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Cost-Effectiveness of Allopurinol and Febuxostat for the Management of Gout

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Background: Gout is the most common inflammatory arthritis in the United States.

Objective: To evaluate the cost-effectiveness of urate-lowering treatment strategies for the management of gout.

Design: Markov model.

Data Sources: Published literature and expert opinion.

Target Population: Patients for whom allopurinol or febuxostat is a suitable initial urate-lowering treatment.

Time Horizon: Lifetime.

Perspective: Health care payer.

Intervention: 5 urate-lowering treatment strategies were evaluated: no treatment; allopurinol- or febuxostat-only therapy; allopurinol–febuxostat sequential therapy; and febuxostat–allopurinol sequential therapy. Two dosing scenarios were investigated: fixed dose (80 mg of febuxostat daily, 0.80 success rate; 300 mg of allopurinol daily, 0.39 success rate) and dose escalation (≤120 mg of febuxostat daily, 0.82 success rate; ≤800 mg of allopurinol daily, 0.78 success rate).

Outcome Measures: Discounted costs, discounted quality-adjusted life-years, and incremental cost-effectiveness ratios.

Results of Base-Case Analysis: In both dosing scenarios, allopurinol-only therapy was cost-saving. Dose-escalation allopurinol–febuxostat sequential therapy was more costly but more effective than dose-escalation allopurinol therapy, with an incremental cost-effectiveness ratio of $39 400 per quality-adjusted life-year.

Results of Sensitivity Analysis: The relative rankings of treatments did not change. Our results were relatively sensitive to several potential variations of model assumptions; however, the cost-effectiveness ratios of dose escalation with allopurinol–febuxostat sequential therapy remained lower than the willingness-to-pay threshold of $109 000 per quality-adjusted life-year.

Limitation: Long-term outcome data for patients with gout, including medication adherence, are limited.

Conclusion: Allopurinol single therapy is cost-saving compared with no treatment. Dose-escalation allopurinol–febuxostat sequential therapy is cost-effective compared with accepted willingness-to-pay thresholds.

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Gout is triggered by crystallization of uric acid in the joints due to hyperuricemia. It constitutes the most common inflammatory arthritis in the United States and affects 3.9% of adults (8.3 million) (1, 2). Acute gout flares are one of the most painful conditions experienced by humans, and chronic tophaceous gout can cause joint deformity, dysfunction, and damage (3).

Although the pathogenesis of gout is well-understood, and efficacious antigout drugs are available, it is often mismanaged in clinical practice (4). Several organizations, including the American College of Rheumatology, have developed evidence-based treatment guidelines that recommend urate-lowering therapy as the primary treatment in patients with tophi or frequent gout attacks (2, 5–7).

Allopurinol (a xanthine oxidase inhibitor), used in up to 95% of treated cases, is generally well-tolerated and relatively inexpensive (5, 6, 8). In 2009, the U.S. Food and Drug Administration approved febuxostat, which is a nonpurine xanthine oxidase inhibitor (9). In clinical trials, febuxostat (80 mg/d) was found to be more effective than allopurinol (≤300 mg/d) in lowering a person's serum uric acid (SUA) level below 360 μmol/L and was as safe as allopurinol (10–13). However, these trials did not compare the efficacy of febuxostat with an escalating dose of allopurinol (for example, ≤800 mg), which is reflective of recommended clinical practice (9, 10, 12–16). Recent studies that used an escalating dose of allopurinol attained up to a 75% to 80% success rate of achieving SUA levels of less than 360 μmol/L (1, 2, 17–19). Finally, febuxostat is substantially more expensive than allopurinol, but the latter is associated with the allopurinol hypersensitivity syndrome, which is a potentially deadly side effect (3, 20, 21).

Although the 2012 American College of Rheumatology gout guidelines recommended that allopurinol and febuxostat be considered as equivalent first-line options, the guideline was developed on the RAND/UCLA Appropriateness Method, which does not consider the costs or cost-effectiveness of available therapies (2). A key point of the 2012 American College of Rheumatology guidelines is that "serum urate level should be lowered sufficiently to durably improve signs and symptoms of gout, with the target <6 mg/dL at a minimum" (2). Of note, a cost-effectiveness analysis of febuxostat submitted to the National Institute for Health and Care Excellence in the United Kingdom was determined to be flawed owing to the failure to incorporate appropriate comparison data with escalating doses of allopurinol (2, 5–7, 16). Further, the 2012 American College of Rheumatology guidelines note that cost-effectiveness analyses that appropriately in-

Context

Prior cost-effectiveness analyses of febuxostat therapy for gout did not include comparisons with escalating doses of allopurinol.

Contribution

Mathematical models compared costs and quality-adjusted life-years of allopurinol and febuxostat as single treatments, allopurinol–febuxostat sequential therapy, febuxostat–allopurinol sequential therapy, and no treatment. The models evaluated fixed-dose (febuxostat, 80 mg/d, vs. allopurinol, 300 mg/d) and dose-escalation regimens (febuxostat, ≤120 mg/d, vs. allopurinol, 800 mg/d).

