JAMA Internal Medicine | Original Investigation

Changes in Prescription Drug and Health Care Use Over 9 Years After the Large Drug Price Increase for Colchicine

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IMPORTANCE Prescription drug prices are a leading concern among patients and policy makers. There have been large and sharp price increases for some drugs, but the long-term implications of large drug price increases remain poorly understood.

OBJECTIVE To examine the association of the large 2010 price increase in colchicine, a common treatment for gout, with long-term changes in colchicine use, substitution with other drugs, and health care use.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study examined MarketScan data from a longitudinal cohort of patients with gout with employer-sponsored insurance from 2007 through 2019.

EXPOSURES The US Food and Drug Administration's discontinuation of lower-priced versions of colchicine from the market in 2010.

MAIN OUTCOMES AND MEASURES Mean price of colchicine; use of colchicine, allopurinol, and oral corticosteroids; and emergency department (ED) and rheumatology visits for gout in year 1 and over the first decade of the policy (through 2019) were calculated. Data were analyzed between November 16, 2021, and January 17, 2023.

RESULTS A total of 2 723 327 patient-year observations were examined from 2007 through 2019 (mean [SD] age of patients, 57.0 [13.8] years; 20.9% documented as female; 79.1% documented as male). The mean price per prescription of colchicine increased sharply from $11.25 (95% CI, $11.23-$11.28) in 2009 to $190.49 (95% CI, $190.07-$190.91) in 2011, a 15.9-fold increase, with the mean out-of-pocket price increasing 4.4-fold from $7.37 (95% CI, $7.37-$7.38) to $39.49 (95% CI, $39.42-$39.56). At the same time, colchicine use declined from 35.0 (95% CI, 34.6-35.5) to 27.3 (95% CI, 26.9-27.6) pills per patient in year 1 and to 22.6 (95% CI, 22.2-23.0) pills per patient in 2019. Adjusted analyses showed a 16.7% reduction in year 1 and a 27.0% reduction over the decade ($P < .001$). Meanwhile, adjusted allopurinol use rose by 7.8 (95% CI, 6.9-8.7) pills per patient in year 1, a 7.6% increase from baseline, and by 33.1 (95% CI, 32.6-33.7) pills per patient through 2019, a 32.0% increase from baseline over the decade ($P < .001$). Moreover, adjusted oral corticosteroid use exhibited no significant change in the first year, then increased by 1.5 (95% CI, 1.3-1.7) pills per patient through 2019, an 8.3% increase from baseline over the decade. Adjusted ED visits for gout rose by 0.02 (95% CI, 0.02-0.03) per patient in year 1, a 21.5% increase, and by 0.05 (95% CI, 0.04-0.05) per patient through 2019, a 39.8% increase over the decade ($P < .001$). Adjusted rheumatology visits for gout increased by 0.02 (95% CI, 0.02-0.03) per patient through 2019, a 10.5% increase over the decade ($P < .001$).

CONCLUSIONS AND RELEVANCE In this cohort study among individuals with gout, the large increase in colchicine prices in 2010 was associated with an immediate decrease in colchicine use that persisted over approximately a decade. Substitution with allopurinol and oral corticosteroids was also evident. Increased ED and rheumatology visits for gout over the same period suggest poorer disease control.

JAMA Intern Med. doi:10.1001/jamainternmed.2023.0898
Published online May 8, 2023.

Supplemental content

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Prescription drug prices in the US are a leading concern among patients and policy makers.[1-3] Large and often sharp increases in drug prices, stemming from manufacturer decisions or policies that lead to reduced competition, have been challenging for patients, employers, and insurers.[4-6] To date, the long-term implications of large price increases remain poorly understood. To address this evidence gap, we examined the case of colchicine, a common treatment for gout, for which there was a large price increase in 2010.

