	3,190 (2.8)	1,274 (1.1)	2.54 (2.54, 2.55)	<0.0001
Topical agents	3,039 (2.7)	464 (0.4)	6.70 (6.69, 6.72)	<0.0001
Intramuscular botox	12 (0.0)	15 (0.0)	0.8 (0.78, 0.82)	<0.0001

CI, confidence interval; COX, cyclooxygenase; NSAIDs, nonsteroidal anti-inflammatory drugs; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitor.
*Fisher's exact tests.
†Includes celecoxib only as other COX-2 inhibitors were not available in the US in 2008.

Table 4. Number of prescription claims for various pain-related medications among osteoarthritis (OA) patients and controls.

Medications	Number of prescriptions*				*p*-value†
	OA (*n* = 112,951)		Control (*n* = 112,951)		
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Long-acting opioids	6.1 (5.9)	3.0 (1.0–11.0)	6.9 (6.0)	5.0 (1.0–12.0)	0.0098
Short-acting opioids	5.1 (5.9)	3.0 (1.0–7.0)	2.7 (3.9)	1.0 (1.0–2.0)	<0.0001
Strong opioids	4.5 (6.4)	2.0 (1.0–5.0)	2.9 (5.0)	1.0 (1.0–2.0)	<0.0001
Weak opioids	4.5 (5.2)	2.0 (1.0–6.0)	2.5 (3.6)	1.0 (1.0–2.0)	<0.0001
Any opioids	5.7 (6.9)	3.0 (1.0–7.0)	2.9 (4.6)	1.0 (1.0–2.0)	<0.0001
COX-2 inhibitors‡	3.8 (3.3)	3.0 (1.0–5.0)	3.2 (3.2)	2.0 (1.0–4.0)	<0.0001
Non-selective NSAIDs	3.6 (3.2)	2.0 (1.0–5.0)	2.2 (2.2)	1.0 (1.0–2.0)	<0.0001
Any NSAIDs	3.9 (3.3)	3.0 (1.0–5.0)	2.3 (2.4)	1.0 (1.0–3.0)	<0.0001
Salicylates	3.3 (3.8)	2.0 (1.0–4.0)	3.5 (4.1)	2.0 (1.0–4.0)	0.3032
Tramadol	3.5 (3.9)	2.0 (1.0–4.0)	2.8 (3.5)	1.0 (1.0–3.0)	<0.0001
Acetaminophen	3.7 (4.5)	2.0 (1.0–4.0)	3.4 (4.9)	1.0 (1.0–3.0)	0.2865
SSRIs	5.9 (3.9)	5.0 (3.0–9.0)	6.3 (3.9)	6.0 (3.0–10.0)	<0.0001
SNRIs	6.2 (4.3)	5.0 (3.0–10.0)	6.7 (4.6)	6.0 (3.0–11.0)	0.0004
Tricyclic antidepressants	5.0 (4.1)	4.0 (1.0–8.0)	5.3 (4.3)	4.0 (1.0–9.0)	0.0381
Tetracyclic and miscellaneous antidepressants	5.7 (4.5)	4.0 (2.0–9.0)	5.8 (4.5)	4.0 (2.0–9.0)	0.4496
Benzodiazepines	4.9 (4.6)	3.0 (1.0–8.0)	4.4 (4.2)	2.0 (1.0–7.0)	<0.0001
Sedative and hypnotics	5.0 (4.5)	3.0 (1.0–8.0)	4.9 (4.7)	3.0 (1.0–7.0)	0.4038
Miscellaneous agents	2.3 (2.9)	1.0 (1.0–2.0)	2.2 (2.6)	1.0 (1.0–2.0)	0.3455
Topical agents	2.0 (1.8)	1.0 (1.0–2.0)	1.7 (1.5)	1.0 (1.0–2.0)	0.0165
Intramuscular botox	2.3 (1.9)	1.0 (1.0–3.0)	1.8 (0.9)	2.0 (1.0–2.0)	0.4199

COX, cyclooxygenase; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.
*Represents magnitude of use among users (individuals with at least one claim) of these medications only.
†Analysis of covariance models with age and gender as covariates.
‡Includes celecoxib only as other COX-2 inhibitors were not available in the US in 2008.

