Intra-articular Hyaluronic Acid for Osteoarthritis of the Knee in the United States: A Systematic Review of Economic Evaluations

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ABSTRACT

BACKGROUND: The economic impact of intra-articular hyaluronic acid (IAHA) for the treatment of knee pain associated with osteoarthritis (OA) has been evaluated in the United States, but not systematically summarized.

OBJECTIVE: We reviewed the literature to determine the economic impact of IAHA for pain associated with knee OA in the United States.

METHODS: A literature review was performed in PubMed (including MEDLINE and MEDLINE In-Process), Embase, the Cochrane Database of Systematic Reviews, and National Health Service Economic Evaluation Database and was limited to English language human studies published from January 2000 to October 2020.

RESULTS: The literature search identified 215 unique abstracts; of these, 47 were selected for full-text review and 21 studies met the inclusion criteria. Intra-articular hyaluronic acid injections delayed progression to total knee arthroplasty (TKA), and repeated courses of treatment successfully delayed TKA by more than 5 years. Intra-articular hyaluronic acid was found to reduce the use of pain medications overall and reduce the number of patients receiving opioid prescriptions by 6% ($P < .001$). Several studies showed that IAHA is more cost-effective in treating pain associated with knee OA compared with conventional care with nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, and corticosteroids, and several authors concluded that IAHA should be the dominant treatment strategy.

CONCLUSIONS: Current studies suggest that IAHA may reduce the use of pain medications, such as NSAIDs and opioids, and impact time to TKA procedures, thus potentially decreasing overall treatment costs of knee OA over time. Furthermore, IAHA was determined to be cost-effective against NSAIDs, corticosteroids, analgesics, and conservative treatment. As the safety and efficacy of IAHA for knee OA have been well established, the findings from our literature review may be used to inform future economic evaluations.

KEYWORDS: IAHA, economics, review, hyaluronan, knee osteoarthritis

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Introduction

Osteoarthritis (OA) is a degenerative joint disease characterized by joint pain and dysfunction that culminates in progressive articular cartilage loss.[1] No curative treatment exists for OA; therefore, the goals for treating OA of the knee are largely palliative and include approaches to relieve pain, slow progression, improve joint biomechanics, increase muscle strength and conditioning, delay total knee arthroplasty (TKA), and preserve functional independence, mobility, and quality of life.[2] Current treatments to alleviate pain and improve daily functioning and disability for patients with OA include physical therapy, weight loss, lifestyle changes, pharmacologic therapies, steroid injections, intra-articular hyaluronic acid (IAHA [also referred to as viscosupplementation]) injections, and surgery.[3,4]

Viscosupplementation with hyaluronic acid (HA) for OA treatment was approved by the US Food and Drug Administration (FDA) as a class III device for the treatment of knee pain associated with OA in 1997.[5,6] Endogenous HA, also referred to as hyaluronate or hyaluronan, is a high-molecular-weight (HMW) biopolymer that is produced by type B synoviocytes and synovial fibroblasts within the joint. The viscoelastic (rheological) properties of HA impart the ability of normal synovial fluid to act as a boundary lubricant and shock absorber to protect cartilage in the joint and permit near frictionless motion in the healthy state.[7] These properties of HA are essentially determined by 2 parameters: molecular weight (the average length of the HA polymer chains) and concentration in the fluid.[8] Patients with knee OA generally display a reduction in both parameters in the synovial fluid of the affected joint, and this loss in viscoelastic synovial fluid function is believed to represent a primary driver in the OA disease process.[8] Accordingly, the premise of viscosupplementation (the supplementation of synovial fluid with exogenous HA to improve the viscoelastic function of the synovial fluid) is to

provide HMW-HA at a concentration that is sufficient to generate a therapeutic effect. Since its initial approval in 1997, various HA formulations have been approved in the US market, including those that were avian and bacteriologically derived and those that were cross-linked.[9] The safety of IAHA is well established,[10] and several meta-analyses of the clinical effectiveness of IAHA have been published.[11-19]

Despite the preponderance of evidence for safety and efficacy, clinical practice guidelines are evolving away from recommendations for IAHA[20-22] in a manner that appears to be unfounded on current evidence. This evolution away from HA without clear alternative therapies has begun to limit patient access to IAHA, which may have significant economic impacts downstream. Many economic evaluations of IAHA for the treatment of knee pain in OA have been conducted, but not systematically summarized. The aim of this study was to systematically review economic evidence regarding the impact of IAHA as a treatment of pain associated with knee OA in the United States.

Methods

Data sources and selection

A flow chart of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) is presented in Figure 1. A literature review was performed in PubMed (including MEDLINE and MEDLINE In-Process), Embase, the Cochrane Database of Systematic Reviews, and the National Health Service Economic Evaluation Database (NHSEED). The database searches were limited to English language human studies published from January 2000 to October 2020. The review was limited to January 2000, as this date represents the timepoint shortly after IAHA was FDA-approved. The search terms included combinations of MeSH (Medical Subject Headings) terms and free text (Table 1).

The titles and abstracts (level 1) and full-text articles (level 2) were screened by 2 researchers using predetermined inclusion and exclusion criteria. Included studies were limited to those providing information on economic evaluations (ie, cost-effectiveness, cost utility, cost minimization, or other comparative economic analysis, and studies related to cost drivers or cost implications for IAHA in adults in the United States). Publications fulfilling the exclusion criteria (ie, those that did not report economic results or outcomes, were not conducted in the United States, were nonsystematic review or opinion articles, and did not report results or outcomes [eg, study design only]) were excluded. Bibliographies of review articles and included papers were reviewed to identify any additional economic publications. Relevant data (eg, study design, patient population, interventions, costs, and efficacy results) were extracted into a table from the selected full-text articles.

Results

The literature search identified 215 unique abstracts; of these, 47 were selected for full-text review and 21 studies met the selection criteria and were extracted (Figure 1). The included economic evaluations comprise 13 retrospective reviews of claims or electronic health records data, 1 cost-of-illness model, 6 cost-effectiveness analyses, and 2 cost-utility analyses.

