Compliance with Allopurinol Therapy Among Managed Care Enrollees with Gout: A Retrospective Analysis of Administrative Claims

AYLIN A. RIEDEL, MICHAEL NELSON, NANCY JOSEPH-RIDGE, KATRINE WALLACE, PATRICIA MacDONALD, and MICHAEL BECKER

ABSTRACT. ***Objective.*** Poor compliance with gout medications has been recognized, but seldom studied. We investigated compliance with allopurinol among managed care enrollees suspected to have gout.

Methods. This was a retrospective, administrative claims-based analysis of patients with gout. Compliance with allopurinol was measured using prescription-fill dates and days-supplied amounts. Compliance was defined for each prescription period as the presumed use of allopurinol on at least 80% of the days of that period.

Results. Of 9482 patients identified, 65.9% filled at least one prescription for allopurinol during the 24 month followup period; 10.4% of allopurinol users filled one prescription and then discontinued use. Of the remaining patients, 13.7% never achieved compliance with therapy; 18% were compliant throughout the entire followup period. Patients were compliant with therapy for an average of 56% of their treatment periods and noncompliant for an average of 44%. In multivariate analysis, male sex was associated with decreased compliance ($p < 0.01$), although the effect was mitigated by increasing age. For subjects of both sexes, increasing age was associated with increased compliance ($p < 0.05$).

Conclusion. Compliance with allopurinol in this population was low. Because untreated gouty arthritis can lead to serious adverse outcomes (such as recurrent gouty arthritis, chronic gouty arthropathy, tophi, and urolithiasis) that are usually avoidable with antihyperuricemic therapy, efforts to achieve better compliance are warranted. (J Rheumatol 2004;31:1575–81)

Key Indexing Terms:
GOUT ALLOPURINOL PATIENT COMPLIANCE
RETROSPECTIVE STUDIES MANAGED CARE PROGRAMS

Gout is characterized by the symptomatic deposition of urate crystals in tissues as a result of urate supersaturation of extracellular fluids, a biochemical aberration indicated by hyperuricemia (serum urate concentrations exceeding 7.0 mg/dl). Although hyperuricemia is a necessary condition for gout, many hyperuricemic persons remain asymptomatic and never develop clinical urate crystal deposition disease (gout). When, however, urate crystal deposition is clinically manifested, the most common events are recurrent acute attacks of inflammatory arthritis and urinary tract stones. Left untreated, urate crystal deposition can result in a chronic deforming arthritis, the development of crystal aggregates (tophi), which can cause destruction of cartilage and bone, and, on occasion, organ dysfunction, especially renal impairment.

Treatment of gout is usually successful, as long as both physician and patient recognize that management involves 3 distinct aims. The first is treatment of acute inflammation, usually accomplished with nonsteroidal antiinflammatory drugs (NSAID), colchicine, systemic or intraarticular steroids, or ACTH. Success in controlling acute attacks of gout, however, does not prevent further episodes and does not affect the hyperuricemic state. The second aim of therapy is prophylaxis against acute attacks of gout during the interval (intercritical period) between attacks, and this is usually achieved with small daily doses of colchicine or an NSAID. Prophylaxis is frequently prescribed as well during the early course of uric acid-lowering therapy, when the frequency of acute gouty attacks is paradoxically increased. The third aim, longterm restoration of a normal serum urate level, usually requires an antihyperuricemic agent. Antihyperuricemic agents currently approved for use in the United States are of 2 classes: the xanthine oxidase inhibitor allopurinol, which blocks formation of uric acid by inhibiting the enzyme responsible for formation of uric acid from hypoxanthine and xanthine; and uricosuric agents

From Ingenix Pharmaceutical Services, Eden Prairie, Minnesota, and TAP Pharmaceutical Products Inc., Lake Forest, Illinois, USA.

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A.A. Riedel, PhD; M.A. Nelson, PharmD, Ingenix Pharmaceutical Services; N. Joseph-Ridge, MD; P. MacDonald, NP, TAP Pharmaceutical Products Inc.; K.L. Wallace, MA, TAP Pharmaceutical Products, Inc. and University of Illinois at Chicago School of Public Health, Chicago, IL; M.A. Becker, MD, University of Chicago, Chicago, IL.

