Applied Health Economics and Health Policy (2022) 20:351–370
https://doi.org/10.1007/s40258-022-00717-0

SYSTEMATIC REVIEW

Cost Effectiveness of Pharmacological Management for Osteoarthritis: A Systematic Review

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Accepted: 16 January 2022 / Published online: 9 February 2022

Abstract

Background and objective Osteoarthritis (OA) is a highly prevalent, disabling disease requiring chronic management that is associated with an enormous individual and societal burden. This systematic review provides a global cost-effectiveness evaluation of pharmacological therapy for the management of OA.

Methods Following Center for Reviews and Dissemination (CRD) guidance, a literature search strategy was undertaken using PubMed, EMBASE, Cochrane Library, Health Technology Assessment (HTA) database, and National Health Service Economic Evaluation database (NHS EED) to identify original articles containing cost-effectiveness evaluation of OA pharmacological treatment published before 4 November 2021. Risk of bias was assessed by two independent reviewers using the Joanna Briggs Institute (JBI) critical appraisal checklist for economic evaluations. The Quality of Health Economic Studies (QHES) instrument was used to assess the reporting quality of included articles.

Results Database searches identified 43 cost-effectiveness analysis studies (CEAs) on pharmacological management of OA that were conducted in 18 countries and four continents, with one study containing multiple continents. A total of four classes of drugs were assessed, including non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, symptomatic slow-acting drugs for osteoarthritis (SYSADOAs), and intra-articular (IA) injections. The methodological approaches of these studies showed substantial heterogeneity. The incremental cost-effectiveness ratios (ICERs) per quality-adjusted life-year (QALY) were (in 2021 US dollars) US$44.40 to US$307,013.56 for NSAIDS, US$11,984.84 to US$128,028.74 for opioids, US$10,930.17 to US$27,799.73 for SYSADOAs, and US$258.36 to US$58,447.97 for IA injections in different continents. The key drivers of cost effectiveness included medical resources, productivity, relative risks, and selected comparators.

Conclusion This review showed substantial heterogeneity among studies, ranging from a finding of dominance to very high ICERs, but most studies found interventions to be cost effective based on specific ICER thresholds. Important challenges in the analysis were related to the standardization and methodological quality of studies, as well as the presentation of results.

1 Introduction

Osteoarthritis (OA) is a highly prevalent musculoskeletal disorder that is associated with a significant health and economic burden. Worldwide, OA affected more than 303 million people in 2017 [1]. It has become an increasing global health concern due to the aging population and the frequent occurrence of multiple co-morbidities, such

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Key Points for Decision Makers

Economic evaluations have expanded to advanced models such as Markova and the Osteoarthritis Policy models that incorporate considerations for longer time ranges, health utility, a wider range of adverse events including cardiovascular events, and additional meaningful outcomes such as the cost per QALY ICERs.

Differences in study design and between health systems of different countries hampered meaningful comparison of results across studies.

The key drivers of cost effectiveness included medical resources, productivity, relative risks, and selected comparators.

as cardiovascular disease and diabetes mellitus, in OA patients. The pain and disability imposed by OA create significant negative impacts on the patient's quality of life, and are important clinical considerations in chronic disease management [2]. OA can affect any joint, but most commonly the knee, hands and hip [3, 4]. OA is comparable to diabetes in disability burden, with both responsible for the largest increases in years lived with disability (YLD) at the global population level compared with the other top 20 causes of disability in 1990–2005 and 2005–2015 [5, 6]. OA accounted for 3.9% of YLD in 2015, and by 2020 it is expected to be the fourth leading cause of YLD globally [7, 8]. In addition to imposing a huge disability burden, the direct and indirect costs of OA are continually increasing, which bring a series of socioeconomic consequences: increased expenditure, reduced productivity, over-utilization of healthcare resources, and an overall decline in quality of life for both patients and caretakers [2, 9]. In addition, due to their age and likely presence of co-morbidities, OA patients have higher risks of experiencing complications than the general population [10, 11]. Pharmacological therapy is associated with a range of adverse events (AEs) in OA patients, leading to an increase in direct costs and adding to the already significant economic burden on patients and healthcare systems [12].

Common pharmacological therapies for OA include non-steroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, symptomatic slow-acting drugs for osteoarthritis (SYSADOAs), and intra-articular (IA) injections of substances such as corticosteroids and hyaluronic acid [13] (Fig. 1). According to the recommended treatment modalities for OA by Osteoarthritis Research Society International (OARSI) [14, 15], When choosing pharmaceuticals for the management of OA patients, it is important to consider the risk of complications. For instance, topical NSAIDs were strongly recommended for individuals with knee OA (Level 1A recommendation: ≥ 75% in favor and > 50% strong recommendation). For individuals with gastrointestinal co-morbidities, COX-2 inhibitors had a Level 1B recommendation and NSAIDs with proton pump inhibitors had a Level 2 recommendation, while for individuals with cardiovascular co-morbidities or frailty, oral NSAIDs were not recommended. Clinical decision making for the pharmacological management of OA should be specific to individual patient conditions. To enable this, physicians should be well informed of the treatment options available, including their relative risks, accessibility, and cost effectiveness.

Health economic evaluations have become increasingly important to support the setting of priorities in healthcare, and to help decision makers allocate healthcare resources efficiently [16]. This is a critical but under-reported aspect in OA management, particularly given the heavy economic burden of OA disability that is likely to worsen due to ongoing population aging, and limited healthcare resources for long-term OA treatment especially in rural or marginalized communities. Most results of economic evaluations are presented using the incremental cost-effectiveness ratio (ICER) [17]. The ICER relates the difference in cost between a medicine and its comparator to the difference in outcomes, and is needed for resource allocation policy making. If the new treatment is less expensive and more clinically effective than the standard treatment, it is said to be dominant. However, if the new treatment is more expensive but also more clinically effective, the new treatment is said to be cost effective if the ICER is less than the willingness to pay (WTP) for each individual country. ICERs can be presented as the cost per quality-adjusted life-year (QALY) gained, where one QALY equates to one year in perfect health.

An overview of existing studies analyzing the cost effectiveness of pharmacological interventions for OA would be useful for identifying the gaps in the current evidence, guiding researchers in designing and conducting high-quality economic evaluations, and helping administrators make decisions based on high-quality evidence. In the absence of a current review on this topic, and in light of previous reviews published in related areas [18–25], the purpose of this study is to systematically review economic evaluations for the pharmacological management of OA.

