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Modifiable Barriers to Optimal Outcomes in Gout Management

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By

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Improving patient outcomes in chronic disease is of critical importance to the future of health care. Gout, affecting 4% of the US population, is a highly treatable chronic disease from which patients experience unnecessarily suboptimal outcomes. In this dissertation, I demonstrate how interrelated patient and provider factors affect patient outcomes in gout. First, I describe how only 14% of gout patients know their serum urate (SU) goal for urate lowering therapy (ULT) despite otherwise being knowledgeable about gout and its treatment. I then demonstrate the importance of multiple patient and provider factors in achieving SU goal. Specifically, I demonstrate that ULT medication adherence, ULT dose escalation and a high ULT starting dose are associated with SU goal attainment. However, I show that a high starting dose is also associated with worse SU goal attainment through its negative impact on medication adherence. These findings demonstrate not only the importance of patient and provider behaviors in achieving optimal outcomes, but also their interrelated nature. Finally, I report that there is no evidence from a large national study that ULT dose escalation reduces mortality among gout patients. In further analysis, I demonstrate that the lack of evidence could be due to inadequate final ULT doses observed even among patients receiving dose escalation. Importantly, the patient and provider factors I identify in this work are all modifiable. Future interventions should address the broad care context outlined in the Chronic Care Model to target these interrelated, modifiable factors and achieve optimal outcomes in gout.

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LIST OF ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ACR	American College of Rheumatology
AIK	Akaike Information Criterion
ARB	Angiotensin II Receptor Blocker
BMI	Body Mass Index
BP	Blood Pressure
CCB	Calcium Channel Blocker
CI	Confidence Interval
CKD	Chronic Kidney Disease
eGFR/GFR	Estimated Glomerular Filtration Rate
EULAR	European League Against Rheumatism
HR	Hazard Ratio
ICD-9/ICD-10	International Classification of Diseases, Ninth Revision or Tenth
MSU	Monosodium Urate
NDI	National Death Index
NSAID	Non-steroidal Anti-inflammatory Drug
OR	Odds Ratio
PAM	Patient Activation Measure
PDC	Proportion of Days Covered
RCT	Randomized Clinical Trial
RDCI	Rheumatologic Disease Comorbidity Index
SD	Standard Deviation
Std. Diff.	Standardized Difference
SU	Serum Urate
ULT	Urate Lowering Therapy
US	United States
VA	Veterans Affairs
VAS	Visual Analog Scale
VHA	Veterans Health Administration (used interchangeable with VA)
VINCI	Veterans Affairs Informatics and Computing Infrastructure
XOI	Xanthine Oxidase Inhibitor

LIST OF PUBLICATIONS

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3. Coburn BW, Bergman DA, Michaud K, Mikuls TR. Allopurinol Dose Escalation and Mortality among Gout Patients with Significant Hyperuricemia. [In Preparation]

Chapter 1: Introduction

1.1 Chronic Illness and Care

Chronic illness has become the single greatest contributor to decreases in individuals' quality of life and has also begun to drive health care cost.[1-3] In the United States (US), approximately half of all adults have one or more chronic illnesses and half of those have at least 2 chronic illnesses.[4] Chronic illnesses such as asthma, diabetes and gout can lead to substantial activity limitations and loss of quality of life.[5-7] Care for patients with one or more chronic illnesses now accounts for over 85% of health care spending today.[3] Yet, despite the ubiquitous and increasing impact of chronic illness, patients and the health care system struggle to achieve optimal, but attainable, outcomes.[2,8]

In 1996, Wagner et al. created one of the first models for understanding and improving chronic illness care: the Chronic Care Model (CCM).[9] The model was developed in response to growing recognition that patients, health care providers and the health care system are too often ill-prepared to address chronic care needs. Patients with one or more chronic illnesses must often engage in more extensive and long-lasting self-management activities than patients with acute illnesses.[10] Yet, many patients burdened by chronic illness are not aware of or prepared for the self-management necessary to achieve desired results.[11,12] Similarly, there is evidence that health care providers deviate from the best practices necessary to support patients with chronic illness in achieving optimal outcomes. More broadly, there is evidence from a systematic review of health systems' chronic care improvement initiatives that broader contextual factors affect chronic illness care outcomes.[13] Wagner and colleagues assembled this

evidence into the CCM in order to depict relevant domains that need to be targeted to improve chronic illness care and outcomes.

Over time, the CCM framework (Figure 1) developed to reflect how chronic care occurs in 3 overlapping environments: the community, the health care system and the health care provider's organization.[14] Within these environments, CCM identifies 6 areas where targeted efforts affect outcomes: community resources and policies, self-management support, delivery system design, decision support, clinical information systems and the organization of health care. Each of these areas contributes to patient outcomes in unique ways, but ultimately facilitate "an informed, activated patient interacting with a prepared, proactive practice team" to produce "high-quality, satisfying encounters and improved outcomes."[14]

In chronic care, CCM recognizes that patients become their own primary caregiver.[10] They are, therefore, required to have a broad range of self-management skills in problem solving and resource utilization.[12] Patients with these skills tend to achieve better outcomes.[15,16] Health care providers, by contrast, provide medical insight, encourage development of problem-solving skills, and help access resources over time.[10] If health care providers are well prepared, knowledgeable, and proactive about specific chronic care needs, patients are more likely to experience improved outcomes. The model suggests that patients and providers together, through productive interactions related to their roles, may achieve optimal care outcomes.[17]

Using CCM as a framework, barriers to optimal outcomes for specific diseases can be better identified and understood. In the following section, I use the CCM as a framework for understanding evidence of suboptimal outcomes in gout with particular attention to the interrelated roles of patients and health care providers.

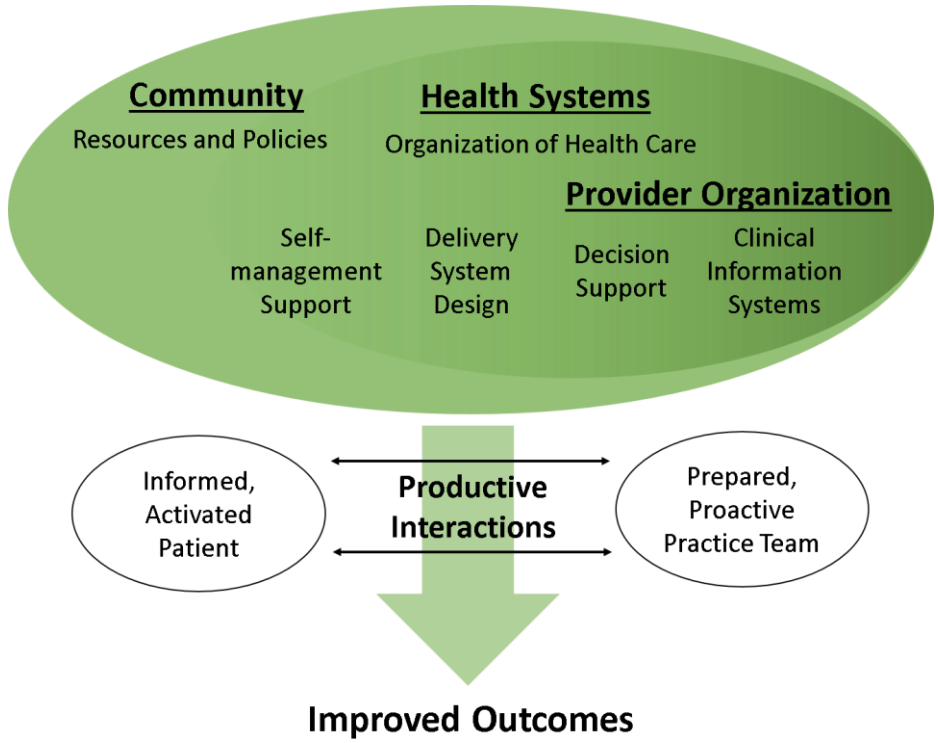

Figure 1 Chronic Care Model

The Chronic Care Model (CCM) places emphasis on productive interactions between an informed, activated patient and a prepared, proactive health care team. These interactions occur within the context of 3 overlapping environments: the community, health systems and provider organizations. Within these environments, the model identifies 6 essential areas that together affect how patients and providers interact to improve outcomes in chronic disease care. Adapted with permission from work by Wagner and colleagues at the MacColl Center for Health Care Innovation.[18]

1.2 Gout and Gout Management

Gout is the most common inflammatory arthritis in the US with a prevalence that has increased in recent decades to nearly 4%.[19,20] Resulting from sustained hyperuricemia, gout can have a considerable, negative impact on individuals' quality of life leading to increased work absenteeism,[21] disability,[22-24] and health care utilization.[25-27] Furthermore, gout and hyperuricemia may be related to an increased risk of mortality.[28-31] Yet, despite the substantial prevalence and health impact of gout, and the availability of highly effective management strategies, suboptimal patient outcomes remain all too common.[32,33]

As with any chronic disease, achievable outcomes in gout are partially a function of the disease process itself as well as available treatments. Gout has a well-defined disease pathogenesis.[34] It is characterized by intermittent, extremely painful bouts of arthritis called attacks or flares.[35] These attacks are induced by the presence of monosodium urate (MSU) crystals in synovial joints and surrounding tissues secondary to persistent hyperuricemia. Attacks typically last 5 to 12 days without treatment[36] and are followed by periods of disease quiescence, often termed intercritical gout.[35] Untreated, the attack frequency increases alongside the body's total MSU crystal burden until a persistent arthritis develops, a severe form of gout characterized by the subcutaneous deposition of MSU termed tophi.[34] Treated properly, however, a diagnosis of gout does not need to result in intractable future gout attacks.

Medical treatment of gout is commonly divided into two parts: short-term alleviation of the pain and inflammation from the attack[37] and long-term urate lowering therapy (ULT) to reduce MSU crystal burden.[38] For short-term therapy targeting attacks, the most common therapies used are anti-inflammatory doses of non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and/or glucocorticoids. For long-term therapy,

xanthine oxidase inhibitors (XOI) are considered first-line therapy and are the most commonly prescribed ULT.[38] Numerous studies have shown that patients on XOIs, especially those achieving and maintaining a serum urate (SU) concentration < 6.0 mg/dl,[39] experience reduced tophi size, frequency of flares, and pain.[40-42] The reduction in MSU crystals resulting from ULT and cessation of gout attacks can be so dramatic after long-term maintenance below SU goal that “cure” is not an uncommon outcome described in the literature.[43,44] However, most patients never achieve SU goal and are thus likely continue to experience gout attacks.[32]

The CCM suggests a framework for achieving optimal outcomes such as SU goal and elimination of future gout attacks.[14] For a chronic disease like gout, the model emphasizes the role of a proactive health care team and an informed, active patient. The model then places the provider and patient in a broader context composed of 6 essential areas. While I return in Chapter 5 to the importance of these 6 areas for the future of gout care, this dissertation first investigates the role of provider and patient behaviors in achieving optimal outcomes.

From the provider perspective, there is myriad evidence demonstrating that gout care is suboptimal. For instance, health care providers may perform suboptimally according to both quality indicators and safe prescribing benchmarks.[45-48] Recognition of these potential issues, in part, prompted the development of evidence- and consensus based guidelines by multiple international groups.[37,38,49,50] Since publication of those guidelines, studies have consistently demonstrated that provider practices remain suboptimal.[32,33,48,51] For instance, the 2012 American College of Rheumatology (ACR) gout management guidelines suggest that health care providers start gout patients on a low ULT dose (e.g. allopurinol ≤ 100 mg/day) followed by gradual dose escalation until SU is < 6.0 mg/dl.[38] Yet, only one in four patients have SU assessments within 6 months

of ULT initiation and less than one-third ever undergo ULT dose escalation.[32] While there have been widespread reports of suboptimal care, there is currently limited knowledge regarding which provider behaviors affect attainment of optimal outcomes in gout such as SU goal < 6.0 mg/dl.[32,52]

From the patient perspective, long-term self-management of gout consists primarily of understanding the disease and its treatment, properly taking ULT, and avoiding life-style risk factors.[38]Like providers, there is evidence that patients struggle in their chronic care role. There are qualitative reports that patients lack understanding of gout and its treatment.[53-55] Medication nonadherence has been well described in gout with approximately 6 out of every 10 patients being considered nonadherent to prescribed ULT.[32,56] However, few studies connect any specific patient behaviors, including ULT adherence to achieving the optimal outcome of SU goal attainment in gout.[32,52] Further work is needed to demonstrate that this association is independent of the many other healthful behaviors in which adherent patients often simultaneously engage.[57]

Taken together, there is burgeoning evidence that patient and provider behaviors are suboptimal in gout, but limited evidence connecting these behaviors to important outcomes. Furthermore, no studies have investigated how these behaviors may relate through potential causal pathways. Further work demonstrating the interrelation of patient and provider factors with outcomes could inform future interventions using the CCM framework to improve outcomes in gout.

1.3 Dissertation Objectives and Contributions

The objective of this dissertation is to develop a model of modifiable patient and provider factors associated with optimal outcomes in gout. In Chapter 2, I describe patients' gout-specific knowledge, including a lack of knowledge regarding an important

therapeutic goal, and the opportunity that this gap in knowledge represents for a goal-oriented care approach. In Chapter 3, I develop a more comprehensive model to test the hypothesis that certain interrelated patient and provider factors are associated with SU goal attainment, including some factors that appear to indirectly impact this outcome through medication adherence. In Chapter 4, I demonstrate the potential importance of these patient and provider behaviors by testing the hypothesis that one provider factor, appropriate ULT dose escalation, is associated with decreased mortality among gout patients. Finally, in Chapter 5, I discuss how the work presented in this dissertation contributes to our understanding of how to improve gout care within the context provided by the CCM framework.

Chapter 2: Target Serum Urate: Do Gout Patients Know Their Goal?

2.1 Background

Self-management is recognized as an important driver of outcomes in chronic diseases, including gout. Treatment goals provide focus for self-management activities and promote integration of valuable feedback for patients regarding their progress.[58,59] A treat-to-target serum urate (SU) strategy for gout patients with an indication for urate lowering therapy (ULT) has been widely endorsed as a means of optimizing clinical outcomes. Achievement of a SU < 6 mg/dL has been associated with improved outcomes, including reductions in gout flare frequency and tophi.[39-42,60,61] Thus, multiple international guidelines support the adoption of such a treatment target.[38,49,50,62] The target is intended to guide health care providers' care, but it also represents a critical domain of patients' gout-specific knowledge. The European League Against Rheumatism (EULAR) reported "that [patient] education on gout and its treatment improves outcome[s]."[49] The recently published American College of Rheumatology

(ACR) guidelines were more explicit in recommending that patients understand the role of uric acid as "the key long-term treatment target."[38]

Although substantial attention in gout has been given to suboptimal adherence to quality of care indicators among providers[45-47] and low SU goal attainment among patients,[32,48] it is largely unknown to what extent patients understand gout and their treatment. Patients report that they are concerned, but uninformed about whether or not ULT triggers gout attacks,[55] a well-recognized event complicating such treatment. Other patients lack familiarity with ULT as a treatment option and do not appear to understand its role in gout management.[54] Furthermore, patients who believe they have little control over their gout or believe that treatment does not help control their gout experience worse musculoskeletal disability over time.[53] The low level of confidence and disease knowledge reported by patients stands in stark contrast to the robust evidence supporting the efficacy of ULT.[40-42]

Many gout educational materials (>50%) fail to address SU goal attainment.[63] It remains largely unknown whether patients understand the role that uric acid plays in gout and the importance of SU goal attainment in chronic disease management. The objective of the present study was to examine gout patients' knowledge of their condition, including the central role of achieving and maintaining SU goal with the use of ULT. Furthermore, I examined, for the first time, factors associated with SU goal knowledge and whether having this knowledge is associated with select health outcomes.

2.2 Methods

Design and Setting

This was a cross-sectional study to determine levels of gout-specific knowledge and factors associated with gout-specific knowledge among a population of gout patients at a single Midwestern Veterans Affairs (VA) medical center. The study was approved by the local VA Institutional Review Board.