Impact of IAHA on TKA

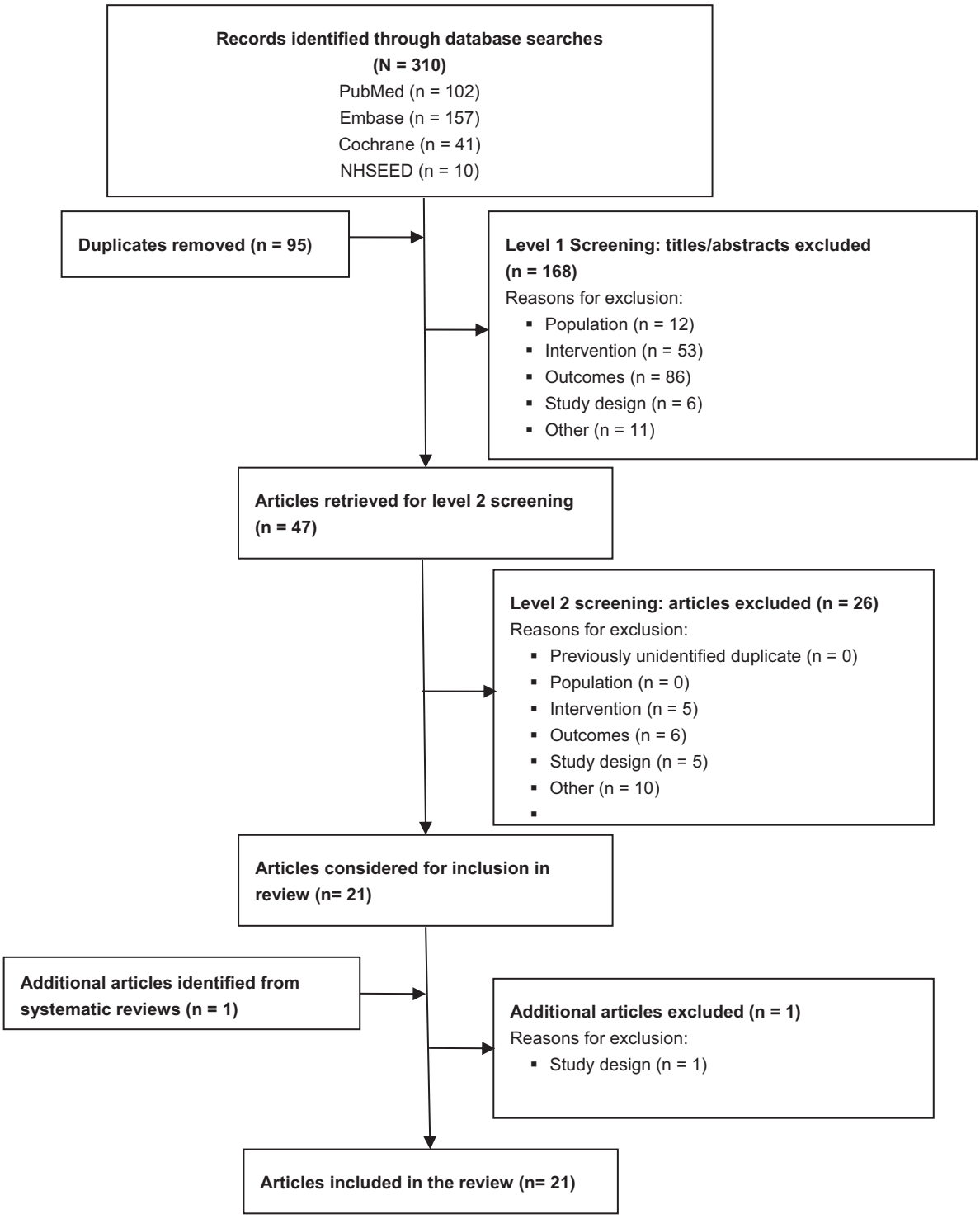
Several studies evaluated the impact of knee OA treatment with IAHA on time to TKA.[23-27] Each of these studies concluded that the use of IAHA is associated with longer time to TKA (Table 2). A retrospective analysis of data from 2006 to 2016 in the Optum Clinformatics database by Ong et al[25] reported a longer median time to TKA of ~7 months for those who received IAHA versus those who did not. Another retrospective analysis using data from 2007 through 2013 in the IMS Health PharMetrics Plus database found that the median time to TKA for those receiving IAHA was more than 4 times longer than it was for those who did not receive IAHA (median: 484 days vs 114 days; $P < .0001$).[23]

Furthermore, these studies also demonstrated that repeated courses of IAHA were associated with longer delays to TKA. Using data from 2007 to 2010 in the IMS Health PharMetrics Plus database, Dasa et al[24] determined that repeated courses of IAHA can delay TKA for up to 3 years. Specifically, the mean times to TKA for those receiving 1, 2, 3, 4, and ⩾5 courses of IAHA were 375.6, 617.6, 777.0, 855.6, and 971.5 days, respectively.[24] Ong et al[25] reported that the median time to TKA after 1 course of an avian-derived, cross-linked IAHA was 21 months (1.8 years); after ⩾5 courses, it was 59 months (4.9 years). The median time to TKA after 1 course of all other IAHA products reported in the data set was 20 months (1.7 years); after ⩾5 courses, it was 61 months (5.1 years). This finding was confirmed in a second retrospective analysis of the Optum Clinformatics database (data from 2006 to 2016) in which the median time from first IAHA treatment to TKA was ~6 months with 1 treatment and approximately 4 years with ⩾5 treatments.[27] Altman et al[23] found that IAHA injections are associated with dose-dependent increase in time to TKA: the mean time to TKA for patients receiving no IAHA was 0.7 years and was 3.6 years for patients who received ⩾5 courses.

Health care resource utilization

Pain management modalities commonly used in patients with knee OA include nonnarcotic analgesics (ie, acetaminophen), nonsteroidal anti-inflammatory drugs (NSAIDs), glucosamine and/or chondroitin sulfate, intra-articular corticosteroids (ICSs), and opioids (ie, tramadol). Inappropriate use of these modalities may be associated with side effects and may pose an economic burden to the health care system.[28-32]

Table 3 presents details on the health care resource utilization studies identified.[3,33-39] Intra-articular HA injection may reduce the use of pain medications (Table 3).[3,33] In a retrospective claims



NHSEED = National Health Service Economic Evaluation Database.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram. NHSEED indicates National Health Service Economic Evaluation Database.

analysis of patients who received their first IAHA injection between 2004 and 2011, McIntyre et al[3] found a 10% reduction in the average number of NSAID prescriptions filled and a 15% reduction in the number of patients receiving any NSAID prescription ($P < .001$). Furthermore, there was a 55% reduction in the average number of steroid injection prescriptions filled and a 57% reduction in the number of patients receiving any steroid prescription ($P < .001$). While the number of opioid prescriptions filled increased by 12%, the number of patients getting any opioid prescription fell by 6% ($P < .001$).