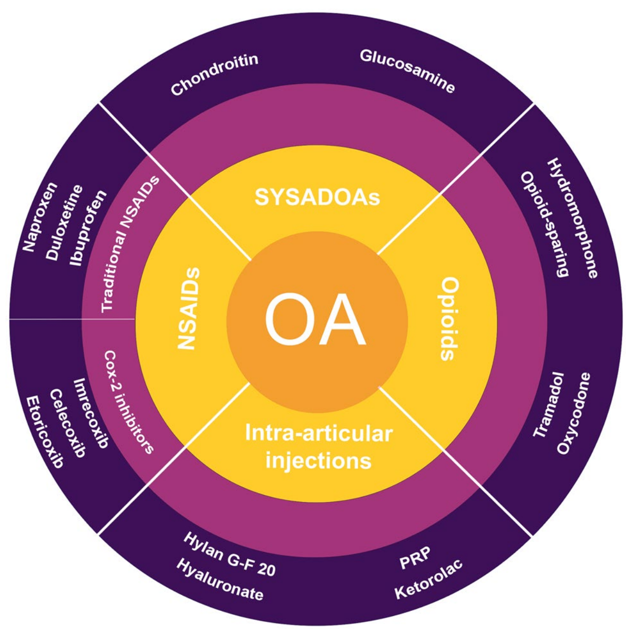

Fig. 1 Classification and types of pharmaceuticals used for osteoarthritis treatment

2 Methods

2.1 Design

A structured systematic literature search was performed in November 2021, using a review protocol based on established standards (Center for Reviews and Dissemination guidelines) and integrated with prior methods [26, 27]. This review protocol aimed to limit bias and ensure the best objectivity of the systematic review (Appendix 1, see electronic supplementary material [ESM]).

2.2 Search Strategy

Published literature from inception to November 2021 reporting the cost effectiveness of pharmacological management of OA was identified by searching the following databases: PubMed, EMBASE, Cochrane Library, the Health Technology Assessment (HTA) database, and the National Health Service Economic Evaluation database (NHS EED) (this database ceased to be updated after March 2015). 'Osteoarthritis' and 'economic evaluation' and free vocabulary terms were used as MeSH/Emtree search terms. Regular alerts were established to update the search until 4 November 2021. In addition, the reference lists of relevant systematic reviews and meta-analyses were scanned to identify potentially eligible studies. The detailed search strategies are presented as supplementary materials (Appendix 2, see ESM). All searches were supplemented by reviewing the bibliography of publications included for full-text review to identify any additional eligible studies.

2.3 Study Selection

Searches were downloaded from each of the databases and uploaded into Endnote X9 for document management. First, duplicates were identified and removed. Second, two reviewers (KNF, ZJF) independently applied inclusion and exclusion criteria (Table 1) to screen titles and abstracts of the remaining articles. Third, the full texts of eligible articles were screened in-depth by two independent reviewers (KNF and ZJF). Any studies resulting in disagreement between the reviewers were presented to a third reviewer (LY) for review and consensus. Subsequently, full-text articles were used for data extraction into an Excel spreadsheet and reviewed by the first author (JYS). Finally, reference lists and citations of eligible articles were checked manually for any additional relevant studies.

2.4 Data Extraction

A standardized data-extraction form was developed to collect data from eligible studies. Study characteristics regarding publication (author, year of publication), study design (country/region, perspective, model type, outcome measure, time horizon, comparators, cost type, discount rates, year of valuation), and study results (costs, effectiveness, base-case ICERs, and sensitivity analysis [SA]) were extracted by two reviewer (ZJF, KNF) and checked by a third reviewer (JYS). Afterwards, for comparability reasons, all extracted costs and ICERs were converted into 2021 US dollars using the yearly inflation rates of the countries involved (http://www.rateinflation.com) and the exchange rate published by the Bank of America (https://www.bankofamerica.com/foreign-exchange/exchange-rates.go).

2.5 Assessment for Risk of Bias

Eligible studies were critically appraised by two independent reviewers (JYS, ZJF) at the study level for methodological quality using the standardized critical appraisal instrument for economic evaluations in the Joanna Briggs Institute

Table 1 Eligibility criteria

Category	Inclusion criteria	Exclusion criteria
Population	A population including OA patients	
Intervention	Any pharmacological intervention given for the treatment of OA	COX2 inhibitors removed from the market (e.g. rofecoxib)
Comparators	Any other strategy, including other pharmacological intervention, usual care, or 'doing nothing'	
Study design	Full health economic evaluations (CEAs) defined by the presentation of at least one incremental cost-effectiveness ratio (ICER) or that found an intervention to be dominant	Partial health economic evaluations (e.g., cost minimization and cost consequence studies were excluded if they did not also include an ICER outcome); case studies; commentaries; editorials; letters; conference abstracts; research protocols; animal studies
Language	English	
Publication date	Published before 3 November 2021	

OA osteoarthritis, *CEA* cost-effectiveness analysis, *ICER* incremental cost-effectiveness ratio

(JBI) System for the Unified Management, Assessment and Review of Information [28–30]. All studies, regardless of their methodological quality, underwent data extraction and synthesis. There was no disagreement among the reviewers during the methodological quality assessment. We determined the level of methodological quality as follows: poor quality = <40% of the items presented; moderate quality = 41%–80% of the items presented; good quality = >80% of the items presented.

2.6 Assessment for Quality of Reporting

We graded the included studies by using the Quality of Health Economic Studies (QHES) instrument that assesses studies for the appropriateness of their methods, the validity and transparency of their results, and the comprehensiveness of how they are reported [31]. The QHES is a 16-item scale that uses a dichotomous 'yes' or 'no' response for each item. A 'yes' is worth a specific number of points for each item (reflecting its relative importance), and a 'no' is worth zero. For each study, the points are summed to get a total score that can range from 0 = 'extremely poor' quality to 100 = 'excellent' quality. The QHES has demonstrated good overall construct validity [31, 32]. Based on the total score threshold recommended by Ofman et al. [24], the included studies were classified as either 'high' (≥ 75 points) or 'low' (< 75 points) quality. Because instruments for assessing the quality of cost-effectiveness analyses have, in general, been found to have poor inter-rater reliability [33], we established a protocol for using the QHES specifically for this review on the basis of Pinto et al. [20] (Appendix 3, see ESM). Two authors (JYS and ZJF) independently assessed the studies by using these guidelines, with final scoring based on consensus; if a consensus could not be reached, a third author (KNF) mediated.

2.7 Data Synthesis

Data extracted from included studies were analyzed and summarized using narrative and tables.

3 Results

3.1 Study Selection and Assessment

The study selection process is presented in Fig. 2. The literature search resulted in 6106 potential articles, of which 43 CEAs on the pharmacological management of OA were included for analysis. The included studies were conducted in 18 countries on four continents, with one study containing data from multiple continents. The categories and types of pharmaceuticals used for OA treatment are presented in Fig. 1. The overall methodological quality of the included studies was moderate (Appendix 4, see ESM). The quality of most of the included studies assessed by QHES was high (mean QHES score 84). Six studies [34–39] missed the 75-point threshold demarcating 'low-quality' studies from 'high-quality' ones (Appendix 5, see ESM).

3.2 Characteristics of Included Studies

Characteristics of the included studies are reported in Table 2. The time periods of publication were 2000–2004 (n = 6) [40–45], 2005–2009 (n = 10) [34, 35, 37, 46–52], 2010–2014 (n = 10) [53–62], and post-2015 (n = 17) [36, 38, 39, 63–76]. The studies were conducted in Europe (n = 15), North America (n = 19) [36, 37, 39, 42, 45, 46, 48, 51, 54–56, 59, 60, 67–72, 75], South America (n = 1) [65], and Asia (n = 7) [35, 44, 62, 66, 73, 74, 76], and there was also a multi-continental study (n = 1) [34]. Study designs included model simulations of OA (n = 33) [37–44, 46–50, 53–60, 65–76], randomized clinical trials (n = 8) [34–36, 45, 51, 52, 61, 64], and observational studies (n = 2) [62, 63].