Address reprint requests to Dr. A.A. Riedel, Research and Data Solutions Group, Ingenix, Inc., 12125 Technology Drive, MN002–0258, Eden Prairie, MN 55344.

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(probenecid, sulfinpyrazone), which promote uric acid excretion by the kidneys.

Uric acid-lowering therapy is recommended for patients with gout and frequent attacks of acute gouty arthritis, chronic gouty joint disease, tophaceous gout, impaired renal function, uric acid nephropathy, and nephrolithiasis[1-3]. Because of a wider range of gout patients in whom it is safe and effective, allopurinol is the most commonly recommended form of uric acid-lowering therapy currently employed. While virtually all patients with gout for whom chronic antihyperuricemic therapy is indicated are candidates for treatment with allopurinol, this agent can result in significant side effects or adverse reactions. The most common of these are gastrointestinal distress and a pruritic, maculopapular rash in 3% to 10% of patients[3,4]. More serious adverse reactions to allopurinol include rashes of increasing extent and severity, hepatic function abnormalities, vasculitis, and a rare but potentially fatal allopurinol hypersensitivity syndrome manifested by fever, toxic epidermal necrolysis, leukocytosis, eosinophilia, hepatitis, and interstitial nephritis[3,5,6].

Compliance of patients with chronic medications has become of increasing interest to practitioners and to health care plans, because of the anticipated relationship between adequate patient compliance and beneficial health outcomes. Poor compliance with gout medications has been recognized, but seldom studied[7]. De Klerk, *et al* found low compliance rates with gout medications among patients in The Netherlands, but study sample sizes were small[8,9]. In a study that examined compliance using electronic medication monitoring, the authors found that patients using antihyperuricemic agents were 84% compliant with the number of doses prescribed and 54% compliant with the dosing schedule[8]. Colchicine users were less compliant, most likely due to gastrointestinal intolerance. Overall, gout patients missed doses on 15% of the days of their observation period.

Effective therapies for the treatment of most patients with gout have been available for more than 30 years. Nevertheless, persistent expression of the symptoms of gout is often encountered even long after treatment is initiated. Patient noncompliance and inadequate patient education about the distinctive aims of treatment appear to play key roles in this situation[7,10,11].

We examined compliance with allopurinol therapy among US managed care enrollees with suspected gout. To date, no other study examines compliance with allopurinol in a large population or in a managed care setting.

MATERIALS AND METHODS

This was a retrospective, administrative claims-based study using subjects who were suspected to have gout and who were enrollees in managed care plans throughout the United States.

Data source. Physician, pharmacy, and facility claims for enrollees in 14 independent practice association (IPA)-network managed care health plans located throughout the US were used in analysis. All plans were discounted, noncapitated, IPA model plans. A subject identification period spanning the period July 1, 1997, to June 20, 1998, was used to identify subjects with gout. During this patient identification period, total plan enrollment was about 2.5 million persons.

Study population. Subjects were included in analysis if they met the following criteria: (1) suspicion of gout, as evidenced by either a diagnosis code for gout (*International Classification of Disease-9-CM* codes 274.xx) present in any position on physician or facility claims OR at least one prescription for colchicine, probenecid, sulfinpyrazone, a probenecid/colchicine combination, or allopurinol during the subject identification period; (2) enrollment in one of 14 commercial managed care health plans with a drug benefit as part of coverage; and (3) continuous enrollment in the health plan for at least 24 months after the first detected claim identifying gout. Because allopurinol may be used in the treatment of hyperuricemia in cancer patients, subjects with a diagnosis of cancer (ICD-9-CM codes 140.xx–208.xx) but not gout and who filled prescriptions for allopurinol (and no other gout medication) were excluded from analysis. The date of a subject's earliest-appearing pharmacy claim for a gout medication or medical claim with a gout diagnosis was defined as the index date for that subject. Twenty-four months of post-index date data were used in analysis.

Measures of compliance. Measures of compliance with allopurinol were based on the compliance rate developed by Rizzo and Simons for research in the area of compliance with antihypertensive medications[12]. A compliance rate, calculated for each pair of prescriptions filled, was defined as: Compliance rate = days supply from 1st prescription filled / [fill date of 2nd prescription filled – fill date of 1st prescription filled].

