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Disease-modifying drugs for knee osteoarthritis: can they be cost-effective?

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SUMMARY

Objective: Disease-modifying osteoarthritis drugs (DMOADs) are under development. Our goal was to determine efficacy, toxicity, and cost thresholds under which DMOADs would be a cost-effective knee OA treatment.

Design: We used the Osteoarthritis Policy Model, a validated computer simulation of knee OA, to compare guideline-concordant care to strategies that insert DMOADs into the care sequence. The guideline-concordant care sequence included conservative pain management, corticosteroid injections, total knee replacement (TKR), and revision TKR. Base case DMOAD characteristics included: 50% chance of suspending progression in the first year (resumption rate of 10% thereafter) and 30% pain relief among those with suspended progression; 0.5%/year risk of major toxicity; and costs of $1,000/year. In sensitivity analyses, we varied suspended progression (20–100%), pain relief (10–100%), major toxicity (0.1–2%), and cost ($1,000–$7,000). Outcomes included costs, quality-adjusted life expectancy, incremental cost-effectiveness ratios (ICERs), and TKR utilization.

Results: Base case DMOADs added 4.00 quality-adjusted life years (QALYs) and $230,000 per 100 persons, with an ICER of $57,500/QALY. DMOADs reduced need for TKR by 15%. Cost-effectiveness was most sensitive to likelihoods of suspended progression and pain relief. DMOADs costing $3,000/year achieved ICERs below $100,000/QALY if the likelihoods of suspended progression and pain relief were 20% and 70%. At a cost of $5,000, these ICERs were attained if the likelihoods of suspended progression and pain relief were both 60%.

Conclusions: Cost, suspended progression, and pain relief are key drivers of value for DMOADs. Plausible combinations of these factors could reduce need for TKR and satisfy commonly cited cost-effectiveness criteria.

Introduction

Knee osteoarthritis (OA) is a prevalent and costly disease characterized by structural changes in cartilage, bone, synovium, and other joint structures[1]. Symptomatic knee OA is a leading cause of disability, afflicting more than 9.3 million US adults[2]. The risk for knee OA is growing substantially due to the aging population, obesity epidemic, and an increasing rate of knee injuries in young, active individuals[1,3–7].

Current guidelines for knee OA care focus on pain relief and functional improvement[8–10]. Pharmacologic therapies are only

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modestly efficacious and have significant associated toxicities. For example, non-steroidal anti-inflammatory drugs (NSAIDs) pose gastrointestinal and cardiovascular risks[11–13]. There are no currently approved OA treatments capable of slowing OA-related structural progression or delaying the need for total knee replacement (TKR). Several large pharmaceutical companies are in the late stages of developing and testing disease-modifying OA drugs (DMOADs), and promising agents that may both halt progression and provide symptom relief are currently being studied[14–17].

In light of ongoing efforts to develop DMOADs, we sought to address several key questions: Can DMOADs be cost-effective, and if so, at what levels of efficacy, toxicity, and cost? How early in the course of treatment should DMOADs be initiated? Do DMOADs have the potential to reduce TKR utilization? To address these key issues, we propose a novel framework in which model-based evaluations of cost-effectiveness can be used to *pre-evaluate* new treatment strategies before the treatments are actually in widespread use. Estimating the effects of particular features of a medication on that medication's cost-effectiveness can inform the design of trials and provide performance targets.

Methods

Analytic overview

We used the Osteoarthritis Policy (OAPol) Model, a validated state-transition computer simulation model, to compare clinical outcomes and costs between subjects receiving guideline-concordant treatments (the standard of care (SoC)) and subjects receiving SoC and DMOADs[18,19]. Outcomes included costs, quality-adjusted life expectancy (QALE), incremental cost-effectiveness ratios (ICERs, the ratio of change in costs to change in QALE), and TKR utilization. In conformity with accepted practice, strategies that increased cost while not increasing QALE relative to an alternative treatment strategy were referred to as "Dominated." We performed the analysis from the health systems perspective (indirect costs were not included), with costs and QALE discounted at a rate of 3%/year, as recommended by the Panel on Cost-Effectiveness in Medicine[20].

The OAPol Model

The OAPol Model is a Monte Carlo simulation with a 1-year cycle length and health states defined by knee OA severity, presence of knee pain, comorbidities, and obesity[18,19]. Each year, subjects may develop a comorbid condition, increase in body mass index (BMI), progress in OA severity, and/or die. Progression of OA is defined as an increase by one Kellgren–Lawrence (K–L) radiographic grade and is dependent on obesity status and sex[21]. The model considers five comorbid conditions: coronary heart disease, diabetes mellitus, chronic obstructive pulmonary disease, cancer, and musculoskeletal disorders other than OA. The prevalences of these comorbid conditions depend on age, sex, race/ethnicity, and obesity[22–24]. Each subject is followed until death, which may occur in any health state. The OAPol Model uses underlying mortality rates from US life tables with excess mortality due to specific comorbid conditions removed[25]. Individuals with comorbid conditions have greater risk of death[26,27]. Subjects with knee OA may receive OA treatments, which are characterized by the ability to relieve pain and suspend OA progression, toxicity, and cost. OA treatments may carry major (e.g., gastrointestinal bleeding) and minor (e.g., dyspepsia, rash) toxicities, both of which decrease quality of life and increase costs. Major toxicities lead to regimen discontinuation and may also cause death.

Each year, subjects accrue costs and changes in quality of life due to OA or OA-related treatments and other underlying medical conditions. Quality of life weights are assigned to capture preferences for health states; a value of 1.0 denotes a state of perfect health while a value of zero denotes health states that are preferentially equivalent to death[28]. Annual medical costs not directly attributable to knee OA are based on comorbidities and age[22,23,30,33]. These data are presented in Table I. Running tallies of survival, quality-adjusted survival, and costs are maintained for each individual and then aggregated to compute average values for the cohort[57]. The following paragraphs describe the means of modeling the SoC and DMOAD regimens.

Guideline-concordant OA care (SoC)

The SoC consists of four, sequentially more invasive regimens: conservative pain management, including NSAIDs, acetaminophen, supportive devices, and physical therapy (Regimen 1); corticosteroid injections (Regimen 2); primary TKR (Regimen 3); and revision TKR (Regimen 4)[8–10]. Subjects progress to the next regimen in the sequence only when the current treatment fails or if a major toxicity occurs. Failure of each regimen is assumed to be detected in the year it occurs. Fundamental treatment characteristics for the SoC are presented in Table I and described in detail in the Technical Appendix.