Another retrospective claims analysis of patients who received high-concentration non-avian HMW-HA injections

Table 1. Study search terms.

KEY TERM	MESH AND FREE-TEXT COMBINATION (EXAMPLES)
Knee OA	"osteoarthritis, knee"[Majr], "osteoarthriti*[Title] AND knee*[Title]"
Hyaluronic acid	"Viscosupplements"[Majr], "Viscosupplements"[Pharmacological Action], "Viscosupplementation"[Majr]
Economics	"Costs and Cost Analysis"[Mesh], "Cost-Benefit Analysis"[Mesh], "Economics, Medical"[Mesh], "Economics, Hospital"[Mesh], "Economics, Nursing"[Mesh], "Economics, Pharmaceutical"[Mesh], "cost analysis"[Text Word], "cost-analysis"[Text Word], "budget impact"[Text Word], "Models, Econometric"[Mesh], "econometric"[Text Word]
Resource utilization	Cost of Illness"[Mesh], "Health Care Costs"[Mesh], "Fees and Charges"[Mesh], "Health Expenditures"[Mesh], "healthcare cost*"[Text Word], "health care cost*"[Text Word]
Health utilities	"health utility"[Text Word], "health utilities"[Text Word], "standard gamble"[Text Word], "time trade off"[Text Word], "EQ5D"[Text Word], "quality adjusted life year"[Text Word], "disability adjusted life year"[Text Word]

Abbreviations: MeSH, Medical Subject Headings; OA, osteoarthritis.

between 2008 and 2015 found that NSAID and steroid prescription use was reduced significantly in the 6-month post-injection period among the study cohort.[33] The proportion of patients filling these prescriptions following non-avian HMW-HA injections was also reduced ($P < .001$). In addition, the number of patients getting any opioid prescription was reduced significantly following non-avian HMW-HA injections ($P < .001$).[33]

Studies suggest that IAHA may reduce the use of pain medications, such as NSAIDs, and delay TKA procedures,[3,23-26] thus potentially decreasing overall treatment costs over time. Two studies reported that IAHA accounts for 16%[34] to 29%[35] of OA treatment–related expenditures in the 12 months leading up to TKA. A large, retrospective analysis of the Blue Cross Blue Shield claims database found that for patients with knee OA, those treated with IAHA had lower 4-year total medical care costs than those treated with ICSs or those who received TKA.[36] Specifically, the 4-year per member per month costs for the IAHA, ICS, and TKA cohorts were $733, $1230, and $1548, respectively.[36] This study also reported lower use and costs of opioids in the IAHA cohort.[36]

Another large claims database analysis determined the contribution of IAHA and TKA to overall knee OA–related direct costs using the Optum Clinformatics data set (2006-2016).[37] The cost of treating patients over a 2-year period following knee OA diagnosis was nearly $5 billion. For the IAHA patients who subsequently underwent TKA within 2 years of diagnosis, the cost of IAHA contributed to only 1.7% of the overall cost of treating those patients. However, a large proportion (84.1%) of IAHA patients did not undergo TKA within 2 years of their diagnosis. The authors reported that if these patients had instead been treated immediately with TKA, it would have cost an estimated $1.84 billion. By not undergoing TKA within 2 years of diagnosis of knee OA, these IAHA patients had potential savings of $1.54 billion, after accounting for other therapies that were used.[37]

A large, retrospective claims analysis of the IMS Health PharMetrics Plus database comparing disease-specific costs and risks of TKA among patients receiving different IAHA treatments reported that meaningful differences in unadjusted mean (median) disease-specific costs exist among IAHA products, ranging from $13 160 ($4804) to $14 959 ($6388).[38] This study also reported that some IAHA products had both a higher proportion of patients who received TKA and a shorter delay to TKA than others.[38] The authors concluded that the analysis of administrative claims data provides real-world evidence that meaningful differences exist among some HA products in disease-specific cost and time to knee replacement surgery.

Using 2012 Medicare Part B claims, Schmajuk et al[39] evaluated patterns of IAHA use across the United States and calculated total payments by Medicare. They reported that Medicare reimbursed for 1 161 924 administrations of IAHA and, on average per administration, paid $179 for the drug and $69 for the injection.[39] The authors suggested that payers and providers should be judicious in their utilization of IAHA within the Medicare population due to the high utilization and cost burden.

Cost-effectiveness

All cost-effectiveness studies identified[40-47] are included in Table 4. Waddell et al[40] developed a cost-of-illness model to demonstrate potential savings associated with IAHA treatment in a managed care setting (Table 4). A hypothetical cohort of patients categorized as having mild, moderate, or severe OA of the knee was followed over a 3-year time period. The 3-year savings associated with adding ⩾1 course of IAHA therapy to the standard treatment pathway for OA of the knee was $8 810 771.[40] The savings per patient with OA receiving IAHA across 3 years was $4706.[40]

Several studies have shown that IAHA is more cost-effective in knee OA compared with conventional care with NSAIDs, analgesic, and corticosteroids.[41-43,47] Several authors conclude that IAHA should therefore be the dominant treatment strategy.

Table 2. Impact of IAHA on time to TKA.