Compliance rates were calculated only for subjects with at least 2 allopurinol prescription fills. Compliance was not assessed for the 651 subjects who filled only one allopurinol prescription (10.4% of the 6248 subjects who filled prescriptions for allopurinol). Rizzo and Simons defined compliance as an average compliance rate > 0.80. Persistence, although noncompliance, was defined as an average compliance rate of 0.30–0.80. Nonpersistence was defined as an average compliance rate < 0.30.

A subject's allopurinol treatment period was identified as the time between the fill date of the first filled allopurinol prescription and (fill date + days supply) of the last filled allopurinol prescription during the 24 month observation period. Based on the Rizzo and Simon methodology, the following measures of compliance were used in analysis: percentage of days compliant during the treatment period; percentage of days noncompliant (although persistent) during the treatment period; percentage of days nonpersistent during the treatment period; and weighted average compliance rate during entire treatment period.

The weighted average compliance rate, a summary measure of compliance, was calculated for each subject who filled at least 2 prescriptions for allopurinol. The weighted average compliance rate is an average compliance rate created by weighting each compliance rate by the number of days over which the compliance rate applied. The weighted average compliance rate provides a more accurate indication of compliance than a simple average of all compliance rates because it takes into account the length of time the patient spent at each level of compliance.

Statistical analysis. Multivariate linear regression of the weighted average compliance rate (the weighted average of all compliance rates) was used to identify factors associated with noncompliance with allopurinol therapy. Robust standard errors were calculated due to heteroskedasticity in the model.

RESULTS

Study population. A total of 9595 subjects fulfilling the 3 criteria for enrollment were identified. Of these, 113 (1.2%) patients prescribed allopurinol, but with diagnosis codes for cancer but not gout, were excluded from the analysis. The final study population included 9482 subjects (Table 1).

Table 1. Study population description.

Total Number of Subjects	9482
Male, n (%)	7783 (82.1)
Age mean yrs (SD), n (%)	51 (11)
0–17	64 (0.7)
18–44	2416 (25.5)
45–64	6195 (65.3)
> 65	807 (8.5)
Gout diagnosis or prescriptions during study period (%)	
At least one claim with a diagnosis code indicating gout	5868 (61.9)
At least one prescription for a medication to treat gout	5972 (63.0)
Two or more prescriptions for medications to treat gout	4848 (51.1)
Both a gout diagnosis code and at least one prescription for a medication to treat gout	2358 (24.9)
Comorbid conditions coded during 24 mo observation period (%)	
Hypertension	5772 (60.9)
Hyperlipidemia	4605 (48.6)
Diabetes	2056 (21.7)
Depression	814 (8.6)
Obesity	800 (8.4)
Osteoarthritis	730 (7.7)
Rheumatoid arthritis	262 (2.8)
Renal failure	247 (2.6)

Table 2. Utilization of gout medications during 24 month followup period.

Gout Medication	Patients, N	Patients, %	No. of Prescriptions*, mean	No. of Prescriptions*, median
Colchicine	1492	15.3	5	3
Probenecid	210	2.2	7	5
Probenecid with colchicine	281	3.0	8	5
Sulfinpyrazone	11	0.1	8	3
Allopurinol	6248	65.9	12	10

* Number of prescriptions among subjects with at least one prescription for the medication.

Table 3. Utilization of gout medications among allopurinol users.

Gout Medication	Subjects*, N	Subjects*, %
Colchicine	1031	16.5
Probenecid	87	1.4
Probenecid with colchicine	107	1.7
Sulfinpyrazone	3	< 0.1

* Among subjects who filled at least one prescription for allopurinol.

The study population (Table 1) was 82.1% male with an average age of 51 years (median 51 yrs). High rates of comorbid conditions were identified in the population during the 24 month post-index date period, including hyperlipidemia (48.6%), hypertension (60.9%), and diabetes (21.7%).