DMOADs

We evaluated treatment strategies where DMOADs were used after the first SoC regimen and before the second SoC regimen. Fig. 1 illustrates the treatment sequence for individuals receiving DMOADs. There are two measures of DMOAD efficacy: structural efficacy and pain relief. Structural efficacy is defined by a relative reduction in the probability of progressing from one K–L grade to the next. Subjects for whom DMOADs suspend OA progression (i.e., DMOADs exhibit structural efficacy) remain at their current K–L grade. Subjects in whom structural progression is suspended may also experience pain relief and improvement in quality of life. To ensure a conservative approach with respect to the clinical value of DMOADs, we assumed that DMOAD-related pain relief is restricted to subjects in whom knee OA progression is suspended. Delaying progression at earlier stages of the disease prevents decrements in quality of life associated with advanced OA (K–L grade 3 or 4). Subjects experiencing toxicity (major or minor) have a decrement in quality of life for that year and incur costs to treat the toxicity. Major toxicity carries a small risk of death. Subjects are removed from DMOADs and move on to the next treatment in the sequence if DMOADs fail to suspend progression and that failure is detected, or if a major toxicity occurs. Fig. 2 shows the OAPol Model process for subjects receiving DMOADs.

Base case DMOAD characteristics and assumptions

As recommended by the Panel on Cost-effectiveness Analyses in Health and Medicine, we chose a set of "base case" estimates of DMOAD efficacy, cost, and toxicity, to reflect the most likely set of parameters of DMOADs based on a review of available literature when possible and otherwise based on extensive discussions with clinicians[20]. In the base case, we assumed that DMOADs suspended OA progression in 50% of subjects. Among those in whom DMOADs succeeded in suspending progression in the first year, there was a 10% failure rate of maintaining the suspension of progression in every subsequent year. We further assumed that once disease progression resumed, it could no longer be suspended via DMOADs. For the base case analysis we chose to anchor pricing for DMOADs at $1,000/year, similar to the cost of prescription NSAIDs[30]. In addition to the baseline cost of DMOADs, we also considered the

Table I
Select OAPol Model inputs

Age at treatment initialization (mean ± standard deviation)			53.54 ± 14.39			Losina *et al.*, 2012[31]
Osteoarthritis progression (*annual likelihood*, %)						
Obesity group	K–L 2 to K–L 3			K–L 3 to K–L 4		Holt *et al.*, 2011[19]
	Male		Female	Male	Female	
Non-obese	5.58		4.00	1.29	1.95	
Obese	12.26		8.95	2.94	4.27	
Quality of life utilities*						
Utility for subjects with severe OA (K–L 3 or 4): 0.690						Losina *et al.*, 2009[32]
Number of comorbidities	Age group	Non-obese		Obese		
		OA pain	No OA pain	OA pain	No OA pain	
0–1	25–44	0.814	0.955	0.781	0.921	NHANES, 2005–08[22,23]
	45–64	0.806	0.952	0.773	0.918	
	65+	0.884	0.943	0.850	0.909	
2–3	25–44	0.721	0.903	0.688	0.870	
	45–64	0.713	0.901	0.679	0.867	
	65+	0.791	0.891	0.757	0.858	
>3		0.662	0.662	0.662	0.662	
Annual direct medical costs (*USD, 2010*)						
Number of comorbidities	Age group	OA pain	No OA pain			Pope *et al.*, 2004[33]
0–1	25–34	$1,506	$1,302			NHANES, 2005–8[22,23]
	35–44	$2,018	$1,814			CPI, 2010[34]
	45–49	$2,635	$2,431			MCBS, 2006[35]
	50–54	$2,636	$2,432			Red Book, 2010[30]
	55–59	$3,443	$3,239			
	60–64	$4,144	$3,940			
	65–69	$4,401	$4,198			
	70–74	$5,092	$4,888			
	75–79	$5,916	$5,712			
	80+	$7,709	$7,505			
2–3	25–34	$6,856	$6,652			
	35–44	$7,368	$7,165			
	45–49	$7,958	$7,755			
	50–54	$7,959	$7,755			
	55–59	$8,436	$8,232			
	60–64	$9,136	$8,933			
	65–69	$9,060	$8,856			
	70–74	$9,750	$9,547			
	75–79	$10,575	$10,371			
	80+	$12,367	$12,163			
>3	25–34	$12,710	$12,506			
	35–44	$13,223	$13,019			
	45–49	$11,954	$11,751			
	50–54	$11,955	$11,751			
	55–59	$13,105	$12,902			
	60–64	$13,806	$13,602			
	65–69	$15,570	$15,366			
	70–74	$16,260	$16,056			
	75–79	$17,084	$16,881			
	80+	$18,877	$18,673			

(*continued on next page*)

Table I (*continued*)

SoC treatments				
Regimen 1: NSAIDs, acetaminophen, physical therapy, assistive devices		First year	Subsequent year failure	
	Pain relief (annual, %)[†]	64.00	24.00	Scott *et al.*, 2000[36]
		First year	Subsequent years	
	Major toxicity (annual, %)	0.38	0.38	Solomon *et al.*, 2005[11], Goldstein *et al.*, 1999[37]
	Minor toxicity (annual, %)	2.95	2.24	Bensen *et al.*, 1999[52], Scott *et al.*, 2000[36], Silverstein *et al.*, 1995[38]
	Cost (USD, 2010)	$643	$483	Medicare, 2010[39–41], Red Book, 2010[30], MCBS, 2006[35], Van Der Esch *et al.*, 2003[42], Grindrod *et al.*, 2010[43]
Regimen 2: Corticosteroid Injections		First year	Subsequent year failure	
	Pain relief (annual, %)[†]	64.00	19.00	Raynauld *et al.*, 2003[44]
		First year	Subsequent years	
	Major toxicity (annual, %)	0.00	0.00	Ayral, 2001[45]
	Minor toxicity (annual, %)	24.00	24.00	Ayral, 2001[45]
	Cost[†] (USD, 2010)	$437	$437	Medicare, 2010[39–41], MCBS, 2006[35]
Regimen 3: Primary TKR		First year	Subsequent year failure	
	Pain relief (annual, %)[‡]	86.20	4.00	Katz *et al.*, 2007[46]
		First year	Subsequent years	
	Major toxicity (annual, %)	1.33	0.00	Paxton *et al.*, 2010[47], Katz *et al.*, 2004[48]
	Minor toxicity (annual, %)	2.94	0.00	Katz *et al.*, 2004[48]
	Cost[†] (USD 2010)	$19,065	$90	Medicare, 2010[39–41], HCUP, 2008[53], Buntin *et al.*, 2005[50], CPI, 2010[34], Teeny *et al.*, 2003[51]
Regimen 4: Revision TKR		First year	Subsequent year failure	
	Pain relief (annual, %)[‡]	74.30	5.60	Katz *et al.*, 2007[46]
		First year	Subsequent years	
	Major toxicity (annual, %)	0.96	0.00	Paxton *et al.*, 2010[47], Katz *et al.*, 2004[48]
	Minor toxicity (annual, %)	3.64	0.00	Katz *et al.*, 2004[48]
	Cost[†] (USD 2010)	$24,631	$90	Medicare, 2010[39–41], HCUP, 2008[53], Buntin *et al.*, 2005[50], CPI, 2010[34], Teeny *et al.*, 2003[51]
DMOADS[§]				
		first year	Subsequent years	
Annual costs (*base case*) (USD, 2010)				
Overall		$1,000–$7,000 (**$1,000**)		
Office visits		$132	$93	2010 Medicare Data[39–41]
Efficacy (*base case*) %, annual		1st year	Subsequent year failure	
Halted progression (K–L 2–3)[‖]		20–100 (**50**)	1–10 (**10**)	
Pain relief[¶] (K–L 2–3)[‖]		10–100 (**30**)	1–10 (**1**)	
Toxicity (*base case*) %, annual		1st year	Subsequent years	
Major		0.5–2.0 (**0.5**)	0.5–2.0 (0.5)	
Minor		9.50	7.27	Scott *et al.*, 2000[36], Bensen *et al.*, 1999[52]
Toxicity outcomes				
Major	Cardiovascular	Likelihood	32.3	Solomon *et al.*, 2005[11]
		Mortality	6.02	HCUP, 2008[53]
		Utility[#]	0.778	Sullivan and Ghushchyan, 2006[54], NHANES, 2005–08[22,23]
		Cost[#]	$18,478	HCUP, 2008[53], CPI, 2010[34]
	Gastrointestinal	Likelihood	67.7	Goldstein 2000[37]
		Mortality	2.93	HCUP 2008[53]
		Utility	0.859	Jansen 2007[55], NHANES 05-08[22,23]
		Cost	$9,408	HCUP 2008[53], CPI 2010[34]