Caution

Other urate-lowering therapies were not assessed.

Implication

Single treatment with allopurinol was cost-saving in both dosing scenarios. Dose-escalation allopurinol–febuxostat sequential therapy is cost-effective at a willingness-to-pay ratio of $109 000 per quality-adjusted life-year.

—The Editors

corporate relevant comparator groups (for example, escalating doses of allopurinol) are needed to aid clinicians and policymakers in choosing appropriate agents for urate-lowering therapy (2, 5, 6, 8).

To address these issues, we evaluated the cost-effectiveness of allopurinol and febuxostat over a lifetime by incorporating both fixed-dose and escalating-dose urate-lowering therapy regimens (4, 9, 10, 12, 13, 22). We also evaluated sequential regimen strategies using each drug as first- or second-line treatments.

METHODS

Model Design and Study Population

We developed a state-transition Markov model with a cycle length of 1 month to project costs and quality-adjusted life-years (QALYs) of 5 urate-lowering therapy strategies over the life of a hypothetical cohort of patients aged 53 years with gout for whom either allopurinol or febuxostat was considered a suitable initial urate-lowering therapy. Our population was consistent with the study populations of the febuxostat trials that compared this drug with allopurinol (10–13). The treatment strategies evaluated were also similar to those in the clinical trials and included no treatment; allopurinol- or febuxostat-only therapy; allopurinol–febuxostat sequential therapy; and febuxostat–allopurinol sequential therapy.

Figure 1 illustrates the Markov model used to evaluate the treatment strategies for this hypothetical cohort of patients with gout, showing the relevant states of health and transitions among states. Both single- and sequential-therapy strategies consisted of 4 main states: controlled SUA (<360 μmol/L) on treatment, uncontrolled SUA (≥360 μmol/L) on treatment, uncontrolled SUA off treatment, and dead. For the evaluation of sequential-therapy strategies, 2 additional states were incorporated: uncontrolled and controlled on second-line therapy. These states reflect the transitions to and potential effectiveness of second-line therapy.

For the 4 strategies, we assumed that the hypothetical cohort of patients would start a urate-lowering therapy option from the uncontrolled-SUA-on-treatment state. From that state, simulated patients could remain uncontrolled, become stabilized (transition to controlled-SUA-on-treatment state), discontinue therapy (transition to uncontrolled-SUA-off-treatment state), switch treatment if allowed (transition to uncontrolled-on-new-treatment state), or die of age- and sex-related causes (9, 11–16). In addition, patients receiving allopurinol faced an additional risk for death due to the allopurinol hypersensitivity syndrome (21, 23). Patients in the controlled-on-treatment state could remain in this state or die. Patients in the no-treatment strategy were assumed to remain in an uncontrolled state until death.

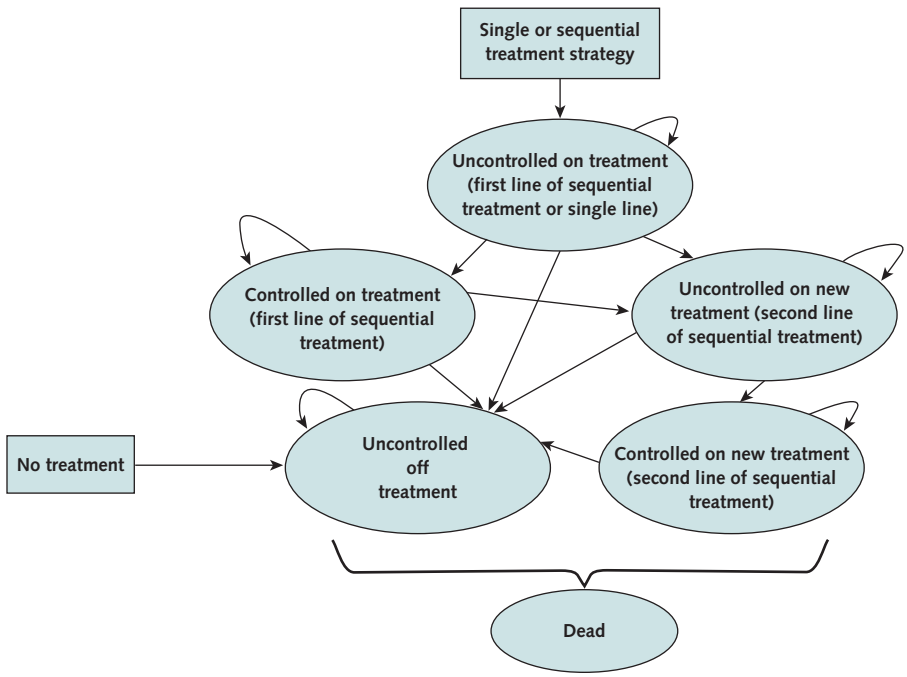
For the sequential-therapy strategies, simulated patients receiving second-line therapy in the uncontrolled state could remain (uncontrolled SUA on second-line treatment), become stabilized (controlled SUA on second-line treatment), discontinue therapy (uncontrolled SUA off treatment), or die. Patients receiving a second-line therapy faced the same transition probabilities as if they had been receiving first-line therapy.