Different analysis perspectives were used to evaluate treatment costs for OA pharmaceuticals. The payer perspective was typically adopted, including third-party payer, private payer, National Health Service (NHS), and Healthcare System (HCS). The majority of articles adopted NHS (n = 8) [38, 43, 49, 50, 53, 57, 58, 74], third-party payer (n = 3) [55, 56, 65], or HCS perspectives (n = 7) [38, 48, 58, 70]. A number of CEAs offered societal perspectives (n = 8) [35, 37, 41, 44, 46, 54, 60, 69]. However, just one such CEA included direct costs and productivity loss [44]. Four offered both NHS and societal perspectives [45, 51, 52, 64] and others adopted various perspectives, while one article did not report a perspective [36].

The treatment selected as the intervention varied across the studies included in this review. Most studies used NSAIDs and/or coxibs as interventions, which were often combined with a proton pump inhibitor (PPI). A total of 13 studies used IA injection as the intervention [36, 39, 45, 59, 68, 71, 72], while three studies used opioids only [34, 49, 61]. Economic evaluation typically compares an intervention with current best practice or usual care, which may vary by clinical setting. The results from the seven articles that defined the comparator as appropriate care [45], usual care (UC) [64, 75], current care [49], standard care [67], and conventional care [59, 68] might not be transferrable because the details of these treatments were unclear.

Numerous sets of cost-effectiveness outcomes were evaluated in the included studies. In addition to cost per minimal perceptible clinical improvement (MPCI) [42], cost per patient improved [45, 51], and cost per life-year gained [40, 41], a variety of gastrointestinal (GI)-related outcomes were used, such as cost per GI event avoided [42], and cost

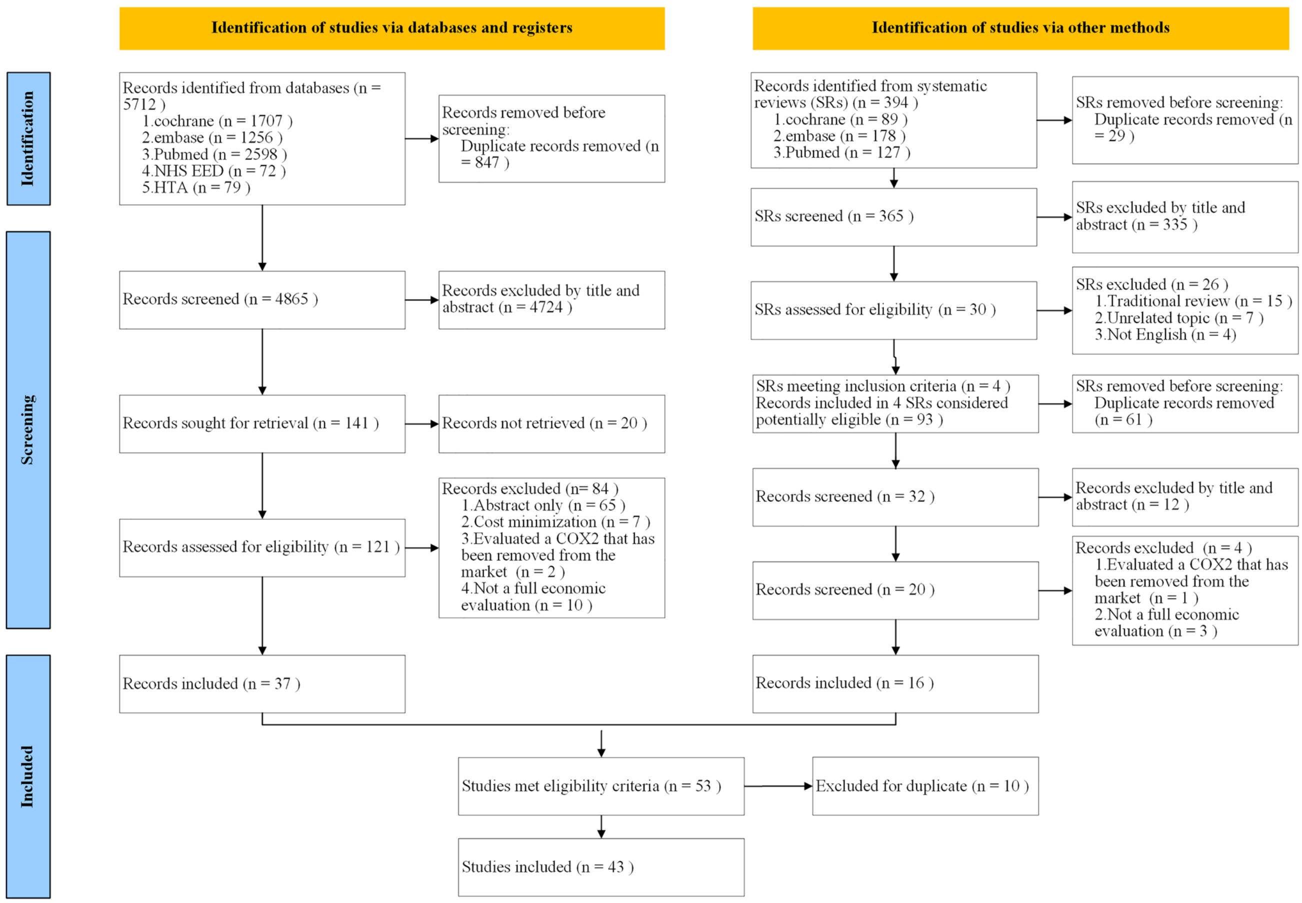

Fig. 2 PRISMA diagram showing the study selection process

per perforation, ulcer or bleed avoided [43]. The use of these variable outcome measures was due to the sources of GI adverse event data included in these studies. The remaining studies reported cost-utility analyses with QALY as the outcome measure. To estimate health utilities for a QALY calculation, the Western Ontario McMaster University Osteoarthritis Index (WOMAC) [77] or another instrument (Sleep Problems Index [SPI]) were often translated into a utility-based instrument (e.g. the EQ-5D or Health Utility Index [HUI]). Four studies [34, 49, 61, 68] translate WOMAC into the HUI and three [50, 53, 66] into EQ-5D, while five studies [52, 56, 62–64] directly used the EQ-5D and three [45, 51, 59] use the HUI3.

3.3 Data Analysis

3.3.1 Cost Effectiveness of Drugs Estimates in Asia

Table 3 identifies seven articles evaluating economic outcomes in Asia [35, 44, 62, 66, 73, 74, 76]. Three evaluations were conducted in the China region [35, 44, 76], two of which were in Taiwan [35, 44], and one evaluation was conducted in each of the following countries: Japan [74], Saudi Arabia [66], and United Arab Emirates [73]. Most of these economic comparisons were made between coxibs (celecoxib or imrecoxib) and NSAIDs with or without gastroprotection. Differences in study design and between health systems in each country hampered meaningful comparison of results across studies. The authors of these studies concluded that coxibs (celecoxib or imrecoxib) were cost effective in these geographical regions based on the local standards. In these studies, the incremental effectiveness between the treatment and control groups varied between 0.0023 and 1.49 QALYs, and the ICERs varied between US$44.40 and US$58,447.97 per QALY gained. In addition, the two articles from Taiwan [35, 44] reported that IA injection was performed. One of these concluded that hyaluronic acid therapy might not be an economically attractive option since Taiwan has fewer health resources than other places, such as Canada and the US [44]. Of the seven studies included, one reported a threshold range, three reported a single threshold, and the remaining three studies did not report a threshold.