Until 2010, colchicine was never formally approved for a particular clinical indication.[7] That year, the US Food and Drug Administration (FDA) approved Colcrys under its Unapproved Drug Initiative after the manufacturer conducted a clinical trial. The FDA awarded Colcrys 3 years of market exclusivity and removed all nonauthorized (non-Colcrys) versions of colchicine from the market in the fall of 2010.[8] Early evidence suggested that the price of colchicine rose and its use declined in the first 2 years after this change.[7-9]

However, longer-term evidence stemming from this FDA policy, such as prices (including patient out-of-pocket cost), use, and substitution with alternative medications, is scant. Moreover, evidence on clinical implications, including emergency department (ED) and specialist encounters for gout that may represent markers for disease control, remains absent. Surveys have shown that patients cut back on medications when facing higher prices.[10-12] Moreover, in other contexts, higher drug prices have led to adverse clinical consequences and downstream health care use, including ED visits.[12,13]

We examined these longer-term outcomes using a large nationwide sample of individuals with employer-sponsored insurance from 2007 through 2019, thus spanning about a decade after the FDA policy. We measured changes in use of colchicine and other medications that can be prescribed with or in place of colchicine for patients with gout, including allopurinol and oral corticosteroids. To assess implications for disease control, we examined changes in ED visits and rheumatology visits for gout.

Key Points

Question What were the long-term implications of the large colchicine price increase in 2010?

Findings In this cohort study of 2 723 327 patient-year observations of patients with gout from 2007 through 2019, the price per colchicine prescription increased 15.9-fold and out-of-pocket price increased 4.4-fold after the US Food and Drug Administration discontinued lower-priced colchicine. The rate of colchicine use decreased, while allopurinol and oral corticosteroid use and emergency department and rheumatology visits for gout increased.

Meaning The study's findings suggest that the large and sharp increase in colchicine prices was associated with a sustained decrease in colchicine use, increased use of other medications for gout, and increased clinical encounters for gout, consistent with poorer disease control.

Methods

Data and Study Population

In this cross-sectional study, we analyzed 2007-2019 MarketScan (IBM) data, comprising a large convenience sample of individuals with employer-sponsored coverage or employer-sponsored Medicare supplemental plans.[14] The prescription drug claims contained in the MarketScan databases detail medication prices and use. We included all enrollees with a diagnosis of gout (*International Classification of Diseases, Ninth Revision* codes beginning with 274 and *Tenth Revision* codes beginning with M10 or M1A[15]) who had medical and prescription drug coverage across all years in which they were enrolled for 12 months. This study was approved by the Harvard Medical School institutional review board with a waiver of informed consent due to the use of deidentified data. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Outcomes

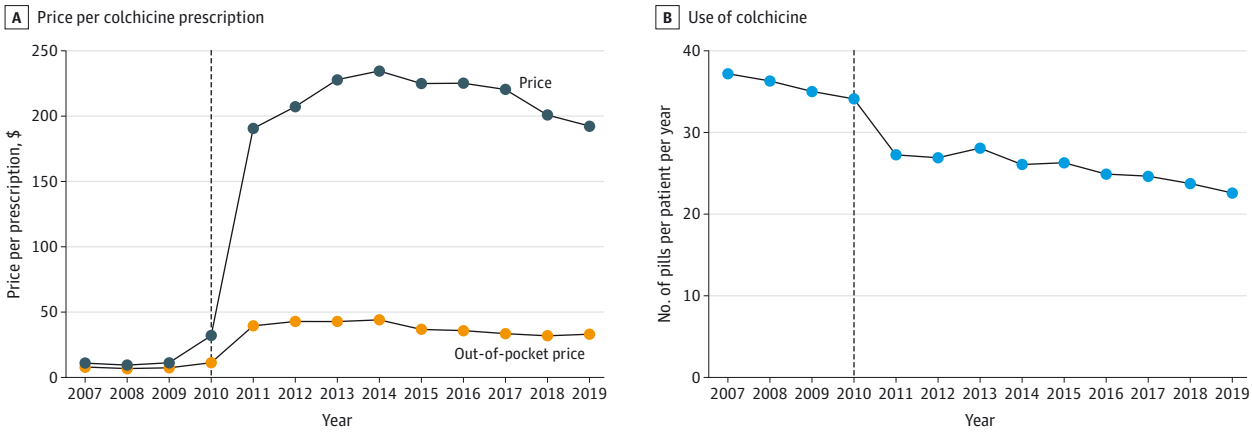
We focused on 3 main outcomes. First, we examined the price of colchicine, defined as the paid amount per prescription and per pill. Transacted prices resulted from negotiations among insurers, their pharmacy benefit managers, and pharmaceutical manufacturers, similar to those used in other studies.[16,17] We also identified patient out-of-pocket price, which included the sum of deductible, copayment, and coinsurance. All dollar values were adjusted to 2019 dollars.