Sample and Procedures

Patients were 19 years or older with at least one gout *International Classification of Diseases (ICD)-9* code (274.XX), excluding gouty nephropathy (274.19, 274.10), and filled at least one allopurinol prescription between August 1, 2011 and July 31, 2012 ("enrollment allopurinol"). Most patients' first allopurinol was prescribed prior to the enrollment allopurinol meaning that a majority of identified patients were prevalent allopurinol users. A total of 1,553 patients met inclusion criteria (Figure 2). Patients were excluded if they were deceased or had one of four conditions, each recognized as a potential alternative indication for allopurinol as recorded by ICD-9 codes: a history of hematologic malignancy, tumor lysis syndrome, stage 5 chronic kidney disease (CKD) or nephrolithiasis.

A total of 1,437 patients, representing all remaining eligible patients, were mailed a recruitment letter and questionnaire in February 2014. A repeat mailing occurred 6 weeks following the initial mailing for non-responders with responses accepted until May 2014 similar to the Dillman method.[64] The questionnaire included 43 questions used to collect socio-demographics, patient activation, health outcomes, gout knowledge, and patients' treatment plan confidence.

Linking responses to administrative data, I reapplied exclusion criteria using laboratory proxies for tumor lysis syndrome (SU > 6 standard deviations above the mean) and CKD stage 5 (estimated glomerular filtration rate (GFR) < 15 ml/min). I required patients to have a pre-enrollment period of at least 6 months of observation with

no allopurinol prescription prior to their first ever allopurinol prescription on record. To determine the 6 month period, I assessed the patient's first observable event in the VA defined as the first clinic visit or pharmacy prescription fill. If the patients' first observable event was greater than 6 months prior to the first allopurinol fill, then they were included in the study. This reduced potential misclassification of allopurinol starting dose and dose escalation as well as anti-inflammatory prophylaxis. Application of these final criteria excluded 274 individuals who had returned their questionnaires.

Questionnaire. The questionnaire was composed of 43 questions, including the following: sociodemographics, a modified version of a gout-specific knowledge questionnaire,[65,66] the Patient Activation Measure (PAM™),[67,68] and self-reported health outcomes. The gout-specific knowledge section was adapted from a longer questionnaire resulting in 6 multiple-choice questions as summarized in Table 1. All questions had 1 correct answer among 5 options with "Don't know" as a possible option for each question. Missing answers were coded as "Don't know." The gout-specific knowledge section of the questionnaire had an excellent response rate with only 0.8 to 2.9% missing data for any question and 98.4% of respondents missing responses for 1 or fewer questions out of 6.

The PAM™ is used to quantify a patient's engagement in their own care regardless of the specific condition they have. It is designed to assess a person's self-perceived knowledge, skills and confidence related to managing their health and health care on a unidimensional, developmental scale from the least activated at 0 to the most activated at 100.[67,68] The most recent version includes 13 questions with strong psychometric properties that can categorize patients into 4 levels (1-4), where 1 is least activated and 4 is most activated.[68] Patients in level 1 tend to be passive partners in their own health care and view their health provider as being in charge, whereas patients at level 4

actively adopt healthful behaviors and see themselves as their own primary health advocate. The PAM was scored according to Insignia Health recommendations.[69]

For self-reported health outcomes, patients were asked to report the number of gout flares they had in the past 6 months and rate their current overall health and gout-specific health on a visual analog scale (0 to 10 cm). For health-related quality of life, all patients completed the EQ-5D-5L.[70]

Electronic Records. Clinical VA laboratory data were a source of many study measures including the determination of whether patients ever achieved SU goal after ULT initiation (< 6.0 mg/dL). ICD-9 codes were used to determine each patient's comorbidity burden as measured by the Rheumatic Disease Comorbidity Index (RDCI).[71,72] Each patient's most recent GFR (ml/min/1.73 m^2) and body mass index (BMI, kg/m^2) were abstracted. The proportion of days covered (PDC) was used to determine medication adherence from prescription dispensing data. The PDC is defined as the number of days the patient has medication available out of the total days of observation (days with medication available/days of observation) after adjusting for early refills and truncating at the end of observation. It is endorsed by the Pharmacy Quality Alliance as the preferred method for quantifying medication adherence using pharmacy claims data.[73] For this study, the PDC was calculated during a fixed, 360-day period initiating on the day of the patient's first allopurinol prescription after August 1, 2011. This provided a fixed time period of sufficient length for medication adherence observation nearest the time of questionnaire completion. National Provider Identifier and Drug Enforcement Administration numbers as well as VA clinic codes were used to determine providers and clinical specialties associated with each gout diagnosis and allopurinol prescription. Treatment duration was defined as the number of years between first allopurinol prescription and final on record. Finally, dose escalation was defined as

an increase in the dose of allopurinol from the first dose in the record to the final dose without regard to intervening doses, also consistent with previous literature.[32]

Statistical Analysis. Demographic and questionnaire data were analyzed using descriptive statistics. Internal consistency for the gout-specific knowledge questions was assessed using Cronbach's Alpha. Chi-squared, Wilcoxon rank-sum and *t*-tests were used to determine factors associated with SU goal knowledge. Multivariable logistic regression with backwards stepwise selection, beginning with factors significant at an alpha ≤ 0.2 level in bivariate analyses, was used to determine independent associations with SU goal knowledge. Two sensitivity analyses were done requiring patients to have 2 or more gout diagnostic codes separated by 30 days or more (n = 69 excluded) and requiring 12 or more months of prior observation (n = 54 excluded). Given the limited number of patients demonstrating this knowledge and the number of possible health outcomes examined, associations of SU goal knowledge with gout outcomes were examined in unadjusted exploratory analyses without statistical correction for multiple comparisons. Considering the number of SU tests following the first ULT on record, the count was modeled using a generalized linear model assuming a negative binomial distribution to account for over-dispersion and a log link. All analyses were done in SAS version 9.4 (SAS Institute, Cary, NC).

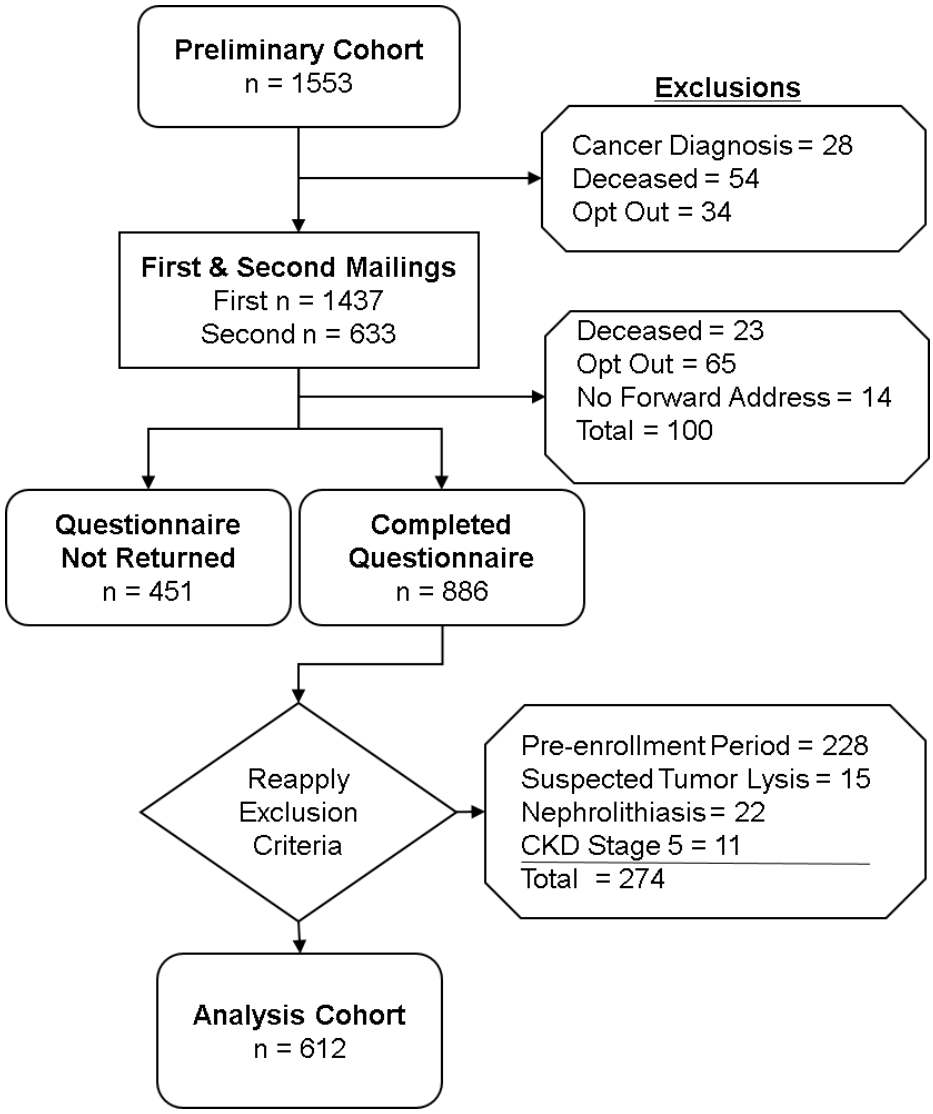

Figure 2 Study Flow Diagram

Study personnel began with a list of 1553 patients already excluding those patients with ICD-9 codes for tumor lysis syndrome, stage 5 chronic kidney disease (CKD), gouty nephropathy or nephrolithiasis. Separate lists of recently deceased patients (n = 54) and patients with a history of cancer (n = 28) who met study inclusion criteria were provided, but subsequently excluded. Prior to the first questionnaire mailing, 34 patients elected to opt out upon receiving the recruitment letter. From the mailing, 100 more opted out, were learned to be deceased or had no forwarding address. Overall, the questionnaire had a 62% response rate (886/1437). Using laboratory proxies, the tumor lysis syndrome and CKD stage 5 exclusion criteria were reapplied. Additionally, a 6-month allopurinol-free pre-enrollment period of observation was required. The final analysis cohort was 612 patients.

2.3 Results

Of the original 1,437 patients mailed a questionnaire, 886 (62%) returned their questionnaires. After exclusion criteria were reapplied, the overall cohort size was 612 patients whose primary indication for allopurinol was gout and who had at least 6 months of prior observation before receiving their first allopurinol prescription. Questionnaire responders were similar to non-responders in age (72.1 years vs. 72.8 years, p = 0.36), proportion that were male (98.2% vs. 99.2%, p=0.15), BMI (32.4 kg/m^2 vs. 32.0 kg/m^2, p = 0.41), comorbidity burden (RDCI 2.8 vs. 3.0, p=0.12), treatment duration (5.9 years vs. 6.2 years, p = 0.59) and GFR (65.5 mL/min vs. 65.5 mL/min, p = 0.99) (Table 2). In contrast, questionnaire responders were more likely than non-responders to have received their first prescription for allopurinol in a rheumatology office vs. primary care or other (6.9% vs. 2.0%, p < 0.001) and were more adherent to allopurinol (PDC median 0.94 vs. 0.91, p = 0.005). Questionnaire responders were also more likely than non-responders to have had a SU level checked within the first 2 years after ULT initiation (66.0% vs. 52.9%, p < 0.001).

Among questionnaire responders, the mean age of first gout attack was 51.6 years, a majority self-reported Caucasian race (89%), and had at least a high school graduate level of education (89%). Using allopurinol prescription fill data, I determined that questionnaire responders received care from a large number of health care providers (n = 405), but that 49 providers (12%) were responsible for 74% of the filled allopurinol prescriptions. A similar distribution was observed when using ICD-9 codes. Providers from two clinics accounted for 91% of prescription fills (89% from primary care and 2% from rheumatology). Rheumatologists were involved at any time in prescribing allopurinol for 74 (12%) of the 612 gout patients.

The proportion of gout patients answering correctly was high for all knowledge questions except SU goal (Table 1). For the 5 questions other than SU goal, 72% of respondents answered correctly on 4 or more questions. By comparison, only 14% knew their SU goal. The vast majority (78%) of responders chose “Don’t know” for the SU goal question compared to only 6 to 35% choosing “Don’t know” for any other question. The six-question gout-specific knowledge section had acceptable internal consistency (0.61) with the SU goal question and was slightly improved without it (0.64).

A variety of demographics, baseline health behaviors and health process factors were associated with SU goal knowledge in bivariate and logistic regression analyses (Table 3). In unadjusted analyses, patients demonstrating SU goal knowledge were younger, had a lower comorbidity burden, were more activated as measured by the PAM, were more likely to get all other gout-specific knowledge questions correct, be treated by a rheumatologist and have their ULT dose escalated during observation. In multivariable logistic regression, patients with rheumatologists as the initial prescriber had 3.0 times the odds of knowing their SU goal as patients with other types of providers (95% CI 1.4 to 6.2). Patients with 1-point higher RDCI had 17% lower odds of knowing their SU goal (95% CI 0.70 to 0.98). As might be expected, patients who knew the other 5 gout-specific questions had 2.1 times the odds of knowing their SU goal compared to patients who correctly answered 4 or fewer questions (95% CI 1.3 to 3.4). Because some patients may interact with rheumatologists later in their care, I also considered whether patients had ever been prescribed allopurinol by a rheumatologist. The adjusted odds ratio for this association increased to 3.8 (95% CI 2.1-6.9) while the estimates for RDCI and High Gout Knowledge remained stable (data not shown).

In exploratory analysis considering major health outcomes (Table 4), SU goal knowledge was not associated with the EQ-5D-5L health utility index ($p = 0.45$), gout

specific health (p = 0.72) or SU goal attainment < 6.0 mg/dL (p = 0.44). However, gout patients with SU goal knowledge reported slightly better overall health on an 11-point VAS compared to patients without that knowledge (8 vs. 7, p = 0.04). Additionally, there was a trend, though not statistically significant, toward patients with SU goal knowledge having more attacks within the past 6 months. SU goal knowledge was associated with an increase in SU tests during 1- and 2-year periods following ULT initiation after controlling for whether a rheumatologist was the initial prescriber. During the first year of therapy, SU goal knowledge was associated with 45% (95% CI 1.10 to 1.92) more SU laboratory tests. Extending to a 2-year follow-up, SU goal knowledge was associated with 56% (95% CI 1.23 to 1.97) more SU laboratory tests.

In sensitivity analyses, limited to patients with at least two diagnostic gout codes or with at least 12 months of prior observation, similar results were observed with respect to the proportion of patients demonstrating SU goal knowledge and its associations with potential predictors and health outcomes (data not shown).