IMPACT OF IAHA ON TIME TO TKA. REFERENCE/ OBJECTIVE	DESIGN	POPULATION	RESULTS	CONCLUSION
Altman et al[23] To evaluate the impact of IAHA use on TKA	▪ Retrospective claims analysis (IMS Health PharMetrics Plus database) ▪ Time frame: 2007-2013	▪ OA patients who received TKA within window	▪ Median time to TKA was 114 days for patients who did not receive IAHA compared with 484 days for patients who received any IAHA injection ($P < .0001$) (more than 4 times longer than the median time to TKA for the non-IAHA group) ▪ Patients who received no IAHA had a median time to TKA of ~0.3 years; with only 1 course of IAHA, the median time to TKA was >1.0 year ($P < .0001$); patients who received ⩾5 courses delayed TKA by a mean of 3.6 years ($P < .0001$).	▪ IAHA injections are associated with dose-dependent increase in time to TKA
Dasa et al[24] To evaluate the effect of repeated courses of IAHA on delay of TKA	▪ Retrospective claims analysis (IMS Health PharMetrics Plus database) ▪ Index time frame: 2007-2010 ▪ Follow-up: 36 months	▪ OA patients with claims indicating IAHA injection	▪ Proportion of patients with TKA within 3 years post index ▪ 1 IAHA course: 28.4% ▪ ⩾5 IAHA courses: 5% ▪ Time to TKA among patients with TKA within 3 years post index: mean days ($P < .001$ for all) • 1 IAHA course: 375.6 days • 2 IAHA courses: 617.6 days • 3 IAHA courses: 777.0 days • 4 IAHA courses: 855.6 days • ⩾5 IAHA courses: 971.5 days	▪ Repeated courses of IAHA are associated with delay of TKA for up to 3 years
Ong et al[25] To evaluate whether an avian-derived, cross-linked IAHA is associated with delay of TKA; to determine whether there is a difference in delay of TKA with number of HA courses	▪ Retrospective analysis (Optum Clinformatics data) ▪ Time frame: 2006-June 2016	▪ OA patients who underwent TKA	▪ Median time to TKA: • No IAHA: 0.9 years • Avian-derived, cross-linked IAHA: 2.0 years • All other IAHA: 2.1 years ▪ Trend toward longer time to TKA the more IAHA treatment courses the patient underwent ▪ Median time to TKA for avian-derived, cross-linked IAHA group: • 1 course: 21 months (1.8 years) • ⩾5 courses: 59 months (4.9 years) ▪ Median time to TKA for all other IAHA groups: • 1 course: 20 months (1.7 years) • ⩾5 courses: 61 months (5.1 years)	▪ IAHA use is associated with longer median time to TKA by at least 7 months ▪ The delay to TKA increased with more IAHA courses
Waddell and Bricker[26] To evaluate the ability of IAHA to delay TKA	▪ Retrospective case series review of electronic health record data from 1 practice ▪ Time frame: October 1997-November 2003	▪ OA patients who initiated treatment with IAHA	▪ Incidence of TKA in IAHA-treated knees (1187 knees; 863 patients) was 19% (n=225 knees) ▪ Median time to TKA: 638 days (1.8 years) ▪ For patients in whom a TKA had not yet occurred during the observation time, the median time of IAHA treatment and patient follow-up was 810 days (2.2 years) ▪ A total of 1978 courses of IAHA given to 1187 knees (average 1.67 courses per knee) resulted in an average cost of $1419.76 per knee to delay TKA by a median of 2.1 years (772 days), the median time of all knees to either TKA or time of last observation ▪ Using cost of $852 including 3 injections with arthrocentesis and 1 office visit ▪ Survival analysis showed that 75% of knees had not had a TKA by 1370 days (3.8 years)	▪ The need for TKA can be delayed with IAHA
Ong et al[27] To evaluate time from initial IAHA to TKA; HCRU for those with ⩾1 course of IAHA	▪ Retrospective claims analysis (Optum Clinformatics Data Mart database) ▪ Time frame: January 1, 2006-June 30, 2016	▪ Knee OA patients with ⩾1 course of IAHA	▪ Over the 10-year study period, 76% of patients treated with IAHA and/or single IA injection did not undergo TKA ▪ Median time from first IAHA treatment to TKA was ~6 months with 1 treatment to approximately 4 years with 5 or more treatments ▪ On average, among patients treated with IAHA, patients who underwent TKA had about twice as many office visits, which included preoperative and postoperative care, as those who did not undergo TKA ▪ Number of claims for opioids, NSAIDs, and PT from first diagnosis of OA to end of follow-up tended to also be greater for those who underwent TKA compared with those who did not ▪ Higher percentages of patients who received TKA had claims for opioids, NSAIDs, and PT compared with those who did not undergo TKA	▪ Patients with a greater number of IAHA treatment courses had a longer time from first diagnosis of knee OA to TKA, with a median time of almost 2 years with 1 treatment to approximately 4-5 years with 5 or more treatments

Abbreviations: HCRU, health care resource utilization; HER, electronic health records; HA, hyaluronic acid; HMW, high molecular weight; IAHA, intra-articular hyaluronic acid; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; PT, physical therapy; Q2, quarter 2; TKA, total knee arthroplasty.

Table 3. Health care resource utilization studies.