Second, we analyzed prescription drug use, defined as the number of pills supplied per patient per year. We used medication reference data (Redbook) within MarketScan data to identify National Drug Codes corresponding to medications of interest. In addition to colchicine, we focused on 2 types of medications that were potential substitutes for colchicine: allopurinol and oral corticosteroids (eTable 1 in Supplement 1); that is, we examined how patients and clinicians adjusted to a large price increase for an important medication, including changing their use of medications that may be imperfect substitutes.

One key hypothesis was that when the price of a therapeutic treatment rises substantially, patients and clinicians may increase their focus on prevention, which may be a beneficial outcome. Allopurinol is considered the first-line medication for prevention of recurrent gout flares, tophi, and disease progression.[18-20] When the patient experiences a gout flare, colchicine or oral corticosteroids may be used to treat the flare. Therefore, another key hypothesis was that when the price of a therapeutic option rises substantially, patients and clinicians may turn to alternative therapeutic medications, such as corticosteroids. Nonsteroidal anti-inflammatory drugs (NSAIDs), which are available over the counter, can also be used for gout flares. Although our data lacked information on over-the-counter medications, we examined prescription NSAIDs in a secondary analysis.

Third, we examined health care visits plausibly associated with changes in the clinical control of gout. Given that gout flares rarely lead to hospitalization, we focused on ED visits

Figure 1. Price and Use of Colchicine, 2007-2019



The vertical dashed line represents the US Food and Drug Administration's discontinuation of lower-priced versions of colchicine from the market in 2010.

and rheumatology visits with a coded diagnosis of gout. Emergency department visits, defined as claims with the place-of-service code for Emergency Room-Hospital, generally address acute presentations of disease, during which stable, chronic diseases are commonly not coded. Thus, the presence of gout diagnoses on ED claims served as a signal of poorer disease control. Similarly, we examined rheumatology visits (defined as claims with provider type rheumatology) that addressed gout. While we did not expect rheumatology visits to increase in the short term given that ED visits may better account for gout flares, we hypothesized that rheumatology visits for gout could increase over the longer term.

Statistical Analysis

We performed the data analyses between November 16, 2021, and January 17, 2023. In unadjusted analyses, we first calculated the mean price and out-of-pocket price for colchicine in each year, both per colchicine prescription and per colchicine pill. Next, for colchicine and its potential substitute drugs, we measured use as the mean number of pills prescribed per patient per year. We preferred this measure of use (the intensive margin) because the number of prescriptions (extensive margin) fails to account for the variation in pills prescribed per prescription. Analogously, we measured the number of ED visits and rheumatology visits for gout per patient per year.

In adjusted analyses, we calculated the difference in means in prescription drug use and medical visits before the FDA removal period (2007-2010) and after the FDA removal period (2011-2019) using an ordinary least squares model. Given that the composition of enrollment in this population with employer-sponsored insurance may change over time, we calculated these differences in outcomes adjusted for patient age, sex, Diagnostic Cost Group risk score, insurance type, and region. The Diagnostic Cost Group risk score is a measure of overall health status commonly used for risk adjustment.