Minor	General minor events	Likelihood	100	
		Mortality	0	
		Utility	0.923	Jansen *et al.*, 2007[55], NHANES, 05–08[22,23]
		Cost	$47	Kamath *et al.*, 2003[56], CPI, 2010[34]

Abbreviations: CPI, consumer price inflation calculator; MCBS, Medicare Current Beneficiary Survey; HCUP, Healthcare Cost and Utilization Project.
*The lowest utility associated with the subject's health state was used by the model: for example, a 45-year-old subject with severe OA and one comorbidity would have a utility of 0.690, whereas, the same subject with three comorbidities would have a utility of 0.662.
† Efficacy for regimens 1 and 2 applies only to individuals who are at K–L grade 2.
‡ Only pain relief efficacy associated with TKR is shown. TKR technical efficacy (e.g., stability of the implant) was greater than 98% for primary and revision TKR.
§ Sensitivity analysis ranges for each parameter have been presented; base case values appear in bold within parentheses.
‖ Pain relief and suspended progression were 0% for subjects who have progressed to K–L grade 4. (K–L 4 represents the most severe level of knee OA, thus patients cannot progress beyond it.)
¶ Pain relief only occurred if there was also suspended progression.
# Toxicity utilities and costs (USD, 2010) were applied only in the year that the event occurred.

cost of one office visit per year: $132 in the first year and $93 in subsequent years (reflecting higher costs for new patient visits)[58].

In practice, monitoring for drug failure is typically triggered when patients report the persistence or recurrence of pain. Since drug failures to suspend disease progression would be accompanied by pain, we therefore assumed that all DMOAD failures would be detected in the year they occurred, resulting in discontinuation of DMOADs and allowing subjects to advance to the next treatment regimen. We assumed in the base case that the likelihood of pain relief was 30% given that progression was suspended (that is, 15% overall likelihood of pain relief). Among patients whose structural progression had been suspended due to DMOADs and who experienced initial pain relief, there was a 1%/year chance of losing pain relief. The failure to sustain pain relief reflects a multitude of factors, including suboptimal adherence and accumulation of additional risk factors such as injury.

We anchored values for both major and minor toxicities of DMOADs to NSAID toxicity characteristics. The cohort of individuals eligible to receive DMOADs will be similar to the population currently utilizing NSAIDs for OA pain; thus, acceptable DMOAD adverse event rates are likely to be comparable to those of NSAIDs. The likelihood of major toxicity was assumed to be 0.5% per year based on the major toxicity risks of Cox-2 selective NSAIDs[11,37]. DMOAD minor toxicity was modeled after the toxicity of non-selective NSAIDs, with 9.50% risk in the first year, and 7.27% risk in all subsequent years[36,52].

Cohort characteristics

We considered cohorts with a mean age of 53.5 years (standard deviation 14.4 years) based on estimates of the average age of OA diagnosis in the US[31]. Race/ethnicity, sex, and obesity distributions for persons with diagnosed knee OA were derived from the National Health Interview Survey (NHIS) 2007–2008[24]. In the absence of efficacious DMOADs, annual OA progression rates (percentage of subjects who worsened in K–L grade in a year) ranged from 1.29% for non-obese, K–L grade 3 males to 12.26% for obese, K–L grade 2 males[19]. Annual underlying (not related to OA management) medical costs (USD, 2010) ranged from $1,302 for young subjects with at most one comorbid condition to $18,877 for older subjects with greater than three comorbid conditions[22,23,30,33–35]. Quality of life weights were derived by converting responses to general health status questions in the National Health and Nutrition Examination Survey (NHANES) 2005–2008 to health status ratings on a scale of 0–1.0[22,23,59,60]. These ratings were then transformed to preference-based utilities[61]. The values ranged from 0.95 for young, healthy subjects with no OA pain to 0.66 for older subjects with several comorbidities and knee pain. Advanced knee OA (defined as symptomatic K–L grades 3 or 4) had a quality of life weight of 0.69[32]. Prevalence of comorbid conditions were derived from NHANES 2005–2008[22,23]. Table I summarizes select cohort input characteristics; additional details have been published elsewhere[18,19] or are presented in the Technical Appendix.