Gout medication use. Seventy-five percent of subjects filled at least one prescription for a medication to treat gout (allopurinol, colchicine, probenecid, probenecid with colchicine, sulfinpyrazone) during the 24 month followup period (Table 2). Allopurinol was the most frequently prescribed gout medication. A total of 6248 subjects (65.9% of the study population) filled at least one prescription for allopurinol during the followup period, with an average of 12 prescriptions per patient among those who filled at least one prescription. The second most frequently prescribed gout medication was colchicine, used by 1492 subjects (15.3% of the study population), with an average of 5 prescriptions per patient (among those with any colchicine use). Combined use of allopurinol and colchicine was common, with 17% of allopurinol users filling at least one prescription for colchicine (Table 3).

Of the 6248 subjects who filled prescriptions for allopurinol during the 24 month followup period, 651 (10.4%) filled only one prescription. Eighty percent of allopurinol users who filled only one allopurinol prescription were male with an average age of 48 years. Of patients who filled only one allopurinol prescription, 22.0% filled colchicine prescriptions, 3.2% filled probenecid prescriptions, and 3.5% filled probenecid/colchicine combination prescriptions during the 24 month followup period.

Compliance with allopurinol therapy. Compliance with allopurinol was analyzed for the 5597 subjects (89.6% of allopurinol users) who filled at least 2 prescriptions for allopurinol. Of these, 769 (13.7%) never achieved compliance with their allopurinol therapy during the 24 month observation period (that is, their compliance rates never reached 0.80).

For each subject, the treatment period was defined as the time between the first allopurinol prescription and fill date + days supply of the last allopurinol prescription. Allopurinol users were compliant with therapy (e.g., achieved a compliance rate ≥ 0.80) during an average of 56% of their treatment periods (Table 4). One-fifth of subjects who filled at least 2 prescriptions for allopurinol were compliant for ≤ 10% of their treatment periods (Figure 1). Only 18% of assessable allopurinol users were compliant with their allopurinol throughout their entire treatment period.

Subjects were noncompliant with allopurinol (e.g., had a compliance rate < 0.80) an average of 44% of treatment-period days (Table 4). Subjects were persistent, although noncompliant (compliance rate 0.30–0.80), an average of 29% of their treatment period and nonpersistent (compliance rate < 0.30) an average of 15% of the treatment period.

The weighted average compliance rate is a summary measure of compliance that accounts for the length of time spent at each level of compliance (Figure 2). The mean average weighted compliance rate was 0.748 (median

Table 4. Percentage of treatment period compliant, persistent (although noncompliant), and nonpersistent with therapy.

Compliance Measure	Mean (SD)	Minimum	Maximum	Percentiles 10th	25th	50th	75th	90th
Treatment period compliant, %	56 (37)	0	100	0	19	65	91	100
Treatment period noncompliant, %	44 (37)	0	100	0	9	35	81	100
Treatment period persistent (and noncompliant), %	29 (30)	0	100	0	0	20	46	78
Treatment period nonpersistent (and noncompliant), %	15 (29)	0	100	0	0	0	17	65