Given the sharp onset of the FDA policy in 2010, we complemented our main estimates with an interrupted time series approach. This strategy modeled the changes in medication use and medical encounters at 2010 as a trend break and separately estimated changes in the slopes of these outcomes after policy implementation vs before (the coefficient of interest), adjusted for covariates. Finally, we performed a falsification test of the 2010 trend break in colchicine use by examining 3 other immunomodulating medications (methotrexate, azathioprine, and hydroxychloroquine) by assessing their outcomes while assuming the same 2010 policy.

We interpreted the FDA policy as an enrollee-level intervention and used robust SEs. *P* values for *t* tests were calculated using 2-sided tests. Statistical significance was defined at $P < .05$. Analyses were performed using Stata, version 16.1 statistical software (StataCorp LLC).

Results

Patient Characteristics

The sample included 2 723 327 patient-year observations of patients with gout from 2007 through 2019. The mean (SD) patient age was 57.0 (13.8) years, and 20.9% were documented as female (vs 79.1% documented as male). Approximately 75% of the sample was younger than 65 years and had commercial plans, while the remaining 25% were retirees with Medicare supplemental coverage (eTable 2 in Supplement 1).

Colchicine Prices

Before the 2010 policy, the mean price of colchicine per prescription was $10.97 (95% CI, $10.95-$10.98) in 2007 and $11.25 (95% CI, $11.23-$11.28) in 2009. During the same period, the mean out-of-pocket price was similarly stable at $7.97 (95% CI, $7.97-$7.98) per prescription in 2007 and $7.37 (95% CI, $7.37-$7.38) per prescription in 2009.

In 2011, immediately after removal of lower-priced versions of colchicine, the mean price per prescription increased to $190.49 (95% CI, $190.07-$190.91)—a 15.9-fold increase—and the mean out-of-pocket price per prescription increased to $39.49 (95% CI, $39.42-$39.56), a 4.4-fold increase. This in-

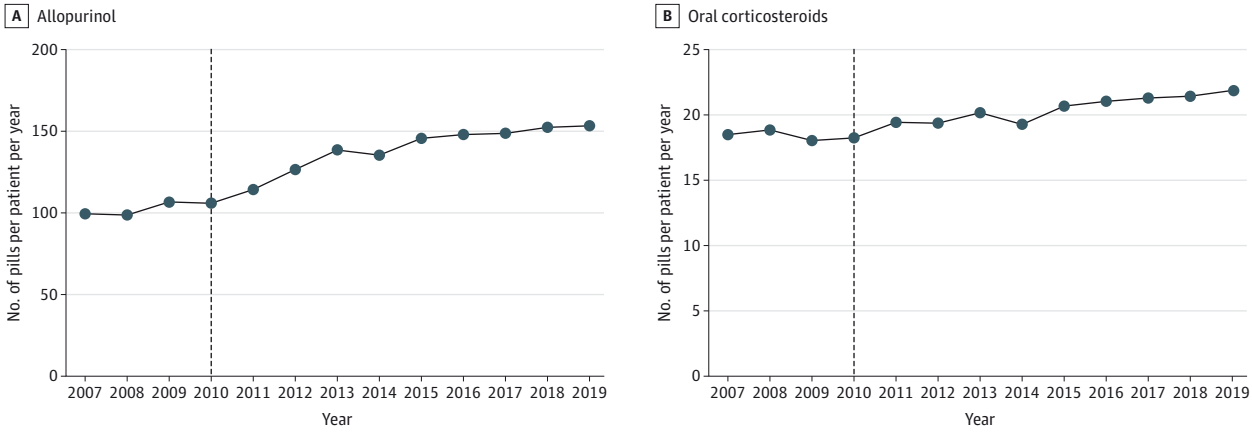
Table. Changes in Prescription Drug and Health Care Use[a]