Table 5. Use of healthcare services among osteoarthritis (OA) patients and controls.

Resource use category	OA ($n=112,951$)			Control ($n=112,951$)			p-value*
	n (%)	Number of visits†		n (%)	Number of visits†		
		Mean (SD)	Median (IQR)		Mean (SD)	Median (IQR)	
Physician office visits							
GP/FP	54,690 (48.4)	4.1 (4.0)	3.0 (2.0–5.0)	41,313 (36.6)	2.5 (2.3)	2.0 (1.0–3.0)	<0.0001
Internal medicine	41,408 (36.7)	3.8 (3.8)	3.0 (2.0–5.0)	37,022 (32.8)	2.9 (3.4)	2.0 (1.0–3.0)	<0.0001
Orthopedists	56,392 (49.9)	2.8 (3.2)	2.0 (1.0–3.0)	6,888 (6.1)	2.0 (1.8)	1.0 (1.0–2.0)	<0.0001
Rheumatologist	15,640 (13.8)	3.0 (2.4)	2.0 (1.0–4.0)	1,549 (1.4)	2.7 (3.0)	2.0 (1.0–3.0)	0.0064
Neurologist	9,276 (8.2)	2.3 (2.1)	2.0 (1.0–3.0)	4,528 (4.0)	2.0 (1.5)	1.0 (1.0–2.0)	<0.0001
Anesthesiologists	2,651 (2.3)	3.0 (3.2)	2.0 (1.0–4.0)	373 (0.3)	2.3 (2.8)	1.0 (1.0–2.0)	0.0072
PT/OT/phys med	19,518 (17.3)	11.1 (11.9)	7.0 (2.0–16.0)	4,845 (4.3)	8.2 (9.1)	5.0 (2.0–11.0)	<0.0001
Any physician office visit	112,316 (99.4)	14.3 (13.2)	10.0 (6.0–18.0)	97,722 (86.5)	6.9 (7.9)	4.0 (2.0–8.0)	<0.0001
Emergency room visits	23,828 (21.1)	1.7 (2.0)	1.0 (1.0–2.0)	12,365 (10.9)	1.4 (0.9)	1.0 (1.0–1.0)	<0.0001
Other outpatient visits	111,610 (98.8)	12.7 (12.0)	9.0 (5.0–16.0)	96,976 (85.9)	6.3 (7.9)	4.0 (2.0–8.0)	<0.0001
Total outpatient visits	112,937 (100.0)	21.7 (18.0)	17.0 (9.0–29.0)	102,769 (91.0)	10.1 (11.3)	7.0 (3.0–13.0)	<0.0001
Hospitalizations	18,998 (16.8)	5.5 (8.0)	3.0 (2.0–6.0)	6,102 (5.4)	5.5 (9.1)	3.0 (2.0–6.0)	0.4051

GP/FP, general practice/family practice; IQR, interquartile range; PT/OT/Phys Med, Physical therapy/occupational therapy/physical medicine and rehabilitation.
*Analysis of covariance models with age and gender as covariates.
†Visits represent unique days of office visits.

Table 6. Direct medical costs of healthcare services among osteoarthritis (OA) patients and controls in US dollars ($) for the calendar year 2008.

Cost category	Costs ($)				p-value*
	OA ($n=112,951$)		Control ($n=112,951$)		
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
Medications	2,363.97 (6,041.30)	907.09 (100.20–2,643.30)	1,368.05 (5,078.03)	281.77 (2.5–1329.5)	<0.0001
Physician office visits	1,267.86 (1,493.41)	845.81 (449.90–1,559.90)	584.12 (820.86)	358.03 (136.6–722.6)	<0.0001
Emergency room visits	271.43 (1,109.28)	0 (0)	100.70 (469.02)	0 (0)	<0.0001
Other outpatient visits	4,964.67 (10,168.93)	2,185.17 (715.50–5,578.20)	1,882.37 (5,397.30)	491.26 (111.20–1,730.80)	<0.0001
Total outpatient visits	6,503.96 (10,892.66)	3,580.49 (1,498.70–7,646.00)	2,567.19 (5,831.51)	1,030.63 (345.00–2,685.80)	<0.0001
Hospitalizations	4,037.07 (15,022.74)	0 (0)	1,163.95 (8,751.73)	0 (0)	<0.0001
Total medical cost	12,905.00 (21,883.79)	6,187.58 (2,645.80–14,865.60)	5,099.19 (13,854.69)	1,879.02 (605.60–4,594.70)	<0.0001