Treatment Effectiveness and Complications

All model estimates were derived from the literature and are shown in **Table 1**. The annual probability of treatment success (that is, controlled SUA) was based on the average effectiveness of therapy and was modeled for 2 dosing scenarios. In the first scenario, we compared a fixed dose of febuxostat (80 mg) with allopurinol (300 mg), which was seen in the febuxostat trials (10–13). In the second scenario, we evaluated the dose escalation of allopurinol (≤800 mg) and febuxostat (≤120 mg) (2, 5, 17–19). The annual probability of transitioning to a controlled state, for both treatment scenarios, was based on the proportion of patients who had an SUA level less than 360 μmol/L at the end of 1 year and was assumed to persist as long as the patient continued receiving medication (10, 11, 17).

The annual probability of experiencing an adverse event while receiving treatment was also obtained from clinical trial data and was slightly higher for patients receiving febuxostat than for those receiving allopurinol (10). Adverse events involving the allopurinol hypersensitivity syndrome have not been observed in the trial data, but we incorporated these events in our models on the basis of observational study findings (21, 23). The annual probability of experiencing a gout flare was dependent on SUA

Figure 1. **Markov model.**



A cycle length of 1 mo was used. Circles represent Markov states, and the arrows represent the probability of moving from 1 state to another. Arrows pointing to the same state represent the probability of staying in a state. In the single-treatment strategy, all patients receiving treatment start in the uncontrolled-on-treatment state. Patients can either remain in this state or transition to the controlled-on-treatment, uncontrolled-off-treatment, or dead state. The uncontrolled-on-new-treatment and controlled-on-new-treatment states represent the switch states (that is, second-line therapy for sequential therapy) and are available only for patients in a sequential-therapy strategy. In the sequential-therapy strategy, all patients start in the uncontrolled-on-treatment state and can remain there or transition to the controlled-on-treatment, uncontrolled-on-new-treatment, uncontrolled-off-treatment, or dead state. Patients in the no-treatment strategy start in the uncontrolled-off-treatment state and remain there until they are dead. Persons can die from all states.

status; patients in the uncontrolled-off-treatment state had a higher probability of experiencing gout flares than patients with controlled or treated SUA (24, 25).

To simulate outcomes in a sequential-therapy strategy, patients could switch medications if their SUA level remained uncontrolled or they had an adverse event while receiving first-line therapy. Patients were allowed to switch treatment after being in an uncontrolled state for 3 months or longer. If patients remained in an uncontrolled state for 9 months and had not already switched, then we assumed that would immediately switch therapy. Finally, patients receiving the first drug in a sequential-therapy strategy, regardless of controlled or uncontrolled state, could also switch medications if they had an adverse event within the first 3 months of therapy.

Simulated patients could discontinue urate-lowering therapy if their SUA level remained uncontrolled (that is, therapeutic failure) or they had an adverse event within the first 3 months of treatment. (The latter was a competing risk for patients who could switch because of an adverse event.) Patients who had nonfatal allopurinol hypersensitivity syndrome discontinued therapy. All patients initially had a decreased risk for discontinuing therapy for the first 3 months in which their SUA levels remained uncontrolled because adjusting to a new medication can take time. For patients whose SUA level remained uncontrolled after 3 months and who could not switch medications, we assumed that they faced an increased risk for discontinuing therapy. Finally, all patients who could not switch medications and whose SUA level remained uncontrolled for 9 months were assumed to discontinue their respective therapy because continuing urate-lowering therapy (particularly the pricey ones) without reaching the well-established target level (2) after 9 months is highly unlikely to be justifiable, despite some gain of QALYs with continued therapy (**Table 1**). Nevertheless, we tested this assumption in our sensitivity analysis.

Health-Related Quality of Life

We assigned health-related quality-of-life weights (that is, utilities) to simulated persons residing in the different health states. For persons with uncontrolled versus controlled SUA levels, we used previously published EuroQol-5 dimension utility weights according to SUA levels (0.75 for $\leq$360 μmol/L, 0.71 for $>$360 μmol/L but $\leq\sim$480 μmol/L, 0.68 for $>\sim$480 μmol/L but $\leq\sim$600