Variable	Unadjusted means		Adjusted difference in year 1 (2011)			Mean adjusted difference (2011-2019)		
	Prepolicy (2007-2010)	Postpolicy (2011-2019)	Difference (95% CI)	% Change	*P* value	Difference (95% CI)	% Change	*P* value
Prescription drugs								
Colchicine	35.4	26.0	−5.9 (−6.3 to −5.5)	−16.7	<.001	−9.6 (−9.8 to −9.3)	−27.0	<.001
Allopurinol	103.4	138.1	7.8 (6.9 to 8.7)	7.6	<.001	33.1 (32.6 to 33.7)	32.0	<.001
Oral corticosteroids	18.4	20.3	−0.3 (−0.7 to 0.0)	−1.8	.07	1.5 (1.3 to 1.7)	8.3	<.001
Visits for gout								
ED visits	0.11	0.15	0.02 (0.02 to 0.03)	21.5	<.001	0.05 (0.04 to 0.05)	39.8	<.001
Rheumatology visits	0.21	0.24	−0.02 (−0.03 to −0.01)	−10.2	<.001	0.02 (0.02 to 0.03)	10.5	<.001

Abbreviation: ED, emergency department.

[a] Prescription drug use and medical visits were defined as the number of pills supplied and visits per patient per year, respectively. Differences in year 1 and over 2011 to 2019 were calculated relative to the prepolicy mean levels of the outcomes. The differences were adjusted for covariates (patient age, sex, Diagnostic Cost Group risk score, insurance type, and region), with robust SEs. The corresponding percent changes were calculated by dividing the adjusted change by the prepolicy mean levels of the outcomes.

Figure 2. Use of Allopurinol and Oral Corticosteroids, 2007-2019



The vertical dashed line represents the US Food and Drug Administration's discontinuation of lower-priced versions of colchicine from the market in 2010.

crease was sustained through 2019 (**Figure 1**A). This sharp increase in overall price and out-of-pocket price after 2010 and continuously elevated prices in the decade that followed were analogous at the pill level (eFigure 1 in Supplement 1).

Prescription Drug Use

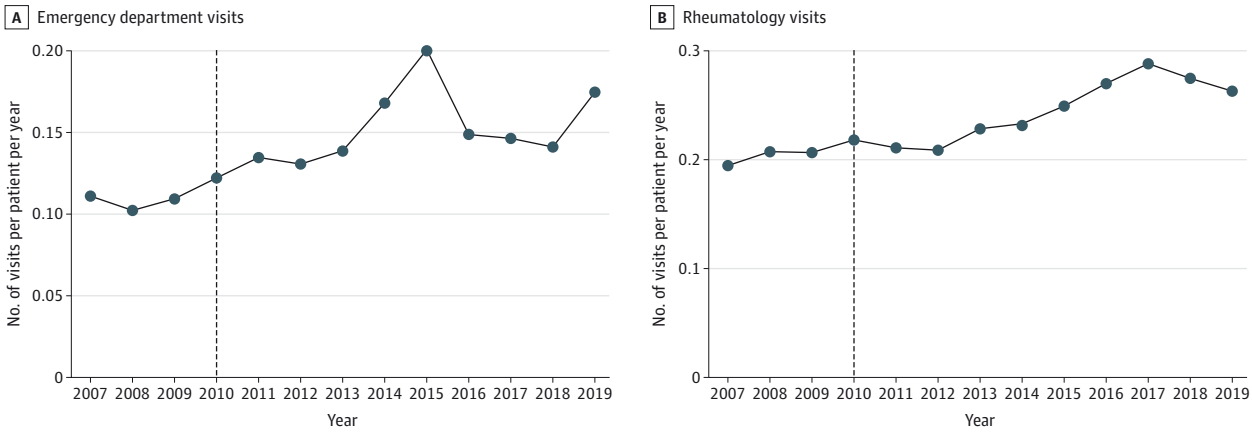
Colchicine use exhibited a sharp reduction shortly after the 2010 policy. In unadjusted analysis, the mean number of colchicine pills per patient was 35.0 (95% CI, 34.6-35.5 pills) in 2009, decreasing to 27.3 (95% CI, 26.9-27.6 pills) in 2011. The mean number of pills further declined to 22.6 (95% CI, 22.2-23.0 pills) in 2019 (Figure 1B). Adjusted for covariates, colchicine use declined by 5.9 (95% CI, −6.3 to −5.5) pills per patient in year 1, a 16.7% reduction from baseline ($P < .001$), and by 9.6 (95% CI, −9.8 to −9.3) pills per patient through 2019, a 27.0% reduction ($P < .001$) (**Table**).