Table 1 Gout-specific Knowledge Questionnaire

	n=612 (%)
1. What is the ideal blood uric acid level to aim for when treating gout? Blood uric acid levels are measured in mg/dL.	
a. Lower than 10	14 (2.3%)
b. Lower than 8	26 (4.3%)
c. Lower than 6	**83 (13.6%)**
d. Lower than 2	14 (2.3%)
e. Don't know	475 (77.6%)
2. What causes gout?	
a. Too little calcium	2 (0.3%)
b. Too much uric acid	**520 (85.0%)**
c. An infection	3 (0.5%)
d. Diabetes	5 (0.8%)
e. Don't know	82 (13.4%)
3. What causes gout attacks?	
a. Infection in the joint	43 (7.0%)
b. Allopurinol in the blood	6 (1.0%)
c. Crystals in the joints	**411 (67.2%)**
d. Calcium in the blood	5 (0.8%)
e. Don't know	147 (24.0%)
4. How do you know if you have a gout attack?	
a. You have a painful swollen joint	**566 (92.5%)**
b. You have a change in your blood tests	3 (0.5%)
c. Your skin gets red and itchy	9 (1.5%)
d. You have a lump in your ear	0 (0.0%)
e. Don't know	34 (5.6%)
5. Lowering your uric acid can help prevent future gout attacks. Which of these drugs can lower your blood uric acid?	
a. Allopurinol	**489 (79.9%)**
b. NSAIDs like ibuprofen, naproxen and indomethacin	11 (1.8%)
c. Prednisone	9 (1.5%)

d. Colchicine	34 (5.6%)
e. Don't know	69 (11.3%)
6. If you are taking a drug to lower your blood uric acid levels, how long do you need to take this drug?	
a. One month	8 (1.3%)
b. One year	5 (0.8%)
c. Two years	5 (0.8%)
d. Forever	**380 (62.1%)**
e. Don't know	214 (35.0%)

* Patients were asked to only mark one option per question. Bold answers represent the correct answer. For the "Primary Attack Symptoms" question, a number of patients recorded multiple symptoms and were given credit if they included the most accurate answer in bold above. For all other questions, multiple answers were counted as incorrect. Questions were adapted from a previously published questionnaire.[65,66]

Table 2 Demographics of Questionnaire Responders and Non-responders

	Responders (n = 612)	Non-responders (n = 501)	P
Demographics			
Age, years	72.1 (10.7)	72.8 (13.1)	0.36
Male	601 (98.2%)	497 (99.2%)	0.15
Caucasian	536 (89.0%)		-
Married	325 (54.4%)		-
≥ High School Graduate	536 (88.9%)		-
Baseline Health			
BMI, kg/m^2	32.4 (6.3)	32.0 (6.8)	0.41
RDCI	2.83 (1.48)	2.97 (1.55)	0.12
GFR, ml/min/1.73 m^2	65.5 (22.3)	65.5 (25.5)	0.99
Age at First Gout Attack, years	51.6 (16.2)		-
Health Behavior			
PDC	0.94 [0.77- 0.99]	0.91 [0.67-0.99]	0.005
Health Processes of Care			
Rheumatologist Prescriber	42 (6.9%)	10 (2.0%)	<0.001
Received Dose Escalation	206 (33.7%)	155 (30.9%)	0.33
SU test within 1 year	298 (48.7%)	209 (41.7%)	0.02
SU test within 2 years	404 (66.0%)	265 (52.9%)	<0.001

Values in bivariate analysis are frequency (%), mean (± SD) or median [Interquartile range]. Percentages represent analysis in non-missing data. Body mass index (BMI); Rheumatic Disease Comorbidity Index (RDCI); glomerular filtration rate (GFR); proportion of days covered (PDC); Patient Activation Measure (PAM); serum urate (SU); Confidence Interval (CI); race/ethnicity, marital status, education, and age of first gout attack not available for non-responders.

Table 3 Association of Patient Characteristics with Target Serum Urate Knowledge

	Unadjusted			Multivariable Adjusted (n=612)	
	Knew SU goal (n = 83)	Did not know SU goal (n = 529)	P	Odds Ratio (95% CI)	P
Demographics					
Age, years	68.7 (10.2)	72.7 (10.6)	<0.001		
Male	82 (99%)	519 (98%)	0.66		
Non-Hispanic Caucasian†	73 (89%)	463 (89%)	0.99		
Married†	46 (57%)	279 (54%)	0.64		
≥ High school graduate†	75 (93%)	461 (88%)	0.25		
Baseline Health					
BMI, kg/m^2	33.1 (5.3)	32.2 (6.4)	0.17		
RDCI	2.46 (1.52)	2.88 (1.47)	0.015	0.83 (0.70 to 0.98)	0.03
GFR, ml/min/1.73 m^2	67.8 (23.1)	65.2 (22.1)	0.32		
Age at first gout attack	48.6 (16.2)	52.1 (16.2)	0.08		
Health Behaviors					
PDC	0.92	0.95	0.18		
	[0.74 - 0.99]	[0.77 - 1.00]			
PAM	62.1 (11.6)	58.6 (11.3)	0.012		
High Gout Knowledge‡	46 (55%)	193 (36%)	0.001	2.1 (1.3 to 3.4)	0.002

	Unadjusted			Multivariable Adjusted (n=612)	
	Knew SU goal (n = 83)	Did not know SU goal (n = 529)	P	Odds Ratio (95% CI)	P
Health Care Process					
Rheumatologist Prescriber	12 (14%)	30 (6%)	0.008	3.0 (1.4 to 6.2)	0.004
Received Dose Escalation	33 (40%)	154 (29%)	0.05		

Values in unadjusted analysis are frequency (%), mean (± SD) or median [Interquartile range]. Percentages represent analysis in non-missing data.

† Variables were dichotomized for analysis: non-Hispanic Caucasian vs. other, currently married vs. not married and high school graduate vs. less than high school graduate.

‡ High Gout Knowledge was defined as answering all 5 of gout-specific questions correctly when excluding the SU goal question. Body mass index (BMI); Rheumatic Disease Comorbidity Index (RDCI); Glomerular filtration rate (GFR); Proportion of days covered (PDC); Patient Activation Measure (PAM); Confidence Interval (CI).

Table 4 Health Outcomes by SU Goal Knowledge

	Knew SU goal (n = 83)	Did not know SU goal (n = 529)	P
EQ-5D-5L	0.79 [0.69 to 0.86]	0.78 [0.66 to 0.83]	0.45
Overall Health, 0 to 11	8 [6 to 9]	7 [5 to 8]	0.04
Gout Specific Health, 0 to 11	8 [7 to 9]	8 [6 to 10]	0.72
SU Goal Attainment < 6.0 mg/dl	60 (75%)	319 (71%)	0.44
Gout Attacks in prior 6 months			0.054
0 attacks	39 (49%)	305 (59%)	
1 attack	12 (15%)	72 (14%)	
> 1 attack	28 (35%)	140 (27%)	

*Values are frequency (%) or median [Interquartile range]. Percentages represent analysis in non-missing data.

2.4 Discussion

This large population of gout patients demonstrated a significant lack of knowledge about an internationally endorsed treatment target in gout. Only 14% of patients responded with the correct SU goal of < 6.0 mg/dL and nearly 80% specifically endorsed a lack of knowledge about their treatment goal. It is now widely accepted that patients should be actively engaged in decision-making regarding their treatment. International guidelines specifically recommend patient education on SU goal and the importance of uric acid as a treatment target.[38,49] This study confirms preliminary evidence from a small questionnaire development study, which showed that only 5 out of 39 U.S. gout patients at a single rheumatology clinic knew their SU goal.[65] The current study is the first to show this in a large population of gout patients seen by both rheumatologists and non-rheumatologists, including primary care providers.

Patient knowledge of disease and treatment is an important part of a complex array of psychosocial factors that have been shown to impact health outcomes. While data supporting the need for specific knowledge is limited, goal setting and goal pursuit are hypothesized to be integral aspects of persuading and motivating patients to adopt positive health behaviors.[58,59] For example, collaborative goal setting has been associated with improved outcomes in other chronic health conditions, including diabetes and hypertension, where treat-to-target approaches have garnered greater support.[74,75] The Chronic Care Model (CCM) suggests that optimal outcomes may be achieved by knowledgeable patients actively engaged in collaborative care with a prepared, proactive medical team.[9,18,76] In support of this model for gout, a proof-of-concept study showed that when health care providers educate and engage gout patients in order to promote positive self-management behaviors, the overwhelming majority (>90%) achieve SU goal.[77] Importantly, patient education specific to SU goal

attainment as part of a treat-to-target approach was a focus of this successful pilot intervention. The current study is the first to show that goal setting with patients is not likely to be a widespread or effectively integrated concept in gout treatment. Even among gout patients most likely to demonstrate SU goal knowledge, those with 1 or more attacks in the past 6 months treated initially by a rheumatologist, less than 40% knew their SU goal.

Prospective studies in hypertension and diabetes have shown that communication about treatment goals within a collaborative treatment setting is associated with improved outcomes.[74,75] In the current study, SU goal knowledge was independently associated with an increase in the number of SU measurements during the first 2 years following ULT initiation. This is important because SU measurement is a prerequisite for proper ULT dose titration leading to SU goal attainment.[38] In other studies, up to 60% of patients do not receive a SU measurement within the first 2 years of observation following prescription of ULT.[48] Although the analyses were limited by the relatively small proportion of subjects demonstrating knowledge (n = 83), SU goal knowledge was associated with slightly better self-reported general health. This same knowledge demonstrated no association with other distal health outcomes, including health related quality of life measured using the EQ-5D-5L. There was a trend, albeit not reaching statistical significance, towards SU goal knowledge being associated with increased gout flares. This result should be interpreted with caution, however, as neither the direction nor reasons for this association can be determined. For instance, it is possible that greater knowledge of gout could lead to increased awareness and reporting of flares. Alternatively, it is possible that an increased number of flares leads to greater pursuit of detailed gout-specific knowledge or receipt of a rheumatology referral where their SU goal may be more likely discussed.

The results of this study should be taken in the context of the population studied and its cross-sectional design. The cross-sectional design precluded my ability to determine causation. The questionnaire design limited my ability to determine the patients' reasons for not knowing SU goal, underscoring the potential for this topic as a promising area of future research. While the majority of the questionnaire required only limited recall, there is a potential for recall bias with 6-month flares questions. However, self-report is increasingly accepted as the critical patient-centered outcome in gout. Initial eligibility was determined by allopurinol receipt during a recent pre-defined 1-year time period. This led to a high proportion of prevalent allopurinol users relative to incident users. Furthermore, included patients were by definition willing to respond to a questionnaire. These two factors likely led to a more engaged and healthy study population as was evidenced in part by the comparison between questionnaire responders and non-responders in Table 2. Importantly, this suggests that the estimate of SU goal knowledge, although quite low, is likely higher than would be seen in a broader patient population. The study also indicated high levels of medication adherence for both questionnaire responders and non-responders relative to other recent studies.[32,56,78-81] The PDC values in this study are higher than other studies likely due to the high proportion of prevalent users in the cohort and the use of mailed prescriptions in the VA system. The mailing service likely reduces barriers to having medication on hand relative to other systems. While an important consideration, the mailing system does not negate the relationship of PDC to actual adherence because VA patients are still required to request a refill each time one is needed. In other words, there is no automatic, time-based refilling system. The primary analysis used a short 6-month allopurinol-free period of observation before first allopurinol prescription, which may have led to misclassification due to allopurinol nonadherence. However, a sensitivity analysis using a 1-year period did not substantially change point estimates.

In summary, I found that a very low proportion of gout patients receiving ULT know their treatment goal. This information provides insight into one broadly untapped pathway to improve the widely reported suboptimal outcomes in gout. More research on prospective strategies to incorporate SU goal information into efforts in shared-decision making, quality improvement projects, self-management programs, or educational materials in gout is needed.

Chapter 3: Medication Adherence as a Mediator of Optimal Outcomes in Gout

3.1 Background

Gout has a well-understood etiology for which efficacious, low-cost, and well-tolerated treatments are available. Additionally, there is broad international consensus on best practices among gout management guidelines,[38,49,50,62] including achievement of optimal outcomes through maintenance of serum urate (SU) below a 6.0 mg/dl target. Recent studies implicate urate lowering therapy (ULT) nonadherence and suboptimal dosing strategies as major barriers to achieving the SU target.[32,47] However, little progress has been made toward improving gout patients' outcomes,[32,82] and it remains largely unknown how patient and provider behaviors interact to facilitate achievement of target SU goals.

Medication adherence to allopurinol among gout patients is widely reported to be low with only 35-45% considered adherent by pharmacy refill measures.[32,56] In a study of more than 13,000 gout patients initiating allopurinol, representing over 90% of prescribed ULTs,[32] adherence was the single strongest predictor of SU goal achievement. Among the first studies to report this finding, adherent patients were more than 2.5-times as likely to achieve SU levels below 6.0 mg/dl compared to nonadherent

patients. However, associations between adherence and treatment outcomes are confounded by the "healthy adherer" effect where adherent individuals tend to also be more actively engaged or "activated" in promoting their health generally.[57] Patient activation is defined as the knowledge, skills and confidence required for patients to be actively involved in their own care and has been associated with many healthful behaviors.[67,68,83] Importantly, there have been no studies accounting for patient activation when examining the association of medication adherence with gout outcomes.

In addition to patient factor effects, current prescribing practices likely contribute to suboptimal outcomes. One of these practices, ULT dose escalation, directly affects SU goal achievement.[32] Importantly, if ULT is initiated, current understanding requires dose escalation to SU goal for its full therapeutic benefits to be realized.[38,49] To maintain a patient on ULT without appropriately escalating the dose is a case of clinical inertia, defined as a provider not initiating or intensifying a treatment when indicated.[84] Other provider factors may indirectly affect outcomes by impacting medication adherence. For instance, gout flares accompanying ULT initiation have been reported as a potential cause of nonadherence.[55,79] These so-called "initiation flares", however, can be limited by using low ULT starting doses and appropriate anti-inflammatory prophylaxis.[85-87] This potential causal pathway connecting low ULT starting dose to SU goal attainment through medication adherence has never, to my knowledge, been studied.

For this study, I adopted the Chronic Care Model (CCM) and chose to focus on patient and provider factors given the strong evidence of their impact. Specifically, I examined the association of patient and provider factors with SU goal achievement among gout patients taking allopurinol. I hypothesized that two patient (medication adherence and patient activation) and three provider factors (allopurinol dose escalation, low starting dose and anti-inflammatory prophylaxis) would be associated with SU goal

attainment. Further, I hypothesized that medication adherence would mediate, at least in part, associations of other patient and provider factors with SU goal achievement.

3.2 Methods

The design, setting, sample and procedures for this study are described in the Section 2.2 Methods. Briefly, this cross-sectional study linked patient questionnaire responses with historical medical and pharmacy dispensing records data from all gout patients receiving care at a single Midwestern VA medical center to determine patient and provider factors associated with optimal gout management. The study used the same inclusion and exclusion criteria for a final cohort of 612 patients (Figure 2)

Primary Outcomes

Laboratory records were used to determine the primary outcome of whether patients ever achieved SU goal (< 6.0 mg/dl) after allopurinol initiation. Two alternative measures of goal attainment were used for sensitivity analyses. Recognizing that some patients may not have a follow-up SU on record, I constructed an alternative measure of SU goal attainment using the same SU goal (< 6.0 mg/dl), but also classifying patients without a SU on record as not achieving goal. This reflects expert consensus that follow-up SU assessments are required for optimal care.[38,49] The second alternative used the final SU value on record to determine goal attainment.

Allopurinol medication adherence was considered as both an outcome and a predictor variable due to its hypothesized role as a mediator. I was interested in the implementation component of adherence.[88] Specifically, I sought to determine the extent that a patients' actual medication taking behavior corresponded to prescribed regimens once both the provider and patient indicated an intent to establish long-term treatment as represented by the first allopurinol fill. Allopurinol adherence was determined by

calculating the proportion of days covered (PDC) during a fixed, 360-day period beginning on the day of the patient's first prescription fill. This provided a sufficiently long, fixed observation period to determine adherence nearest therapy initiation ("early" adherence). A secondary measure of adherence used in sensitivity analysis was the PDC calculated during a 360-day period beginning the day of the patient's first allopurinol prescription fill after August 1, 2011 ("recent" adherence). Together, the two measures provided a method for understanding the potential effect of temporal distance between measures. A PDC ≥ 0.8 was considered adherent and can be intuitively defined as any patient who was likely to have allopurinol available to use on at least 8 out of every 10 days observed.[32,56,79]

Predictor Variables

As noted in Chapter 2, the Patient Activation Measure (PAM™) was used to quantify self-perceived knowledge, skills, and confidence needed to manage health.[67,68] Importantly, if a patients' PAM increases over time, their health behaviors improve also suggesting that activation could be a target for future interventions.[89,90] The PAM score distribution for this study was similar to the mean ± standard deviation (SD) of 56.8 ± 10.0 observed in a large sample of chronic disease patients.[91] Importantly, PAM was correlated with gout-specific knowledge ($r = 0.24$, $p < 0.001$) and confidence in gout treatment plan ($r = 0.38$, $p < 0.001$) which were collected in this study to assess PAM's convergent validity in gout. Gout-specific knowledge was assessed using the six multiple choice questions from Chapter 2 (Table 1). Patients' confidence in their treatment plan was assessed using the mean score from four 11-cm visual analog scales (VAS) with anchors from "not at all confident" to "completely confident" that covered the following topics: 1) discussed medication options to control gout, 2) discussed lifestyle and diet

options, 3) able to summarize treatment plan and 4) able to do all tasks in treatment plan.