*Kruskal–Wallis test.

assistive device during the study period. As would be expected, the proportions of patients undergoing OA-related surgeries and procedures were significantly higher ($p<0.0001$) in the OA group relative to controls (<0.5% except for intraarticular injections [2%]). Among OA patients who received intraarticular injections, over half (54.9%) received at least two injections compared to a majority (82.6%) of the controls who received only one such injection during the study period ($p<0.0001$); among users of acupuncture in the OA group, the mean number of sessions was 9.1 (SD 9.8) with a median of 6.0 (IQR 3.0–12.0), compared with a mean of 7.0 (SD 6.2) and a median of 5.0 (IQR 2.0–9.0) ($p<0.0001$) among controls.

As shown in Table 6, total medication costs (rounded to the nearest dollar) for the OA group (mean $2364 [SD $6041]; 95% confidence interval [CI] $2329–2399; median $907, IQR $100–2643) were significantly higher ($p<0.0001$) than controls (mean $1368 [SD $5078], 95% CI $1338–1398; median $282, IQR $3–1330). The direct costs of physician office visits, ER visits, outpatient visits, hospitalizations, and total direct medical costs during the study period were all significantly higher ($p<0.0001$) in the OA group compared with controls: physician office visits (OA: $1268 [SD $1493], 95% CI $1259–1277; controls: $584 [SD $821], 95% CI $579–589); ER visits (OA: $271 [SD $1109], 95% CI $265–278; controls: $101 [SD $469], 95% CI $98–103); other outpatient visits (OA: $4965 [SD $10,169], 95% CI $4905–5024; controls: $1882 [SD $5397], 95% CI $1851–1914); hospitalizations (OA: $4037 [$15,023], 95% CI $3949–4124; controls: $1164 [SD $8752], 95% CI $1113–1215); and total direct medical costs (OA: $12,905 [SD $21,884],

95% CI $12,777–13,032; controls: $5099 [SD $13,855], 95% CI $5018–5180).

Discussion

Despite the high prevalence of OA and its association with well-recognized patient and economic burdens, these burdens have been poorly characterized with regard to use of pain-related medications and other healthcare resources. The data presented here, from a large and geographically diverse population, demonstrate that patients with OA have significantly higher ($p<0.0001$) prevalence of comorbid conditions characterized by a substantial medication burden relative to age- and gender-matched controls from the same geographic regions.

Our observation of the presence of a variety of comorbidities across body systems and disease categories is consistent with other studies suggesting that patients presenting with OA are characterized by a high comorbidity burden that contributes to reduced function and increased mortality[32,34–36].

In particular, hypertension and hyperlipidemia were present in more than half of the OA patients compared with approximately one-third of controls. Since controls were matched for age, the higher prevalence of these comorbidities among the OA patients cannot be ascribed to older age. The reason for the increased odds of these comorbidities, as well as for other cardiovascular disorders is unclear, although an increased presence of metabolic syndrome has been reported in patients with OA, which may be further ascribed to the observed relationship between obesity and OA[5,37,38].

The cause–effect relationship between OA and other comorbidities has not been fully elucidated. However, increased sleep disturbances, present in 12% of our OA patients (OR 3.1), as well as depression (12%, OR 2.1) and anxiety (7%, OR 1.9) have previously been identified as factors impacting function and disability in OA patients[39–41]. The presence and importance of these comorbidities may in part relate to their reciprocal relationship with pain, especially in chronic pain conditions[42–47].