Allopurinol use increased from a mean of 106.8 (95% CI, 106.0-107.5) pills per patient in 2009 to 114.4 (95% CI, 113.7-115.1) pills per patient in 2011, further rising to 153.4 (95% CI, 152.2-154.6) pills per patient by 2019 (**Figure 2**A). Adjusted for covariates, this increase was a mean 7.8 (95% CI, 6.9-8.7) pills per patient or 7.6% in year 1 ($P < .001$) and 33.1 (95% CI, 32.6-33.7) pills per patient over the decade, a 32.0% increase from baseline ($P < .001$) (Table).

Use of oral corticosteroids demonstrated a less clear change relative to baseline, with unadjusted means of 18.0 (95% CI, 17.7-18.4) pills per patient in 2009, 19.4 (95% CI, 19.1-19.7) pills per patient in 2011, and 21.9 (95% CI, 21.5-22.3) pills per patient in 2019 (Figure 2B). Adjusted for covariates, we observed no significant changes in year 1 of the policy, but a mean increase of 1.5 (95% CI, 1.3-1.7) pills per patient over the subsequent decade, an 8.3% increase ($P < .001$) (Table).

Changes in slope of use after the FDA policy were modest (eTable 3 in Supplement 1). Colchicine use, after dropping sharply following the FDA policy, slowed its slope of decline by a mean 0.5 (95% CI, 0.2-0.7) tablets per patient per year, or 1.4% annually over the decade ($P < .001$). The slopes of allopurinol and oral corticosteroid use similarly increased by 2.6% (coefficient, 2.7; 95% CI, 2.3-3.1) and 3.8% (coefficient, 0.7; 95% CI, 0.5-0.9), respectively, after the policy relative to before ($P < .001$). In our secondary analysis, the secular decline in prescription NSAIDs slowed after 2010 (eFigure 2 and eTable 3 in Supplement 1).

Figure 3. Emergency Department and Rheumatology Visits for Gout, 2007-2019



The vertical dashed line represents the US Food and Drug Administration's discontinuation of lower-priced versions of colchicine from the market in 2010.

In our falsification test, methotrexate, azathioprine, and hydroxychloroquine exhibited no significant change in use in year 1 (mean, 0.1 tablets per patient per year; 95% CI, −0.2 to 0.3 tablets per patient per year; P = .47) and no change in the slope of use thereafter relative to prepolicy trends (mean, 0.0 tablets per patient per year; 95% CI, −0.1 to 0.2 tablets per patient per year; P = .45). In a sensitivity analysis, use of colchicine in a 5-year continuously enrolled sample of patients with gout showed qualitatively similar results (eFigure 3 in Supplement 1).

Medical Use

Emergency department visits for gout increased from a mean of 0.11 (95% CI, 0.11-0.11) per patient in 2009 to 0.13 (95% CI, 0.13-0.14) per patient in 2011, and further increased to 0.20 (95% CI, 0.19-0.21) per patient in 2015. After newer colchicine competitors were introduced in 2015, ED visits for gout declined to a mean of 0.17 (95% CI, 0.17-0.18) per patient by 2019 (**Figure 3**A). Adjusted for covariates, mean ED visits for gout rose by 0.02 (95% CI, 0.02-0.03) per patient in year 1, a 21.5% increase (P < .001). By 2019, ED visits for gout had risen by a mean of 0.05 (95% CI, 0.04-0.05) per patient, or a 39.8% increase relative to the pre-FDA policy mean (P < .001) (Table).