Table 2 Characteristics of CEA studies in the pharmacological management of OA (43 studies)

Study/QHES score	Country/region	Type of study	Perspective	Comparators	Time period/discount rate	Costs	Outcome	Year, currency	SA
Haglund 2000 [40]/75	Sweden	Swedish ACCES model	Sweden direct medical costs	Celecoxib vs NSAID monotherapy Celecoxib vs base case	1 y/5%	Direct costs	GI event averted LYG	1998, SEK	One-way SA
Svarvar 2000 [41]/84	Norway	ACCES model	Societal	Celecoxib vs NSAID monotherapy Celecoxib vs base case	6 mo/5%	Direct costs	GI event averted LYG	1999, USD	One-way SA
Torrance 2002 [45]/94	Canada	Multicenter, open-label randomized parallel-group design	Societal and HCS	Hylan G-F 20 + appropriate care vs appropriate care	1 y/NA	Direct costs, productivity loss, other indirect costs	QALY (HUI3) WOMAC	1999, CAD	DSA
Kamath 2003 [42]/88	USA	Decision tree	Healthcare payer	Ibuprofen vs acetaminophen	6 mo/NA	Direct costs	GI event averted MPCI (WOMAC)	2000, USD	DSA PSA
Moore 2004 [43]/82	UK	Decision-analytic model	NHS	Etoricoxib vs NSAIDs alone Etoricoxib vs NSAIDs + H_2A	1 y/1.5%	Direct costs	PUB avoided QALY	2002, GBP	One-way SA, PSA
Yen 2004 [44]/94	Taiwan	Decision tree	Societal	Celecoxib vs naproxen	26 wk/NR	Direct costs, productivity loss	QALY (standard gamble)	2002, USD	DSA
Marshall 2006 [51]/94	USA	Multicenter, open-label randomized parallel-group design	HCS and societal	Oxycodone vs oxycodone-paracetamol	4 mo/NR	Direct costs, productivity loss	QALY (HUI3) WOMAC	2005, USD	DSA, PSA
Loyd 2007 [46]/91	USA	Decision tree	Societal	Celecoxib vs NSAIDs	Lifetime/3%	Direct costs	QALY	2006, USD	One-way SA
Ward 2007 [47]/84	Germany	Discrete event simulation	German health insurance system	OROS hydromorphone vs ER oxycodone	1 y/NR	Direct costs	QALY (translate SPI to SF-6D)	2005, EUR	DSA, PSA
Contreras-Hernandez 2008 [37]/68	Mexico	Decision tree	Societal	Celecoxib vs NSAIDs	6 mo/NA	Direct costs	No. of patients with pain control and no AE	2008, USD	DSA, PSA
Castelnuovo 2008 [52]/94	UK	TOIB	NHS and societal	Oral vs topical ibuprofen	1 & 2 y/6%	Direct costs	QALY (EQ-5D)	2005, GBP	DSA, PSA
Bruyère 2009 [34]/73	France, Belgium, Switzerland, Austria, USA	STOPP	Public	Chondroitin sulfate vs placebo	2 y/NR	Drug costs	QALY (translate WOMAC to HUI)	2009, EUR	DSA

Table 2 (continued)

Study/QHES score	Country/region	Type of study	Perspective	Comparators	Time period/discount rate	Costs	Outcome	Year, currency	SA
Chou 2009 [35]/70	Taiwan	NR	Societal	Hylan G-F 20 vs sodium hyaluronate	6 mo/NR	Direct costs	QALY (VAS), HSS, WOMAC, Lequesne's index	2006, TWD	NR
Bessette 2009 [48]/85	Canada	Markov model	A third-party payer	Celecoxib as first- vs second-line treatment	5 y/3%	Direct costs	QALY	2005, CAD	One-way SA
Black 2009 [49]/87	UK	Cohort simulation	NHS	Glucosamine sulfate + current care vs current care	Lifetime/NR	Direct costs	QALY (translate WOMAC to HUI)	2008, GBP	DSA, PSA
Latimer 2009 [50]/94	UK	Markov model	NHS	Celecoxib + PPI vs etoricoxib + PPI	3 mo/3.5%	Direct costs	QALY (translate WOMAC to EQ-5D)	2007, GBP	DSA, PSA
Scholtissen 2010 [61]/91	Spain, Portugal	GUIDE	HCS	Glucosamine sulfate vs paracetamol	6 mo/NR	Drug costs	QALY (translate WOMAC to HUI)	2010, EUR	PSA
Brereton 2012 [53]/94	UK	Markov model	NHS	Celecoxib + PPI vs diclofenac + PPI	3 mo/3.5%	Direct costs	QALY (translate WOMAC to EQ-5D)	2011, GBP	DSA, PSA
Turajane 2012 [62]/84	Thailand	Prospective observational study	HCS	Celecoxib vs NSAIDs	6 mo/NR	Direct costs	QALY (EQ-5D)	2011, THB	NR
Wielage 2013 [54]/76	Canada	Markov model	Societal	Duloxetine vs celecoxib	3 mo/5%	Direct costs	QALY (translate patient-level pain to EQ-5D)	2011, CAD	One-way SA, PSA
Wielage 2013 [55]/86	USA	Discrete-state, time-dependent semi-Markov model	US private payer	Duloxetine vs naproxen	Lifetime/3%	Direct costs	QALY, WOMAC	2011, USD	One-way SA, PSA
Wielage 2013 [56]/75	USA	Markov model	US private payer	Duloxetine vs naproxen	Lifetime/16%	Direct costs	QALY (EQ-5D)	2011, USD	One-way SA, PSA
Brereton 2014 [57]/79	Sweden	NICE OA model	NHS	Celecoxib + PPI vs diclofenac + PPI	Lifetime/3%	Direct costs	QALY	2012, USD	PSA

Table 2 (continued)