Sensitivity analyses

Two-way sensitivity analyses of DMOAD characteristics

We conducted 21 sets of two-way sensitivity analyses, varying likelihood of suspending OA progression, pain relief, major toxicity, loss of pain relief and/or resumption of OA progression, and costs. We tested the sensitivity of DMOAD cost-effectiveness to variations in the initial likelihood of suspended progression (20–100%), failure to suspend progression in subsequent years (1–10%), initial pain relief (10–100%), failure to relieve pain in subsequent years (1–10%), cost ($1,000–$7,000), and major toxicity (0.1–2%)

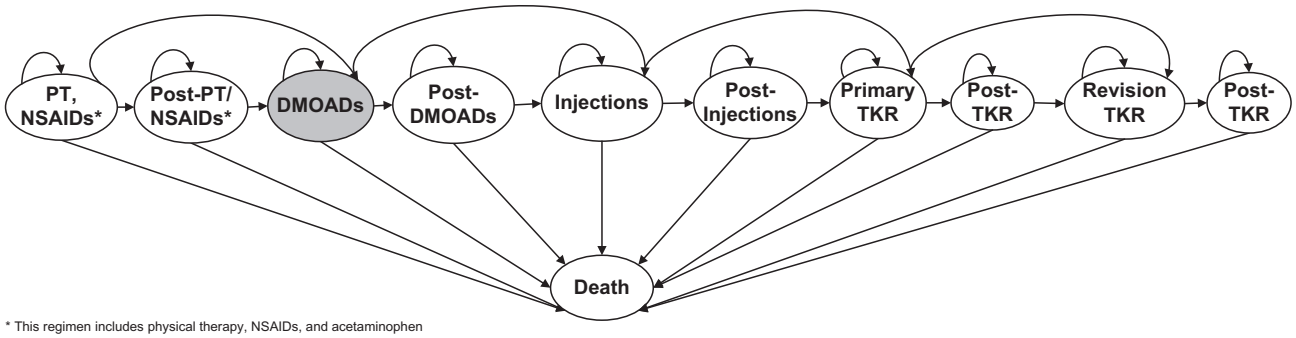


Fig. 1. This figure shows the treatment sequence that each model subject will receive. Initially, subjects are on the first regimen, which consists of NSAIDs, acetaminophen, and physical therapy. Each year on the regimen, subjects are evaluated for regimen failure and for major toxicity. If the regimen fails or a major toxicity occurs, the subject will be removed from the regimen and will move on either to the next regimen or to a post-treatment waiting period. Subjects will remain in the post-treatment waiting period until they are determined to be eligible for the next treatment. Subjects in the DMOADs cohorts are eligible to receive DMOADs after the first regimen (subjects not in the DMOADs cohort move on to corticosteroid injections). Once DMOADs fail to relieve pain or a major toxicity occurs, subjects move on to receive corticosteroid injections either immediately, or after a waiting period. This process continues through to TKR. Each year, subjects are evaluated for death; a subject may die at any point.

in a series of two-way sensitivity analyses. By modeling DMOADs with low levels of pain relief (10%), we incorporated the possibility that DMOADs may not necessarily provide pain relief, even if they suspend progression. These ranges were chosen to cover the spectrum of possible DMOAD characteristics. Costs and toxicity were anchored to known values for NSAIDs, based on recommendations from experts in the field.

Additional sensitivity analyses

In addition to varying levels of DMOAD efficacy, toxicity, and cost, we varied the timing of DMOAD administration, defined by where DMOADs are inserted in the current SoC sequence. We also varied the placement of the regimens by switching the order of Regimen 1 (NSAIDs, physical therapy, acetaminophen) and Regimen 2 (corticosteroid injections). We also tested the effect of removing Regimen 2 (corticosteroid injections) from the treatment sequence.

In a separate sensitivity analysis, we examined the value of DMOADs while varying the baseline K–L grade distribution: (1) initialized with 100% K–L grade 1 OA, and (2) initialized with 50% K–L grade 1 and 50% K–L grade 2 OA.

Finally, we conducted a sensitivity analysis using data for doxycycline, which has been suggested to have disease-modifying properties. One published study showed that doxycycline could reduce progression by up to 40% while doxycycline has not been shown to have any effect on symptoms[29]. We modeled minor gastrointestinal toxicities (the most significant toxicity reported in the study) occurring at a rate of 7% annually. Costs were estimated at $200 annually according to the Red Book[30].

Results

Base case analysis (Table II, top row)

Clinical benefits of DMOADs

The QALE among persons with knee OA who received the SoC was estimated at 14.21 quality-adjusted life years (QALYs) discounted (22.22 QALYs undiscounted). Adding base case DMOADs as the second-line regimen in the treatment sequence (after NSAIDs and physical therapy but before corticosteroid injections) led to an estimated QALE of 14.25 QALYs.

Among knee OA patients receiving the current SoC, 11.00% underwent TKR within 10 years of treatment initiation, with a 52.37% lifetime risk of primary TKR. Adding base case DMOADs as the second-line regimen reduced the 10-year risk of TKR by 46%, with 5.99% of the DMOADs cohort receiving TKR within 10 years of treatment initiation. Moreover, DMOADs reduced lifetime risk of TKR by 15%, with 44.35% of the DMOADs cohort receiving primary TKR.