Rheumatology visits for gout, adjusted for covariates, decreased by a mean of 0.02 (95% CI, −0.03 to −0.01) per patient in year 1. However, over the ensuing decade, rheumatology visits increased by a mean of 0.02 (95% CI, 0.02-0.03) per patient, adjusted for covariates, which amounted to a 10.5% increase relative to baseline (Figure 3B; Table). Neither ED nor rheumatology visit use showed a measurable change in slope after the FDA policy (eTable 3 in Supplement 1).

Discussion

In a large, nationwide data set comprising commercially and Medicare-insured patients with gout, this retrospective cohort study found that FDA removal of lower-priced competitors to Colcrys in 2010 led to a sharp and substantial increase in price and patient cost sharing for colchicine that was associated with an immediate decrease in use of colchicine. Meanwhile, use of allopurinol and oral corticosteroids increased in patients with gout, suggesting a substitution effect and potentially greater efforts to prevent gout flares, which had become more expensive to treat. The policy was also followed by an increase in ED and rheumatology visits for gout over the ensuing decade.

To treat gout flares, colchicine was substituted with oral corticosteroids, though the substitution was modest, with a mean increase of 8.3% over the decade compared with the mean decline of 27.0% in colchicine use. The use of allopurinol, not a direct substitute for colchicine but used alongside colchicine to prevent gout flares, increased substantially by 32.0%. These findings suggest that as gout flares became more expensive to treat, patients and clinicians may have been more aggressive in preventing such flares by increasing allopurinol use; that is, when the price of a treatment rises, prevention may receive more attention, which is beneficial. However, on net, prevention efforts may have been exceeded by worsened disease control, given the increase in clinical visits for gout. Although disease severity was difficult to assess, colchicine is typically effective for treating acute flares and for gout flare prophylaxis in the early stages of using allopurinol. Thus, colchicine's mechanism is consistent with our empirical findings.

Given the lack of a control group, our estimates are susceptible to secular trends, such as a decline in primary care visits that may explain a slowdown in prescription volume. However, prescriptions per capita increased over this period,[21] and prescriptions are commonly issued without a visit (eg, electronic refills). Meanwhile, specialist visits remained stable in the commercially insured population,[22,23] and ED visits also were stable over this period.[24]

Taken together, our results suggest that a large price increase, especially a large out-of-pocket price increase, in medications that have few or no substitutes could have adverse eco-

nomic and clinical consequences. These results indicate a similar pattern as findings in the literature for insulin, for which surveys suggest substantial price-related medication nonadherence.[25] In addition, although we found a fairly large decrease in colchicine use among patients with gout, this decrease may not have been as large as one might expect given the magnitude of the out-of-pocket price increase. This less-than-expected decrease suggests that patients and insurers may largely absorb price increases in medications that lack substitutes, and for those who do lower their use, adverse clinical outcomes may follow.

Our findings are directionally consistent with a prior study of the 2010 FDA colchicine policy that focused on the likelihood of initiating colchicine based on data from 2009 to 2012.[9] Our use of data starting in 2007 allows for a fuller sense of trends prior to the 2010 policy. Our study, which extends to 2019, provides more time to examine changes in colchicine use, substitution away from colchicine, and possible clinical implications of such use patterns, all of which may not be immediately apparent within 2 years of a large price increase. In addition, other research has found lower prescription drug use in response to increased patient cost sharing.[10-13] However, these studies in general did not examine substitution patterns and possible clinical outcomes in response to large and sharp price increases in medications, which have different policy implications than changes in cost sharing.