Study/QHES score	Country/region	Type of study	Perspective	Comparators	Time period/discount rate	Costs	Outcome	Year, currency	SA
Capel 2014 [58]/86	Spain	Markov model	NHS	Naproxen + esomeprazole vs ibuprofen + PPI Naproxen + esomeprazole vs naproxen + PPI	1 y/NA	Direct costs	QALY, WOMAC	2012, EUR	DSA, PSA
Hatoum 2014 [59]/86	USA	Decision analytic model	Payer	Bioengineered hyaluronic acid + conventional care vs conventional care	52 wk/NR	Direct costs	QALY (HUI3), WOMAC	2012, USD	One-way SA, PSA
Wielage 2014 [60]/77	Canada	Semi-Markov model	Societal	Celecoxib vs diclofenac	3 mo/5%	Direct costs	QALY, WOMAC	2011, CAD	One-way SA, PSA
Castro 2015 [65]/83	Colombia	Discrete-event simulation model	Third-party payer	Hylan G-F 20 vs CST	5–20 y/3%	Direct costs	QALY (WOMAC)	2012, USD	PSA
Nasef 2015 [66]/83	Saudi Arabia	Markov model	Patient	Ibuprofen + PPI vs no treatment	3 mo/3%	Direct costs	QALY (translate WOMAC to EQ-5D)	2013, USD	PSA
Katz 2016 [67]/86	USA	OAPol model	Clinical policy	OTC naproxen vs ibuprofen Naproxen Rx + OTC PPI vs OTC naproxen	5 y/3%	Direct costs	QALY, WOMAC	2013, USD	One- and two-way SA, PSA
Rosen 2016 [68]/94	USA	Grootendorst model	Payer	Euflexxa + conventional care vs conventional care	6 mo/NR	Direct costs	QALY (translate WOMAC to HUI-3)	2015, USD	One-way SA
Bellamy 2016 [36]/72	USA	Randomized, double-blind, prospective study	NR	Ketorolac vs corticosteroid (injection)	3 y/NR	Direct costs	QALY, VAS, WOMAC, KSS, TL Knee Scoring Scale, SF-36, UCLA activity score	2015, USD	NR
Thomas 2017 [63]/87	France	Observational, prospective and multicenter study	Third-party payer	HA (Arthrum H 2%) vs NSAIDs	6 mo/NR	Direct costs	QALY (EQ-5D), WOMAC, EQ-VAS	2014, EUR	NR

Table 2 (continued)

Study/QHES score	Country/region	Type of study	Perspective	Comparators	Time period/discount rate	Costs	Outcome	Year, currency	SA
Smith 2017 [69]/86	USA	OAPol model	Societal	Tramadol vs opioid-sparing Tramadol + oxycodone vs opioid-sparing	3–12 mo/3%	Direct costs	QALY, delay and reduction of utilization of TKA	2014, USD	PSA
Hermans 2018 [64]/84	Netherlands	Randomized clinical trial	Societal and HCS	Usual care + HMW-HA (Hylan G-F 20) vs usual care	52 wk/NR	Productivity and medical costs	QALY (EQ-5D)	2010, EUR	PSA
Losina 2018 [70]/86	USA	OAPol model	HCS	Celecoxib vs OTC naproxen OTC naproxen + OTC PPIs vs OTC naproxen	Lifetime/3%	Direct costs	QALY, WOMAC	2015, USD	PSA
Migliore 2019 [38]/68	Italy	Markov model	NHS	Hylan G-F 20 (1×6 mL) vs acetaminophen Hylan G-F 20 (3×2 mL) vs acetaminophen	5 y/3.5%	Direct costs	QALY, no. of patients with reduction in knee OA symptoms	2016, EUR	One-way SA, PSA
Rosen 2019 [39]/73	USA	Tree diagram	Payer	HMW HA vs NSAID/analgesic medication	6 mo/NR	Direct costs	QALY	2019, USD	One-way SA
Rosen 2020 [71]/79	USA	Decision analytic models	Payer	HMW HA vs LMW HA	6 mo/NR	Direct costs	QALY	2019, USD	One-way SA
Samuelson 2020 [72]/90	USA	Tree diagram	Payer	PRP vs HA	1 y/3%	Direct costs	QALY, WOMAC (EQ-5D)	2019, USD	TSA
Karasawa 2021 [74]/93	Japan	Markov model	NHS	Celecoxib vs ioxoprofen	Lifetime/2%	Direct costs	QALY PUB avoided	2021, JPY/USD	One-way SA, PSA
Sun 2021 [76]/80	China	Markov model	Healthcare	Diclofenac vs diclofenac + PPI Diclofenac vs imrecoxib Imrecoxib vs imrecoxib + PPI Diclofenac + PPI vs imrecoxib + PPI	Lifetime/5%	Direct costs	QALY	2019, USD	PSA, DSA

Table 2 (continued)

Study/QHES score	Country/region	Type of study	Perspective	Comparators	Time period/discount rate	Costs	Outcome	Year, currency	SA
Sullivan 2021 [75]/94	USA	OAPol model	Healthcare	Usual care vs duloxetine + usual care	Lifetime/3%	Direct costs	QALY	2018, USD	One-way SA, Two-way SA, PSA
Chirikov 2021 [73]/80	United Arab Emirates	Discrete-state Markov model	Payer	Celecoxib vs ibuprofen Celecoxib vs naproxen	30 mo/3%	Direct costs	QALY	2019, USD	PSA, DSA

ACCES Arthritis Cost Consequence Evaluation System, *AE* adverse event, *CAD* Canadian dollar, *CEA* cost-effectiveness analysis, *CST* conventional supportive therapy, *DSA* deterministic sensitivity analysis, *ER* extended-release, *EUR* Euro, *GBP* British pound sterling, *GI* gastrointestinal, *GUIDE* Glucosamine Unum In Die Efficacy trial, *HA* hyaluronic acid, *HCS* the health care system, *HMW* high molecular weight, *HSS* hospital for special surgery, *HUI* Health Utility Index, *JPY* Japanese yen, *KSS* Knee Society Score, *LMW* low molecular weight, *LYG* life-year gained, *MPCI* minimal perceptible clinical improvement, *NA* not applicable, *NHS* National Health Service, *NICE* National Institute for Health and Care Excellence, *NR* not reported, *NSAID* non-steroidal anti-inflammatory drug, *OA* osteoarthritis, *OAPol model* Osteoarthritis Policy model, *OROS* osmotic-controlled release oral delivery system, *OTC* over-the-counter, *PPI* proton pump inhibitor, *PRP* platelet-rich plasma, *PSA* probabilistic sensitivity analysis, *PUB* perforation, ulcers and/or bleeding, *QALY* quality-adjusted life-year, *QHES* Quality of Health Economic Studies, *SA* sensitivity analysis, *SEK* Swedish kronor, *SF-36* Short Form-36, *SPI* Sleep Problems Index, *STOPP* Study on Osteoarthritis Progression Prevention, *THB* Thai Baht, *TKA* total knee arthroplasty, *TL* Tegner/Lysholm, *TOIB* Topical or Oral Ibuprofen study, *TSA* threshold sensitivity analysis, *TWD* New Taiwan dollar, *UCLA* University of California Los Angeles, *USD* US dollars, *VAS* visual analog scale, *WOMAC* the Western Ontario McMaster University Osteoarthritis Index

3.4 Cost Effectiveness of Drugs Estimates in Europe

Table 4 presents a total of 15 studies conducted in nine European countries, with one study involving two countries [61]. The UK and Sweden were the only countries in which more than one study was conducted. NSAIDs were the most common comparator to celecoxib. Most studies concluded that celecoxib was cost effective compared with other active treatment options based on local standards, and at times dominated comparators (was more effective and less costly) in some countries [37, 40, 41]. The cost and incremental effectiveness between the treatment and control groups varied between US$0.00755 and US$450.98, and 0.002 and 0.038 QALYs, respectively. The ICERs ranged from US$6461.63 to US$38,686.79 per QALY gained. Other articles reported IA injections, opioids, and SYSADOAs, and the intervention group showed cost effectiveness compared with the comparators. For IA injections, the cost and incremental effectiveness between the treatment and control groups varied between US$10.85 and US$1647.84, and 0.042 and 0.35116 QALYs, respectively. The ICERs ranged from US$258.36 to US$10,702.23 per QALY gained. There are three articles reporting a threshold interval and nine reporting a single threshold, while the remaining one did not report a threshold.