Cost-effectiveness of DMOADs

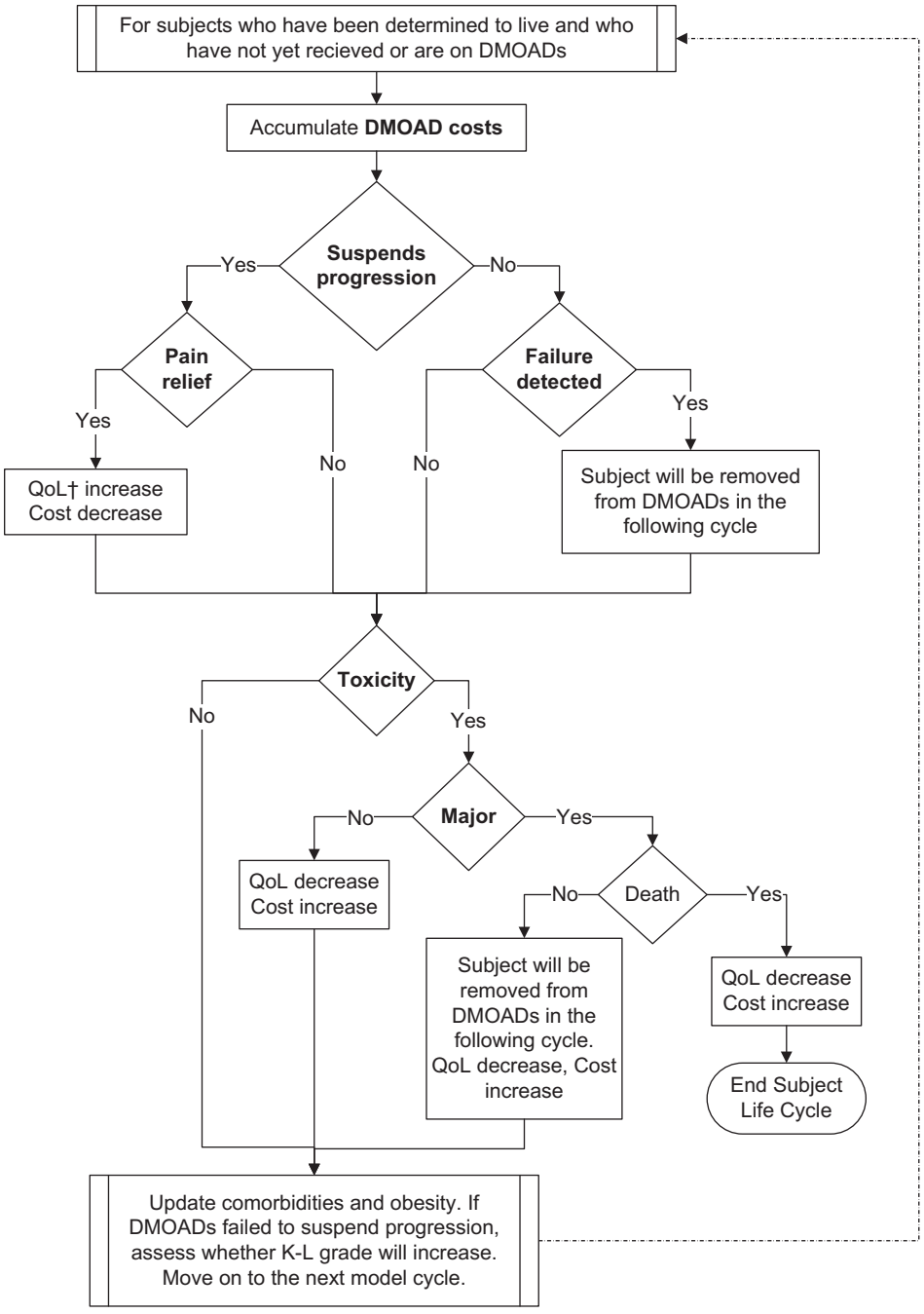
Priced at $1,000 annually, the cost-effectiveness of DMOADs offered as the second-line regimen for those diagnosed with knee OA was estimated at $57,500/QALY gained.

Guidance for the prospective evaluation of DMOADs regimens

Fig. 3 shows the minimum degree of structural OA progression suspension and pain relief at which DMOADs might be considered cost-effective using three different cost-effectiveness thresholds: $50,000/QALY, $100,000/QALY, and $150,000/QALY. Assuming DMOADs are associated with 0.5% risk of major toxicity and failure of DMOADs is diagnosed in the year it occurs, DMOADs costing $1,000/person/year would achieve ICERs below $50,000/QALY if they could suspend OA progression by at least 60% and provide concurrent pain relief in at least 30% of those with suspended OA progression. DMOADs that cost $3,000 or $5,000 would attain ICERs below $100,000/QALY if they could suspend OA progression/lead to pain relief by at least 20%/70% or 60%/60%. ICERs below $150,000/QALY could be achieved by DMOADs costing $7,000/person/year if they could suspend structural progression by at least 20% and lead to concomitant pain relief in at least 90% of those with suspended OA progression. Fig. 3 shows that DMOADs costing $1,000, suspending progression in 100% of cases, and leading to 20% pain relief would provide similar value as more expensive DMOADs ($3,000/person/year) that suspend progression in 20% of cases, and relieve pain in 70% of cases. The same value would also be achieved by a more expensive DMOAD ($5,000) with pain relief and suspended progression at 60%. DMOADs costing $7,000 were unlikely to attain ICERs of $50,000/QALY, even if they were 100% effective in both suspending structural progression and relieving pain.

Sensitivity analyses

Select, two-way sensitivity analyses are presented in Fig. 4 and Tables II and III. Additional two-way sensitivity analyses are presented in the Technical Appendix. The timing of DMOAD administration (anywhere in the sequence prior to TKR) did not have a meaningful impact on the cost-effectiveness of DMOAD therapy (results not shown).



†*QoL – quality of life*

Fig. 2. This figure depicts the pathway of a hypothetical subject in the OAPol Model receiving DMOADs. When DMOADs are discontinued, subjects will be evaluated for the treatment immediately following DMOADs.

Table II presents results of two-way sensitivity analyses that varied the degree of suspended progression and pain relief within clinically plausible ranges (50–70% for suspended progression and 30–50% for pain relief). When DMOADs were priced at $1,000/year with major toxicity risks at 0.5%/year, DMOADs were likely to have cost-effectiveness ratios below $100,000 compared to the SoC (no DMOADs). The proportion of the cohort receiving TKR depended on the likelihood that DMOADs suspended progression; base case DMOADs as the second-line regimen (50% suspended progression, 30% concomitant pain relief) resulted in 44.35% lifetime risk for TKR. Increasing suspended progression to 70% decreased lifetime risk of TKR to 41.31%. Fig. 4 (upper left box) portrays cost-effectiveness ratios of DMOADs-based strategies for expanded ranges of suspended progression and pain relief. Results of these two-way sensitivity analyses suggest that pain relief 10% or lower led to a lower QALE in patients receiving DMOADs compared to those who did not have a DMOADs-based regimen as a part of their treatment strategy. Pain relief levels of 20% or lower resulted in either lower QALE (in scenarios where suspended OA progression was <60%) or ICERs greater than $150,000 if suspended progression rates ranged from 60 to 70%.

Table II
Two-way sensitivity analysis of DMOAD pain relief and suspended progression

Suspended progression	Pain relief	Treatment strategy	Avg. QALE	Avg. cost	ICER	Proportion of cohort receiving primary TKR
50%	Base case 30% (15% overall)‡	SoC*	14.21	$115,800		52.37%
		SoC + DMOADs†	14.25	$118,100	$57,500	44.35%
	40% (20% overall)	SoC	14.21	$115,800		52.37%
		SoC + DMOADs	14.28	$118,000	$31,400	44.34%
	50% (25% overall)	SoC	14.21	$115,800		52.37%
		SoC + DMOADs	14.32	$118,000	$20,000	44.33%
60%	30% (18% overall)	SoC	14.21	$115,800		52.37%
		SoC + DMOADs	14.26	$118,400	$52,000	42.82%
	40% (24% overall)	SoC	14.21	$115,800		52.37%
		SoC + DMOADs	14.30	$118,300	$27,800	42.82%
	50% (30% overall)	SoC	14.21	$115,800		52.37%
		SoC + DMOADs	14.35	$118,200	$17,100	42.83%
70%	30% (21% overall)	SoC	14.21	$115,800		52.37%
		SoC + DMOADs	14.28	$118,600	$40,000	41.31%
	40% (28% overall)	SoC	14.21	$115,800		52.37%
		SoC + DMOADs	14.33	$118,600	$23,300	41.30%
	50% (35% overall)	SoC	14.21	$115,800		52.37%
		SoC + DMOADs	14.38	$118,500	$15,900	41.31%

* SoC sequence: conservative pain management (NSAIDs, acetaminophen, physical therapy), corticosteroid injections, primary TKR, revision TKR.
† SoC + DMOADs sequence: conservative pain management, DMOADs, corticosteroid injections, primary TKR, revision TKR.
‡ Overall pain relief is calculated as (% pain relief given suspended progression) × (% suspended progression); the top row of this table corresponds with 30% pain relief given suspended progression, 50% suspended progression, and thus 15% overall pain relief.