VA medical and pharmacy refill records were used to determine provider factors in gout care including allopurinol starting dose, dose escalation and anti-inflammatory prophylaxis. A low starting dose was defined as ≤ 100 mg/day, consistent with ACR gout management guidelines.[38] Dose escalation was defined as any increase in allopurinol from the first dose to the final dose.[32] Anti-inflammatory prophylaxis was assessed by determining whether a prescription was filled for non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids or colchicine during a window 30 days prior to or within seven days after the patients' first ever allopurinol fill on record or if the patients' days of supply for anti-inflammatory lasted until after the date of their first ever allopurinol fill.

Other Measures

A number of covariates were collected from the questionnaire including marital status (married versus not), age at first gout attack, and education level (high school graduate if patient completed ≥ 12 years of school). To further describe the gout burden in the cohort and potential need for improvements in health outcomes, I report patients' self-reported number of gout flares in the past six months.

VA medical and pharmacy dispensing records were used to determine patients' gender, comorbidity burden, estimated glomerular filtration rate most proximate to questionnaire completion (GFR, ml/min), body mass index most proximate to questionnaire completion (BMI, kg/m^2), and concomitant medication use. Comorbidity burden was assessed using ICD-9 codes to determine the patient's Rheumatic Disease Comorbidity Index (RDCI) over a 2-year period bracketing the enrollment allopurinol fill date.[71] Concomitant medication use was determined by counting the number of unique medications filled during a 1-year period beginning August 1, 2011. I used the 25th

percentile (seven unique medications) as a cut-off for defining high versus low concomitant medication use. I also identified providers' primary medical specialty to account for important practice and patient population differences among specialties.[32] To determine the providers' primary medical specialty, I used a combination of unique National Provider Identifier and Drug Enforcement Administration codes. I then assigned providers' primary medical specialty according to which clinic code was most often associated with their prescriptions. For descriptive purposes, medical specialty was reported in 3 categories (rheumatology, primary care, and other). For analysis, two categories were used (rheumatology versus other) because the primary care and other categories performed similarly.

Statistical Analysis

Chi-squared, Fisher's exact, Wilcoxon rank sum and *t* tests were used for comparisons of group characteristics as appropriate. As preliminary analysis for mediation testing, the association of patient activation and three provider factors (allopurinol dose escalation, low-dose initiation, and anti-inflammatory prophylaxis) with medication adherence was examined using multivariable logistic regression. All four pre-specified factors were entered into the model and maintained regardless of statistical significance. Covariates from Table 5 were entered into the model if the univariate p-value was < 0.20 to ensure important independent variables were not overlooked. Covariates maintained in the model were identified through a manual backwards stepwise selection using a $p > 0.05$ criterion. Interaction terms were considered for the four patient and provider factors and also removed at $p>0.05$. A similar process was used to determine associations with SU goal attainment while including medication adherence as a patient factor. To determine the optimal combination of five patient and

provider factors, I used the Akaike Information Criteria (AIC) where the lowest AIC indicated the best fitting model.

Mediation by medication adherence was tested using a counter-factual approach with delta-method 95% confidence intervals.[92] Specifically, I examined whether medication adherence mediated the association of the other four pre-specified factors with achievement of SU goal. Mediation analysis is useful for understanding many types of potential causal pathways, but it can be especially helpful when a predictor variable X has a direct association with an outcome Y, but may be inversely associated with the same outcome through a mediator M.[93] A hypothetical example of this "inconsistent model" would be workers' ability to make error-free widgets where a worker's intelligence (X) is directly associated with fewer errors (Y), but where intelligence also promotes boredom (M) in turn increasing errors.[94] To further illustrate mediation and inconsistent models, I provide a directed acyclic graph depicting a hypothesized inconsistent model of mediation proposed in this study (Figure 3).

In sensitivity analyses, I determined whether results substantially changed when considering whether patients used non-VA pharmacies for any medications, if they received help taking medications, or had non-VA providers help manage their gout, obtained through self-report. I considered alternative measures of SU goal attainment and medication adherence as described above. Given the low frequency of missing data, complete case analysis was used with the exception of sensitivity analyses where missing SU goal attainment values were imputed as described under primary outcomes. Analyses were conducted using SAS v9.4 (SAS Institute, Inc.).

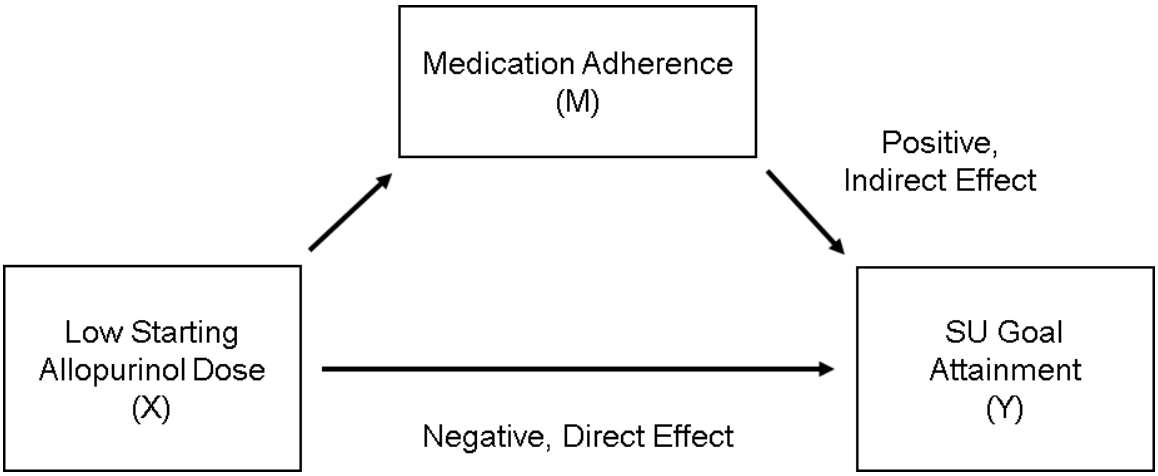

Figure 3 Conceptual Diagram of an Inconsistent Mediation Model in Gout

Mediation analysis is useful for understanding potential causal pathways. It can be especially helpful for understanding "inconsistent models" where a predictor variable X has a direct association with an outcome Y, but may be inversely associated with the same outcome through a mediator M (25). Here I depict an inconsistent model proposed in this study. A low starting dose (X) is directly associated with a lower odds of reach serum urate (SU) goal attainment (Y), but a low starting dose also promotes medication adherence (M) thereby increasing the odds of SU goal attainment.

3.3 Results

As previously reported in Chapter 2, the questionnaire response rate was 62% (n = 886). The cohort size for the primary analysis, after applying final exclusion criteria, was 612 individuals (Figure 2). Questionnaire responders were similar to non-responders, except that responders were more likely to receive their first prescription from a rheumatology office than a primary care or other office, were more adherent to allopurinol, and were more likely to have their SU checked within the first 2 years after allopurinol initiation.

The median duration from first allopurinol prescription to questionnaire mailing was 6.0 years (interquartile range 3.2 to 10.3). The prevalence of ever reaching SU goal was 71% (379/531) in patients whose SU was measured following allopurinol initiation and 62% (379/612) when absence of SU measurement during follow-up was considered as a failure to achieve goal. Forty-nine percent (49%) of patients had their SU checked within 1 year of allopurinol initiation while 66% had SU checked by the end of 2 years. Overall, 43% of gout patients experienced at least one attack in the previous 6 months with a substantial number (28%) reporting more than one attack during that period. Table 5 displays other patient characteristics.

Associations with Medication Adherence

Considering unadjusted bivariate associations for early adherence (Table 5), adherent patients (63% of cohort) were slightly older than nonadherent patients (72.8 vs. 70.9 years, p = 0.036), had their first gout attack at an older age (52.7 vs. 49.7 years, p = 0.028), higher BMI (32.8 vs. 31.7 kg/m^2, p = 0.033), greater comorbidity (RDCI 2.9 vs. 2.7, p = 0.030), lower activation scores (PAM 58.3 vs. 60.3, p = 0.0497) and were more likely to receive a low starting dose of allopurinol (36% vs. 27%, p = 0.014). Neither dose

escalation nor anti-inflammatory prophylaxis were associated with medication adherence. In sensitivity analysis assessing recent adherence rather than early adherence, activation and low starting dose were no longer associated with adherence (data not shown). Early and recent adherence were moderately correlated ($r = 0.49$, $p < 0.001$). Other factors reaching the threshold for initial inclusion in the adjusted model were gender, marital status, loop diuretic use, concomitant medication use, and RDCI. Of the five patient and provider factors examined in adjusted models, only low starting dose was associated with higher treatment adherence (OR 1.82, 95% CI 1.20 to 2.76) (Table 6).

Associations with SU Goal Attainment

Considering unadjusted associations with SU goal attainment, patients at SU goal had higher activation scores (59.8 vs. 56.2, $p = 0.01$) and were more likely to be adherent (76% vs. 66%, $p = 0.014$) than those not at SU goal. Patients at SU goal were less likely to receive a low starting dose (27% vs. 48%, $p < 0.001$). Only 7.5% of all patients received a final dose over 300 mg/day including only 12 (6%) of the 200 patients who began at a low starting dose. Though not statistically significant, patients achieving SU goal were more likely to receive allopurinol dose escalation (36% vs. 28%, $p=0.08$). Patients achieving SU goal had a higher GFR (68.6 vs. 58.2 ml/min, $p < 0.001$) and were more likely to be seen by a rheumatologist (7% vs. 1%, $p = 0.036$) compared to patients not achieving SU goal. Loop diuretic use and male gender also reached the threshold ($p < 0.20$) for consideration in the adjusted model.

In multivariable analysis, three of the five patient and provider factors were associated with SU goal attainment while a fourth, patient activation, did not reach statistical significance, but did improve model performance (AIC 514 with activation vs. 516 without). While both medication adherence (OR 2.35; 95% CI 1.50 to 3.68) and

dose escalation (OR 2.48; 95% CI 1.45 to 4.25) were strongly associated with SU goal attainment, low starting dose demonstrated an inverse association (OR 0.21; 95% CI 0.12 to 0.35).

Medication Adherence as a Mediating Factor

In the mediation model, I isolated a positive effect of low starting dose on SU goal attainment indirectly through early adherence (OR 1.11; 95% CI 1.02 to 1.20) (Table 6). Isolating this effect maintained the direct, inverse relationship of low starting dose with SU goal attainment (OR 0.21; 95% CI 0.12 to 0.37). Small effect size increases were noted for the direct effect of medication adherence and dose escalation in the mediation model relative to the multivariable logistic regression model.

Sensitivity Analyses

In sensitivity analysis considering recent adherence (Table 7), the association between low starting dose and adherence was, as expected, attenuated and no longer significant. The change did not substantially increase the association of adherence with patient activation, as might have been expected given the shorter temporal distance between the two after the change. Associations between adherence and provider factors were also unaffected by the change to recent adherence. Other listed sensitivity analyses for achieving SU goal are available in Table 8. In general, effect size changes were modest while the direction and relative effects of the five patient and provider factors remained largely consistent.

Table 5 Bivariate Associations with Adherence and Serum Urate Goal Attainment

	Overall n = 612	Adherent (PDC ≥ 0.8) n = 363	Nonadherent (PDC < 0.8) n = 229	Serum Urate < 6.0 mg/dL n = 379	Serum Urate ≥ 6.0 mg/dL n = 152
Age, yrs.	72.1 (10.7)	**72.8 (10.0)**	**70.9 (11.6)**	71.8 (10.4)	72.4 (10.4)
Male, %	98	98	99	99 †	97 †
Married, %	54	57	50	54	54
Age at first Attack, yrs.	51.6 (16.2)	**52.7 (16.5)**	**49.7 (15.6)**	51.0 (15.8)	51.7 (17.0)
BMI, kg/m^2	32.5 (6.3)	**32.8 (6.5)**	**31.7 (5.8)**	32.5 (6.3)	33.1 (6.9)
GFR, ml/min	65.5 (22.3)	65.0 (21.7)	66.3 (23.2)	**68.6 (21.8)**	**58.2 (21.5)**
RDCI	2.8 (1.5)	**2.9 (1.5)**	**2.7 (1.5)**	2.8 (1.4)	2.8 (1.5)
High School Graduate, %	89	89	88	89	89
Diuretic Use, %					
Loop	27	30	22	26	33
Thiazide	22	22	21	21	22
Concomitant Med Use, %	74	77	66	75	72
Duration of Allopurinol Use, yrs	6.0 [3.2–10.3]	6.2 [3.2–10.4]	5.9 [3.2–10.0]	**6.8 [3.5–10.9]**	**5.1 [2.8–9.8]**
Activation Score	59.1 (11.4)	**58.3 (11.0)**	**60.3 (12.0)**	**59.8 (11.2)**	**56.9 (12.1)**
PDC	0.79 (0.25)	-	-	**0.95 [0.81 – 1.00]***	**0.92 [0.65 – 0.99]***
Adherent, %	63	-	-	**76**	**66**

Low Starting Dose, %	33	**36**	**27**	**27**	**48**
Anti-Inflammatory Proph, %	54	54	55	56	55
Dose Escalation, %	31	30	31	36	28
Prescriber Specialty, %					
Rheumatology	5	5	4	**7**	**1**
Primary Care	87	88	87	**84**	**92**
Other	8	8	8	**10**	**7**

All values are %, mean (standard deviation) or median [interquartile range]. Bold values represent statistically significant differences at $p < 0.05$. † Fischer's Exact Test. * Wilcoxon rank sum test. Analysis represents non-missing data. No variable had >3% missing data except age at first attack (6.5%), activation score (7.5%) and serum urate (13%).

PDC, proportion of days covered; BMI, body mass index; GFR, estimated glomerular filtration rate; RDCI, Rheumatic Disease Comorbidity index

Table 6 Adjusted Associations of Early Adherence and SU Goal Attainment

	Adherent (PDC ≥ 0.8)†	Serum Urate < 6.0 mg/dL ‡	Indirect Effect Via Adherence*	Direct Effect*
Patient Factors				
Activation Score	0.99 [0.98 to 1.01]	1.02 [1.00 to 1.03]	1.00 [1.00 to 1.00]	**1.02 [1.00 to 1.04]**
Adherent (PDC ≥ 0.8)	-	**2.35 [1.50 to 3.68]**	-	**2.39 [1.51 to 3.78]**
Provider Factors				
Low Starting Dose	**1.82 [1.20 to 2.76]**	**0.21 [0.12 to 0.35]**	**1.11 [1.02 to 1.20]**	**0.21 [0.12 to 0.37]**
Anti-Inflammatory Proph	0.91 [0.63 to 1.30]	1.07 [0.69 to 1.66]	0.98 [0.93 to 1.05]	1.15 [0.74 to 1.82]
Dose Escalation	0.80 [0.53 to 1.23]	**2.48 [1.45 to 4.25]**	0.97 [0.89 to 1.04]	**2.52 [1.47 to 4.34]**

All values represent odds ratio [95% confidence interval]. The 95% confidence intervals for direct and indirect effects were determined using the delta method. † Model adjusts for age and body mass index. ‡ Model adjusts for estimated glomerular filtration rate and provider specialty. * Model adjusts for all covariates in early adherence and serum urate goal attainment models listed above. Bold terms represent significance using 95% confidence intervals. PDC, Proportion of Days Covered; SU, serum urate.