Table 1. **Model Inputs***

Model Estimate	Annual Point Estimate (Range)		Reference
	Febuxostat	Allopurinol	
Probability of treatment success			
Transition to controlled state; fixed dose†	0.81 (0.75–0.87)	0.39 (0.32–0.46)	10
Transition to controlled state; dose escalation	0.82 (0.75–0.89)	0.78 (0.67–0.87)	10, 17
Probability of an event			
Adverse event	0.25 (0.12–0.35)	0.23 (0.12–0.35)	10
The hypersensitivity syndrome‡	0.00	0.004 (0.02–0.06)	23
Death due to the hypersensitivity syndrome§	0.00	0.27 (0.135–0.405)	21
Flare SUA controlled on treatment	0.23 (0.12–0.35)		24
Flare SUA uncontrolled on treatment	0.36 (0.18–0.54)		24
Flare SUA uncontrolled off treatment	0.45 (0.23–0.68)		24
Probability of switching therapy after being in the uncontrolled state for some time			
1–3 mo‖	0.00	0.00	Clinical assumption
4–6 mo	0.20 (0.12–0.28)	0.20 (0.12–0.28)	Clinical assumption
7–9 mo	0.30 (0.21–0.39)	0.30 (0.21–0.39)	Clinical assumption
9 mo	1.00	1.00	Clinical assumption
Adverse event¶	0.11 (0.05–0.17)	0.11 (0.05–0.17)	17
Probability of discontinuing treatment because of therapeutic failure			
1–3 mo**	0.10 (0.05–0.15)	0.10 (0.05–0.15)	Clinical assumption
4–6 mo	0.20 (0.10–0.30)	0.20 (0.10–0.30)	Clinical assumption
7–9 mo	0.30 (0.15–0.45)	0.30 (0.15–0.45)	Clinical assumption
9 mo	1.00	1.00	Clinical assumption
Adverse event††	0.06 (0.03–0.09)	0.03 (0.015–0.045)	10
State utility by SUA status			
Controlled SUA on treatment	0.75 (0.38–1.00)		26
Uncontrolled SUA on treatment	0.70 (0.35–0.75)		26
Uncontrolled SUA off treatment	0.66 (0.33–0.75)		26
Event disutility			
Flare	0.01 (0.005–0.015)		14
Adverse event	0.03 (0.015–0.045)		Clinical assumption
Hypersensitivity‡‡	0.35 (0.18–0.53)		27
Nonpharmacologic costs of treatment by SUA status, $§§			
Controlled SUA in persons aged <65 y	396 (198–1820)		29, 30
Controlled SUA in persons aged ≥65 y	312 (156–1577)		29, 30
Uncontrolled SUA on treatment in persons aged <65 y	444 (222–1525)		29, 30
Uncontrolled SUA on treatment in persons aged ≥65 y	372 (186–1255)		29, 30
Uncontrolled SUA off treatment in persons aged <65 y	684 (342–1883)		29, 30
Uncontrolled SUA off treatment in persons aged ≥65 y	552 (276–1498)		29, 30
Drug costs, $			
Flares	26 (14–39)		20
Fixed dose‖‖	2075 (1037–3112)	67 (33–100)	20
Dose escalation	2385 (1192–3578)	96 (48–145)	20

SUA = serum uric acid.

* When probabilities in studies were not reported on a monthly basis, the authors adjusted using rates and then transformed rates into monthly probabilities. All cost estimates are reported in 2013 U.S. dollars.

† The upper range for the effectiveness of febuxostat was based on 10% of the mean value.

‡ Probability was assumed to persist for the first year of receiving allopurinol.

§ Probability is conditional on experiencing the syndrome.

‖ Probability of switching is only for scenarios that model a switch strategy. The probability of switching due to being in an uncontrolled state is conditional on patients remaining in the uncontrolled-on-therapy state for 3 mo. If patients remain in the uncontrolled-on-therapy state for 9 mo and have not already switched, then they immediately change therapies.

¶ Probability of switching is only for scenarios that model a switch strategy. Switching due to an adverse event is conditional on patients experiencing an adverse event within 3 mo of starting therapy. Patients can switch therapy because of an adverse event, regardless of being in a controlled or an uncontrolled state.

** Discontinuation due to therapeutic failure is defined as the probability of discontinuing treatment conditional on staying in an uncontrolled state for a given period.

†† Discontinuation due to adverse event is conditional on experiencing an adverse event and is assumed to persist for the first 3 mo of treatment.

‡‡ Utility associated with having the hypersensitivity syndrome is 0.35 regardless of the state in which a person resides.

§§ The low estimate in the price range is 50% of the mean value. The high estimate is the upper 95% CI derived from the probabilistic sensitivity analysis.

‖‖ The low estimate in the price range is derived from single technology appraisal submission to the U.K. National Institute for Health and Care Excellence. The high estimate in the range is 50% of the mean estimate.

μmol/L, and 0.64 for >~600 μmol/L) (26). We assigned a utility value of 0.75 to patients with a controlled SUA level. To determine the utility associated with an uncontrolled SUA level and receiving medication, we took the utilities associated with having SUA levels greater than 360 μmol/L but less than or equal to ~480 μmol/L, greater than ~480 μmol/L but less than or equal to ~600 μmol/L, and greater than ~600 μmol/L and weighted them by the distribution of patients reported in the clinical trial data that matched each SUA category (22, 26). The distribution of patients by SUA status was similar for patients receiving febuxostat and allopurinol, and therefore we used the same distribution for both drugs (26). Using this method, we assigned a utility value of 0.70 to patients who were receiving therapy but had uncontrolled SUA. Finally, we assigned a utility of 0.66 to patients in an uncontrolled state but not receiving medication, which was derived using the distribution of SUA for patients in the placebo group of the clinical trial (26).