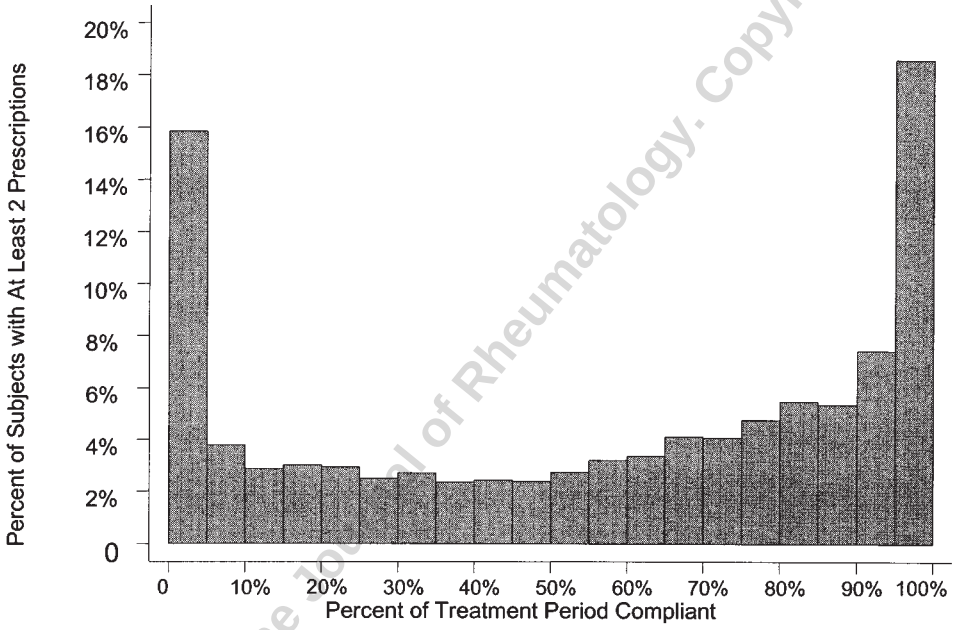

Figure 1. Percentage of treatment period compliant with allopurinol (subjects who filled at least 2 allopurinol prescriptions, n = 5597).

0.841), indicating that on average, patients filled prescriptions with a frequency that provided them with daily doses of allopurinol on 75% of the days in the treatment period. Female subjects had higher weighted average compliance rates compared to male subjects, and subjects in the 19–44 year age group had lower weighted average compliance rates compared to subjects in all other age categories (Table 5).

Multivariate linear regression of the weighted average compliance rate was used to determine variables that are independently related to noncompliance with allopurinol (Table 6). Male sex was found to significantly decrease compliance rates ($p < 0.01$), while increasing age was found to increase compliance ($p < 0.05$). The interaction between age and sex indicates that the influence of male sex on noncompliance decreases with increasing age. While the effect of sex on compliance was minimal for the average-age subject (51 yrs), among 40-year-old subjects, female sex was associated with an increase of 1.5 days of compliance per 30 days of treatment compared to male sex. For 30-year-olds, female sex was associated with an increase of 2 days of compliance per 30 days compared to male sex. The presence of diabetes and/or hypertension during the 24 month followup period was found to be associated with increased compliance with allopurinol. A subject with both hypertension and diabetes would have, on average, 3 more days of compliance during a 30 day treatment period compared to a subject without these conditions. Increasing dose of allopurinol was found to be associated with decreased compliance, with each 100 mg increase in dose associated with one less day of compliance per 30 day treatment period. The model had an $R^2 = 0.0531$, indicating that only 5% of the variance in compliance rates in the population was explained by factors included in the model.

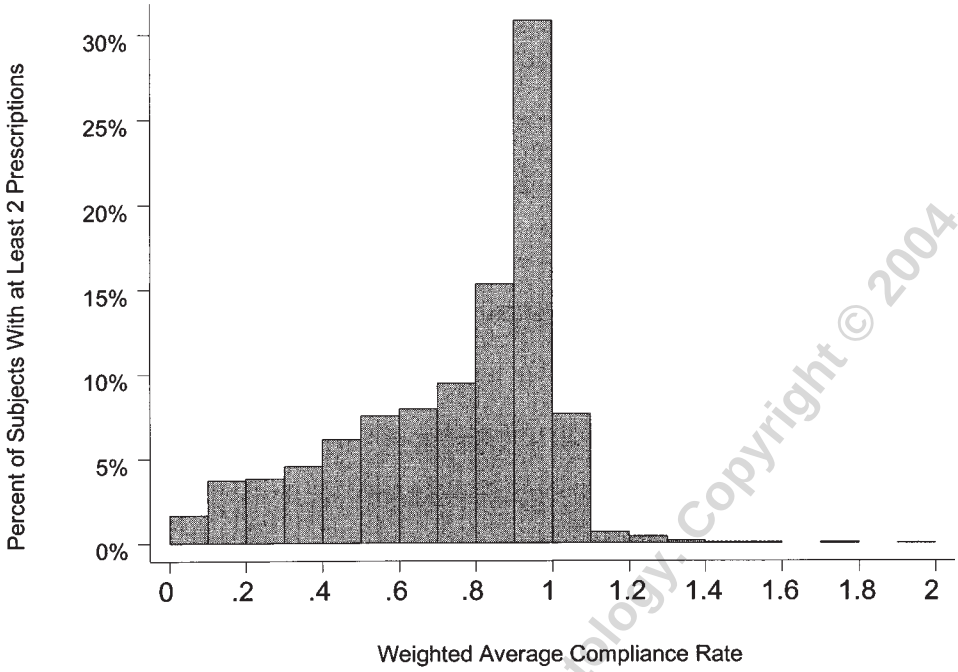

Figure 2. Weighted average compliance rate.

