

# A Pharmacist-Staffed, Virtual Gout Management Clinic for Achieving Target Serum Uric Acid Levels: A Randomized Clinical Trial

Robert Goldfien, MD; Alice Pressman, PhD, MS;  
Alice Jacobson, MS; Michele Ng, PharmD; Andrew Avins, MD, MPH

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## ABSTRACT

**Context:** Relatively few patients with gout receive appropriate treatment.

**Objective:** To determine whether a pharmacist-staffed gout management program is more effective than usual care in achieving target serum uric acid (sUA) levels in gout patients.

**Design:** A parallel-group, randomized controlled trial of a pharmacist-staffed, telephone-based program for managing hyperuricemia vs usual care. Trial duration was 26 weeks.

**Main Outcome Measures:** Primary outcome measure was achieving sUA levels at or below 6 mg/dL at the 26-week visit. Secondary outcome was mean change in sUA levels in the control and intervention groups. Participants were adults with recurrent gout and sUA levels above 6.0 mg/dL. Participants were randomly assigned to management by a clinical pharmacist following protocol or to monitoring of sUA levels but management of their gout by their usual treating physician.

**Results:** Of 102 patients who met eligibility criteria, 77 subjects obtained a baseline sUA measurement and were entered into the trial. Among 37 participants in the intervention group, 13 (35%) had sUA levels at or below 6.0 mg/dL at 26 weeks, compared with 5 (13%) of 40 participants in the control group (risk ratio = 2.8, 95% confidence interval [CI] = 1.1 to 7.1,  $p = 0.03$ ). The mean change in sUA levels among controls was +0.1 mg/dL compared with -1.5 mg/dL in the intervention group (sUA difference = -1.6, 95% CI = -0.9 to -2.4,  $p < 0.001$ ).

**Conclusions:** A structured pharmacist-staffed program was more effective than usual care for achieving target sUA levels. These results suggest a structured program could greatly improve gout management.

including poor patient adherence; the need for better patient education; and a lack of awareness of management guidelines, especially among primary care physicians. Notably, unlike other forms of inflammatory arthritis (eg, rheumatoid arthritis), there is a straightforward and easily monitored outcome measure that correlates with optimal long-term outcomes in gout. Both the European League Against Rheumatism<sup>15</sup> and the American College of Rheumatology<sup>16</sup> recommend that patients with tophaceous or recurrent gout be treated with urate-lowering therapy (ULT) to a target sUA level below 6.0 mg/dL. Maintaining the sUA at that level eventually leads to cessation of gout flares.<sup>17</sup> This fact is particularly notable given the burden of gout in the US. One study found there were 3.9 million outpatient visits for gout in the US in 2002.<sup>18</sup> Unfortunately, only a minority of patients with gout receives appropriate treatment, including doses of ULT sufficient to achieve this target.<sup>11,19</sup> Specifically, deficiencies in ULT management include a lack of appropriate monitoring, failure to treat-to-target, and fear of ULT dose escalation in some patients, particularly those with chronic kidney disease.<sup>12,13</sup> Thus, there is a need for new, practical, and more effective approaches to the management of gout.

To address the problem of inadequate adherence to gout treatment guidelines, we previously developed a management model consisting of a telephone-based “clinic” composed of a clinical pharmacist under the supervision of a board-certified

## INTRODUCTION

Gout is the most common inflammatory arthritis in men.<sup>1,2</sup> It is well recognized that successful long-term management of gout and hyperuricemia remains elusive.<sup>3-5</sup> Unlike other common forms of inflammatory arthritis, gout is not an autoimmune disease and instead is understood to be a manifestation of chronic elevation of serum uric acid (sUA). Studies of gouty arthritis have provided important insights into other inflammatory conditions that are of great interest to rheumatologists.<sup>6,7</sup>

There is also a growing literature documenting the association of chronic hyperuricemia and gout with diabetes, chronic kidney disease, and adverse cardiovascular outcomes.<sup>8-11</sup> Therefore, improving the long-term management of gout may lead to other important health benefits as well.