We assumed that simulated patients experienced a disutility of 0.01 if they had a gout flare or an adverse event (except for the allopurinol hypersensitivity syndrome), regardless of disease or treatment status (14). If a patient had an allopurinol hypersensitivity event, we assigned a utility of 0.35, regardless of their health state (27, 28).

Cost

Costs were evaluated from a payer perspective. Nonpharmacologic costs (inpatient, emergency department, outpatient, and other medical services associated with the treatment of gout) were derived from a study that reported annual costs per SUA level (29). Costs were adjusted for inflation to reflect 2013 U.S. dollars. We further adjusted costs to be representative of private and public payers (Medicaid and Medicare) (30). In our model, costs are from the perspective of private payers and Medicaid for persons younger than 65 years. We assumed that Medicaid covered 21% of the population (31). For persons older than 65 years, costs are from the perspective of Medicare. The average inflation-adjusted nonpharmacologic cost of treating a patient younger than 65 years was $396 per year ($312 for patients >65 years) in the controlled state, $444 per year ($372 for patients >65 years) for patients in the uncontrolled-but-on-treatment state, and $684 ($552 for patients >65 years) for patients in the uncontrolled-but-off-treatment state (29).

The cost of medication (either febuxostat or allopurinol) was added as a further cost to each state depending on which urate-lowering therapy was used. Drug costs represent the average wholesale price, but the federal upper limit was used when available. The inflation-adjusted cost per year of fixed-dose allopurinol and febuxostat therapy was estimated at $67 per year ($5.60 per month) and $2075 per year ($172 per month), respectively (20). The cost of medication was adjusted in the dose-escalation strategies to reflect the increase in medication use. Finally, the pharmacologic cost of treating gout flares was $26, based on the average cost of a 7-day treatment of colchicine, nonsteroidal anti-inflammatory drugs (naproxen and indomethacin), and prednisone (2, 20).

Statistical Analysis

All statistical analyses were conducted using TreeAge Pro 2009 (TreeAge Software).

Cost-Effectiveness Analysis

To evaluate urate-lowering therapy strategies, we did an incremental cost-effectiveness analysis. We first removed strategies that were more costly and less effective than another strategy (that is, dominated strategies). Then, we ordered the remaining urate-lowering therapy strategies by increasing costs and effectiveness and calculated incremental cost-effectiveness ratios (ICERs), defined as the additional cost of a strategy divided by the additional benefit compared with the next most costly strategy. Strategies that were less effective and more costly than a combination of 2 other strategies (that is, dominated by extension) were eliminated from consideration. We applied a 3% annual discount rate to future costs and benefits to account for the time preference of money and health (32).

Sensitivity Analysis

To test for uncertainty in the model estimates, we performed 1-way sensitivity analyses on all of the variables in **Table 1**. Point estimates were tested between their 95% CI bounds when available. If CIs were not reported, then point estimates were tested between ±50% of their mean value (**Table 1**). In addition, we tested the effect of 4 structural assumptions of our model: Second-line therapy is as effective as first-line therapy, patients in controlled states remain as such, patients would discontinue therapy if they remained in an uncontrolled state for 9 months, and patients have perfect adherence.

To assess the effect of simultaneous change, we conducted a probabilistic sensitivity analysis. We assigned β distributions to treatment effectiveness; γ distributions to the cost of being in each state; and normal distributions to the difference in utility between the on-treatment states (both controlled and uncontrolled) and the uncontrolled states (both on and off treatment) (33).

Role of the Funding Source

The Agency for Healthcare Research and Quality had no role in the design, analysis, or reporting of results.

RESULTS

Base-Case Results

Results from the base-case analysis are presented in **Table 2**. Although clinical guidelines call for dose escalation in clinical practice, most providers use only fixed dosing (2, 34). In addition, previous cost-effectiveness analyses of febuxostat have generally only presented results under a fixed-dose assumption (16, 35). Our results are therefore presented separately for the fixed-dose and all dosing sce-