Regardless of causality, the increased presence of comorbid conditions among OA patients not only adds to the cost of treatment[10], but increases the complexity of managing these patients[48]. In the current study, this complexity was manifested by the significantly higher ($p<0.0001$) medication burden among patients with OA, and by the significantly greater ($p<0.0001$) proportion of these patients who were prescribed combinations of pain and adjunctive medications, including medications for insomnia and mood disorders. It is important to note that the total medication burden of patients with OA is likely to be underestimated in the current study because information contained in the database on medications was limited only to prescription medications. Consequently, it is not known to what extent these patients may have been taking over-the-counter medications for OA-related pain, which would further contribute to the medication and economic burden. Information on alternative treatments including acupuncture, physical therapy, vitamins, chondroitin and glucosamine, and related treatments was limited in the database because only treatments/services that were reimbursed by health insurance providers were captured, further compounding the potential underestimation of OA burden.

Opioids and opioid combinations were the most frequently prescribed medication class, exceeding even NSAIDs that are generally considered first-line. This high rate of opioid prescribing is in accord with other studies that have shown opioids to be the most frequently prescribed pain-related medications in patients with OA[11,32], with 68.4% being prescribed a short-acting opioid[32]. Opioids, especially short-acting opioids, are generally used as rescue pain medications or on an 'as needed' basis, and thus it is not surprising to see high rates of prescribing of these medications in patients with chronic pain conditions. Overall, in our study, there was a higher rate of prescribing of all evaluated pain-related medications among OA patients, and the number of prescriptions for these medications was also significantly higher ($p<0.05$) relative to controls.

The high rate of prescribing was paralleled by mean medication costs among OA patients nearly twice that of controls, and median costs more than 3-fold higher. High medication costs relative to matched individuals without OA have been reported elsewhere in the literature[49]. As in previous studies that reported high rates of healthcare utilization among OA patients[10,32,49], we observed substantial resource utilization significantly greater ($p<0.0001$) than controls across categories except for number of hospitalizations. Despite the comparable rate of hospitalizations (mean of 5.5 hospitalizations in both cohorts), the overall proportion of hospitalizations was higher (16.8 vs. 5.4%) and costs of hospitalizations among OA patients were nearly four times ($p<0.0001$) those of controls, potentially attributable to the higher rate of OA-related surgeries and procedures.

Patients with OA utilized significantly greater ($p<0.001$) outpatient resources than controls, including emergency room visits and physician office visits regardless of specialty, averaging nearly two outpatient visits each month during the study period. This resource utilization was reflected by significantly higher ($p<0.0001$) mean costs for these resource categories that were at least twice that of the control cohort. The mean annualized total direct medical costs (medications + inpatient + outpatient) for patients with OA, calculated at $12,905 per patient in CY 2008 dollars, was comparable to what has

been reported by White and *et al.*[32]: $11,542 for CY 2005 and $12,718 after adjusting for inflation. Our estimated costs were somewhat lower than the $19,938 recently reported by Dunn and Pill[11], who based their costs on submitted charges rather than reimbursed costs. However, consistent with Dunn and Pill[11], outpatient costs were the primary driver of direct medical costs.

The significantly higher costs and resource utilization among OA patients compared to controls, may in part be attributable to the treatment of comorbid conditions, factors related to overall health status including obesity (a significant risk factor for OA) for which information is not available in claims databases, or diagnoses and treatment of other underlying conditions (which may have otherwise remained undiagnosed) during physician office visits initiated by patients to address OA-related complaints. Conversely, persons in poorer health might also be more likely to seek healthcare and consequently more likely to be diagnosed with and treated for OA as well as other medical conditions contributing to higher costs and resource utilization among these patients. Further since insurance claims databases essentially constitute a de-identified longitudinal record of payments made to healthcare providers on behalf of patients, and the data are de-linked from patient medical charts, it is not possible to accurately attribute costs to any particular diagnosis or condition. Accordingly, although costs were higher among OA patients relative to non-OA controls, we cannot overemphasize that it is not possible to determine the proportion of these costs that are directly attributable to OA.