Guidelines for the treatment of acute gout and the optimal management of hyperuricemia have been evolving and have been the subject of several recent reviews.<sup>12-14</sup> These reviews highlight several barriers to optimal gout management,

Robert Goldfien, MD, is the Chair of the Chiefs of Rheumatology for The Permanente Medical Group in Richmond, CA. E-mail: robert.goldfien@kp.org. Alice Pressman, PhD, MS, is the Director of Analytics and Evaluation in the Department of Research, Development, and Dissemination for Sutter Health in Walnut Creek, CA. E-mail: pressmar@sutterhealth.org. Alice Jacobson, MS, is a Senior Statistical Analyst in the Department of Research, Development, and Dissemination for Sutter Health in Walnut Creek, CA. E-mail: jacobsa1@sutterhealth.org. Michele Ng, PharmD, is a Clinical Pharmacist in the Department of Outpatient Pharmacy at the Oakland Medical Center in CA. E-mail: michele.s.ng@kp.org. Andrew Avins, MD, MPH, is a Research Scientist at the Division of Research in Oakland, CA. E-mail: andy.l.avins@kp.org.

rheumatologist.<sup>20</sup> In this model, the pharmacist uses telephone encounters to implement a simple protocol, initiating and adjusting standard gout medications in patients referred by their primary care physicians for management of recurrent or tophaceous gout. Patients are monitored by the clinic until they have 2 consecutive target sUA results at least 3 months apart; they are then discharged back to the care of their primary physician. We previously reported a case series from this pilot study, analyzing the outcomes of the first 100 patients referred to the program. The results of this pilot were encouraging, and the current study (Gout Uric Acid Reduction, or GUARD trial) was conducted to test whether this model would be more effective than usual care in the context of a randomized controlled trial.

## METHODS

### Design

The GUARD study was a randomized, parallel-group, open-label clinical trial of a pharmacist-staffed, structured gout management program compared with usual care.

### Patient Selection

The study sample was recruited from the Kaiser Permanente Northern California (KPNC) patient population. Inclusion criteria included at least 2 consecutive years of Health Plan membership, an established diagnosis of gout (International Classification of Diseases, Ninth Revision Code 274.XX), and clear documentation of at least 2 distinct episodes of acute gouty arthritis in the preceding 12 months. To be eligible for randomization, patients between the ages of 21 and 80 years had either a most recent sUA level above 7.0 mg/dL or no measurement of sUA in the past year. Patients were excluded if they had a current cancer diagnosis with active treatment, were believed to be terminally ill (as judged by the Principal Investigator before randomization), were pregnant or lactating, or had end-stage renal disease or dementia.

For each patient fulfilling the eligibility criteria, an e-mail was sent to his/her primary care physician. This e-mail included a brief description of the trial, including the expectation that those assigned to receive “usual care” would be instructed to continue to manage their gout under

the care of their primary care physician or rheumatologist. If physician consent was obtained, patients were contacted by letter accompanied by a description of the study and a written informed consent document. The program pharmacist telephoned the potential subject and described the study, answered any questions, and then obtained verbal consent. Each participant was provided written educational material on gout at the time of program entry. Randomization was accomplished by assigning an identification number using a balanced, blocked randomization list with variable block sizes (used to reduce the likelihood of an unbalanced or biased randomization).

After randomization, a baseline laboratory assessment was required of all potential participants to begin the trial. (The laboratory measurements were obtained after randomization for practical implementation reasons.) This panel included sUA and alanine aminotransferase values, estimated glomerular filtration rate, and complete blood cell count. The trial protocol was approved by the Kaiser Foundation Research Institute’s institutional review board.

### Group Assignments

Control subjects were asked to complete baseline, 12-week, and 26-week laboratory assessments. We defined measurement windows of between 10 weeks and 16 weeks for the 12-week measurement of sUA in the control group, and between 24 weeks and 30 weeks for the closeout measurement.