3.5 Cost Effectiveness of Drugs Estimates in the Americas

Table 5 lists 20 articles assessing the economic evaluations in the Americas, performed in three countries (US, Canada, and Colombia). Similar to other continents, celecoxib was considered cost effective when compared with NSAIDs. The ICERs varied between US$875.91 and US$307,013.56 per QALY gained. The ICER estimates also varied with the subject's pain and age [75]. However, a study comparing celecoxib with over-the-counter (OTC) naproxen showed that celecoxib was not cost effective because of its exorbitant annual price of US$880 [70]. In addition, one study comparing opioid-based strategies showed that celecoxib was not cost effective because it diminishes the effectiveness of total knee arthroplasty (TKA) [69].

3.6 Cost Effectiveness of Drugs Estimates Across Continents

Table 6 lists one article assessing the economic evaluations across continents, performed in five countries (France, Belgium, Austria, Switzerland, and USA). The ICER estimates also varied with the time period.

Table 3 Cost-effectiveness estimates in Asia (7 studies)

References	Country/region	Intervention and comparator	Δ Cost (US$)	Δ Effectiveness (QALY)	ICER (US$)	Cost-effectiveness threshold (US$)	Intervention cost effective? (+/−)
Traditional NSAIDs and/or coxibs							
Turajane 2012 [62]	Thailand	Celecoxib vs NSAID	$0.84	0.019	$44.4/QALY	NR	+
Nasef 2015 [66]	Saudi Arabia	Celecoxib + PPI vs ibuprofen + PPI	$120.32	0.06	$1980.88	$2255/QALY	+
		Ibuprofen + PPI vs no treatment	$1460.39	0.34	$4242.90	$2255/QALY	+
Karasawa 2021 [74]	Japan	Celecoxib vs loxoprofen	$62.02	0.024	$53,466.92	NR	+
Sun 2021 [76]	China	Imrecoxib vs diclofenac (lower risk of GI and CV events)	$614.22	1.49	$413.90	$30,921/QALY	+
		Imrecoxib vs diclofenac (higher risk of GI and CV events)	$571.06	1.13	$507.89	$30,921/QALY	+
Chirikov 2021 [73]	United Arab Emirates	Celecoxib vs ibuprofen	$38.77	0.0032	$11,854.92	$41,227–$123,682/QALY	+
		Celecoxib vs naproxen	$84.22	0.002	$40,999.56	$41,227–$123,682/QALY	+
IA injections							
Yen 2004 [44]	Taiwan	Celecoxib vs naproxen	$67.94	0.0023	$29,178.43	2002 Taiwan GDP per capita ($18,399) $46,773/QALY	+
Yen 2004 [44]	Taiwan	Hyaluronan vs celecoxib	$181.19	0.0031	$58,447.97	2002 Taiwan GDP per capita ($18,399) $46,773/QALY	−
Chou 2009 [35]	Taiwan	Hylan G-F 20 vs sodium hyaluronate	$51.27	0.019	Dominant	NR	+

CV cardiovascular disease, *GI* gastrointestinal, *IA* intra-articular, *ICER* incremental cost-effectiveness ratio, *NR* not reported, *NSAID* non-steroidal anti-inflammatory drug, *PPI* proton pump inhibitor, *QALY* quality-adjusted life-year

3.7 Subgroup Analyses

Subgroup analyses were conducted by type of study (trial-based or model-based), and time period (≤1 year, 1–5 years, lifetime). The results are presented as tables in the supplementary materials (Appendix 6, see ESM).

4 Discussion

In this study, we have addressed gaps (differences in study design and between health systems in each country) in the current evidence by separating the analysis of the cost effectiveness of OA drugs into different continents, and providing up-to-date analyses that would be useful for healthcare providers and payers, as well as researchers for conducting high-quality economic evaluations in the future.

OA is a chronic condition characterized by a long course of disease progression, often associated with severe impacts on the patient's quality of life and risk of mortality from other co-morbidities [78, 79]. The OA disease burden is growing faster than any other health condition globally [5, 80]. Improving patient quality of life and joint function are the primary goals of OA management strategies, for which the choice of appropriate healthcare interventions is critical in the light of rising costs for the OA patient population. Health economic evaluations provide a critical piece of the

Table 4 Cost-effectiveness estimates in Europe (15 studies)

Study	Country/region	Intervention and comparator	Δ Cost (US$)	Δ Effectiveness (QALY)	ICER (US$)	Cost-effectiveness threshold (US$)	Intervention cost effective? (+/−)
Traditional NSAIDs and/or coxibs							
Haglund 2000 [40]	Sweden	Celecoxib vs NSAID monotherapy	NR	NR	Dominant	NR	+
Svarvar2000 [41]	Norway	Celecoxib vs NSAID monotherapy	NR	NR	Dominant	NR	+
Contreras 2008 [37]	Mexico	Celecoxib vs NSAIDs	−$0.00755	0.0097	Dominant	Cost-effectiveness acceptability curves	+
Latimer 2009 [50]	UK	Celecoxib + PPI vs etoricoxib + PPI	$36.28	0.002	$18,343.27	$35,243/QALY	+
Brereton 2012 [53]	UK	Celecoxib + PPI vs diclofenac + PPI	$84.40	0.006	$14,131.82	$31,498/QALY	+
Brereton 2014 [57]	Sweden	Celecoxib+ PPI vs diclofenac + PPI	$87.93	0.006	$13,519.23	100,000 SEK ($16,971/QALY)	+
Castelnuovo 2008 [52]	UK	Oral vs topical ibuprofen (SP)	$120.32	0.038	$21,588.60	$16,548 – $22,065/QALY	+
		Oral vs topical ibuprofen (HP)	$450.98	0.038	$38,686.79	$16,548 – $22,065/QALY	+
Moore 2004 [43]	UK	Etoricoxib vs NSAIDs alone	$362.12	0.0097	$36,998.82	$57,341/QALY	+
		Etoricoxib vs NSAIDs + H2A	$169.95	0.0097	$17,364.45	$57,341/QALY	+
Capel 2014 [58]	Spain	Naproxen+ esomeprazole vs ibuprofen+ PPI	$78.73	0.0041	$18,824.96	$38,294/QALY	+
		Naproxen + esomeprazole vs naproxen+ PPI	$44.23	0.0068	$6461.63	$38,294/QALY	+
IA injections							
Thomas 2017 [63]	France	HA (Arthrum H 2%) vs NSAIDs	$10.85	0.042	$258.36	$55,549/QALY	+
Hermans 2018 [64]	Netherlands	Usual care + HMW-HA (Hylan G-F 20) vs usual care (SP)	$561.04	0.052	$10,702.23	$26,646/QALY	+
		Usual care + HMW-HA (Hylan G-F 20) vs usual care (HP)	$538.60	0.052	$10,702.23	$26,646/QALY	+
Migliore 2019 [38]	Italy	Hylan G-F 20 (1×6 mL) vs acetaminophen	$1354.25	0.35116	$3856.54	$24,462/QALY	+
		Hylan G-F 20 (3×2 mL) vs acetaminophen	$1647.84	0.35116	$4692.61	$24,462/QALY	+
Opioids							
Ward 2007 [47]	Germany	OROS hydromorphone vs ER oxycodone	$174.43	0.017	$11,984.84	NR	+