Table 5. Weighted average compliance rate among allopurinol users who filled at least 2 allopurinol prescriptions. A compliance rate was calculated for the time between 2 allopurinol prescription fills as [(days supply from first prescription)/(fill date of 2nd prescription – fill date of 1st prescription)]. The weighted average compliance rate is a weighted average of all compliance rates during a patient's treatment period.

Weighted average compliance rate	
Mean (SD)	0.748 (0.296)
Median	0.841
Minimum, maximum	0.04, 2.00
25th–75th percentile	0.568–0.961
Mean (SD) by sex	
Male	0.744 (0.302)
Female	0.774 (0.261)
Mean (SD) by age group, yrs	
0–17	0.754 (0.320)
18–44	0.663 (0.282)
45–64	0.763 (0.303)
65 and older	0.831 (0.231)

DISCUSSION

This was a retrospective administrative claims-based study that examined gout medication use among 9482 managed care enrollees suspected to have gout. Specifically, the study examined compliance with allopurinol therapy among the 6248 patients who filled prescriptions for this medication. Subjects were followed for 24 months after their initial identification.

Of allopurinol users, 10.4% filled only one prescription in the 24 month followup period. It is likely that, in some cases, early cessation of allopurinol occurred as a result of medication-related recurrences of acute gouty arthritis. Nevertheless, compliance with allopurinol treatment was less than optimal even among subjects who refilled prescriptions. Of subjects who filled at least 2 prescriptions for allopurinol, 13.7% were never compliant with this medication. Only 18% of subjects who filled 2 or more allopurinol prescriptions were compliant throughout their treatment period. On average, subjects who filled at least 2 prescriptions were compliant with allopurinol therapy 56% of the days in their treatment periods and noncompliant with therapy for 44% of the days. Male sex was associated with decreased compliance, although the effect of sex diminished with increasing age. Increased compliance was associated with increasing age in both sexes and with the presence of diabetes or hypertension.

The choice to define compliance as a compliance rate ≥ 0.80 and nonpersistence as a compliance rate < 0.30 was based on thresholds devised by Rizzo and Simons for a study of compliance with hypertension[12]. While the choice of these boundaries for a study of gout is arbitrary, they were selected because of their use in the literature and because of the similarity between treatment for gout and treatment for hypertension. Both conditions are chronic diseases that require longterm pharmacotherapy, and both conditions can be asymptomatic for a long period of time, despite patient

Table 6. Results of multivariate regression model of weighted compliance rate.

Independent Variables	ß	SE	95% CI	
Sex, male	–0.151***	0.052	–0.253	–0.049
Age	0.002**	0.001	0.000	0.003
Age × sex	0.003***	0.001	0.001	0.005
Prescriptions filled				
Sulfinpyrazone	–0.034	0.128	–0.285	0.217
Probenecid	–0.002	0.004	–0.011	0.006
Colchicine	0.002	0.004	–0.005	0.009
Probenecid/colchicine	–0.005	0.006	–0.018	0.007
Average dose of allopurinol (100 mg)	–0.029***	0.004	–0.037	–0.021
Comorbid conditions detected				
Diabetes	0.039***	0.008	0.023	0.054
Osteoarthritis	–0.004	0.014	–0.032	0.024
Hypertension	0.046***	0.009	0.027	0.065
Renal failure	–0.024	0.020	–0.062	0.015
Depression	0.000	0.013	–0.025	0.025
Rheumatoid arthritis	0.040	0.073	–0.102	0.183
Obesity	–0.004	0.012	–0.027	0.018
Constant	0.700***	0.049	0.604	0.796

** $p < 0.05$, *** $p < 0.01$. Model $F = 25.84$ ($p = 0.000$), model $R^2 = 0.0531$.

noncompliance with therapy. When the boundaries that define compliance and persistence were varied, study results varied modestly. That is, at a threshold of 0.80, allopurinol users were compliant for an average of 56% of the days of their treatment period. When the standard for compliance was varied from 0.85 to 0.75, the percentage of days compliant with allopurinol decreased from 61% to 49%.