In the intervention group, the clinical pharmacist, under a protocol approved by the KPNC East Bay Pharmacy and Therapeutics Committee, was authorized to order relevant laboratory tests and to initiate or to change orders for the medications used for ULT and for flare prophylaxis. In the event of acute flares or abnormal laboratory results, the pharmacist consulted with the rheumatologist, who could prescribe treatment or advice if outside the scope of the pharmacy protocol. The ULT was either initiated or adjusted if the sUA level was above 6.0 mg/dL. Prophylaxis of gout flares was prescribed in all cases (see next paragraph). Subjects already receiving ULT treatment had their medications titrated but not changed. Subjects not receiving ULT at the start of the trial were started on a regimen of allopurinol,

100 mg/day (if the estimated glomerular filtration rate was less than 30 mL/min, the starting dose was 50 mg/day), unless there was a known allergy or other contraindication to allopurinol. After any change in ULT, subjects were instructed to return for laboratory assessment (sUA, alanine aminotransferase, complete blood cell count, and estimated glomerular filtration rate) in 2 weeks to 3 weeks, and report any adverse drug reactions or gout flares. Dose titration was in increments of 100 mg/day. The titration process was continued in an iterative fashion until a target sUA level was achieved and maintained, or until the trial ended at 26 weeks. In all cases, the primary outcome—sUA level at or below 6.0 mg/dL—was determined by either a second consecutive target result or the most recent result at 26 weeks (with a window of 24 weeks to 30 weeks).

Probenecid and febuxostat were second-line agents and used if allopurinol was not tolerated. Flare prophylaxis in most cases consisted of daily oral colchicine or any nonsteroidal anti-inflammatory drug and was continued throughout the study in the intervention group. At the conclusion of the trial, each subject’s primary physician was informed whether or not the patient achieved the target, and the most recent sUA level. If the patient had achieved the target, the physician was advised to continue the current medication and dose of ULT. For patients not at target, the physician was reminded of the target level.

### Outcome Variables

The primary outcome was achieving an sUA level of 6.0 mg/dL or below at the 26-week closeout visit. Secondary outcomes included the absolute change in sUA level from baseline to 26 weeks and achieving at least a 2 mg/dL decrease in sUA level at the closeout visit.

### Statistical Analyses

All analyses of continuous variables were conducted with the Student *t*-test. Categorical variables were analyzed with the Fisher exact test or its generalization for more than 2 levels.<sup>21</sup> Analyses were conducted and are reported here both under the principle of intention-to-treat, with the last value carried forward (the primary analysis), and as a per-protocol