Table 4 (continued)

Study	Country/region	Intervention and comparator	Δ Cost (US$)	Δ Effectiveness (QALY)	ICER (US$)	Cost-effectiveness threshold (US$)	Intervention cost effective? (+/−)
SYSADOAs							
Black 2009 [49]	UK	Glucosamine sulfate + current care vs current care	NR	NR	$17,480.64	$51,675/QALY	+
Scholtissen 2010 [61]	Spain and Portugal	Glucosamine sulfate vs paracetamol	−$12.69	0.01	Dominant	$30,643 $46,630/QALY	+

ER extended-release, *HA* hyaluronic acid, *HMW* high molecular weight, *HP* healthcare system perspective, *H2A* histamine H2 receptor antagonist, *IA* intra-articular, *ICER* incremental cost-effectiveness ratio, *NR* not reported, *NSAID* non-steroidal anti-inflammatory drug, *OROS* Osmotic-controlled Release Oral delivery System, *PPI* proton pump inhibitor, *QALY* quality-adjusted life-year, *SEK* Swedish kronor, *SP* social perspective, *SYSADOAs* symptomatic slow-acting drugs for osteoarthritis

puzzle for informing clinical decision making related to OA interventions.

In this study, we performed a systematic review of the literature on cost-effectiveness analysis of OA pharmacological interventions, and provided insights into the changes seen in the methodology of these economic evaluations over the past two decades. Over the past years, such evaluations are no longer limited to decision trees and short time ranges that considered only gastrointestinal events, but have expanded to advanced models such as Markov [38, 48, 50, 53–56, 58, 60, 66, 73, 74, 76] and Osteoarthritis Policy models [67, 69, 70, 75] that incorporate considerations for longer time ranges, health utility, a wider range of adverse events including cardiovascular events, and more meaningful outcomes such as the cost per QALY ICERs. Depending on the continents, type of drug, the control group, and duration of follow-up, cost-effectiveness analyses for OA pharmacological interventions reported different ranges of ICER estimates.

Despite a significant growth in pharmacoeconomic evaluation studies of OA in recent years, as well as some innovations in trial and model design, the comparability among various studies remains poor due to a lack of standardized research methods and designs. For instance, our analysis indicated that most studies found celecoxib to be economically attractive compared with NSAIDs with or without gastric protective agents. However, due to significant heterogeneity in the methodology and design of the included studies, it is not possible to provide a confident recommendation. Several sources of study heterogeneity should be considered when interpreting the results of our review. First, different perspectives of cost analysis were adopted among the included studies, such as a payer or societal perspective, introducing inconsistencies into the types of resources that should and should not be compared to evaluate the cost effectiveness of pharmacological interventions. This is complicated by the fact that the effects of OA are multi-dimensional, involving not only individual disability and reduced quality of life, but also major impacts on overall societal productivity. This level of complexity is rarely being addressed in the current design of CEAs. Second, the included studies used a range of different comparators, such as comparing against baseline (standard care or no intervention) or comparing against other pharmacological interventions, which reduces the ability to make accurate comparisons among studies [81, 82]. Finally, it is important to note that for a chronic condition such as OA, clinical trials or models spanning only a few months (as seen in a major portion of the included studies) are unlikely to provide evidence that is representative of the entire course of disease. These identified challenges have been discussed in more detail elsewhere [83, 84].

Several key drivers of cost effectiveness were identified in our systematic review, which might have contributed to the variations seen in cost and effectiveness measures across continents. These include medical resources, productivity, relative risks, and selected comparators. Variation in medical resources could lead to different cost effectiveness of OA drugs in different geographical regions. Some economically under-developed areas may have less health resources than economically developed areas, and so some measures that achieve certain benefits but cost more may not be supported [44, 70]. Two trial studies reported that decreased productivity is the most influential parameter to changes in the cost effectiveness of OA drugs [51, 64]. The time lost by patients had a relatively strong effect on the estimated incremental net monetary benefit from a societal perspective.

It has been noted that the main driver of the cost effectiveness of OA drugs is the relative risk of the drugs, which affects the results of the model. The relative risk of the drug drives the absolute risk of the population, which in turn drives the projected cost of side effects and the risk and

Table 5 Cost-effectiveness estimates in the Americas (20 studies)

Study	Country/region	Intervention and comparator	Δ Cost (US$)	Δ Effectiveness (QALY)	ICER (US$)	Cost-effectiveness threshold (US$)	Intervention cost effective? (+/−)
Traditional NSAIDs and/or coxibs							
Loyd 2007 [46]	US	Celecoxib vs NSAIDs	$5205.96	0.1304	$39,436.80	$79,515/QALY	+
Bessette 2009 [48]	Canada	Celecoxib as first- vs second-line treatment	$1331.45	0.02	$51,656.40	NR	+
Wielage 2014 [60]	Canada	Celecoxib vs diclofenac	$53.10	0.0024	$23,818.81	$59,345/QALY	+
Losina 2018 [70]	US	Celecoxib vs OTC naproxen	$450.98	0.005	$307,013.56	$109,325/QALY	–
		OTC naproxen + OTC PPIs vs OTC naproxen	$450.98	0.007	$63,639.81	$109,325/QALY	–
Kamath 2003 [42]	US	Ibuprofen vs acetaminophen	$71.23	0.08	$875.91	Cost-effectiveness acceptability curves	+
Wielage 2013 [54]	Canada	Duloxetine vs celecoxib	$624.72	0.0169	$36,613.26	$59,345/QALY	+
Wielage 2013 [55]	US	Duloxetine vs naproxen	$1458.94	0.0266	$54,188.77	$59,345/QALY	+
Wielage 2013 [56]	US	Duloxetine vs naproxen	$1533.73	0.0266	$67,594.46	$59,345/QALY	+
Katz 2016 [67]	US	Naproxen OTC vs ibuprofen	$426.13	0.007	$60,139.76	$112,726/QALY	+
		Naproxen Rx + PPI OTC vs naproxen OTC	$2130.31	0.025	$84,173.71	$112,726/QALY	+
Sullivan 2021 [75]	US	Duloxetine + usual care vs usual care (57 years old and WOMAC pain 55)	$950.27	0.009	$93,442.99	$93,443/QALY	+
		Duloxetine + usual care vs usual care (65 years old and WOMAC pain 55)	$844.68	0.005	$167,458.29	$93,443/QALY	+
		Duloxetine + usual care vs usual care (75 years old and WOMAC pain 55)	$739.10	0	Dominated[2]	$93,443/QALY	+
		Duloxetine + usual care vs usual care (57 years old and WOMAC pain 25)	$1372.61	0.031	$45,296.09	$93,443/QALY	+
		Duloxetine + usual care vs usual care (65 years old and WOMAC pain 25)	$1267.02	0.03	$40,755.93	$93,443/QALY	+
		Duloxetine + usual care vs usual care (75 years old and WOMAC pain 25)	$1161.44	0.03	$40,755.93	$93,443/QALY	+

cost of post-event switch in therapy [37], and also reduces quality of life, resulting in an increase in ICER [41, 53, 54, 57]. Some studies have shown that cost effectiveness varies among the selected comparators. The adverse events rate and PPI utilization rate may vary when different comparators are used, which have a great impact on the results of the