There are some inherent limitations to a study that is solely based on claims analysis. One is the retrospective, uncontrolled structure of the investigation and lack of clinical validation. The lack of clinical information in administrative claims data prohibits analysis of disease severity or examination of certain clinical factors that may have driven treatment decisions. Second, there are limitations to the use of prescription refilling as a proxy for patient compliance. The presence of a prescription claim does not necessarily mean a drug was taken. Similarly, patients could have received drugs without the presence of a prescription claim either by receiving drug samples or filling prescriptions outside the health plan's pharmacy system (although this is likely to be rare).

It is important that the study population consisted of subjects suspected of having gout. A medical claim with a diagnosis code for gout was present for 42.6% of subjects; the remaining subjects were identified because they filled prescriptions for medications used in the treatment of gout and hyperuricemia. Because of the chronic and frequently asymptomatic nature of gout, it is not surprising that a large segment of the population did not have a diagnosis code for gout in their claims data. These subjects likely did not seek medical treatment (other than pharmacotherapy) for their gout during the study period. A compliance assessment for the subgroup of subjects with a diagnosis code for gout was carried out and compared with that of the entire study population. The results of these assessments were found to be similar.

Despite some limitations, administrative claims data remain a powerful tool for characterizing medication use patterns in large, chronically ill populations. This data source provides an economically efficient method of describing health service use patterns among large study cohorts and reflects pharmacy and medical service use in a "real-world" setting, in contrast to the tightly controlled environment of clinical trials.

The literature regarding patient compliance with prescribed therapies is expansive and frequently provides contradictory information about factors that are important predictors of compliant behavior. Our findings are consistent with studies that have examined determinants of compliance with drug therapy in gout as well as with other conditions that are chronic, require longterm pharmacotherapy, and often remain asymptomatic despite noncompliance. De Klerk, *et al* found that male sex and the passage of time were both associated with increasing noncompliance with gout medications[8]. These authors also found greater compliance with symptom-controlling medications than with agents aimed at maintaining symptom-free intervals[8]. Patients with a greater number of comorbid conditions have been found to be more compliant with statin therapy than patients with fewer comorbidities[13,14], presumably because the former group of patients are already taking medications

for other conditions. In a review of studies of medication compliance, Hughes, *et al* noted that compliance with medication regimens is lowest among patients with asymptomatic conditions[15].

Several studies examining the influence of compliance rates with medications on health outcomes and health care costs identified the following factors influencing compliance behavior: the efficacy of the medication involved, the cost of the medication, and the severity and immediacy of effect of lapses in therapy[15-21].

Hurley, *et al* examined the effect of noncompliance with hormone replacement therapy (HRT) on short term healthcare costs and utilization in the Lovelace health care system[19]. Subjects poorly compliant with HRT had significantly more emergency room visits and mental health visits compared with compliant subjects, although there was no difference in total health care costs between compliant and noncompliant subjects. Urquhart, *et al*, in a study of compliance with lipid-lowering agents, noted costs associated with prescriptions filled and not taken[20].

Compliance with allopurinol in this commercially insured, managed care population was low. Among specific reasons that may be suggested to contribute to this finding in a population with gout are: absence of widely accepted management guidelines for gout, resulting in limited ability of prescribing physicians to communicate to patients the distinct aims and means of treatment; an apparent increase in the risk for acute gouty flares during the early months of antihyperuricemic therapy with allopurinol or uricosuric agents; inadequate use of either colchicine prophylaxis or titrated allopurinol against the risk; and a high prevalence among gout patients of other comorbidities (such as ethanol abuse and obesity) typically associated with lesser compliance.

Because untreated gout can lead to serious adverse outcomes (such as recurrent gouty arthritis, chronic gouty arthropathy, tophi, and urolithiasis), efforts to achieve improved compliance with treatment regimens are warranted. Such efforts should, in our opinion, begin with the establishment of treatment guidelines for gout and the education of physicians and patients in the details and options for treatment. Studies of the reasons underlying noncompliance with relatively inexpensive chronic medications like allopurinol may also provide a useful model for in-depth examination of the influence of patient education, physician-patient communication, and adverse drug related events on morbidity and healthcare costs.

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