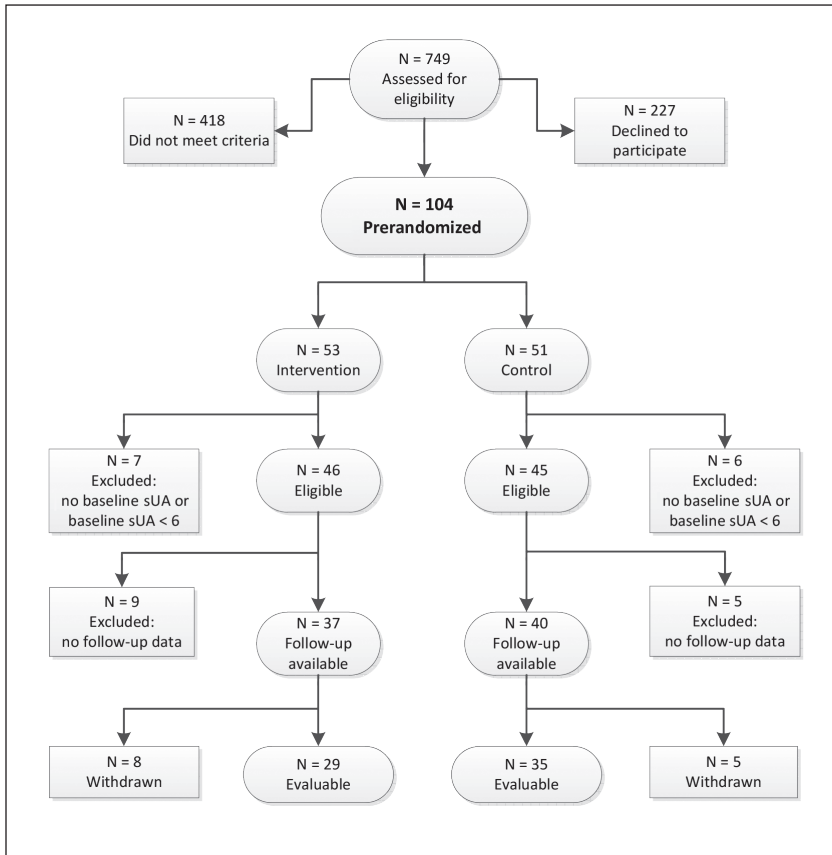


Figure 1. Flow diagram of design of Gout Uric Acid ReDuction study.  
sUA = serum uric acid level (mg/dL).

analysis, including only observed values. All reported p values were 2-sided with the experimental error rate set to  $\alpha = 0.05$ , and no adjustments were made for multiple testing. Analyses were performed with SAS Version 9.3 (SAS Institute, Cary, NC) and STATA 12 (StataCorp LP, College Station, TX).

**RESULTS**

The outcomes of the selection, consent, randomization, and trial progress are shown in Figure 1. We identified 1860 potentially eligible patients from KPNC electronic health records. The records were placed in random order, and charts were then reviewed for eligibility by a board-certified rheumatologist (RG) to validate the inclusion and exclusion criteria. We screened the charts of the first 749 patients and identified 329 who were eligible for inclusion in the study. Of the 418 who were not eligible, the most common reasons were insufficient documentation of at least 2 gout flares in the prior year (n = 226, 54%), a most recent sUA level of 7.0 mg/dL or less (n = 93, 22%), and excluded comorbidities (n = 15, 4%).

Ultimately, 104 patients consented to participate and were randomly assigned to receive either active intervention or usual care. Three patients gave consent and were randomized but, on baseline laboratory evaluation, were found to have sUA levels at or below 6.0 mg/dL. Of the 99 remaining subjects, 51 were randomly assigned to the intervention group and 48 to the control group. Of these, 12 subjects never completed the baseline sUA assessment (7 in the treatment group and 5 in the control group). A total of 22 participants dropped out of the study after obtaining their baseline sUA measurements (8 in the control group and 14 in the intervention group); all but 1 (whose insurance lapsed) failed to obtain required laboratory assessments despite repeated attempts by the study pharmacist. Of the 37 participants randomized to the intervention group, 32 (86%) remained in the trial at the 12-week time point and 29 (78%) at the 26-week closeout call; the corresponding lab adherence numbers for the control group were 36 (90%) of 40 participants at 12 weeks and 35 (88%) at 26 weeks. Table 1 shows the demographic

Table 1. Baseline demographic and clinical characteristics, overall and by study group			
Characteristic	All participants (N = 77)	Intervention group (n = 37)	Control group (n = 40)
<b>Demographic characteristic</b>			
Age (years), mean (SD)	59.4 (1.4)	60.9 (2.0)	58.0 (2.0)
Male sex, no. (%)	68 (88)	36 (97)	32 (80)
<b>Race/ethnicity, no. (%)</b>			
Native American	1 (1)	1 (3)	0 (0)
Asian	9 (12)	7 (19)	2 (5)
African American	12 (16)	5 (14)	7 (18)
Pacific Islander	17 (22)	7 (19)	10 (25)
White	23 (30)	9 (24)	14 (35)
Hispanic	14 (18)	7 (19)	7 (18)
Unknown	1 (1)	1 (3)	0 (0)
<b>Clinical characteristic</b>			
Hypertension, no. (%)	49 (64)	25 (68)	24 (62)
Chronic kidney disease, no. (%)	23 (30)	13 (35)	10 (26)
Diabetes mellitus, no. (%)	19 (25)	9 (24)	10 (26)
Serum uric acid (mg/dL), mean (SD)	8.3 (1.4)	8.5 (1.5)	8.2 (1.3)
Serum creatinine (mg/dL), mean (SD)	1.2 (0.4)	1.3 (0.5)	1.1 (0.3)

SD = standard deviation.

and baseline information for all subjects entering the study (n = 77).