HEALTH CARE RESOURCE UTILIZATION STUDIES. REFERENCE/OBJECTIVE	DESIGN	POPULATION	RESULTS	CONCLUSIONS
McIntyre et al[3] To evaluate the impact of IAHA injections on utilization of other pain management modalities	▪ Retrospective pre-post design with Truven MarketScan Commercial Claims and Encounters data ▪ Time frame: January 2004-December 2011	▪ All patients who received IAHA injection within time frame	▪ Difference in average number of prescriptions filled • NSAIDs: –10% • Steroids: –55% • Opioids: 12% ○ TKA: 175% ○ Non-TKA: –6% ▪ Difference in the number of patients getting any prescription • NSAIDs: –15% • Steroids: –57% • Opioids: –6% ○ TKA: 85% ○ Non-TKA: –15%	IAHA treatment may help reduce the use of other pain medications such as steroids, NSAIDs, and opioids
Chitnis et al[33] To evaluate the impact of high-concentration non-avian HMW-HA on utilization patterns of 3 prescription pain management pharmacotherapies commonly used in patients with knee OA: NSAIDs, corticosteroid injections, and opioids	▪ Retrospective pretest-posttest design with IBM MarketScan commercial data ▪ Time frame: January 2008-June 2015	▪ Patients (aged 18-64 years) who received non-avian HMW-HA	▪ Difference in the average number of prescriptions filled • NSAID: –9% ($P < .001$) • Steroid: –60% ($P < .001$) • Opioids: –7% ($P < .001$) ▪ Difference in the proportion of patients filling prescriptions • NSAID: –6% ($P < .001$) • Steroid: –28% ($P < .001$) • Opioids: –4% ($P < .001$)	▪ Non-avian HMW-HA may offer effective pain alleviation among knee OA patients while reducing prescription pain medications such as steroids, NSAIDs, and opioids
Bedard et al[35] Determine the costs associated with nonarthroplasty management in the year prior to TKA	▪ Retrospective analysis (Humana administrative claims data) ▪ Time frame: 2007-Q2 2015	▪ All patients who underwent primary TKA	▪ An average cost of $506 per patient for noninpatient management of knee OA ▪ The 3 most common treatments: corticosteroid injections, IAHA injections, and opioids ▪ Top 3 average cost per patient receiving treatment: $822 for IAHA, $405 for physical therapy, and $344 for knee brace ▪ Top 3 average costs for single treatment event: $331 for knee brace, $294 for IAHA injection, and $84 for physical therapy session	▪ In the year prior to TKA, over half of the noninpatient costs associated with knee OA were from injections, therapy, prosthetics, and prescriptions; approximately 29% of these costs were due to IAHA
Dasa et al[38] To compare disease-specific costs and risk of TKA among patients receiving different HA treatments	▪ Retrospective claims analysis (IMS Health PharMetrics Plus database) ▪ Time frame: July 2007-June 2010 ▪ Follow-up: 36 months	▪ OA patients initiating IAHA during time frame	▪ More than 50% of patients in the avian-derived, non–cross-linked IAHA cohort received fewer than 5 injections for the index course, and 26.3% of the patients in the avian-derived non–cross-linked IAHA cohort received 3 injections for the index course ▪ Unadjusted health care costs over the post-index period, mean (median) • Bacteriologically derived, non–cross-linked IAHA cohort: $13 160 ($4808) • Avian-derived, non–cross-linked IAHA cohort: $13 947 ($5720) • Bacteriologically derived IAHA cohort: $14 224 ($6188) • Avian-derived, cross-linked, IAHA cohort: $14 959 ($6388) ▪ Avian-derived, cross-linked, IAHA-injected patients and bacteriologically derived IAHA-injected patients had greater disease-specific costs compared with avian-derived, non–cross-linked, IAHA-injected patients (9.0%, $P < .0001$% and 6.8%, $P = .0050$, respectively) ▪ Patients treated with avian-derived, non–cross-linked IAHA; bacteriologically derived, non–cross-linked IAHA; and bacteriologically derived IAHA had longer delays to TKA than those treated with avian-derived, cross-linked IAHA	▪ Meaningful differences exist among some HA products in disease-specific cost and time to knee replacement surgery

(Continued)

Table 3. (Continued)

HEALTH CARE RESOURCE UTILIZATION STUDIES. REFERENCE/OBJECTIVE	DESIGN	POPULATION	RESULTS	CONCLUSIONS
Mackowiak et al[36] To compare the medical costs associated with treatments for knee OA: ICS and IAHA	▪ Retrospective medical and pharmacy claims analysis (Blue Cross/Blue Shield) ▪ Time frame: July 2012-December 31, 2017	▪ Knee OA patients with claim in 2013	▪ Adjusted 4-year per patient per month costs: ▪ IAHA cohort: $733 ▪ ICS cohort: $1230 ▪ TKA cohort: $1548 ▪ Per-patient opioid and analgesic prescriptions were consistently and significantly lower in the IAHA (range, 0.70-0.96) vs ICS cohort (range, 2.0-2.26) for years 1 through 4 ▪ Usage rates were significantly lower in the IAHA cohort vs TKA cohort in year 1 (0.96 vs 4.77) and not different in years 2 through 4 (TKA range, 0.76-1.08) ▪ In year 1, opioid and prescription analgesic costs were significantly lower in the IAHA vs ICS and TKA cohorts ($3.45 vs $11.14 and $12.82) ▪ After year 1, opioid and prescription analgesic costs were significantly higher in the ICS (range, $13.83-$15.96) vs IAHA (range, $3.02-$3.87) and TKA cohorts (range, $3.43-$4.97)	▪ Patients in the IAHA cohort had lower total medical care costs, fewer adverse outcomes, and lower use/costs of opioids and prescription analgesics vs patients in the ICS and TKA cohorts
Schmajuk et al[39] To examine patterns of IAHA use across the United States	▪ Retrospective analysis (Medicare Part B claims) ▪ Time frame: 2012	▪ Administrations for all formulations of HA	▪ Medicare Part B reimbursed for 1 161 924 administrations of IAHA among 423 669 unique patients ▪ On average per administration, Medicare paid $179 for the drug and $69 for the injection ▪ Medicare paid $207 million for HA product and $80 million for the associated large-joint injection CPT code	▪ IAHA was administered frequently to Medicare beneficiaries in 2012 at significant cost
Weick et al[34] To assess utilization and payments for IAHA in the 12 months prior to TKA	▪ Retrospective cohort (MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits [Truven Health Analytics]) ▪ Time frame: 2005-2012	▪ Patients who underwent TKA	▪ Among the 14.7% of the study population who received ⩾1 IAHA injection in the 12 months preceding TKA, the mean number of injections received was 3.6 ▪ Between 2004 and 2012, the number of HA injections per 100 000 patients in the study population ranged from a low of 24 030 in 2004 to a high of 30 914 in 2008 ▪ Total payments associated with IAHA injections in the study cohort amounted to $40 547 881 over the study period ▪ The mean payment per individual IAHA injection was $310, and the mean total payment for HA injections per patient receiving an IAHA injection (all IAHA injections for a patient) was $1128 ▪ IAHA injections accounted for 25.2% of treatment-specific payments	▪ IAHA injections accounted for 16.4% of all knee OA–related health care payments in the study population
Ong et al[37] To determine the contribution of IAHA and TKA to the overall knee OA–related direct costs and to evaluate cost savings from the use of IAHA	▪ Claims analysis (Optum Clinformatics data set) ▪ Time frame: 2006-end Q2 2016	▪ Patients with knee OA	▪ 15.9% of the IAHA patients underwent TKA within 2 years, but IAHA only contributed 1.7% to the total costs for these patients ▪ The remaining 84.1% of IAHA patients did not undergo TKA, which saved an estimated total of $1.54 billion (average $20,740 per patient) or 83.9%, after accounting for their non-TKA therapies	▪ Substantial cost savings were observed for a large percentage of IAHA patients who did not undergo TKA

Abbreviations: CPT, Current Procedural Terminology; HA, hyaluronic acid; HMW, high molecular weight; IAHA, intra-articular hyaluronic acid; ICS, intra-articular corticosteroids; NSAID, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PT, physical therapy; Q2, quarter 2; TKA, total knee arthroplasty.