Table 7 Sensitivity Analysis: Adjusted Associations of Recent Adherence and Serum Urate Goal Attainment

	Adherent (PDC ≥ 0.8)†	Serum Urate < 6.0 mg/dL ‡	Indirect Effect Via Adherence*	Direct Effect*
Patient Factors				
Activation Score	1.01 [1.00 to 1.03]	1.02 [1.00 to 1.04]	1.00 [1.00 to 1.00]	1.02 [1.00 to 1.04]
Adherent (PDC ≥ 0.8)	-	2.25 [1.40 to 3.62]	-	2.22 [1.36 to 3.61]
Provider Factors				
Low Starting Dose	1.38 [0.88 to 2.17]	0.23 [0.14 to 0.38]	1.05 [0.99 to 1.11]	0.22 [0.13 to 0.37]
Anti-Inflammatory Proph	0.88 [0.59 to 1.31]	1.10 [0.71 to 1.70]	0.99 [0.94 to 1.03]	1.17 [0.74 to 1.83]
Dose Escalation	0.65 [0.42 to 1.03]	2.50 [1.46 to 4.27]	0.94 [0.88 to 1.01]	2.52 [1.46 to 4.35]

All values represent odds ratio [95% confidence interval]. The 95% confidence intervals for direct and indirect effects were determined using the delta method. † Model adjusts for age, body mass index and concomitant medication use (greater than 7 concomitant medications). ‡ Model adjusts for estimated glomerular filtration rate and provider specialty. * Model adjusts for all covariates in adherent and serum urate goal attainment models listed above. PDC, Proportion of Days Covered.

Table 8 Sensitivity Analyses: Adjusted Associations with Early Adherence and Serum Urate Goal Attainment

	Original Serum Urate Goal Attainment Model (n=490)	Excluding Patients Whose Family helps with Medications (n=407)	Excluding Patients with non-VA Providers Involved in Gout Care (n=427)	Excluding Patients with any Prescriptions from Pharmacy other than VA (n=394)
Patient Factors				
Activation Score	1.02 [1.00 to 1.03]	1.02 [1.00 to 1.05]	1.02 [1.00 to 1.04]	1.02 [1.00 to 1.05]
Adherent (PDC ≥ 0.8)	2.35 [1.50 to 3.68]	2.23 [1.37 to 3.62]	2.12 [1.32 to 3.41]	2.26 [1.38 to 3.70]
Provider Factors				
Low Starting Dose	0.21 [0.12 to 0.35]	0.23 [0.13 to 0.41]	0.25 [0.15 to 0.43]	0.22 [0.12 to 0.39]
Anti-Inflammatory Proph	1.07 [0.69 to 1.66]	1.15 [0.71 to 1.86]	0.98 [0.61 to 1.56]	1.10 [0.67 to 1.79]
Dose Escalation	2.48 [1.45 to 4.25]	2.54 [1.41 to 4.57]	1.98 [1.13 to 3.45]	2.36 [1.31 to 4.22]

All values represent odds ratio [95% confidence interval]. All models adjust for estimated glomerular filtration rate and provider specialty. PDC, Proportion of Days Covered.

Table 8 Sensitivity Analyses Continued: Adjusted Associations with Early Adherence and Serum Urate Goal Attainment

	Original Serum Urate Goal Attainment Model* (n=490)	Classifying Patients with no SU measurements as not achieving SU goal (n=562)	Using last SU on record (n=490)	Using last SU on record & classifying no SU measurements as not achieving SU goal (n=562)
Patient Factors				
Activation Score	1.02 [1.00 to 1.03]	1.01 [1.00 to 1.03]	1.00 [0.99 to 1.02]	1.00 [0.99 to 1.02]
Adherent (PDC ≥ 0.8)	2.35 [1.50 to 3.68]	1.88 [1.28 to 2.77]	2.09 [1.40 to 3.10]	1.88 [1.30 to 2.72]
Provider Factors				
Low Starting Dose	0.21 [0.12 to 0.35]	0.25 [0.15 to 0.39]	0.30 [0.19 to 0.48]	0.31 [0.20 to 0.48]
Anti-Inflammatory Proph	1.07 [0.69 to 1.66]	1.16 [0.80 to 1.70]	1.08 [0.73 to 1.58]	1.13 [0.79 to 1.62]
Dose Escalation	2.48 [1.45 to 4.25]	3.68 [2.24 to 6.05]	2.12 [1.33 to 3.38]	2.92 [1.86 to 4.58]

* This column is repeated to facilitate easy comparison. All values represent odds ratio [95% confidence interval]. All models adjust for estimated glomerular filtration rate and provider specialty. PDC, Proportion of Days Covered.

3.4 Discussion

In gout patients treated with allopurinol, medication adherence, dose escalation, and low starting dose were all strongly associated with SU goal attainment even after adjustment for patient activation and other relevant covariates. Interestingly, in the mediation model, low starting dose was indirectly associated with better SU goal attainment through its positive effect on early adherence while simultaneously being directly associated with worse SU goal attainment. The positive effect of low starting dose on medication adherence reflects evidence that smaller decreases in SU level during treatment initiation are associated with fewer treatment "initiation flares" and better adherence among patients.[55,86] I observed that the direct association with SU goal attainment was likely driven by the low prevalence of dose escalation observed in this study. Only about 1 in 3 patients ever received dose escalation of allopurinol, and only about 1 in 17 initiating allopurinol at a low starting dose ever progressed beyond 300 mg/day, a dose that is insufficient in up to 60% of patients.[40] These novel findings suggest that a strategy of low allopurinol starting dose followed by appropriate dose escalation to SU goal maximizes goal attainment by promoting both early allopurinol adherence and long-term lowering of SU.

Contrary to my initial hypothesis, an important and novel finding is the relatively weak association observed between patient activation and SU goal attainment. Patient activation is one of the most promising measures currently available for ascertainment of a patient's engagement in promoting their health. It is associated with health maintenance behaviors, such as proper diet, exercise and self-reported medication adherence,[83,89-91] all of which are promoted in gout management guidelines.[38,49] In this study, higher activation scores were associated with higher levels of both gout-specific knowledge and confidence in treatment plans indicating the PAM measures some level

of gout-specific engagement. However, this study's findings suggest that patient activation may have limited impact on whether or not a gout patient reaches SU goal. This is consistent with literature showing that health behaviors such as targeted dietary modifications do not typically bring SU levels below target concentrations.[95] Future studies will be needed to confirm whether or not patient activation is associated medication adherence as this study appears to be the first to investigate the association using an objective measure of adherence.

Beyond the novel findings regarding patient activation and mediation by adherence, results of this study are consistent with other studies of SU goal attainment in observational settings. The finding of an association between medication adherence and SU goal attainment (OR 2.35; 95% CI 1.50 to 3.68) is consistent with the OR of 2.52 (95% CI 2.41 to 3.01) observed in the only other study to assess this association.[32] My finding that dose escalation is strongly associated with SU goal attainment is novel, but consistent with other studies showing increasing odds based on final allopurinol dose.[32,96] I also verified that, in the context of inadequate dose escalation, a low starting dose of allopurinol is directly associated with failure to reach SU goal.[32] Given the importance of low starting dose in both promoting early adherence and minimizing risk of allopurinol hypersensitivity reactions,[97] overcoming clinical inertia related to dose titration represents a key target for future interventions.

Anti-inflammatory prophylaxis was not associated with adherence or SU goal attainment. However, the findings should be considered in the larger context of the literature. Clinical trial data indicates that anti-inflammatory prophylaxis is effective at reducing attacks during therapy initiation.[85-87] Thus, anti-inflammatory prophylaxis remains an important best practice in optimal gout management.[37]

While care was taken to ensure appropriate relative timing of measures from electronic records, linkage with questionnaire data makes the study inherently cross-sectional precluding causal interpretations. Additionally, the study design promoted a predominantly prevalent user cohort which in turn likely led to more individuals being adherent (63%) and achieving SU goal (62-71%) in this study relative to other studies using electronic health records.[32] As I showed, it is important to recognize the ways in which questionnaire responders differ from non-responders. Notwithstanding this caveat, the high response rate (62%) and representative distribution of PAM scores gives us confidence that the estimates of associations are robust within the inherent limitations of mailed questionnaires.[91] Finally, the measure of adherence was based on prescription refill data, which likely overestimates the number of days medication was taken correctly.

The World Health Organization and others have identified patients and health care system design as important dimensions for improving medication adherence and patient outcomes.[98,99] Approaches targeting these dimensions would be appropriate for improving important modifiable factors in this study. Specifically, improved adherence, a strong predictor of SU goal attainment in this study, among patients with similar diseases has been achieved by direct-to-patient communication and modifying patient routines.[100-102] Furthermore, health care system factors, such as clinical decision support or system redesign efforts, have shown promise in improving prescribing behaviors.[103,104] By implementing these approaches in gout care, we may begin to address the important barriers to optimal outcomes reported here.

In conclusion, medication adherence and low allopurinol starting dose combined with appropriate ULT dose escalation represent promising targets for future gout quality improvement efforts. While targeting patient activation or engagement in personal health

maintenance may have other important health benefits, this study indicates that such efforts may have a limited impact on SU goal attainment.

Chapter 4: Allopurinol Dose Escalation and Mortality Among Gout Patients

4.1 Background

Hyperuricemia and gout are independently associated with increased mortality.[28,30,31,105] A majority of this increase in mortality risk is thought to be attributable to excess cardiovascular disease,[106] but may also be associated with increased cancer mortality.[107] Multiple studies have shown that hyperuricemia increases interstitial inflammation and decreases endothelial function, a well-characterized surrogate for cardiovascular risk.[106,108] By contrast, urate lowering therapies (ULTs) such as allopurinol have been associated with improved endothelial function, reduced blood pressure, and improved glomerular filtration rate (GFR).[109-111] Dubreuil et al. and others have gone further to show that allopurinol may even lower mortality risk among gout patients.[112,113] However, it remains unknown whether a dose relationship exists between ULT and reductions in mortality.

Allopurinol dosing strategies are a critical point of interest in gout care. Current guidelines recommend that patients be started on a low dose, ≤ 100 mg daily, and then titrated up slowly.[38] While past randomized clinical trials (RCTs) of ULTs have used static dosing strategies,[40-42] such strategies are suboptimal and should now be considered unethical. Future studies will likely be required to dose escalate therapy until patients meet serum urate (SU) goal. This ethical requirement, however, impedes our ability to understand if ULT dose escalation strategies reduce mortality in gout. Further limiting are the large sample sizes and lengthy follow-up duration required to determine

whether appropriate ULT dose escalation favorably impacts mortality and other long-term outcomes. Evidence that these requirements are substantial challenges for study design and cost can be observed in recent diabetes efforts.[114,115]

Observational studies of comparative effectiveness can be an important complement to RCTs especially for definitive long-term outcomes such as mortality.[116] It has been shown that a substantial portion of primary care providers, responsible for approximately 95% of gout management, use a static ULT dosing strategy for gout patients.[32] However, a small but meaningful number of providers use a dose escalation strategy providing a potential opportunity for comparison. Using a national population of gout patients, I investigated the effect of ULT dose escalation on mortality. Specifically, I hypothesized that patients receiving dose escalation would have a lower all-cause and cause-specific cardiovascular and cancer mortality relative to similar gout patients receiving a static dosing strategy.

4.2 Methods

Study Setting

I identified a population of gout patients using Veterans Health Administration (VHA) data from 1999 to 2010. The VHA has provided care for between 5 and 10 million retired US military enrollees each year since 2001. Data from the VHA's electronic medical records and pharmacy prescribing represent longitudinal care provided at 152 medical centers and 1,400 additional community-based outpatient clinics nationwide. This data, including demographics, outpatient and inpatient visits, laboratory results, and pharmacy dispensing, was accessed in the VHA's Corporate Data Warehouse through the VA Informatics and Computing Infrastructure (VINCI).[117] Many studies indicate the completeness and validity of various CDW data including gout diagnostic codes.[118,119]

Study Population

The target cohort for this study was defined as any gout patient ≥ 40 years old prescribed incident allopurinol between October 2001 and December 2008. Gout for this study was defined as having at least 1 *International Classification of Disease* (ICD-9) code for gout prior to the incident allopurinol fill with a second ICD-9 code for gout separated by at least 30 days and occurring prior to the beginning of time at risk (described below). Also considered to be a first-line ULT,[38] febuxostat was approved on February 2009 and only available to clinical trial participants prior to that date. Patients were required to have a record of hyperuricemia, defined for this study as SU ≥ 8.0 mg/dl to reflect a gout population most likely to need dose escalation, and at least 1 year of observability without allopurinol prior to the incident allopurinol date. Observability was defined as having at least 1 annual VHA primary care or rheumatology visit and filling at least one prescription every 6 months.[120] Patients were excluded if they had an estimated glomerular filtration rate < 30 ml/min, were involved in a clinical trial for ULT during observation, or had history of dialysis, organ transplantation, malignancy, or tumor lysis syndrome.[112,113] These exclusions were intended to limit the population of interest to patients for whom gout was the primary indication for allopurinol receipt. A total of 31,336 patients met the eligibility criteria for the study and 25,379 of those had complete data required for propensity score matching as described below (Figure 4).

Mortality Outcomes

The primary outcomes for this study were all-cause and cause-specific cardiovascular and cancer mortality as defined using the National Death Index (NDI). The NDI is a centralized database of death record information reflecting state vital statistic office records and maintained by the Centers for Disease Control and Prevention. Death records were requested from and matched by VHA staff at the

Suicide Data Repository which maintains NDI records for VHA. The records include date of death and cause of death as recorded by ICD-10 codes. Cardiovascular mortality was defined as any mortality attributed to an ICD-10 code within Chapter IX (I00-I99) and cancer mortality was defined as an ICD-10 within Chapter II (C00-D48). Competing risks for cardiovascular and cancer mortality were other causes of mortality and cancer or cardiovascular mortality, respectively. All-cause mortality was also assessed.

Primary Predictor Variable

Allopurinol dose escalation was the primary predictor variable. Dose escalation was defined over a 2-year 'dose escalation' period which I estimated would encompass planned dose escalation strategies in practice. Using the dataset in Chapters 2 and 3, I found that approximately 70% of all allopurinol dose escalation events occurred within 2 years of a new allopurinol prescription. Patients were identified as "dose escalators" if their final average daily dose within the 2-year period was greater than their initial average daily dose. Patients were allowed to switch to febuxostat and dose equivalencies to allopurinol were estimated based on clinic trial data demonstrating that similar proportions of patients on 300 mg/day of allopurinol and 40 mg/day of febuxostat reach SU goal (42% vs. 45%, respectively).[42] Thus, a patient switching from allopurinol 100 mg daily to febuxostat 40 mg daily was considered to be a dose escalator. For this analysis, I estimated that the three febuxostat doses observed during follow-up (40, 80 and 120 mg/day) were approximately equivalent to 300, 600 and 900 mg/day of allopurinol, respectively. Within-prescription dose escalations were accounted for by review of the medical label instructions (commonly referred to as the medication sig). Patients having within-prescription dose escalations were categorized as dose escalators if the final average daily dose of the sig for their last prescription fill during the dose escalation period was greater than the initial dose from the sig of the incident

allopurinol fill. To identify dose escalation sigs, unique sigs were reviewed randomly and iteratively in samples of 200 to detect common characteristics of dose escalation sigs. Any sigs matching those characteristics were removed for full analysis where each unique sig was reviewed individually and labeled with the starting average daily dose and final average daily dose by two reviewers. Any discrepancies were reviewed together to establish consensus or decided by a third reviewer if no consensus could be reached. After 2 consecutive random draws found no new common identifiers, 1,000 of the remaining unreviewed sigs were randomly drawn to estimate the sensitivity of this identification method. Only 0.5% of the 1,000-sig random sample were identified as dose escalation sigs translating into an estimated 98% sensitivity for using this method on all sigs. Because each sig identified for full analysis was individually assessed and verified by a second reviewer, the specificity is expected to approach 100%.