Table 2 reports the results of the primary outcome measure. In the intention-to-treat analysis using the method of last-value-carried-forward, 13 (35%) of 37 subjects in the intervention group (95% confidence interval [CI] = 20% to 52%). However, only 5 (13%) of 40 subjects (95% CI = 4% to 27%) in the control group achieved an sUA level of 6.0 mg/dL or below at 26 weeks (Figure 2; risk ratio [RR] = 2.8, 95% CI = 1.1 to 7.1, p = 0.03). This difference was greater at the 12-week time point with 15 participants (41%, 95% CI = 25% to 58%) in the intervention group and 3 participants (8%, 95% CI = 2% to 20%) in the control group achieving the targeted study outcome of sUA levels of 6.0 or less (RR = 5.4, 95% CI = 1.7 to 17.2, p = 0.001).

The control group experienced a mean increase in the sUA level at 26 weeks of 0.1 mg/dL (95% CI = -0.45 to 0.69), whereas the sUA in the intervention group decreased by an average of 1.5 mg/dL (95% CI = -1.0 to -2.0). The intergroup difference in sUA levels was -1.6 mg/dL (95% CI = -0.9 to -2.4, p < .001). Results

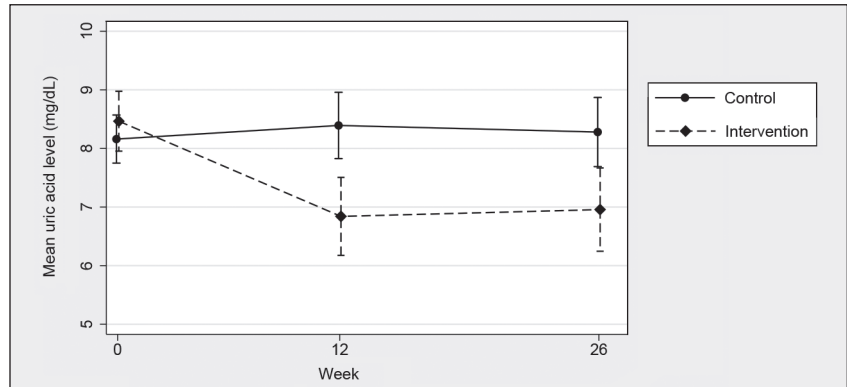


Figure 2. Comparison of mean serum uric acid during study period. Values shown are at each study time point, with error bars indicating 95% confidence intervals (intention-to-treat analysis).

were similar, although somewhat more pronounced, for the less-conservative per-protocol analysis, which did not include imputed data (Table 2).

Figure 2 shows the mean sUA levels at baseline, 12 weeks, and 26 weeks for both groups for the intention-to-treat analysis. In the control group, there was no significant change in sUA levels at either time point, whereas the intervention group had significant reductions of sUA at both time points.

To elucidate the range of outcomes among subjects in the control and intervention groups, we plotted the individual change in sUA levels at week 26 for all participants completing the protocol (Figure 3).