Table 2. **Results From the Base-Case Analysis**

Strategy	Lifetime Costs, $	Incremental Costs, $	QALYs	QALYs Gained	ICER, $/QALY
Fixed-dose single-line treatment options					
Allopurinol only	9542	–	12.723	–	Reference
No treatment	10 335	–	12.332	–	Dominated
Febuxostat only	31 433	21 890	13.265	0.542	40 400
All single-line treatment options					
Allopurinol only (dose escalation)	9037	–	13.199	–	Reference
Allopurinol only (fixed dose)	9542	–	12.723	–	Dominated
No treatment	10 335	–	12.332	–	Dominated
Febuxostat only (fixed dose)	31 433	–	13.265	–	Dominated by extension
Febuxostat only (dose escalation)	35 391	26 354	13.281	0.082	322 800
All fixed-dose treatment options					
Allopurinol only	9542	–	12.723	–	Reference
No treatment	10 335	–	12.332	–	Dominated
Allopurinol–febuxostat sequential therapy	21 661	12 119	13.193	0.470	25 800
Febuxostat–allopurinol sequential therapy	28 856	7194	13.283	0.090	80 000
Febuxostat only	31 433	–	13.265	–	Dominated
All treatment options					
Allopurinol only (dose escalation)	9037	–	13.199	–	Reference
Allopurinol only (fixed dose)	9542	–	12.723	–	Dominated
No treatment	10 335	–	12.332	–	Dominated
Allopurinol–febuxostat sequential therapy (dose escalation)	17 793	8756	13.422	0.222	39 400
Allopurinol–febuxostat sequential therapy (fixed dose)	21 661	–	13.193	–	Dominated
Febuxostat–allopurinol sequential therapy (fixed dose)	28 856	–	13.283	–	Dominated
Febuxostat only (fixed dose)	31 433	–	13.265	–	Dominated
Febuxostat–allopurinol sequential therapy (dose escalation)	32 249	14 456	13.447	0.025	563 800
Febuxostat only (dose escalation)	35 391	–	13.281	–	Dominated

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

narios. When evaluating fixed-dose and single-therapy options (as opposed to sequential-therapy options), we found that allopurinol is less costly and more effective than no treatment. The incremental cost-effectiveness of fixed-dose febuxostat therapy is $40 400 per QALY. In contrast, when all single-therapy options were evaluated, dose-escalation febuxostat was more costly and more effective than dose-escalation allopurinol and had an ICER of $322 800 per QALY.

When all 5 treatment options and all dosing scenarios were evaluated, dose-escalation allopurinol therapy was the least costly strategy and more effective than no treatment. Dose-escalation allopurinol–febuxostat sequential therapy costs $8756 more than dose-escalation allopurinol therapy, was associated with an increase in benefit of 0.222 QALY, and had an ICER of $39 400 per QALY. Dose-escalation febuxostat–allopurinol sequential therapy was more costly and more effective than dose-escalation allopurinol–febuxostat sequential therapy and had an ICER of $563 800 per QALY. All other strategies were ruled out by dominance.

Sensitivity Analysis

Table 3 presents results from the 1-way sensitivity analyses of sequential therapy for the fixed-dose and all dosing scenarios. These sensitivity analyses indicate that our results are moderately sensitive to the difference in utility between the controlled- and uncontrolled-on-treatment states. As the utility difference between the uncontrolled- and controlled-on-treatment states (**Figure 1**) increases, allopurinol–febuxostat sequential therapy has a lower ICER in both the fixed-dose and dose-escalation scenarios.

Table 4 presents results from the sensitivity analyses on the structural assumptions. Our results were sensitive to several structural assumptions; however, the ICERs of dose-escalation allopurinol–febuxostat sequential therapy remained lower than the willingness-to-pay threshold of $109 000 per QALY (**Table 4**). When all structural assumptions are set to the midpoint of their tested range, the ICER of dose-escalation allopurinol–febuxostat sequential therapy is $68 800 per QALY (**Table 4**).

We further evaluated an extreme scenario in which there is no discontinuation of the last therapy for any patients despite failure to achieve the therapeutic target (SUA level <360 μmol/L) for the remainder of their lives. In this unlikely scenario, the ICER of dose-escalation allopurinol–febuxostat sequential therapy became $118 400 per QALY.

Figure 2 illustrates the acceptability curves for all strategies and dosing scenarios. When willingness to pay is less than $40 100 per QALY, dose-escalation allopurinol therapy has the highest probability of being cost-effective. When the willingness-to-pay threshold is between $40 100 and $561 000 per QALY, dose-escalation allopurinol–febuxostat sequential therapy has the highest probability of being cost-effective. Finally, when the willingness-to-pay threshold is greater than $561 000 per QALY, dose-

escalation febuxostat–allopurinol sequential therapy has the highest probability of being cost-effective.

DISCUSSION

Our objective was to inform clinicians and policymakers about the costs, health benefits, and cost-effectiveness of 5 urate-lowering therapies using allopurinol and febuxostat for the management of chronic gout. Of note, our analyses incorporated dose escalation of allopurinol as a relevant reference group (as called for by the 2012 American College of Rheumatology gout guidelines) and dose escalation of febuxostat as an alternative (2). Although no willingness-to-pay threshold is universally accepted in the United States, certain studies have shown that persons are willing to pay approximately $109 000 per QALY (36, 37). Our primary analyses are based on data available to date and the most probable clinical assumptions; however, our results were more sensitive to several potential variations of model structure assumptions than conventional 1-way sensitivity analyses. Nevertheless, the ICERs of dose-escalation allopurinol–febuxostat sequential therapy remained lower than the willingness-to-pay threshold of $109 000 per QALY. The ICER of dose-escalation allopurinol–febuxostat sequential therapy exceeded the willingness-to-pay threshold of $109 000 per QALY only in the unlikely scenario when discontinuation of therapy was not allowed in any patients despite failure to achieve therapeutic target. Finally, febuxostat alone and febuxostat–allopurinol sequential therapy are unlikely to be cost-effective.