Table 4. Cost-effectiveness studies.

COST-EFFECTIVENESS STUDIES.REFERENCE/ OBJECTIVE	DESIGN	POPULATION	RESULTS	CONCLUSION
Waddell et al[40] To demonstrate potential savings associated with the new treatment modality of IAHA in a managed care setting	▪ Cost-of-illness model ▪ Data sources • Literature • Clinical trial data • Expert opinion • Claims data	▪ Mild, moderate, or severe OA	▪ The 3-year savings associated with adding 1 or more courses of IAHA therapy to the standard treatment pathway for OA of the knee was $8 810 771 ▪ The total average savings per OA patient receiving IAHA was $4706 (over 3 years) ▪ The number of TKAs avoided was 808 ▪ The model was highly sensitive to the durability of IAHA; increasing and decreasing durability within a reasonable range resulted in 3-year savings of $9 131 879 and $2 012 082, respectively	▪ Appropriate use of IAHA could delay the need for TKAs and generate savings in the managed care setting ▪ Using IAHA generated savings in a managed care setting over 3 years
Hatoum et al[41] To determine the cost-effectiveness of bioengineered IAHA injections in treating OA knee pain in poor responders to conventional care, including NSAIDs and analgesics	▪ Cost-effectiveness model ▪ Treatments: • IAHA • NSAIDs • Corticosteroids • Analgesics • Surgery	▪ Moderate-to-severe knee pain due to OA in patients who either failed to respond or responded poorly to conventional therapy ▪ Data source: • FLEXX Trial and Extension Study	▪ IAHA was less costly and more effective than conventional care with NSAIDs and analgesics and was the dominant treatment strategy; when IAHA was compared with escalating conventional care cost due to disease progression, it was found to have an ICER of $38 741/QALY Scenario 1: no assumption of disease progression IAHA: $3469; 0.163 QALYs; Dominant Conventional care: $4562; 0.000 QALYs Scenario 2: escalating care cost due to disease progression IAHA: $1446; 0.164 QALYs; $38 741 Conventional care: $516; 0.140 QALYs	▪ IAHA is the dominant treatment strategy
Miller and Block[42] To determine the cost-effectiveness of an 8-week multimodal knee OA treatment program administered in a real-world setting	▪ Cost-effectiveness model ▪ Treatments: • IAHA • Physical therapy • Knee bracing • Patient education	▪ Patients with symptomatic knee OA	▪ A single, multimodal, 8-week knee OA treatment program including 3 to 5 weekly IAHA knee injections was cost-effective ($12 800/QALY) and may delay the need for knee arthroplasty through 2 years' follow-up	▪ Treatment was cost-effective
Miller et al[47] To report long-term clinical outcomes and cost utility in a subgroup of patients who were treated with IAHA	▪ Cost-effectiveness model ▪ Treatments: • IAHA • Physical therapy • Knee bracing • Patient education	▪ Patients with symptomatic knee OA	▪ A single, multimodal, 8-week knee OA treatment program that included 1 cycle of 5 IAHA knee injections was highly cost-effective ($6000/QALY); the percentage of simulations with an ICER below WTP limits was 97.2% for a WTP of $50 000/QALY, 98.9% for a WTP of $100 000/QALY, and 99.4% for a WTP of $150 000/QALY	▪ Treatment was cost-effective
Rosen et al[43] To evaluate the cost-effectiveness of treating patients with knee OA with HMW-HA compared with LMW and conservative treatment while taking into account disease stage	▪ Cost-effectiveness ▪ Treatments: • HMW IAHA • LMW IAHA ▪ Conservative treatment • Physical therapy/ exercise, braces/orthosis, medications (such as NSAIDs), and analgesics	▪ Patients with knee OA	▪ IAHA, particularly HMW formulations, demonstrates cost-effectiveness when compared with conservative treatment options and LMW IAHA in patients with early/mid-stage knee OA ▪ The cost-effectiveness of HMW IAHA in patients with later stage knee OA was not as apparent, particularly because of the uncertainty in the proportion of patients with late-stage OA who have a meaningful improvement after receiving IAHA	▪ HMW IAHA was cost-effective compared with conservative treatment and LMW IAHA in early/mid-stage knee OA

(Continued)

Table 4. (Continued)

COST-EFFECTIVENESS STUDIES.REFERENCE/ OBJECTIVE	DESIGN	POPULATION	RESULTS	CONCLUSION
Samuelson et al[44] To examine the cost-effectiveness of a series (total of 3 injections) of IA PRP injections in comparison with that of IAHA for the treatment of symptomatic knee OA	▪ Cost-effectiveness ▪ Treatments: • IAHA • IA PRP	▪ Symptomatic knee OA ▪ Data source • Literature	▪ A series of either PRP ($8635.23/QALY) or IAHA ($5331.75/QALY) injections for the treatment of symptomatic knee osteoarthritis would be considered cost-effective (cost per QALY <$50 000) ▪ However, PRP was significantly more effective at 1 year, and as it was associated with an ICER of $12 628.15/QALY when compared with IAHA, a series of PRP injections should be considered a reasonable and acceptable alternative to IAHA injections for the treatment of symptomatic knee osteoarthritis	▪ PRP injections were not more cost-effective than IAHA injections
Rosen et al[45] To examine the single payer cost-effectiveness of various HA products in the treatment of knee OA	▪ Cost utility	▪ Symptomatic knee OA	▪ Across all IAHA products, a bacteriologically derived, non–cross-linked IAHA preparation had the most favorable cost-utility ratio (2015 US dollar: $5785.52/QALY); when compared with conventional care, all IAHA products were cost-effective based on the assumption of WTP threshold of $50 0000/QALY	▪ All IAHA products were cost-effective
Rosen et al[46] To determine the current and potential impact that a biologically derived HMW IAHA may have on QALYs if used more widely for patients with knee OA	▪ Cost utility	▪ Symptomatic knee OA	▪ A bacteriologically derived, non–cross-linked IAHA preparation was estimated to save 36 730 QALY/year among the US population and has the potential to save an additional 369 181 QALY/year if used by all eligible patients	▪ IAHAs, such as a bacteriologically derived, non–cross-linked IAHA preparation, have the potential to save substantial QALYs

Abbreviations: HMW, high molecular weight; IAHA, intra-articular hyaluronic acid; ICER, incremental cost-effectiveness ratio; LMW, low molecular weight; NSAID, nonsteroidal anti-inflammatory drug; OA, osteoarthritis; PRP, platelet-rich plasma; PT, physical therapy; QALY, quality-adjusted life-year; TKA, total knee arthroplasty; WTP, willingness to pay.