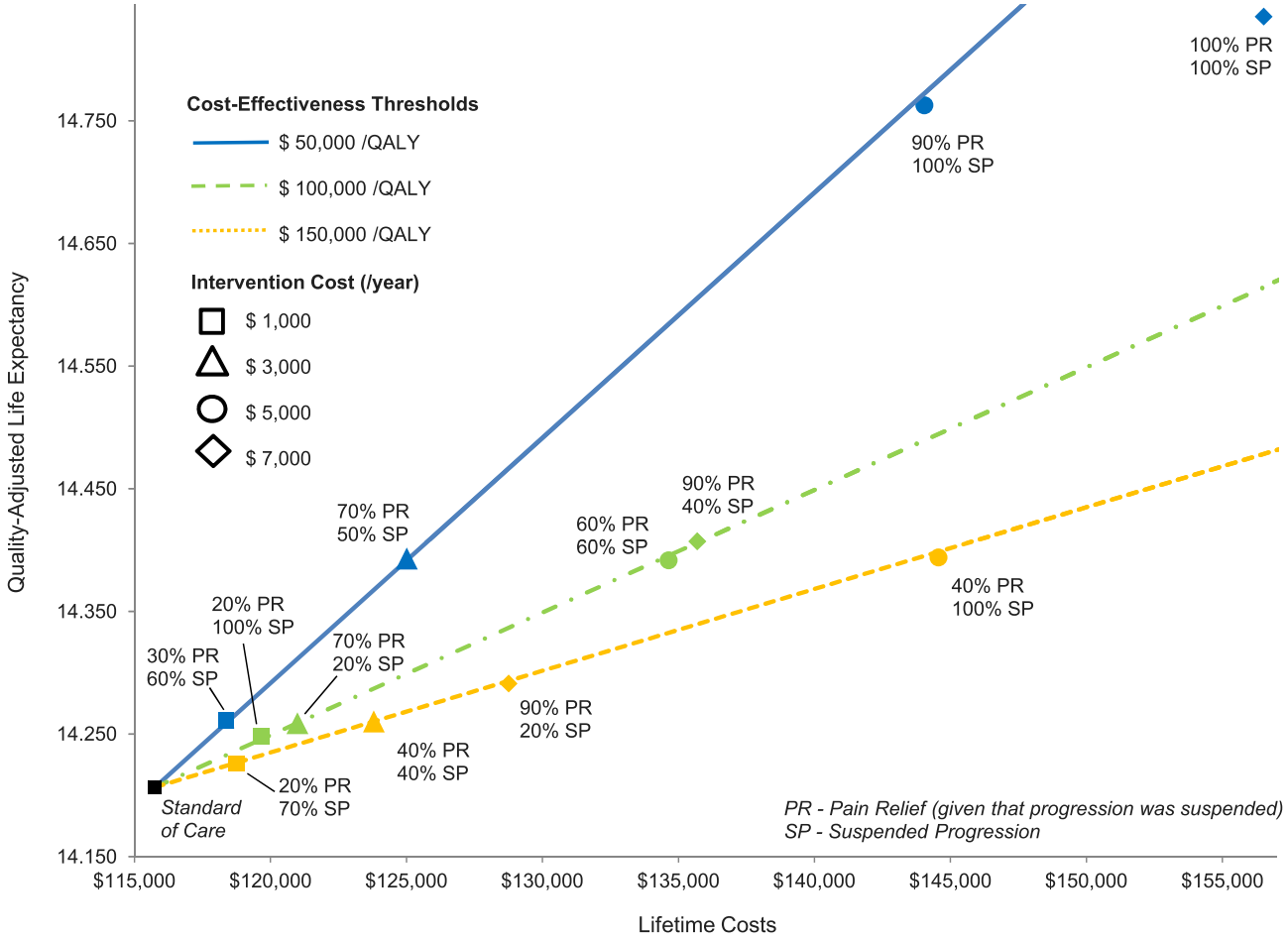


Fig. 3. Threshold efficacy, cost, and life expectancy associated with DMOADs treatment. This figure describes threshold efficacy for alternative willingness-to-pay thresholds, shown in blue ($50,000/QALY), green ($100,000/QALY), and yellow ($150,000/QALY). Squares represent efficacy thresholds for DMOADs costing $1,000/person/year, triangles – $3,000/person/year, circles – $5,000/person/year, and diamonds – $7,000/person/year. The vertical axis shows the per person discounted QALE and the horizontal axis shows the per person discounted lifetime cost. The black square in the lower left corner represents the per person life expectancy and lifetime cost in a program with no DMOADs intervention.