Our analytic approach is considerably different from the few previous studies, which have used short time horizons and decision trees to evaluate the cost-effectiveness of urate-lowering therapy for the management of gout. Ferraz and O'Brien (38) used a 1-year time horizon and a Canadian payer's perspective to evaluate the cost-effectiveness of reducing gout attacks (the disease-specific outcome, as opposed to QALY in our study) with allopurinol in patients with chronic gout compared with no treatment. They found that urate-lowering therapy (allopurinol and indomethacin) was cost-saving in patients who have 3 or more flares per year. Despite the limited scope of the analytic approach in their study, these findings are largely consistent with our cost-saving findings of allopurinol compared with no treatment.

In a more recent analysis of urate-lowering therapies, Meltzer and colleagues (39) compared the cost-effectiveness of febuxostat–allopurinol with allopurinol–febuxostat sequential therapy. The time horizon was 1 year, and effectiveness was measured as a controlled case

Table 3. **Results From 1-Way Sensitivity Analysis***

Strategy	Difference in Utility Between Controlled SUA and Uncontrolled-on-Therapy SUA (0.025–0.066; Base Case, 0.05)		Difference in Utility Between Uncontrolled-on-Therapy SUA and Uncontrolled-off-Therapy SUA (0.035–0.041; Base Case, 0.04)		Time Until Patients Must Discontinue due to Remaining in Uncontrolled-on-Therapy State (6–12 mo; Base Case, 9 mo)		Cost of Febuxostat ($1037–$3112; Base Case, $2075)		Starting Age of Patient (25–85 y; Base Case, 53 y)	
	ICER (Difference, 0.025), *$/QALY*	ICER (Difference, 0.066), *$/QALY*	ICER (Difference, 0.035), *$/QALY*	ICER (Difference, 0.041), *$/QALY*	ICER (Time, 6 mo), *$/QALY*	ICER (Time, 12 mo), *$/QALY*	ICER (Cost, $1037), *$/QALY*	ICER (Cost, $3112), *$/QALY*	ICER (Age 25 y), *$/QALY*	ICER (Age 85 y), *$/QALY*
Fixed-dose strategy										
Allopurinol–febuxostat sequential therapy	33 300	20 200	26 300	22 471	22 900	28 900	11 200	40 000	25 300	26 800
Febuxostat–allopurinol sequential therapy	116 600	71 000	90 400	79 733	74 000	105 900	41 700	135 300	88 800	80 000
All dosing strategies										
Allopurinol–febuxostat sequential therapy (dose escalation)	50 600	30 700	39 900	34 200	29 000	53 300	17 600	60 200	38 500	41 100
Allopurinol–febuxostat sequential therapy (fixed dose)					Dominated					
Febuxostat–allopurinol sequential therapy (fixed dose)					Dominated					
Febuxostat–allopurinol sequential therapy (dose escalation)	705 700	491 300	591 700	534 000	558 200	574 300	277 300	886 800	582 000	521 900

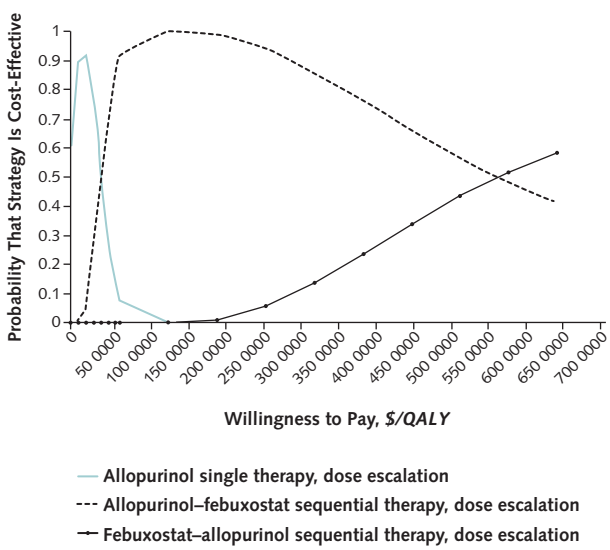
ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SUA = serum uric acid.
* Only results from the switch strategy are shown. In the fixed-dose scenario, allopurinol therapy is the reference case for first-line allopurinol. In all dosing strategies, dose-escalation allopurinol therapy is the reference case. Column headers indicate variables that varied and their range. Strategies are ordered by increasing cost and effectiveness. The ICER represents the additional cost per QALY of the next-most-expensive strategy. If strategies are dominated, they are not used to evaluate an ICER.