**DISCUSSION**

Our premise for this study was that an important failure in the management of chronic gout has been the lack of a systematic approach for identifying inadequately

Table 2. Primary and secondary outcome measures by study group						
Outcome	Intention-to-treat analysis			Per-protocol analysis		
	Intervention group (n = 37)	Control group (n = 40)	p value	Intervention group (n = 29) <sup>a</sup>	Control group (n = 35) <sup>a</sup>	p value
<b>sUA level ≤ 6 mg/dL, no. (%)</b>						
12 weeks	15 (41)	3 (8)	0.001 <sup>b</sup>	15 (47)	3 (8)	0.001 <sup>c</sup>
26 weeks	13 (35)	5 (13)	0.03 <sup>d</sup>	13 (45)	3 (9)	0.001 <sup>e</sup>
<b>sUA level change from baseline (mg/dL), mean ± SE</b>						
12 weeks	-1.6 ± 0.2	0.2 ± 0.2	< 0.001	-1.9 ± 0.2	0.3 ± 0.3	< 0.001
26 weeks	-1.5 ± 0.3	0.1 ± 0.3	< 0.001	-1.8 ± 0.3	0.1 ± 0.3	< 0.001
<b>Decrease in sUA level by ≥ 2 mg/dL, no. (%)</b>						
12 weeks	16 (43)	4 (10)	0.001	16 (50)	4 (11)	0.001
26 weeks	14 (38)	5 (13)	0.02	14 (48)	3 (9)	< 0.001
<b>ALT level change from baseline (mg/dL), mean ± SE</b>						
12 weeks	8.4 ± 3.1	-2.4 ± 1.5	0.002	8.6 ± 3.2	-2.8 ± 1.7	0.003
26 weeks (mg/dL) mean ± SE	8.1 ± 3.9	-1.3 ± 1.8	0.03	6.7 ± 4.8	-0.7 ± 1.9	0.13
<b>Creatinine level change from baseline (mg/dL), mean ± SE</b>						
12 weeks	0.01 ± 0.02	-0.02 ± 0.02	0.28	0.1 ± 0.02	-0.2 ± .02	0.27
26 weeks	0.006 ± 0.03	0.005 ± 0.03	0.99	-0.003 ± 0.03	0.2 ± .02	0.61

<sup>a</sup> Numbers refer to participants assessed at the 26-week time point. For the 12-week time point, there were 32 evaluable participants in the intervention group and 36 participants in the control group.

<sup>b</sup> RR = 5.4 (95% CI = 1.7 to 17.2).

<sup>c</sup> RR = 5.6 (95% CI = 1.8 to 17.7).

<sup>d</sup> RR = 2.8 (95% CI = 1.1 to 7.1).

<sup>e</sup> RR = 5.2 (95% CI = 1.6 to 16.6).

ALT = alanine aminotransferase; CI = confidence interval; RR = risk ratio; SE = standard error; sUA = serum uric acid.

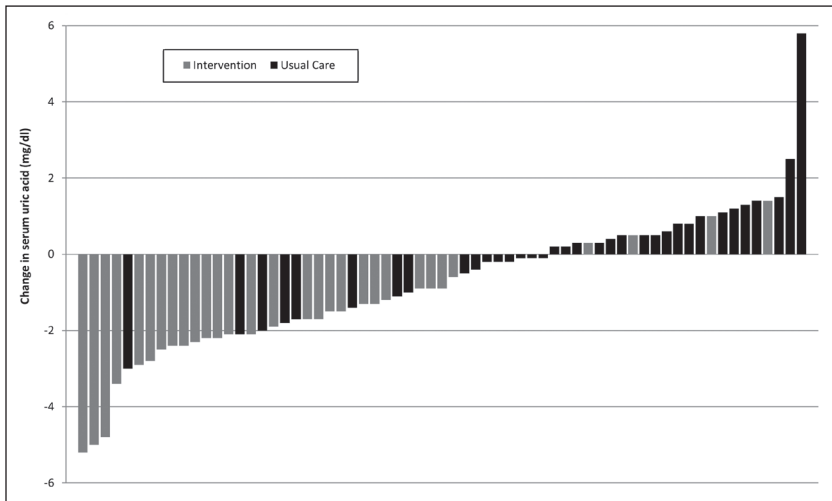


Figure 3. Net change in serum uric acid among individual evaluable participants in the intervention and usual care groups.