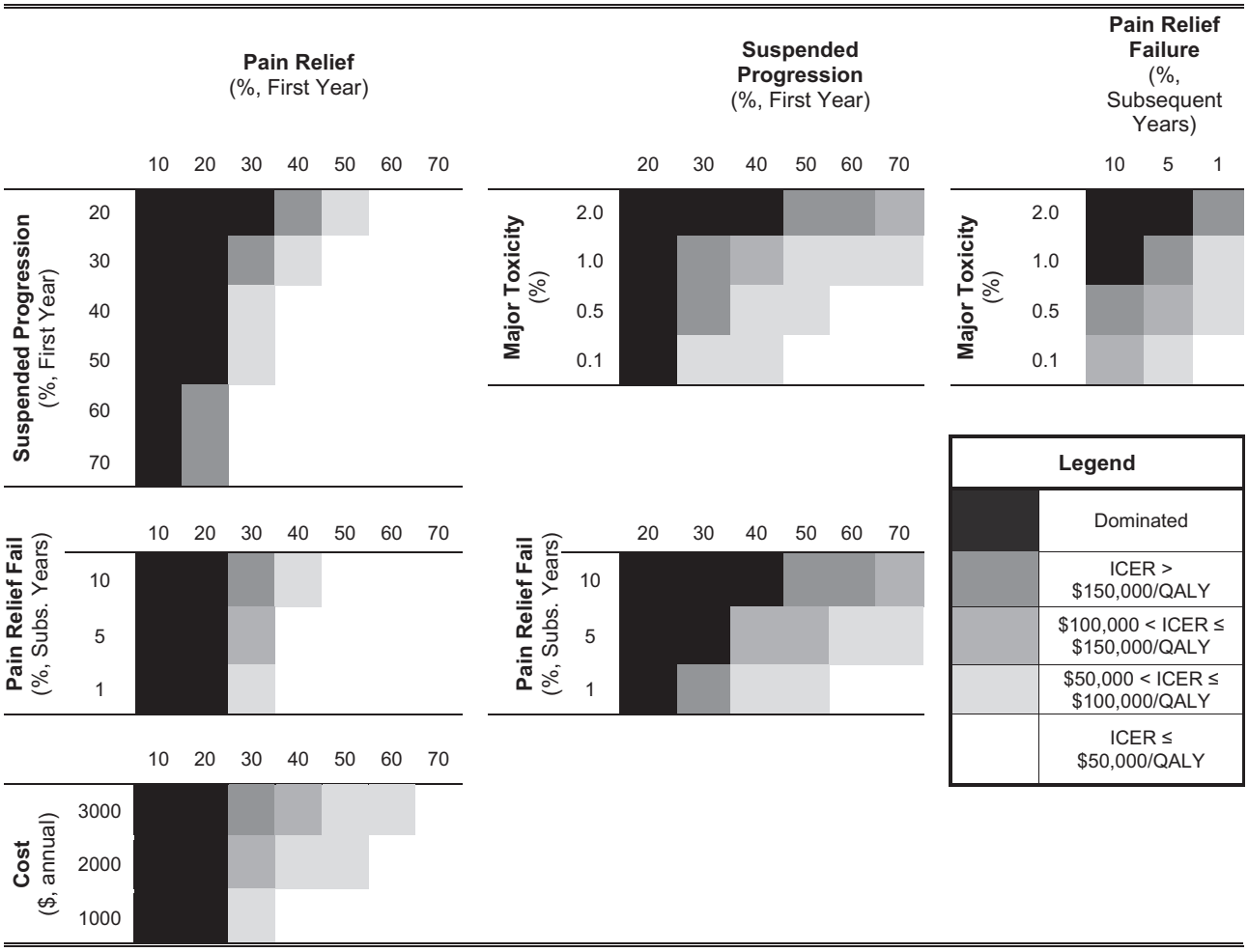


Fig. 4. Each box in this figure represents a single two-way analysis – for instance varying cost ($1,000–$3,000) and toxicity (0.1–2%) of DMOADs. The shade of each block in the quadrant represents the level of cost-effectiveness for that particular DMOAD in comparison to the SoC. The darkest shades are the lowest levels of cost-effectiveness, and the lightest shades represent the highest levels of cost-effectiveness. Blocks are shaded black if the particular DMOAD *decreased* QALE relative to the SoC, and thus were dominated. The quadrants are organized such that the most beneficial combination of DMOAD parameters appears in the bottom right-hand corner of each square (for example, lowest cost, $1,000, and highest level of pain relief, 70%), and the least beneficial combination of DMOAD parameters appears in the top left-hand corner of each square (for example, highest cost, $3,000, and lowest pain relief, 10%).

Table III
Two-way sensitivity analysis of DMOAD cost and pain relief, suspended progression, or major toxicity

Treatment strategy			Avg. QALE	$1,000		$2,000		$3,000	
				Avg. cost	ICER	Avg. cost	ICER	Avg. cost	ICER
Pain relief	30% (base case)	SoC*	14.21	$115,800		$115,800		$115,800	
		SoC + DMOADs†	14.25	$118,100	$57,500	$121,600	$145,000	$125,200	$235,000
	40%	SoC	14.21	$115,800		$115,800		$115,800	
		SoC + DMOADs	14.28	$118,000	$31,400	$121,600	$82,900	$125,100	$132,900
	50%	SoC	14.21	$115,800		$115,800		$115,800	
		SoC + DMOADs	14.32	$118,000	$20,000	$121,500	$51,800	$125,100	$84,500
Suspended progression	50% (base case)	SoC	14.21	$115,800		$115,800		$115,800	
		SoC + DMOADs	14.25	$118,100	$57,500	$121,600	$145,000	$125,200	$235,000
	60%	SoC	14.21	$115,800		$115,800		$115,800	
		SoC + DMOADs	14.26	$118,400	$52,000	$122,500	$134,000	$126,600	$216,000
	70%	SoC	14.21	$115,800		$115,800		$115,800	
		SoC + DMOADs	14.28	$118,600	$40,000	$123,300	$107,100	$128,000	$174,300
Major toxicity	1%	SoC	14.21	$115,800		$115,800		$115,800	
		SoC + DMOADs	14.24	$118,100	$76,700	$121,700	$196,700	$125,100	$310,000
	0.5% (base case)	SoC	14.21	$115,800		$115,800		$115,800	
		SoC + DMOADs	14.25	$118,100	$57,500	$121,600	$145,000	$125,200	$235,000
	0.1%	SoC	14.21	$115,800		$115,800		$115,800	
		SoC + DMOADs	14.26	$118,000	$44,000	$121,700	$118,000	$125,300	$190,000

* SoC sequence includes: conservative pain management (NSAIDs, acetaminophen, physical therapy), corticosteroid injections, primary TKR, revision TKR.
† SoC + DMOADs sequence includes: conservative pain management, DMOADs, corticosteroid injections, primary TKR, revision TKR.

Fig. 4 also suggests that the cost-effectiveness of DMOADs was very sensitive to the degree of initial pain relief, as well as loss of pain relief benefits in subsequent years, if initial pain relief was between 30% and 50%. Major toxicity rates played an important role, especially if levels of suspended progression were modest (20–50%).

Table III presents results of two-way sensitivity analyses examining the impact of DMOAD cost, efficacy, and toxicity. Improved pain relief (50%) achieved concurrently with suspended progression of 50% led to very favorable cost-effectiveness ratios (<$50,000/QALY); however, ICERs increased over $50,000/QALY when DMOADs were priced at $2,000 or $3,000 annually. Priced at $1,000/year, DMOADs had favorable ICERs across a wide range of plausible values for pain relief, toxicity, and likelihood of suspended progression.

ICERs for DMOADs did not vary substantially when we varied the order of the regimens. When corticosteroid injections (Regimen 2) were received before Regimen 1 in the treatment sequence, DMOADs still carried an ICER of $75,000/QALY. If corticosteroid injections were removed from the treatment sequence altogether, DMOADs carried an ICER of $31,000/QALY.