The cost-effectiveness of IAHA in adults with moderate-to-severe knee pain due to OA who either failed to respond or responded poorly to conventional therapy was evaluated in the US marketplace. Two decision analytic models were developed that compared IAHA treatment with either continuation of patients' baseline conventional care (NSAIDs, acetaminophen, physical therapy, and assistive devices) with an assumption of no disease progression (model 1) or escalating conventional care (NSAIDs and analgesics, corticosteroid injections, and surgery), which included escalating costs because of disease progression (model 2).[41] In model 1, the average utility gain among patients treated with IAHA (n = 214) was 0.163 quality-adjusted life-years (QALYs) (95% confidence interval [CI],–0.162 to 0.488) over 52 weeks. For the conventional care group, patients in this simulation were maintained on their prescribed OA care and did not gain any QALYs. Total treatment costs were $3469 for the IAHA group and $4562 for the conventional care group treated with NSAIDs and analgesics. Because IAHA treatment was effective and less costly than conventional care, IAHA was the dominant strategy and no incremental cost-effectiveness ratio (ICER) was calculated. Furthermore, sensitivity analyses showed that IAHA remained the dominant treatment strategy except when QALYs were set at the lowest end of the 95% CI. In model 2, among patients achieving a response after 2 courses of IAHA, an average of 0.23 QALYs were gained over the 1-year period. Among non-responders (those who failed to achieve a ⩾20% improvement from baseline on Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] pain score), the average QALYs gained was 0.08. Total treatment cost over 1 year was $1446 for the IAHA group and $516 for the conventional care group. The number of QALYs gained was 0.16 for the IAHA group and 0.14 for the conventional care group. The average cost-effectiveness ratio was $8816/QALY for IAHA and $3686/QALY for escalating conventional care. The ICER for IAHA, with conventional treatment as the baseline strategy, was $38 741/QALY gained.[41] Results from 1-way sensitivity analyses showed that the ICER calculated for IAHA was most sensitive to response rates in both the IAHA and the conventional care groups. Furthermore, in a probabilistic sensitivity analysis with Monte Carlo simulation, when the willingness-to-pay level was set at $50 000/QALY, IAHA was shown to be a cost-effective strategy for OA treatment in ~70% of simulations.[41]

Another economic study evaluated a single, 8-week multimodal knee OA treatment program, which included weekly IAHA injections for 3 to 5 weeks along with physical therapy, rehabilitation, and education.[42] Findings suggest that IAHA was cost-effective and lowered knee arthroplasty use through 2 years of follow-up; however, it is unclear whether the cost-effectiveness was driven by IAHA, physical therapy, or both.

Miller et al[47] constructed a cost-effectiveness model from long-term clinical outcomes and cost utility in a subgroup of patients treated with an avian-derived, non–cross-linked HA from a previous study.[42] The cost-effectiveness of a single, 8-week multimodal knee OA treatment program (1 cycle of 5 intra-articular knee injections of sodium hyaluronate given at weekly intervals along with physical therapy, rehabilitation, and education) was compared with usual care in a hypothetical control group that did not participate in the program.[47] The multimodal knee OA treatment program was highly cost-effective compared with usual care, with a base-case ICER of $6000/QALY. The percentage of simulations with an ICER below a $50 000 willingness-to-pay limit was 97.2%.

Rosen et al[43] evaluated the cost-effectiveness of treating patients with knee OA with HMW IAHA compared with low-molecular-weight (LMW) HA and conservative treatment while considering the disease stage. Decision-analytic models were created for early/moderate OA, as well as late-stage knee OA. Models for late-stage knee OA assumed a range of response rates to IAHA treatments (10%-50%) and included conservative treatment (physical therapy/exercise, braces/orthosis) and medications (NSAIDs and analgesics). The models compared the cost/QALY gained for these treatments with the use of either LMW or HMW IAHA. Incremental cost-effectiveness ratios were calculated for each treatment in relation to HMW IAHA. For early to moderate knee OA, HMW IAHA was dominant over LMW IAHA and physical therapy/exercise, as it was less expensive and provided greater benefit. Only HMW IAHA was cost-effective versus braces/orthosis and NSAID/analgesic medications based on a willingness-to-pay threshold of $50 000. In the model of 50% response rate to IAHA for late-stage OA, HMW IAHA remained cost-effective compared with physical therapy/exercise and braces/orthosis, but not with NSAID/analgesic medications, at a willingness-to-pay threshold of $50 000. In the worst-case scenario (10% responder rate to IAHA), HMW IAHA was no longer cost-effective in any circumstance.[43]

Samuelson et al[44] examined the cost-effectiveness of a series of intra-articular platelet-rich plasma injections (total of 3 injections) compared with IAHA for the treatment of symptomatic knee OA. In the model, the base case assumes an otherwise healthy individual presenting to an orthopedist's office as a new patient for the evaluation and treatment of symptomatic knee OA. The authors concluded that both treatment options would be considered cost-effective, and platelet-rich plasma injections were not more cost-effective than IAHA injections.[44]

Rosen et al[45] examined and compared the cost utility of different IAHA products relative to one another and to conventional care. A single US payer economic evaluation was conducted comparing multiple IAHA products. Across all IAHA products, a bacteriologically derived, non–cross-linked IAHA preparation had the most favorable cost-utility ratio ($US 2015: $5785.52/QALY). When compared with

conventional care, all IAHA products were cost-effective based on the assumption of a willingness-to-pay threshold of $50 000/QALY.

An economic model was developed to estimate the current and potential impact that a bacteriologically derived, non–cross-linked HMW IAHA preparation may have on QALYs in the US population with symptomatic knee OA.[46] The number of US patients with symptomatic knee OA in 2015 and the number of patients with TKA were used to estimate the projected total number of eligible patients who may benefit from the use of HMW IAHA versus conventional care. Results demonstrated that with current use, a bacteriologically derived, non–cross-linked HMW IAHA is estimated to save 36 730 QALY/year among the US population and has the potential to save an additional 369 181 QALY/year if used by all eligible patients.