treated patients and then to treat and monitor them in a structured, target-driven way. In our organization, the management of other chronic diseases has improved substantially by using such an approach.<sup>22</sup> We previously published results of a pilot program designed to assess the feasibility of using a pharmacist to manage ULT in patients with gout under the supervision of a rheumatologist.<sup>20</sup> The outcomes in this single-cohort study were encouraging, but it was an uncontrolled study. The present study, which included a randomized usual-care control group, confirmed that a higher percentage of patients randomly assigned to a structured, goal-directed program did

**... an important failure in the management of chronic gout has been the lack of a systematic approach for identifying inadequately treated patients and then to treat and monitor them in a structured, target-driven way.**

indeed achieve and maintain a target sUA level at or below 6.0 mg/dL. In addition, we found a statistically significant greater mean improvement in sUA level among patients in the intervention group.

The percentage of subjects in the intervention group who achieved the primary outcome (35% in the intention-to-treat

analysis, 45% in the per-protocol analysis) was considerably lower than what we were able to achieve in our pilot program (82%), but much higher than the percentage seen in the control group (8%). In our current trial, the lower rate of success without the intervention was notable but must be interpreted within the context of the study. In particular, unlike the pilot program, the study recruited patients not referred by their primary physicians, which may have resulted in a cohort of less-motivated patients. Although greater in the intervention group, there was also a higher dropout rate compared with that seen in our pilot program. It is also possible that the lower success rate was partially caused by limitations imposed by the study protocol. Specifically, unlike the present trial, the pilot study allowed the continuation of the program beyond 26 weeks if the sUA target was not maintained for at least 3 months. Because adherence to ULT is known to be low compared with treatment of other chronic conditions,<sup>23</sup> the successful long-term management of gout must eventually account for this by building in a continued monitoring scheme that will identify nonadherent patients and allow further intervention. In the current study, limited to 26 weeks, we were not able to address this need. Nonetheless, initiating and adequately titrating pharmacologic treatment to lower sUA level is a necessary step toward long-term control, and one

that is achieved in a relatively low percentage of patients with gout in the absence of a structured program. We believe that the results in the pilot study may well be a better reflection of how well our program would perform outside the constraints of the study design and length.

Our study had several strengths, including a comparable randomized control group; a clear, structured intervention protocol; and objective outcome measurements. However, several limitations should be noted. First, there was a relatively high dropout rate from the program (22%), which was higher in the intervention group than the control group. This difference did not reach statistical significance,  $p = 0.232$ . Despite this difference, both the per-protocol and intent-to-treat analyses showed a statistically significant improvement in attaining the primary outcome in our intervention group. Moreover, we were not able to use a control group that strictly reflected usual care. This is because our primary outcome measure required that every participant be tested at least two times for sUA during the study. Under true “usual care,” it was unrealistic to expect that all the patients with gout would have been tested, and thus we would have been unable to assess our primary outcome. Indeed, we have reviewed KPNC data for sUA among patients with a gout diagnosis and found that 29% had no sUA level measured in the 5-year period before their last encounter for gout (unpublished data). If anything, we believe this monitoring requirement may have biased our results against an intervention effect because the lack of an sUA measurement during the study would more likely lead to a lack of initiation or titration of treatment.

## CONCLUSION

The fact that we were able to demonstrate improved outcomes even with a restrictive and time-limited intervention suggests that an ongoing monitoring program integrated within a primary care-centered medical system could be highly effective in achieving sustained reduction of sUA levels in patients with gout. Moreover, if managed efficiently by a pharmacist or other physician extender, this approach could result in a

cost-effective program and, over time, in a large reduction in health care utilization and cost of caring for patients with gout, with improved clinical outcomes. ❖

#### Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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## Favoring Disease

Gout would thus appear at least partly to depend on a loss of power ... of the "uric-acid-exerting function" of the kidneys ... . Any undue *formation* of this compound would favour the occurrence of the disease; and hence the connection between gout and uric acid, gravel and calculi ... and the influence of high living, wine, porter, want of exercise, etc, in inducing it.

— Sir Alfred Baring Garrod, FRS, 1819-1907,  
English physician credited with coining the term "rheumatoid arthritis"