Altering K–L grade distribution at the time of knee OA diagnosis did not lead to qualitative changes in ICERs. The DMOAD ICERs for cohorts who were 100% K–L grade 1 at the time of diagnosis were $38,000/QALY. The ICER for the 50% K–L grade 1 and 50% KL grade 2 cohort was $43,000/QALY.

Results of the sensitivity analyses modeling doxycycline as a potential DMOAD showed that doxycycline was a dominated strategy as it did not lead to meaningful improvements in quality of life.

Discussion

Using the OAPol Model, a validated computer simulation of the epidemiology and management of knee OA, we have demonstrated that cost, efficacy, and pain relief are the key drivers of value in DMOADs. We have shown how these drivers trade off with one another. In addition, we have described the many plausible combinations of these drivers which could reduce the need for TKR and satisfy commonly cited cost-effectiveness criteria. There is no general agreement about what defines “cost-effective.” In the United States, maximum willingness-to-pay thresholds ranging from $50,000/QALY to $150,000/QALY and beyond are widely cited[62–64].

The cost-effectiveness of DMOADs was highly sensitive to variations in those parameters with direct effects on quality of life, particularly pain relief. Variations in the level of pain relief revealed a distinct threshold of 20%, below which DMOADs would not offer clinical benefits relative to standard care. DMOADs with no intrinsic pain-relieving capacity could only improve quality of life if slowing down progression ultimately reduced pain. Our results validate the importance of targeting pathways which will both reduce progression and offer pain relief.

Since improvements in quality of life are anchored in pain relief, the cost-effectiveness of DMOADs ultimately depends on the level of overall symptom relief achieved by suspended structural progression. Greater rates of suspended OA progression were associated with a lower proportion of the cohort receiving TKR; however, the reduced TKR rates did not translate to greater cost-effectiveness unless DMOADs also offered pain relief because while TKR is costly, it consistently provides pain relief. Thus, in order to justify prolonged DMOAD use before TKR, even in cases of suspended progression, DMOADs must offer pain relief.

Several important limitations of our analyses should be noted. We used the K–L grade as a measure of OA progression[65,66]. While a magnetic resonance imaging -based (MRI) definition of OA and its progression is receiving growing attention, the validation of MRI-based markers is ongoing[67]. In order to address this limitation and maintain conservative estimates of pain relief, we did not model pain relief as automatically occurring in cases of suspended progression; rather, in the base case, only 30% of subjects experiencing suspended progression also experienced pain relief. Moreover, in the model, the efficacy of DMOADs was expressed in terms of slowing or ‘suspending’ progression based on K–L grade. However, K–L grade is a relatively unresponsive marker of radiographic change and its use may lead to increased time until DMOAD failure detection[68]. Since conventional radiographs are a current SoC, our analysis is consistent with clinical practice.

We assumed that failure of DMOADs is detected in the year it occurs. While this assumption biases the results in favor of DMOADs, it seems reasonable since monitoring for failure is triggered by continuous or newly occurring pain.

We chose not to model indirect costs because, at present, there are no data available on the impact of DMOADs on disability or absenteeism. As more data become available, this will be a rich area for future research.

NHIS instruments did not allow for separation between OA occurring at the knee and OA occurring at other sites. The NHIS also did not distinguish OA from gout, RA, lupus, or fibromyalgia. These ambiguities may distort the distributions of sex, BMI and race assigned to persons with knee OA.

This analysis did not consider high-tibial osteotomy (a treatment option for subjects with uni-compartmental disease) as part of the standard treatment sequence because these procedures are performed infrequently in the US[49]. To ensure that results are generalizable to the overall population with knee OA, we chose to simulate the most common OA treatments.

The cost-effectiveness thresholds will vary from country to country. The results presented in this paper are based on cost and quality of life data measured in the US. This paper offers methodology that could be used to assess cost-effectiveness of DMOADs in other countries, using country-specific data on OA natural history, progression, treatment costs, and potentially alternative thresholds for economic value.

Although we only modeled the use of one DMOAD as part of the OA treatment sequence, it is likely that multiple DMOADs will ultimately become available to patients. It is also possible that DMOADs are more likely to offer pain relief for subjects at earlier stages of OA. However, we did not model varying levels of pain relief based on current K–L grade. In this case, it would be critical to offer DMOADs early in the treatment sequence, thus catching patients before they progress to more severe OA.

The results of our analyses showed that in the absence of DMOADs, the lifetime risk of TKR among those with symptomatic knee OA was approximately 50%. These results suggest higher TKR rates than estimated in data derived from large cohort studies such as the Osteoarthritis Initiative (OAI)[69]. There are several reasons for the difference between our model-based estimates and OAI data: (1) persons intending to undergo TKR within 18 months were excluded from OAI, and (2) OAI-based estimates, which indicate a 1%/year conversion to TKR, include data from both incident and prevalent cohorts, with a substantial number of persons at K–L grade 1. In contrast, our model-based estimates used incidence of TKR data derived from the Multicenter Osteoarthritis Study (MOST), which assumes that only subjects with K–L grade 3 or greater were eligible for TKR. Among subjects in the OAI with K–L grade 3 or 4 OA, the conversion to TKR was estimated at about 10%/year[69,70]. Furthermore, this rate of conversion to TKR among those at K–L grade 3 or 4 was consistent with nationwide estimates of the number of TKRs performed in the US[71].

To the best of our knowledge, the results of the analyses documented here comprise the first pre-evaluation of the effectiveness, costs, and cost-effectiveness of DMOAD therapy for knee OA. We have examined the sensitivity of DMOAD value to variations in a wide spectrum of characteristics, most notably efficacy, toxicity, and costs. Our findings may provide critical insights for clinical trial planning and ensure that drug manufacturers focus the development of new regimens on parameters that will affect quality of life, in particular, pain relief. These analyses also offer a new approach in which simulation modeling can be efficiently used to evaluate new treatment strategies under development before the implementation of costly clinical trials.

Author contributions

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Analysis and interpretation of the data: Losina, Daigle, Suter, Hunter, Solomon, Walensky, Jordan, Burbine, Paltiel, Katz

Drafting of the article: Losina, Daigle, Katz

Critical revision of the article for important intellectual content: Losina, Daigle, Suter, Hunter, Solomon, Walensky, Jordan, Burbine, Paltiel, Katz

Final approval of the article: Losina, Daigle, Suter, Hunter, Solomon, Walensky, Jordan, Burbine, Paltiel, Katz

Provision of study materials or patients: Losina

Statistical expertise: Losina

Obtaining of funding: Losina

Collection and assembly of data: Losina, Daigle

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Conflict of interest

The authors do not have any conflict of interest with respect to the context of this paper.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.joca.2013.01.016.

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