Propensity Matching

While some differences in whether an individual patient is appropriately dose escalated may be due to random chance, patients receiving dose escalation may also systematically differ from those not receiving dose escalation. In order to mitigate confounding by indication, I used propensity score matching to balance baseline confounders and prognostic variables between two groups: dose escalators and non-escalators. My methods build on prior work by Dubreuil et al*.* who designed a propensity matching approach for allopurinol use among hyperuricemic patients with and without gout.[112] For each patient, I calculated the predicted probability (propensity score) of receiving dose escalation over the 2-year dose escalation period using a logistic regression equation. To address time trends in allopurinol use and confounders prior to matching, patients were sorted into accrual blocks of approximately 6-months in length from October 2001 to December 2008 (14 blocks) based on the date of the incident

allopurinol fill. Within each accrual block, I created a matched sample by matching dose escalators and non-escalators 1:1 based on the logit of the propensity score using calipers to limit the allowable difference in scores between matches. I used a caliper of 0.2 times the standard deviation of the logit.[121] I used a greedy match algorithm such that, after matching to a dose escalator, non-escalators were removed from the pool of potential matches.[121]

The variables used to develop the propensity score estimation were assessed over a baseline period of up to 2-years prior to the incident allopurinol date. Baseline characteristics included demographics, body mass index (BMI, kg/m^2), comorbidities, medication use, laboratory values indicating cardiovascular risk, health care utilization and gout-specific factors. Demographic variables were defined for age at incident allopurinol date and sex. Comorbidities included hypertension, cardiovascular disease and diabetes identified by ICD-9 codes. Patients' comorbidity burden was further described using the validated Rheumatic Disease Comorbidity Index (RDCI).[71] Medication use related to cardiovascular risk was recorded for each of the following categories: β blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), loop diuretics, thiazides, statins, fibrates, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), metformin, other oral hypoglycemic agents, and insulin. Laboratory values for total cholesterol (g/dL), albumin (g/dL) and estimated glomerular filtration rate (eGFR, mL/min/1.73 m^3 based on serum creatinine using the Modification of Diet in Renal Disease equation)[122] were identified using available laboratory data from the date nearest incident allopurinol during the 2-year baseline period. The total number of primary care visits during this baseline period was used as a proxy for health care utilization. The number of outpatient gout diagnoses on record and the presence of an inpatient gout diagnosis as the primary

discharge diagnosis during the baseline period were used as proxies for gout burden. Patients were also classified based on presence of a rheumatology visit or consult during the baseline 2-year period. Finally, the patients' baseline SU concentration nearest incident allopurinol date and the index allopurinol dose were included as gout-specific factors.

Assessments for Quality of Care as a Residual Confounder

Propensity matching may not effectively control for confounding if quality of care concurrent to ULT dose escalation is markedly different between dose escalators and non-escalators for common comorbidities. For instance, if ULT dose escalators treated for hypertension tend to have better control of blood pressure than ULT non-escalators, we may be concerned that unmeasured confounding is biasing estimates. In other words, it may be that concurrently improving care or healthful behaviors explain some or all of the association estimated. To assess for this possibility, I report baseline and 2-year follow-up values for two process quality variables: percentage of patients with blood pressure readings ≥ 140 systolic or 90 diastolic mm/Hg among those treated for hypertension (beta-blockers, calcium channel blockers, thiazides, loop diuretics, ACE inhibitors or ARBs) and the percentage of patients with a cholesterol > 200 mg/dl among those treated for hyperlipidemia (statins or fibrates). I also report the percent of patients with complete observability during the 2-year dose escalation period using the same aforementioned definition applied to the pre-index period. Patients had to be considered 'observable' during both year periods to be considered observable for the 2-year dose escalation period.

Statistical Analysis

Baseline characteristics of eligible dose escalators and non-escalators were assessed using standardized differences.[123] All listed baseline characteristics (Table 10)

were used for matching. Balance diagnostics were used to assess the means and distributions of baseline characteristics of the matched groups. Means of the matched groups were compared using standardized differences.[121] Standardized differences of < 0.1 were considered negligible.[121] Continuous variable distributions were compared using variance ratios, quantile-quantile plots, and non-parametric density plots.[124] I confirmed that all variance ratios fell within *F*-distribution 95% confidence intervals.[124] The plots were visually assessed for deviations in distributions between groups. Non-linear and interaction terms were subsequently considered if balance diagnostics indicated that matching did not adequately balance the means or distributions of baseline characteristics.[124,125]

Time at risk for both groups began 2 years after the date of incident allopurinol. This consistent time period between groups eliminates the potential for immortal time to bias risk estimates.[126] For instance, an alternative, but naïve approach may have been to start time at risk for non-escalators at the time of first allopurinol while waiting for time at risk to begin for dose escalators until escalation had occurred. Because only living dose escalators would be included in the study using this method, an 'immortal' period before the escalation event would exist for dose escalators, but not non-escalators. My method of determining time at risk eliminates the potential that immortal time could bias risk estimates in favor of the dose escalation group. Competing risks regression and cumulative incidence plots were used to assess the effect of dose escalation on cardiovascular and cancer mortality in the presence of other causes of mortality. A Cox proportional hazards model was used to estimate the effect of dose escalation on all-cause mortality with 95% confidence intervals (CI) based on robust variance estimates to account for matching.[125,127]

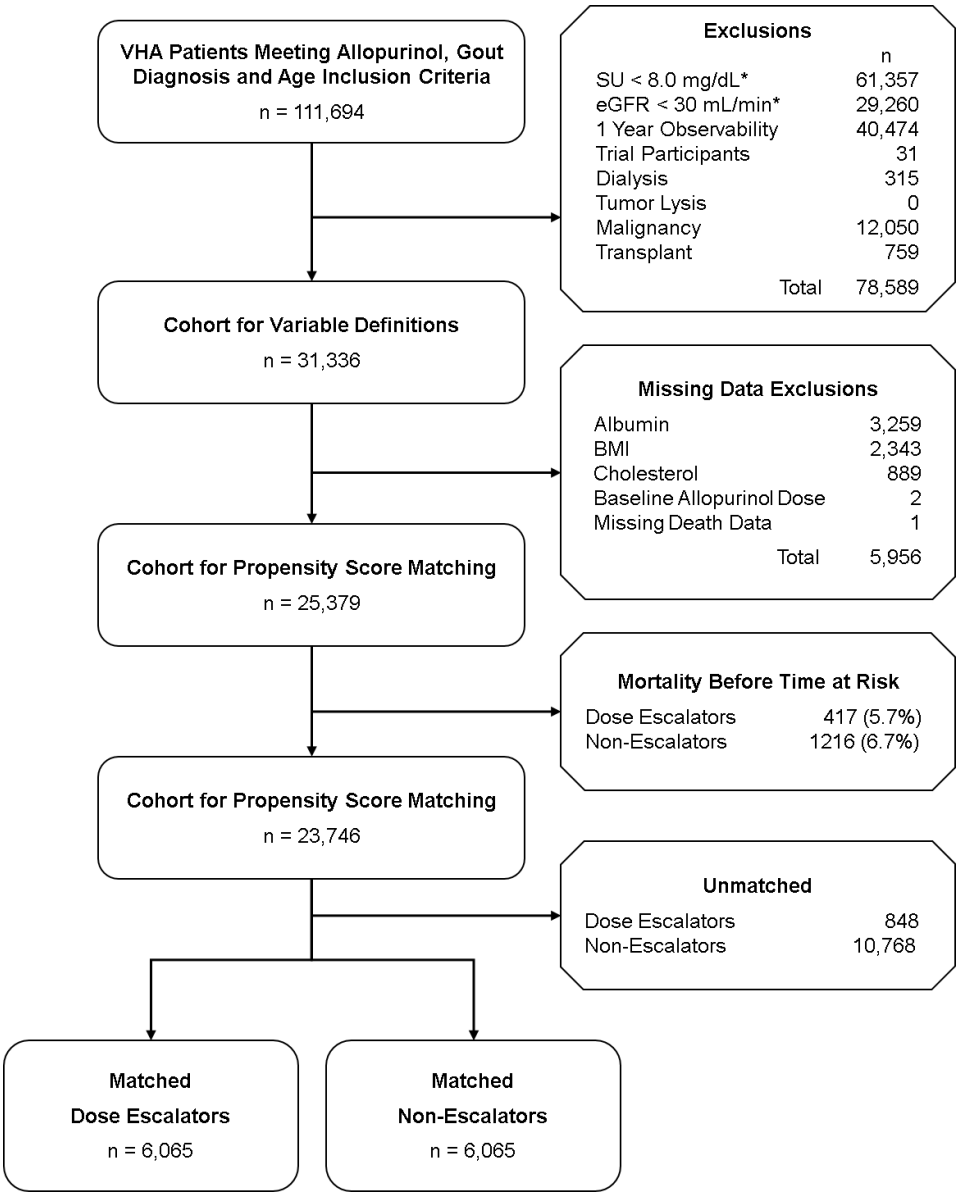

Figure 4 National Mortality Study Flow Diagram

Any gout patient ≥ 40 years old prescribed incident allopurinol between October 2001 and December 2008 was considered for this study. Gout for this study was defined as having at least 1 *International Classification of Disease* (ICD-9) code for gout prior to the incident allopurinol fill with a second gout ICD-9 code separated by at least 30 days and occurring prior to the beginning of time at risk. At total of 111,694 met this inclusion criteria. A total of 78,589 patients were excluded based on one or more exclusion criteria. Baseline variables were defined for 31,336 eligible patients. Complete data and survival through the dose escalation were required for matching leading to the final cohort of 23,746 patients for propensity matching. Out of these, 12,130 (51%) were matched using 1:1 propensity score matching. * The SU and eGFR exclusions included patients missing 2-year baseline data values: 42,914 and 25,427 patients, respectively.

4.3 Results

Prior to matching, the 6,931 dose escalators were similar to 16,833 non-escalators for a majority of the baseline characteristics (Table 9). Only health care utilization measures and SU exceeded a standardized difference of 0.1. As expected, those receiving dose escalation had a higher average baseline SU (9.6 mg/dL vs. 9.4 mg/dL), lower median incident allopurinol dose (100 mg/day vs. 200 mg/day), greater median number of baseline primary care visits (9 visits vs. 8 visits over 2 years) and were more likely to have a rheumatologist involved in their care (18% vs. 6% with a rheumatologist prescribing the baseline allopurinol and 24% vs. 11% with a rheumatology clinic visit during baseline).

Propensity Matching

Incident allopurinol dates were well distributed over time with the number of eligible dose escalators and non-escalators during each accrual block ranging from 345 to 724 and 896 to 1,474, respectively. After propensity score matching, all baseline characteristics were balanced based on standardized differences (all <0.03, Table 9). Variance ratios and visual inspection of distributions indicated balanced distributions between groups for all continuous baseline variables. Importantly, 99.8% of patients had baseline allopurinol doses within 100 mg/d, 76.6% started on the same dose, and those with higher doses than their match were evenly distributed between dose escalators and non-escalators (11.7% and 11.8%, respectively). Consistent with a VA gout population, the mean age was 64 years and over 99% were male.[47] The majority of patients had comorbid hypertension, cardiovascular disease or diabetes; use of medications for these conditions was common. The propensity matched cohort had similar rheumatology contact with 11% having their baseline allopurinol prescribed by a rheumatologist and 17% having a rheumatology clinic visit.

Dose Escalation Practices and Follow-up SU Concentrations

As noted, 99.8% of patients had baseline doses of allopurinol within 100 mg/day of their matched pair. The median dose increase for dose escalators over the 2-year follow-up was 100 mg/day with 90% of increases ranging from 50 to 300 mg/day. Only 10% of patients in the dose escalation group escalated to a final dose greater than 300 mg/day (Table 11). As expected, dose escalators had greater SU goal attainment during follow-up (31% vs. 12%). However, even among dose escalators, SU goal was achieved by a minority of patients.

All-Cause Mortality

There were 2,179 deaths occurred during observation with 1,067 occurring in the dose escalation group and 1,112 in the non-escalation group. The mortality rates were 48.4 and 46.3 per 1,000 person-years for dose escalators and non-escalators, respectively. This represents a 4% reduction in mortality risk for dose escalators not reaching statistical significance (HR 0.96; 95% CI 0.88 to 1.04). Using a cumulative incidence plot, there is only a negligible difference in mortality incidence over time (Figure 5).

Cause-Specific Mortality

There were 479 cardiovascular deaths among dose escalators and 490 cardiovascular deaths among non-escalators leading to cardiovascular mortality rates of 20.8 and 21.3 per 1,000 person-years, respectively. For cancer, there were 187 deaths among dose escalators and 203 deaths among non-escalators translating to cancer mortality rates 8.1 and 8.8 per 1,000 person-years, respectively. Dose escalation was not associated with a statistically significant reduction in cardiovascular (HR 0.97; 95% CI 0.86 to 1.10) or cancer mortality (HR 0.92; 95% CI 0.75 to 1.12). Referring again to

the cumulative incidence plots (Figure 5), there were only small differences in time to death between dose escalators and non-escalators after accounting for competing risks.

Assessment for Quality of Care Residual Confounding

Assessments for quality of care were done at baseline and follow-up to determine whether other factors reflecting quality of care may have changed concurrently with dose escalation (Table 12). Observability during follow-up was slightly better for dose escalators relative to non-escalators (94% vs. 91%, standardized difference = 0.1), but was high overall for both groups. There was no difference in the proportion of patients at blood pressure goal at baseline or follow-up among those treated for hypertension. At baseline, cholesterol control was similar for dose escalators and non-escalators. By the end of follow-up slightly more dose escalators had achieved cholesterol goal than non-escalators, but the standardized difference remained less than 0.1 (80% vs 78%, standardized difference = 0.06). Overall, these findings indicate minimal differences in concurrent quality of care indicators between dose escalators and non-escalators.

Table 9 Baseline Characteristics of Unmatched and Matched Cohorts

Baseline Characteristics	Unmatched Cohorts			Propensity Matched Cohorts		
	Dose Escalators (n = 6,913)	Non-Escalators (n = 16,833)	Std. Diff.	Dose Escalators (n = 6,065)	Non-Escalators (n = 6,065)	Std. Diff.
Demographics						
Age, years	63.8 ± 10.3	64.4 ± 10.6	0.05	64.0 ± 10.4	64.0 ± 10.3	0.01
Male, %	99.6	99.7	0.02	99.6	99.7	0.01
BMI, kg/m^2	32.6 ± 6.4	32.0 ± 6.2	0.09	32.4 ± 6.3	32.4 ± 6.3	0.01
Comorbidity						
Hypertension, %	90	89	0.03	90	90	0.02
Cardiovascular Disease,%	50	47	0.06	49	49	<0.01
Diabetes, %	38	35	0.06	37	37	0.01
RDCI, mean	2 [1-3]	2 [1-3]	0.06	2 [1-3]	2 [1-3]	<0.01
Medications						
B-blockers, %	60	57	0.07	59	59	<0.01
ACE Inhibitors, %	67	66	0.02	67	67	0.01
ARBs, %	13	12	0.05	13	13	<0.01
CCBs, %	43	41	0.03	42	43	<0.01
Loop Diuretics, %	34	30	0.07	33	33	<0.01
Thiazides, %	51	50	0.02	51	50	0.01
Statins, %	63	61	0.03	63	63	0.01
Fibrates, %	15	13	0.04	14	14	<0.01
Aspirin, %	33	31	0.03	33	32	<0.01
NSAIDs, %	71	70	0.02	71	71	<0.01
Metformin, %	15	15	0.02	15	15	0.01
Other Hypoglycemics, %	23	21	0.03	22	22	0.01
Insulin, %	12	10	0.09	11	11	0.01
Laboratory Measurements						
Serum Urate, mg/dL	9.6 ± 1.6	9.4 ± 1.5	**0.18**	9.6 ± 1.5	9.6 ± 1.5	0.01
Cholesterol, mg/dL	180 ± 44	181 ± 43	0.02	181 ± 44	181 ± 43	<0.01
eGFR, mL/min/1.73 m^2	65 ± 21	66 ± 20	0.06	65 ± 21	65 ± 21	<0.01
Albumin, g/dL	4.0 ± 0.5	4.0 ± 0.5	0.01	4.0 ± 0.5	4.0 ± 0.5	0.01
Health Utilization Measures						
Incident Allo Dose, mg/d	100 [100-100]	200 [100-300]	**1.09**	100 [100-100]	100 [100-100]	<0.01
Primary Care Visits, n	9 [6-14]	8 [6-13]	**0.10**	6 [9-14]	6 [9-14]	<0.01
Gout Diagnoses, n	3 [1-5]	3 [1-5]	0.09	3 [1-5]	3 [2-5]	0.02
Inpatient Gout Diagnosis, %	3	2	0.06	2	2	0.01
Rheumatology Prescriber,%	18	6	**0.35**	11	11	0.01
Rheumatology Consult, %	24	11	**0.34**	17	17	0.01

Baseline characteristics for each group are mean ± SD, percent, or median [interquartile range]. Standardized differences (Std. Diff.) are reported for each baseline variable and values less than 0.1 are considered negligible. Values are **bolded** if they are above the 0.1 threshold. Standardized differences are the preferred statistic for between group comparisons in propensity studies because the statistic is independent of sample size providing a consistent measure before and after matching.[124] Review of standardized differences in the far right column for the matched cohort indicate successful matching and negligible differences in baseline differences between groups.