Limitations of the study

Since a retrospective insurance claims database was used in this study, it is important to consider the limitations associated with such a study design, including potential errors in coding and recording, which could potentially result in misclassification of diagnosis or miscoding. The code that we used, 715.XX, has consistently been used to identify OA cohorts in other database-based burden of illness studies[32,50–52]. Nevertheless, it is possible that some patients who in fact did not have OA were assigned this diagnosis as a result of misdiagnosis, miscoding, or ease by the practitioner for defining other diffuse acute or chronic pain conditions of unknown etiology. To minimize this possibility and increase specificity, we required that all OA patients have at least one diagnosis of OA in each of two consecutive years.

However, the comorbidity burden might be overestimated in our study, since the presence of comorbidities was identified based on one or more claims for each comorbidity during the 1-year study period. Thus, an individual who had only one claim with a specific comorbidity was included. However, if there was a potential coding or recording error on that claim, including this particular patient in the count for that specific comorbidity would represent an overestimation of the proportion of patients who had that comorbidity. Although this might be a potential limitation, any overestimation is likely to be random and unlikely to differentially affect either group, thus maintaining the validity of the reported differences in the comorbidity profiles between the two groups. Moreover, recently published studies describing the burden of OA using insurance claims databases have used a similar definition as in our study (one or more claims for each comorbidity during a specified period of time) thus rendering our findings consistent and comparable to the literature[32,52].

An additional limitation is the inability to link the condition of interest, OA, with the prescribing of a particular pain or adjunctive medication. While this may be relevant to populations characterized by multiple comorbidities, the data nevertheless suggest that regardless of prescribing reason, patients with OA had a significantly greater medication burden relative to the matched control cohort. A similar limitation is that since patient compliance cannot be ascertained in retrospective database studies, the prescribing of a particular medication does not necessarily imply that the patient actually took the medication as directed.

Another limitation stems from the inadequate representation of older individuals (≥65 years old) in all commercial insurance claims databases in the US, as is the case with the LifeLink database used in this study (10.3% of OA patients and controls in our study were ≥65 years old). Thus, the comorbidity profiles and economic burden in older adults with OA and a corresponding comparison group might be entirely different from that reported in our study, thereby restricting the generalizability of our findings. Also, since OA of the lower leg tends to occur at a later age, and can result in substantial costs and morbidity due to the need for knee replacement surgery in many patients, it is likely that costs in older OA patients are higher than those reported in our study. The average age of patients in our study (57 years) was slightly higher than the 51 and 55 years in the OA cohorts in two recently published studies utilizing claims data[32,52]. This difference in age is due to the fact that the LifeLink database does include some Medicare beneficiaries who participate in Medicare advantage plans and for whom it is possible to have complete claims histories.

Lastly, our study reports direct costs among OA patients and controls from the third party payer (commercial insurance) perspective. Since insurance companies often set reimbursement limits for physician, inpatient and outpatient services, it is not only possible but very likely that our study underestimates the true costs of OA from both societal and patient perspectives. Further, indirect costs due to absenteeism and presenteeism (lost productivity

on the job) that contribute substantially to the economic burden of OA[7–9,53,54], are also not reflected in our study.

Conclusions

Despite the above limitations, this study extends our knowledge of the burden of OA. The analyses presented here characterize OA patients with respect to the significantly greater frequency of comorbid conditions that are present relative to those without OA, as well as to the higher use of analgesic and adjunctive medications and resource utilization. These data may help inform clinical decisions regarding appropriate management strategies.

Transparency

Declaration of funding
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Declaration of interest
M.G. and K.-S.T. are employees of Avalon Health Solutions Inc, who were paid consultants to Pfizer in connection with the development of this manuscript; M.G. also owns stock in Pfizer. A.S. is an employee of Pfizer and owns stock in Pfizer. D.L. was paid an honorarium for his participation in this research and for his review and input to this article by Avalon Health Solutions, Inc; he has also performed consulting for Kurron Bermuda Ltd. B.S. has received consulting fees from Pfizer, Boehringer-Ingelheim, Endo Pharmaceuticals, and Astra Zeneca, and has received research support from Astra Zeneca and Pfizer.

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