Although the case of colchicine may be unique given the FDA removal of generic competitors from the market, the economic basis for the subsequent price increase ultimately rests in the reduction in competition, a familiar mechanism that underlies other increases in prescription drug prices stemming from a drug's market power. Therefore, despite the unique policy intervention that gave rise to colchicine's price increase, our findings may nevertheless be applicable to large future increases in drug prices. Such price increases could include, for example, manufacturers' responses to the Inflation Reduction Act,[26] which gives Medicare the ability to negotiate prices of select drugs. Because a proposal to cap drug price growth in the commercial population was not included in the legislation, reductions in Medicare drug prices might lead to compensatory increases in commercial drug prices, for which this study may offer a useful data point.

Limitations

This study has several limitations. First, without a control group, our estimates were susceptible to unmeasured confounding. We relied on the sharp trend break in colchicine prices and the immediate change in colchicine use from prepolicy levels as the identification strategy. We also relied on prepolicy trends as the counterfactual in interrupted time series analyses (although the trends in colchicine use and in ED and rheumatology visits before 2010 remain a concern). Our falsification test supported the findings. However, in the absence of exogenous variation in colchicine prices and ideal counterfactual medications to colchicine, results should not be interpreted as causal. Moreover, changes in outcomes farther out from the date of the price change are plausibly more susceptible to secular effects (eg, economic changes and health care system changes) and other sources of confounding. Second, patient mix could evolve over time, as enrollees could enter and leave the sample in each year, though we required 12-month enrollment within each year. However, a sensitivity analysis of individuals with gout continuously enrolled for 5 years yielded qualitatively similar results (eFigure 3 in Supplement 1). Third, clinical details such as gout severity and functional impairment were unobservable in claims. Similarly, the presence of a gout diagnosis on a claim may not mean that acute gout was contributory. For example, it is possible that ED visits with gout recorded were instead focused on a different medical issue with gout recorded as a comorbidity. Fourth, over-the-counter medications (eg, NSAIDs) were unobservable in claims, and we could not rigorously evaluate opioid use relative to the policy given the changing opioid landscape during this period. However, to the extent that over-the-counter NSAIDs or opioids were used as substitutes for colchicine, our findings of increased allopurinol and corticosteroid use may be a conservative reflection of overall substitution. Fifth, our findings may not generalize to populations outside of patients with employer-sponsored insurance or Medicare supplemental coverage, such as patients with traditional Medicare or Medicaid. The findings also may not generalize to large price increases for medications other than colchicine, which may pertain to different clinical situations and have different (or possibly no) substitutes that lead to different patterns of use and clinical implications.

Conclusions

The findings of this retrospective cohort study suggest that after a 4.4-fold increase in out-of-pocket colchicine prices nationwide, patients with gout used less colchicine, used more substitute medications, and may have experienced poorer disease control over 9 years. Increasing drug prices where competition is lacking could have important implications for patients and payers in the long term.

ARTICLE INFORMATION

Accepted for Publication: February 21, 2023.

Published Online: May 8, 2023. doi:10.1001/jamainternmed.2023.0898

Author Contributions: Ms Giuriato and Dr Song had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Ly, Song.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Ly, Giuriato.
Critical revision of the manuscript for important intellectual content: Ly, Song.
Statistical analysis: All authors.
Obtained funding: Song.
Administrative, technical, or material support: Song.
Supervision: Song.

Conflict of Interest Disclosures: Dr Song reported receiving personal fees from the Research Triangle Institute for work on Medicare risk adjustment, Google Ventures, VBID Health, and the International Foundation of Employee Benefit Plans for academic lectures, and for providing consultation in legal cases outside the submitted work. No other disclosures were reported.

Funding/Support: This work was supported by Director's Early Independence Award

DP5-OD024564 and grant P01-AG032952 from the National Institutes of Health (Dr Song) and grant 20-04402 from Arnold Ventures (Dr Song).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily represent the views of the US Department of Veterans Affairs or the US government.

Data Sharing Statement: See Supplement 2.

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