BMI = body mass index; RDCI = Rheumatic Disease Comorbidity Index; ACE inhibitors = angiotensin converting enzyme inhibitors; ARBs = angiotensin receptor blockers; CCBs = calcium channel blockers; NSAIDs = non-steroidal anti-inflammatory drugs (NSAIDs); eGFR = estimated glomerular filtration rate based on the Modification of Diet in Renal Disease equation; Allo = allopurinol.

Table 10 Baseline and Follow-up Allopurinol Dosing by Group

	Baseline		Follow-up	
	Non-Escalators	Dose Escalators	Non-Escalators†	Dose Escalators
Allopurinol Dose*	(n = 6,065)	(n = 6,065)	(n = 6,065)	(n = 6,065)
≤ 100	76%	76%	78%	<1%
> 100 & < 300	19%	19%	18%	38%
300	5%	5%	4%	51%
> 300	<1%	<1%	<1%	10%

* Dose represents the average daily dose with allopurinol equivalents used for febuxostat in follow-up calculations. † A small proportion of non-escalators (4%) had their dose decreased during the 2-year follow-up.

Table 11 Follow-up Serum Urate (SU) by Group

	Dose Escalators (n = 6,065)	Non-Escalators (n = 6,065)
SU Tested	91%	77%
At SU Goal < 6.0 mg/dL*	31%	12%
Follow-up SU, mean mg/dL	6.9 ± 1.9	7.6 ± 1.7

Values are percentages and mean ± SD. Only the last value on record for follow-up was used if there were multiple. * Calculation includes those missing SU tests. Among only those with follow-up testing 34% of dose escalators and 16% of non-escalators were at SU goal.

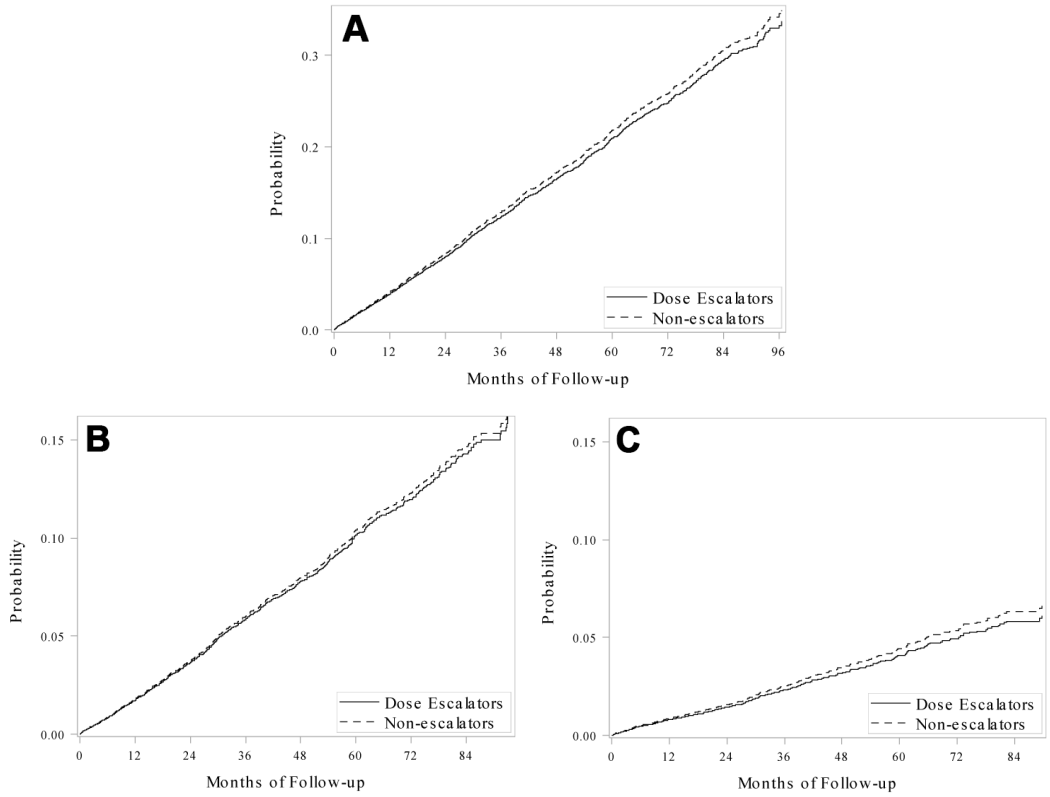

Figure 5 Time to Death for Propensity Matched Dose Escalators and Non-escalators

The cumulative incidence of (A) all-cause mortality, (B) cardiovascular mortality, (C) cancer mortality during follow-up. In all graphs, dose escalators are represented by the solid line and non-escalators by the dashed line.

Table 12 Assessment of Quality of Care as a Residual Confounder

	Baseline		Follow-up	
	Dose Escalators	Non-Escalators	Dose Escalators	Non-Escalators
Observability*	100%	100%	94%	91%
BP < 140/90 mmHg	63%	63%	68%	68%
Cholesterol < 200 mg/dL	72%	71%	80%	78%

* Observability at baseline was defined for a 1-year period, but was defined for the full 2-year dose escalation period for follow-up. A patient was considered observable for the period if they were observable for both 1-year periods. All lab values are the last on record during the 2-year follow-up if more than one was available.

BP = blood pressure

4.4 Discussion

In this study, there was no evidence that current dose escalation practices reduce mortality risk, all-cause or cause-specific. ULT dose escalation produced a statistically insignificant 4% reduction in all-cause mortality risk as well as non-significant 3% and 8% reductions in cause-specific mortality of cardiovascular and cancer etiology, respectively. The lack of statistical significance was despite this being the largest study to date of ULT treatment effects on gout patient mortality.[112,113,128] However, I also showed that patients receiving ULT dose escalation were not dose escalated to a level typically required for proper gout control.[38,39] Such clinical inertia, especially among those receiving dose escalation, limited my ability to determine the effect of appropriate dose escalation on mortality. These results add to the persistent uncertainty regarding the role of ULT in reducing mortality risk.[107,129]

This study has a number of design strengths that further inform our understanding of ULT and mortality risks. First, I successfully linked a large national cohort of gout patients to cause-specific mortality data. Previous studies have typically reported all-cause mortality thus limiting understanding about the relative impact of therapy on causes of mortality such as cardiovascular disease or cancer.[112,113] While most studies have focused on the potential cardiovascular benefits of ULTs that may lead to reduced mortality,[129] there is a potential that reducing hyperuricemia may also have effects on cancer mortality.[107] While neither were statistically significant in this study, the point estimate for reductions in cancer mortality was stronger than reductions for cardiovascular mortality. Few conclusions should be drawn from these findings other than to emphasize that until a more definitive link is determined, assertions regarding cause-specific cardiovascular mortality reductions from all-cause mortality data are likely pre-mature.

This study employs a new-user, active-comparator design novel among studies of ULT treatment associations with mortality among gout and hyperuricemic patients. This approach is particularly robust as it better reflects treatment decisions and treatment recommendations for gout and hyperuricemia than study designs using comparisons against non-initiator groups (patient never treated with allopurinol). Comparing to patients not initiated on therapy is likely a comparison against a heterogeneous group.[130] Specifically, not all gout patients are recommended for ULT, such as those experiencing infrequent gout attacks and lacking tophi or evidence of gout-related joint damage.[38,49] Additionally, patients with asymptomatic hyperuricemia are not recommended for ULT initiation.[38,49] These two groups comprise a low-risk subpopulation of non-initiators. The non-initiator group likely also contains a high-risk population of patients, potentially near death, for whom prescribers are less likely to initiate a new medication.[130] Studies in other diseases have termed this the risk-treatment mismatch or paradox.[131,132] This study mitigates this potential bias by comparing two groups both initiating ULT therapy. The similarity of the dose escalator and non-escalator groups is reflected in the unmatched baseline characteristic comparisons in Table 9. This study further balanced residual differences between groups through a rigorous propensity score method.[124,125,133] Together, these methods likely led to a less biased estimate of treatment effect.

Here and elsewhere, I have demonstrated that clinical inertia, or the lack of increasing treatment intensity when indicated,[84] is common in gout management even among those receiving initial dose escalation.[32] In this study, only 30% of dose escalation patients completed the 2-year follow-up period at SU goal. It is possible that the clinical inertia observed in this study greatly limited my ability to determine ULT dose effects on mortality risk reduction. The potential that such under-dosing limited my

findings is consistent with at least one study showing that increases in forearm blood flow, a measure of endothelial function, were significantly greater for patients randomized to 600 mg/day allopurinol doses than for those assigned to 300 mg/day or a placebo.[111] Additionally, if the mortality reduction hypothesized to be attributable to ULT is associated with reductions in cumulative systemic inflammation from gout attacks,[134] then dosing practices reported in this study are unlikely to decrease such inflammation. International guidelines, supported by evidence-based studies, recognize that dose escalation until SU is below 6.0 mg/dL is typically required for long-term reduction in gout attacks.[38,49] Without SU goal achievement, allopurinol initiation may only serve to transiently increase systemic inflammation associated with treatment initiation attacks while not serving to significantly reduce long-term attack risk.[85-87]

In the place of ULT dose escalation, I could have considered the effect of SU goal attainment or SU change on mortality risk similar to a recent study.[128] That approach would have directly investigated one of the hypothesized causal links, SU concentration, between ULT and mortality reduction.[107,129] However, I chose to focus on dose escalation for a number of reasons. First, the approach frames the issue as an RCT would by comparing the effect of treatment strategies. Second, investigating dose effects more broadly reflects the many hypothesized mechanisms through which allopurinol or febuxostat may reduce mortality. Specifically, studies indicate that allopurinol may improve endothelial function through its inhibition of xanthine oxidase and corresponding reduction in reactive oxygen species rather than its urate lowering effect.[111,129] Third, there exists a significant deficit in periodic SU evaluation among observational cohorts creating a potentially insurmountable missing data problem. Specifically, estimates of follow-up SU testing range from 15-30% at 6 months to 50% at 4 years.[48] Such infrequent testing and likely baseline differences between those with follow-up SU

testing versus those without would have made even the best imputation techniques inadequate. Thus, my decision to investigate dosing strategies reflects my belief that it better reflects provider treatment choices, the totality of hypothesized causal effects, and the limitations of available data.

Despite the many strengths of this study, interpretation must account for its limitations. As previously noted, my ability to fully understand the dose effects of ULT was limited by the clinical inertia observed in practice. This study is observational in nature. While the new-user, active-comparator design and use of propensity matching likely mitigated potential confounding by many measured and unmeasured risk factors, I cannot eliminate the potential for residual unmeasured confounding. To specifically address gout severity as a residual unmeasured confounder, I included baseline SU level, rheumatologist care and number gout diagnostic codes on record as proxies for severity. While these methods were improvements over past studies, current medical records are limited in their ability to determine gout severity with no validated and systematically documented measures that would fulfill this need. Finally, the population largely reflects the patient population typically being treated with ULT for gout. However, females comprised less than 1% of the population limiting external validity of the results for females.

In conclusion, I found no association between ULT dose escalation and reduced mortality. The findings were likely limited by suboptimal ULT dosing observed in practice even among dose escalators. While I hoped that this study would add to the evidence that appropriate dose escalation has significant benefits for gout patients, clinical inertia during appropriate dose escalation is so prevalent that I cannot make a definitive assessment. Interventions to overcome clinical inertia in ULT dose escalation may be

needed before understanding about dose effects can be made, including the potential benefits for mortality.

Chapter 5: Discussion

5.1 Summary

Gout is the most common form of inflammatory arthritis, but it is also considered one of the most treatable. In this dissertation, I have applied the patient and provider portion of the Chronic Care Model (CCM) framework to draw further insight into modifiable barriers to optimal outcomes in gout. Importantly, this work builds on prior studies that identified deficits related to quality indicators, safe prescribing or patient adherence to therapy by assessing their association with optimal outcomes in an observational setting. These findings build a foundation for future work to target important modifiable factors identified here.

Patients' engagement in their own care is increasingly recognized as a critical pathway toward improved outcomes.[14] In this dissertation, I demonstrated that gout patients may have a deficit in treatment goal knowledge relative to other knowledge about gout. Only 14% of patients knew their serum urate (SU) goal. Yet, over 70% answered at least 4 out of the other 5 gout knowledge questions correctly indicating an otherwise good understanding of their disease. This discrepancy between knowledge of gout as a disease and knowledge of a critical treatment goal raises the potential that goal setting is underutilized in gout care. Literature on goal setting in health suggests that it may be an important aspect of obtaining optimal outcomes for chronic diseases.[59,74,75] More broadly, knowledge of goals and goal-setting processes are highlighted in numerous behavior change and theoretical models including CCM.[10,11,58] In the following section, I identify initiatives where SU goal is currently being promoted

and demonstrate the many ways that a goal-setting framework can be incorporated into comprehensive approaches to CCM-based improvement initiatives.

Recently, more emphasis has been placed on a collaborative patient-provider approach to achieving optimal outcomes in chronic disease.[59,76,135] In this dissertation, I demonstrated that current practices in gout management may benefit from greater use of a collaborative approach. Specifically, both patients' adherence to urate lowering therapy (ULT) and providers' dosing practices were strongly associated with SU goal attainment. For provider dosing practices, dose escalation and high starting dose were significantly associated with SU goal attainment, but high starting dose was also associated with worse SU goal attainment through its negative effects on ULT adherence. The effect of a provider's choice for starting ULT dose on patient's ULT adherence illustrates a specific area of potential impact for a more collaborative approach. If providers start on lower ULT doses and work with patients to overcome initiation attacks and other challenges that arise when starting a new ULT, patients would likely achieve better outcomes. Demonstration of the interrelation between patient and provider behaviors is not limited to my findings. In diabetes, studies show that low patient medication adherence is associated with clinical inertia in potentially appropriate treatment intensification.[136,137] This is a potentially intuitive finding. Providers may recognize that some patients are nonadherent creating uncertainty regarding the appropriateness of treatment intensification. Thus, if patients remain nonadherent, then interventions focusing strictly on dose escalation practices may be incongruent with the realities of practice and thus fail to impact outcomes. The interrelated nature of patient and provider behaviors increases the need for multi-faceted interventions. I explore potential components of multifaceted approaches in the following section on future work.

The difficulty of demonstrating associations of certain modifiable patient and provider behaviors with long-term outcomes has been a major barrier in developing an evidence-based approach to improving patient outcomes in practice.[138] In Chapter 4, I developed a promising and methodologically rigorous approach to understanding the effect of ULT dose escalation on mortality outcomes in gout. I used a new-user, active-comparator design and propensity score matching approach to investigate whether a ULT dose escalation strategy was associated with decreased mortality relative to a static dose strategy. While I found no difference in mortality outcomes between the two dosing strategies, conclusions were limited due to pervasive clinical inertia even among dose escalators. With only 30% of patients achieving SU goal and only 10% being escalated above 300 mg/day of allopurinol, I was forced to conclude that current dose escalation efforts are insufficient to determine the effect of appropriate dose escalation. While limiting for understanding associations of ULT with mortality outcomes in gout, the findings further emphasize the importance of developing methods to target patient and provider factors identified in this dissertation as important for achieving SU goal.