Table 5 (continued)

Study	Country/region	Intervention and comparator	Δ Cost (US$)	Δ Effectiveness (QALY)	ICER (US$)	Cost-effectiveness threshold (US$)	Intervention cost effective? (+/−)
IA injections							
Torrance 2002 [45]	Canada	Hylan G-F 20 + appropriate care vs appropriate care (SP)	$791.71	0.071	$11,150.83	$31,754/QALY	+
		(HP)	$786.13	0.071	$11,072.71	$31,754/QALY	+
Hatoum 2014 [59]	US	BioHA + conventional care vs conventional care	$1048.13	0.024	$43,671.75	$57,529/QALY	+
Bellamy 2016 [36]	US	Ketorolac vs corticosteroid (injection)	NR	NR	Dominant	NR	+
Rosen 2016 [68]	US	Euflexxa + conventional care vs conventional care	$574.82	0.115	$4,998.46	$54,663/QALY	+
Rosen 2019 [39]	US	HMW HA vs NSAID/analgesic medication	$273.33	0.026	$10,512.77	$51,534/QALY	+
Rosen 2020 [71]	US	HMW HA vs LMW HA	$87.61	0.029	$3020.96	$51,534/QALY	+
Samuelson 2020 [72]	US	PRP vs HA	$1477.66	0.11	$13,015.63	$51,534/QALY	+
Castro 2015 [65]	Colombia	Hylan G-F 20 vs CST	NR	NR	Dominant	NR	+
Opioids							
Marshall 2006 [51]	US	Oxycodone vs oxycodone + paracetamol	$1054.90	0.0105	$100,467.71	$68,511–$137,022/QALY	+
Smith 2017 [69]	US	Tramadol vs opioid-sparing	$1999.77	0.04	$42,765.01	$111,098/QALY	-
		Tramadol + oxycodone vs opioid-sparing	$5777.11	0.05	$128,028.74	$111,098/QALY	-

CST conventional supportive therapy, *HA* hyaluronic acid, *HMW* high molecular weight, *HP* health care system perspective, *IA* intra-articular, *ICER* incremental cost-effectiveness ratio, *LMW* low molecular weight, *NR* not reported, *NSAID* non-steroidal anti-inflammatory drug, *OTC* over-the-counter, *PPI* proton pump inhibitor, *PRP* platelet-rich plasma, *QALY* quality-adjusted life-year, *SP* social perspective, *WOMAC* the Western Ontario McMaster University Osteoarthritis Index

Table 6 Cost-effectiveness estimates across continents (1 study)

References	Country/region	Intervention and comparator	Δ Cost (US$)	Δ Effectiveness (QALY)	ICER (US$)	Cost-effectiveness threshold (US$)	Intervention cost effective? (+/−)
SYSADOAs							
Bruyère 2009 [34]	France, Belgium, Austria, Switzerland, US	Chondroitin sulfate vs placebo (6 mo)	$120.45–$193.57	0.011	$10930.17–$27799.73	$40,085/QALY	+
		(12 mo)	$240.91–$387.14	0.011	$12688.80–$20392.15	$40,085/QALY	+
		(24 mo)	$481.81–$774.26	0.011	$17299.89–$27799.73	$40,085/QALY	+

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year, *SYSADOAs* symptomatic slow-acting drugs for osteoarthritis model. Therefore, the importance of selecting an appropriate comparator is becoming increasingly apparent, and the interpretation of cost-effectiveness analysis between active comparators requires some caution [60].

Threshold ICER plays a central role in the methodology and application of CEAs, since the intervention ICERs are compared against the threshold to determine whether new interventions offer good value for money. There are several factors requiring consideration here. (i) There are fundamental differences in the threshold values for cost per QALY between different countries or healthcare systems. (ii) Some studies have specified a threshold range rather than a single value [51, 61]. (iii) In some studies, the threshold value against which the intervention ICERs should be compared is unknown. These factors may support the current view that a single ICER threshold should not be applied in CEAs involving a diverse range of technologies and conditions [85]. Moreover, defining an ICER threshold value might be more appropriate in a national health service system, where healthcare budgets are well-defined and more fixed than in a social security system, where the maximum level of total co-payments of the entire population is undefined [85–89]. To ensure efficient healthcare resource allocation, such issues surrounding the definition of ICER thresholds need to be thoroughly considered together with the study population involved.

Our review provides a different perspective on CEA evaluations on the pharmacological management of OA. Although a number of previous reviews have been published on different aspects of this topic [21, 24, 90–94], they have typically described a limited range of therapies and were mostly published more than 5 years ago. Our study provides up-to-date, comprehensive information on a more complete range of OA pharmacological interventions, including oral drugs and IA injections. In addition, in light of limited reviews reporting standardized inflation rates, our study presented pooled economic results that were adjusted by 'purchasing power parity' (PPP) and time period, and normalized across different countries. It is interesting to note that 87% of the studies included in our review were conducted in Europe and North America, which may suggest an increasing OA burden in these regions, but is also reflective of strong HTA institutions and the use of economics in decision making and market value.

The interpretation of findings presented in our review is subject to a few limitations. First, high-quality studies that were not published in English but otherwise satisfy the inclusion criteria were not considered in our analysis, which may have made our results more relevant for English-speaking countries. Second, our investigation was limited to pharmacoeconomic analyses that presented ICERs or found an intervention to be dominant. We are aware of cost-minimization studies in which certain treatments have been found cost-saving, and which were analogous to the included CEAs, but were not considered in our analysis since ICERs were not calculated [95–100]. Finally, since the included studies span a period of approximately two decades, some of the pharmaceutical prices have dropped significantly since these studies were published, particularly if they were in the 2000s. The findings of these studies therefore may not accurately depict the current market value of the same pharmaceuticals.

5 Conclusion

The findings of this systematic review suggest substantial uncertainty regarding the ICER estimates for OA pharmacological therapies, due to the heterogeneity of the included studies. Nevertheless, the results of most studies indicated cost effectiveness of the intervention based on specific ICER thresholds. There are fundamental differences in the threshold values for cost per QALY in studies, which is contributed by the difference in the threshold determination method used. Further efforts are needed to increase the standardization and quality of applied methods, and future studies should report the threshold that was used to determine cost effectiveness.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40258-022-00717-0.

Declarations

Funding Open Access funding enabled and organized by CAUL and its Member Institutions. This study was supported by the National Natural Science Foundation of China (81802204), China Postdoctoral Science Foundation (2020M671453), Natural Science Foundation of Shanxi Province (201801D221117), Program for the Outstanding Innovative Teams of Higher Learning Institutions of Shanxi (2019L0410), and National Health and Medical Research Council (Australia; GNT1120249).

Conflict of interest The authors declare that we have no financial or personal relationships with other people or organizations that could inappropriately influence our work.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material All data generated or analyzed during this study are included in this published article and its supplementary information files.

Code availability Not applicable.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by JYS, KNF, LY, ZJF, FL, GSW, HMY, JJL, and BW. The first draft of the manuscript was written by JYS, JJL, and BW and all authors provided comment and revision on subsequent versions of the manuscript. All authors read and approved the final manuscript.

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