Table 4. **Structural Assumptions***

Strategy	All Structural Assumptions Set to the Midpoint of the Tested Range			Structural Assumption of Baseline Model and Testing							
	Lifetime Costs, $	QALYs	ICER, $/QALY	Second-Line Therapy Is as Effective as First-Line Therapy: Reduce the Effect of Second-Line Therapy Between 0% and 50% (Midpoint, 25%)		Once Controlled Patients Remained Controlled: Annual Probability of Becoming Uncontrolled† Varied Between 0.00 and 0.15 (Midpoint, 0.075)		Patients Discontinued Therapy if They Remained Uncontrolled for 9 mo: Probability of Becoming Uncontrolled on Therapy if Uncontrolled for 9 mo Varied Between 0.00 and 1.00 (Midpoint, 0.50)		Patients Have Perfect Adherence: Annual Probability of Nonadherence Varied Between 0.00 and 0.50 (Midpoint, 0.25)	
				ICER (Low Range Value, 0%), $/QALY	ICER (High Range Value, 50%), $/QALY	ICER (Low Range Value, 0.00), $/QALY	ICER (High Range Value, 0.15), $/QALY	ICER (Low Range Value, 0.00), $/QALY	ICER (High Range Value, 1.00), $/QALY	ICER (Low Range Value, 0.00), $/QALY	ICER (High Range Value, 0.50), $/QALY
Allopurinol only (dose escalation)	10 353	12.473	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Allopurinol–febuxostat sequential therapy (dose escalation)	11 791	12.493	68 800	58 800	93 300	61 700	75 000	51 100	94 600	91 300	66 600
Febuxostat–allopurinol sequential therapy (dose escalation)	14 519	12.504	271 900	278 100	261 500	259 400	281 400	289 300	254 600	609 700	188 200

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
* Results from sensitivity analyses on the key structural assumptions of the model. The first column presents the ICER when all structural assumptions are set to the midpoint of their tested range. Only results from nondominated strategies for all treatment options are shown. Column headers indicate the structural assumption and how it was tested. Strategies are ordered by increasing cost and effectiveness. The ICER represents the additional cost per QALY of the next-most-expensive strategy. If strategies are dominated, they are not used to evaluate an ICER.
† Assumed to remain in uncontrolled-on-therapy state for life.

Figure 2. **Acceptability curves for all treatment strategies.**



The acceptability curve shows the urate-lowering therapy strategy with the highest probability of being cost-effective for a given willingness-to-pay threshold. When willingness-to-pay per QALY is less than $40 100, dose escalation of allopurinol alone is the optimal treatment. QALY = quality-adjusted life-year.

defined by an SUA level less than 360 μmol/L. The authors reported that the cost-effectiveness of febuxostat–allopurinol compared with allopurinol–febuxostat sequential therapy was $1185 per additional case controlled case. This result also complements our findings that allopurinol's low cost and effectiveness make it a favorable first-line treatment.

The National Institute for Health and Care Excellence in the United Kingdom released a technology appraisal of febuxostat for the treatment of gout (35). In the appraisal, a decision analysis was used to compare allopurinol with febuxostat using a 2-year time horizon and a United Kingdom National Health Service payer perspective. Results showed that the ICER of fixed-dose febuxostat compared with fixed-dose allopurinol was $35 448 per QALY gained (adjusted to U.S. dollars and adjusted for inflation). This is consistent with our findings in the fixed-dose scenario. However, the technology appraisal was criticized for not incorporating dose escalation of allopurinol, sequential-therapy options, or complications from the allopurinol hypersensitivity syndrome (16).

Similarly, a recent Scottish Medicines Consortium technology appraisal for febuxostat did not incorporate dose escalation of allopurinol in the base-case analysis or complications from the allopurinol hypersensitivity syndrome, and a short time horizon was used (5 years) (26).

Comparisons with our model are difficult because of the use of different time horizons and treatment options.

In contrast to these previous studies, the strengths of our analyses include the use of a lifetime time horizon, evaluation of dose escalation of allopurinol and febuxostat, incorporation of both single and sequential therapies, and accounting for the allopurinol hypersensitivity syndrome.

Our study has several limitations. Due to a lack of data, our analyses are based on several key assumptions (for example, effectiveness of second-line therapy). Although we tested these assumptions in sensitivity analyses, incorporation of concrete data in future analyses will be valuable. Our main objective was to compare allopurinol and febuxostat, which are the most commonly used urate-lowering therapy options in the United States. However, several other options and strategies of urate-lowering therapy are available, including probenecid, combination urate-lowering therapy (for example, allopurinol or febuxostat combined with probenecid), and pegloticase. Although these options are less commonly prescribed in current practice, future comprehensive cost-effectiveness analyses could incorporate them. Finally, febuxostat may be more effective than allopurinol in decreasing SUA levels in patients with higher starting SUA levels and those with renal impairment (12). In these subpopulations, the incremental cost-effectiveness of febuxostat compared with allopurinol may potentially improve.

In conclusion, our analyses indicate that allopurinol as a single-therapy option is cost-saving compared with no treatment, and dose-escalation allopurinol–febuxostat sequential therapy seems to be cost-effective. Further, febuxostat single therapy and febuxostat–allopurinol sequential therapy are unlikely to be cost-effective.

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