Discussion

Intra-articular HA injections constitute a mature nonpharmacological therapeutic product market for knee pain in OA. A US retrospective claims database analysis estimated that 3 million patients with knee OA were eligible to receive IAHA treatment; however, only approximately 40% (1 238 353/3 051 968) of patients received treatment.[46] Furthermore, some major insurance carriers still do not pay for IAHA injections or require that patients fail conservative therapies, such as over-the-counter therapies, prior to the use of IAHA. The current continuum of care includes use of over-the-counter therapies followed by prescription pain medicines, corticosteroid injections, IAHA treatments, and, finally, end-stage joint replacement. Delaying the use of IAHA until patients present with advanced OA (grade IV) has been theorized to reduce its effectiveness and is inconsistent with published appropriate use criteria, which state an "uncertain" benefit in patients with advanced OA.[48] In addition, the conservative therapies currently being leveraged are palliative and are intended to alleviate pain through pharmacologic means, which may contribute to adverse events (AEs) associated with polypharmacy and drug interactions that may require acute and emergency intervention. The physiologic state of the knee with OA does not improve or remain static but continues to degrade over time. Thus, palliative therapies, such as corticosteroids, that can cause tissue atrophy and mask pain may alter innate repair and adaptive and protective mechanisms.[40] This may exacerbate and potentially accelerate degeneration of the osteoarthritic knee and the need for TKA.[49]

The results of this literature review focusing on the US market demonstrate that using IAHA may delay time to TKA for up to 5 years. This finding is important because not all patients are ready for TKA when it is indicated, and because of comorbidities, many patients are contraindicated for TKA. Although no published research shows that IAHA reduces the direct incidence and corresponding cost of TKA, IAHA provides substantial clinical and economic benefits by delaying TKA. Our review identified evidence that with IAHA use, medical costs were lower (adjusted 4-year per patient per month costs) for patients treated with IAHA than for those treated with ICSs or TKA,[36] use of other pain medications was reduced,[3,33,36] and substantial cost savings were feasible.[37,40] Furthermore, IAHA was determined to be cost-effective against NSAIDs, corticosteroids, analgesics,[41] and conservative treatment.[43]

Nonsteroidal anti-inflammatory drugs are often recommended and prescribed to treat pain in OA; however, if not used appropriately, they can be associated with adverse effects, including gastrointestinal toxicity, cardiovascular toxicity, and risk of acute myocardial infarction and heart failure.[31] This is of particular concern when treating older patients with OA, and these added complications may pose a significant economic burden to the US health care system.[28]

Similarly, recent meta-analyses assessing the efficacy and safety of opioids versus placebo in patients with OA showed little evidence that opioids are beneficial for pain or function and reported high rates of AEs.[50] Any reduction in opioid use can have far-reaching economic benefits for society, especially given that current data indicate that narcotics are no more effective than NSAIDs in this population.[29,51] Finally, growing evidence shows that multiple-course, intra-articular steroid injections lack long-term efficacy and may actually be detrimental, especially with chronic administration in patients with OA.[49,52] Recent studies have demonstrated that AEs after intra-articular steroid injection, which include accelerated OA progression, subchondral insufficiency fracture, complications of osteonecrosis, and rapid joint destruction with bone loss, are becoming more recognized by physicians.[32] These AEs may add additional economic burden to the US health care system. Overall, the utilization of cost-effective, nonpharmacological treatment modalities with improved safety profiles, such as IAHA injections, is important and may provide cost-saving opportunities for the health care system.

While these findings are focused on the US market, and thus are generalizable only to the US market, studies in other countries have reported similar findings. In Canada, studies have determined that IAHA may be cost-effective.[53,54] In the Netherlands, researchers reported that IAHA added to usual care (defined according to guidelines of the Dutch Orthopedic Association) for knee OA is probably cost-effective.[55] In France, HA may provide medical benefits at an acceptable cost.[56] In Spain, IAHA may reduce health system economic burden by delaying the implantation of a prosthetic knee.[57] Similarly, in Italy IAHA use resulted in reduced economic burden by decreasing medication consumption and drug-related AEs and by delaying surgery; the authors note that IAHA was likely cost-effective.[58]

Reducing total medical care costs, minimizing opioid and analgesic utilization to an appropriate amount, and improving patient quality of life should be treatment goals of physicians

selecting therapies for patients with knee OA. Achieving these goals will be ever more crucial with the movement from traditional fee-for-service payment models to value-based payment models. As IAHA injections have been widely studied in mild to moderate knee OA where they have been proven to benefit patients, these treatments need to come sooner in the continuum of care. Given the emerging evidence for potentially contraindicating steroid injections in the treatment of knee OA, perhaps the time has come to consider a new continuum of care that obviates the need for steroid injections for a patient to become eligible for nonpharmacologic IAHA treatment.

Limitations

Our study is not without limitations. One limitation of this systematic literature review is that we did not assess the quality of these studies on a quality assessment rating scale. Second, the age of certain studies may make them less relevant in the current health care environment, as treatment modalities and costs for knee OA have changed over the last 20 years. Finally, many of these studies (62%) are retrospective reviews of claims or electronic health records. Retrospective database reviews present inherent limitations, including the limited ability to measure disease severity. Furthermore, the results of these database studies are only representative of the patient populations within those databases.

Conclusions

As economic spending on health care continues to rise within the US, it is becoming ever more important to evaluate the economic value of treatment modalities to help support evidence-based decision-making. Our literature review shows that IAHA is cost-effective for the treatment of pain associated with knee OA and suggests that IAHA may reduce the use of pain medications, such as NSAIDs and opioids, and impact time to TKA procedures. As the disease burden is projected to increase for patients with knee OA, it will be important that researchers take a broader methodological approach when evaluating the economic value of IAHA, such as consideration for work-related time off due to OA, effects of QALYs, additional costs related to adverse effects of other treatments, and TKA or need for revision procedures. The findings from our literature review may be used to form future economic evaluations and inform payers regarding potential cost savings associated with IAHA treatments.

Author Contributions

WP and BB conceived the study, contributed to the study design, secured funding, and critically reviewed and revised the manuscript. MM designed the study; acquired, analyzed, and interpreted the data; provided study supervision; and drafted the manuscript. CM and KC-M contributed to the study design and study concepts, interpreted the data, and critically reviewed and revised the manuscript.

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