5.2 Future Work

Chronic diseases are likely to remain a primary driver of health care utilization for the foreseeable future. For this reason, methods for improving patient outcomes in chronic disease will need to evolve to address the ever growing demand. Often, the quick and easy solution suggested by researchers who identify gaps in quality of care is to provide more education to patients and providers, but decades of research indicate that such an approach has limited effectiveness.[58,139,140] Knowledge, alone, is not sufficient. Instead, there is convergence from research in a number of fields, including treatment adherence,[141] clinical decision support,[142] and dissemination and implementation research[138] indicating that successful interventions are most often multi-level (e.g. target

individuals, systems and/or organizations) and multi-faceted (e.g. use two or more methods flexibly for accomplishing the same outcome). The CCM, supplemented by other work, provides a foundation for developing multi-level, multi-faceted approaches for improving quality and patient outcomes in gout care.

First, there is a critical need for development of clinical information systems that better reflect the diagnostic process, shared-decision making, clinical context, and uncertainty. For the studies reported here, I used a common medical coding system and medication prescribing to identify gout patients for whom treatment was initiated. This approach is commonly used in health services research and beyond, but it has limitations. Medical coding, developed primarily for billing purposes, does not equate to disease presence. For this reason, there are efforts to develop 'computable phenotypes' for diseases with the idea that differing combinations of diagnostic codes, timing of codes, and other factors can improve the sensitivity and specificity for disease identification.[143] Well-documented and validated computable phenotypes will improve identification, but still lack the functional meaning that would facilitate improvements in quality of care. Efforts to improve care based on electronic health records would benefit from greater detail about the goal of treatment or lack of treatment to guide understanding of expected outcomes. This information could even incorporate shared-decision making, or the process of patients and providers reviewing evidence to collaboratively determine the best course of action for a particular patient.[144] For instance, in gout there is little debate that health care providers should suggest long-term ULT for patients severely affected by gout, but for patients with infrequent attacks who do not want to take a daily medication there is uncertainty about the benefits of long-term therapy. [38] Shared-decision making may be particularly useful in cases where uncertainty is highest. Similarly, the A1c treatment goal for diabetic patients can vary

depending on their risk for developing dangerous hypoglycemic episodes creating uncertainty in the optimal goal.[145] Clinical information systems should be able to reflect therapeutic goals that develop over time and respond to patients' changing conditions. Understanding the goal of treatment and the input of patients could deepen understanding of quality beyond the one-size-fits-all approach often imposed in research studies due to current record-keeping limitations. Indeed, some suggest that evidence-based medicine loses significance without inclusion of patient preferences.[142,144] Until clinical information systems better track varied circumstances of treatment and goals, our ability to understand quality using these systems will be limited to sometimes overly generalized assumptions.

Clinical decision support is an approach addressed by CCM that has enormous potential to assist health care providers in overcoming barriers to outcomes identified in this dissertation. Clinical decision support relies on the idea that a health care provider working in partnership with a well-designed, user-centered information resource will perform better than a provider on their own.[146] A potential approach in gout and other chronic diseases would be to create disease dashboards[147,148] that would simultaneously allow the provider to review a patient's disease-specific history and nudge them to make decisions consistent with the patient and current evidence-based recommendations. For instance, a gout dashboard could display a patient's history of gout attacks, a graph of their historical SU levels with relevant ULT doses, and one-click ordering for SU testing or ULT. The system could even nudge providers by making the default option for ULT a dose escalation if the patient is below SU goal or a reorder (static dose) if the patient is at SU goal. Since chart review is where providers spend a large share of their time when using electronic health records,[149] convenient organization of disease information and

ordering could simultaneously improve efficiency and help overcome clinical inertia in dosing practices.

Another opportunity identified by CCM is delivery system design. Bodenheimer and colleagues suggest that the 'tyranny of the urgent' during clinic visits overwhelms the periodic steps required for optimal chronic disease management.[14] A potential method of addressing this is to allow the primary health care provider to initiate treatment strategies that are efficiently operationalized by a health care team and potentially facilitated by technology. Interestingly, this approach is currently being studied as part of a pragmatic randomized trial for gout treatment within a large integrated health system.[150] In the trial, gout patients are identified through electronic medical records shortly after initiating allopurinol. An ambulatory care pharmacist and an automated calling system are then used to provide protocolized care promoting SU goal attainment. Consistent with findings in this dissertation, the protocol emphasizes improving medication adherence among patients who report poor ULT adherence and then dose escalating patients who fail to achieve SU goal despite being adherent. This is but one approach to system redesign that could improve outcomes by separating the predictable sequences of care required to achieve optimal chronic disease outcomes from the primary care provider's important role in identifying disease, initiating therapy strategies, and addressing critical issues that arise overtime in care.

The CCM suggests that for chronic conditions, self-management support should involve "collaboratively helping patients and their families acquire skills and confidence to manage their chronic illness, providing self-management tools…, and routinely assessing problems and accomplishments."[14] The level of self-management support changes in direct proportion to the pervasiveness of the disease and treatment impact on the patient's day-to-day life. For instance, intensive self-management programs were

developed for rheumatoid arthritis patients during the 1990's when the disease was often crippling despite therapy.[15] Fortunately for most gout patients, self-management is limited to eating a good diet, exercising, and properly using medications. However, as I demonstrated in Chapter 2, even these self-management activities can pose substantial challenges. When a patient is initiated on ULT, they may experience initiation attacks causing them to discontinue therapy without notifying their health care provider. Appropriate response to gout attacks is a critical self-management skill for gout patients that may not be required for months after first learning from the doctor what to do, if they are informed at all. In addition to the finding that patients may be inappropriately discontinuing therapy, one study suggests that patients who visit their health care provider during an attack may actually be more likely to use therapy inappropriately following their visit.[151] Recognizing the limitations of early in-office patient education, these findings suggest that direct-to-patient resources providing timely and patient-centered information may have a role in optimizing self-management. For instance, a smartphone app could allow patients to review long-term management[152] and also push time-sensitive information to patients. In gout, patients could be given access to track progress toward SU goal over time, which may provide the conceptual link between their medication use and health that is necessary to promote adherence. Beyond tracking treatment progress, smart phones could use predictive analytics to identify when a patient is likely to be having a gout attack and provide the patient with in-the-moment instructions for medication use. These approaches represent important opportunities to develop better self-management among patients and could translate into improved long-term outcomes.

In addition to the above 4 areas, CCM identifies two broader areas where targeted efforts may improve outcomes: community resources and policies and health care

organization. Communities can significantly impact patients' chronic disease outcomes through the availability of healthful food,[153] safe outdoor exercise areas,[154] and social support groups.[155,156] In gout, community norms surrounding each of these has the potential to reduce the number of people developing gout as well as reducing consumption of common triggers of gout attacks (e.g. purine-rich meats, high-fructose drinks, and beer).[157] In addition to communities, the organization of health care can have an outsized impact on chronic disease outcomes.[158-160] For instance, government and health care businesses can promote or discourage certain care practices through incentives.[161,162] It is now widely recognized that the US health care system payment structure primarily incentivizes the volume of health care, such as the number of short clinic visits and procedures, more heavily than quality which may require more time dedicated to care follow-up and behavioral change approaches.[163] More recently, efforts have been aimed at altering incentives to better reflect the type of chronic care that patients like those with gout require. For instance, payment models are being developed that may make it more financially feasible to use clinic time to coordinate chronic care.[164,165] While the community and health care organization elements of the CCM are sometimes more difficult to target in research, their effects can be far reaching and should not be over looked.

5.3 Conclusion

Improving patient outcomes in chronic disease is of critical importance to the future of health care. Gout, affecting 4% of the US population, is a highly treatable chronic disease from which patients experience unnecessarily suboptimal outcomes. In this dissertation, I demonstrate how interrelated patient and provider factors affect patient outcomes in gout. Importantly, the factors, including low knowledge of SU goal, low patient ULT adherence and suboptimal ULT dosing practices by providers, are all readily

modifiable. Historically, efforts to improve patient and provider behaviors have focused on education and outreach, but future interventions will likely find greater success addressing the broad care context outlined in the CCM to target these interrelated, modifiable factors and achieve optimal outcomes in gout.

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Appendix A: Questionnaire

Gout Quality Improvement Project

Department of Veterans Affairs Nebraska-Western Iowa Health Care System

Date you completed this questionnaire:

☐☐ / ☐☐ / ☐☐☐☐

(mm/dd/yyyy)

Please do NOT write your name or identifying information on this questionnaire.

By filling out this questionnaire, you are consenting to be in the study and have your medical records reviewed.

Instructions

1. You will need a blue or black pen that won't bleed through the paper. Please do not use pencil or red ink.

2 . You will see a lot of small squares like this: ☐ Yes ☐ No

These squares should be marked with an X like this: ☒ Yes ☐ No

Be sure to make your X inside the box, and fairly heavy, so the computer can read it.

3. You will also see some scales like the one below. You will need to make a mark in the box that best corresponds to your answer. These scales are usually 0-10. Read carefully to determine what the question is asking. In this example, the box marked with an X represents a person having a great deal of pain.

	0									**10**	
NO PAIN	☐	☐	☐	☐	☒	☐	☐	☐	☐	☐	☐ SEVERE PAIN

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Background

The following questions are meant to gather background information about you.

1. How old were you when you had your first gout attack? ☐☐ years old

2. Does someone else, such as a family member, help you take your medications? ☐ Yes ☐ No

3. Do any non-VA, private providers manage your gout? ☐ Yes ☐ No

4. Do you receive any prescription medications from a pharmacy other than the VA pharmacy? ☐ Yes ☐ No

Treatment Plan

The following are questions about the treatment plan you and your doctor have decided on for your gout. For each question, please place an x on the 0-10 scale to show how confident you are.

1. How confident are you that you and your doctor have discussed the medication options available to control your gout?

	0										10	
Not at all confident	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	**Completely confident**

2. How confident are you that you and your doctor have discussed lifestyle and diet changes that may help control your gout?

	0										10	
Not at all confident	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	**Completely confident**

3. How confident are you that you could summarize the treatment plan you and your doctor have chosen to control your gout?

	0										10	
Not at all confident	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	**Completely confident**

4. How confident are you that you can do all the tasks in the treatment plan?

	0										10	
Not at all confident	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	**Completely confident**

Personal Views about Health

Below are statements that people sometimes make when they talk about their health. Place an X in a box to the right of each statement according to how much you agree or disagree with it. When answering please consider your health generally. Your answers should be true for you and not just what you think others want you to say.

If the statement does not apply to you, place an X in the box for N/A.

	Strongly Disagree	Disagree	Agree	Strongly Agree	N/A
1. When all is said and done, I am the person who is responsible for taking care of my health.	☐	☐	☐	☐	☐
2. Taking an active role in my own health care is the most important thing that affects my health.	☐	☐	☐	☐	☐
3. I am confident I can help prevent or reduce problems associated with my health.	☐	☐	☐	☐	☐
4. I know what each of my prescribed medications do.	☐	☐	☐	☐	☐
5. I am confident that I can tell whether I need to go to the doctor or whether I can take care of a health problem myself.	☐	☐	☐	☐	☐
6. I am confident that I can tell a doctor concerns I have even when he or she does not ask.	☐	☐	☐	☐	☐
7. I am confident that I can follow through on medical treatments I may need to do at home.	☐	☐	☐	☐	☐
8. I understand my health problems and what causes them.	☐	☐	☐	☐	☐
9. I know what treatments are available for my health problems.	☐	☐	☐	☐	☐
10. I have been able to maintain (keep up with) lifestyle changes, like eating right or exercising.	☐	☐	☐	☐	☐
11. I know how to prevent problems with my health.	☐	☐	☐	☐	☐
12. I am confident I can figure out solutions when new problems arise with my health.	☐	☐	☐	☐	☐
13. I am confident that I can maintain lifestyle changes, like eating right and exercising, even during times of stress.	☐	☐	☐	☐	☐

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Medications

The following questions ask for your views about anti-gout medication. Please place an X in the box to show how much you agree or disagree with each of the following statements.

1. My anti-gout medication works for me.

☐ Strongly disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly agree

2. My anti-gout medication makes me feel worse.

☐ Strongly disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly agree

Over the past 7 days:

1. I took all doses of my anti-gout medication.

☐ Strongly disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly agree

2. I missed or skipped at least one dose of my anti-gout medication.

☐ Strongly disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly agree

3. I was not able to take all of my anti-gout medication.

☐ Strongly disagree ☐ Disagree ☐ Neutral ☐ Agree ☐ Strongly agree

Health

The following questions ask you to share your views about your health and how gout affects it.

Place an X in the box that best describes how you are doing.

1. Considering your HEALTH OVERALL, rate how you are doing on the following scale.

	0										**10**	
VERY POOR	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	VERY WELL

2. Considering ALL THE WAYS THAT GOUT AFFECTS YOU, rate how you are doing on the following scale.

	0										**10**	
VERY POOR	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	VERY WELL

3. How many acute gouty arthritis flares or attacks have you had in the past 6 months?

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ more than 6

Health, continued

For each question below, place an X in the one box that best describes your overall health today.

MOBILITY

- ☐ I have no problems walking
- ☐ I have slight problems walking
- ☐ I have moderate problems walking
- ☐ I have severe problems walking
- ☐ I am unable to walk

ANXIETY/DEPRESSION

- ☐ I am not anxious or depressed
- ☐ I am slightly anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am severely anxious or depressed
- ☐ I am extremely anxious or depressed

PAIN/DISCOMFORT

- ☐ I have no pain or discomfort
- ☐ I have slight pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have severe pain or discomfort
- ☐ I have extreme pain or discomfort

USUAL ACTIVITIES ***(e.g. work, cooking, housework, family or leisure activities)***

- ☐ I have no problems doing my usual activities
- ☐ I have slight problems doing my usual activities
- ☐ I have moderate problems doing my usual activities
- ☐ I have severe problems doing my usual activities
- ☐ I am unable to do my usual activities

SELF-CARE

- ☐ I have no problems washing or dressing myself
- ☐ I have slight problems washing or dressing myself
- ☐ I have moderate problems washing or dressing myself
- ☐ I have severe problems washing or dressing myself
- ☐ I am unable to wash or dress myself

Gout Knowledge

The following questions ask you to share what you know about gout. Since we are hoping to determine if certain knowledge is useful for you, it is important that you answer these questions without any help. Please select only 1 answer for each question.

1. What causes gout?

☐ Too little calcium ☐ Too much uric acid ☐ An infection ☐ Diabetes ☐ Don't know

2. What causes gout attacks? ☐ Infection in the joint ☐ Allopurinol in the blood
☐ Crystals in the joint ☐ Calcium in the blood ☐ Don't know

3. How do you know if you have a gout attack?

☐ You have a painful swollen joint ☐ You have a change in your blood tests ☐ Don't know
☐ Your skin gets red and itchy ☐ You have a lump on your ear

4. Lowering your uric acid can help prevent future gout attacks. Which of these drugs can lower your blood uric acid?

☐ Allopurinol ☐ NSAIDs like ibuprofen, naproxen and indomethacin
☐ Prednisone ☐ Colchicine ☐ Don't know

5. What is the ideal blood uric acid level to aim for when treating gout?
Blood uric acid levels are measured in mg/dL.

☐ Lower than 10 ☐ Lower than 8 ☐ Lower than 6 ☐ Lower than 2 ☐ Don't know

6. If you are taking a drug to lower your blood uric acid levels, how long do you need to take this drug?

☐ One month ☐ One year ☐ Two years ☐ Forever ☐ Don't know

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1. How many years of school have you completed? Please X the box to the left of the number of years of school you have had.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ 11 ☐ 12 ☐ 13 ☐ 14 ☐ 15 ☐ 16 ☐ 17+
- - - - - - - - - - -Grade School - - - - - - - - - - High School- - - - - - - - - - -College- - - - - - - - - - - -

2. Please tell us your ethnic background:

☐ White, not of hispanic origin ☐ Asian or Pacific Islander ☐ American Indian or Alaska Native
☐ Black, not of hispanic origin ☐ Hispanic ☐ Other

3. Current marital status? (check one) ☐ Never married ☐ Separated ☐ Widowed ☐ Remarried after divorce
☐ Married ☐ Divorced ☐ Remarried after death of spouse

Thank you for completing the survey. Please place it into the envelope provided and return it by US mail. The envelope has already been addressed and stamped for return so there is no cost for you!

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