PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of a pharmacist-based gout care management program in a large integrated health plan: Results from a pilot study
AUTHORS	Goldfien, Robert; Ng, Michele; Yip, Goldie; Hwe, Alice; Jacobson, Alice; Pressman, Alice; Avins, Andrew

VERSION 1 - REVIEW

REVIEWER	Liote, Fredric Hôpital Lariboisière
REVIEW RETURNED	26-Aug-2013

THE STUDY	Goldfien et al raised an important issue: how to enhance ULT monitoring in gout. They have designed a smart flow chart and methodology including one clinical pharmacist and one rheumatologist. They reprot results from a pilot study raising interesting questions in terms of faisability. Patient description should be improved (table 1), including - % of patients with at least one clinical tophus, - with chronic arthropathy - CKD should be clarified giving the number of patients in each CKD class. It is unclear from the methodology section which ULT was first chosen (allopurinol in all?), at which INITIAL dosage; similarly it appears that a few number recevide febuxostat: reason in unclear. Indeed at that methodology section and in the result section, it is essential to associate allopurinol dosages AND CKD levels. (maximal dosage ..) Prophylaxis should be precised with respect to counter indication. In the abstract a shor tsentence or in brackets should expalin why patients did not complete the study.
RESULTS & CONCLUSIONS	This study provides an elegant way to monitor ULT dosage and compliance, at least in part. It seems to contribute to reduce therapeutic inertia (Lioté F & Choi HK, ARD 2013). This point should be discussed However the reviewer is not convinced that two SUA<6.0 mg/dL 3 months apart are sufficient to insure good compliance. A formal one year SUA after begining the study for each patient would have been more appropriate. Please add if available. Or update the SUA follow-up. Total follow up duration before discharge is missing. Also titration period duration is missing.

	Another pitfall is to discharge patients after achieving these 2 "good SUA levels"... what is the results of further F/Up? Please comment and add data. Prophylaxis details should be added: please refer to the Ree's study in which few patients received colchicine. Should be added the number of patients under colchicine, duration and maximal dose, combination with NSAID's? number of flares?
GENERAL COMMENTS	This elegant structured treat to target protocol does not take into account other key aspects of gout management, namely patient education, life style changes including diet. Please acknowledge these points in the discussion section

REVIEWER	Sautner, Judith State Hospital Stockerau
REVIEW RETURNED	29-Aug-2013

GENERAL COMMENTS	The paper is definitely of interest and reads well. The goal to improve the management of gout eg to more effective lowering of sUA to the target level is very well understandable. - The chosen setting with pharmacists being involved and even in a decisive position in the therapeutic process as such is quite unusual in Europe and would not be possible in our understanding. But I assume this was done due to local customs and in order to leverage physician time - as mentioned in the discussion of the manuscript. In my opinion this is definitely a limitation of the study because the setting is not freely transferable to other countries and would fe not pass the Ethics committee in Austria. - page 7, line 15: it is mentioned that Allopurinol is used up to 300mg and in some patients up to 450 mg. on page 10, line 51 it is mentioned that 2 patients even required a dosage of 600mg. Please correct. - Albeit flare prophylaxis in 100% of patients, which is described as sufficient, a flare rate of 34% is pretty high. Maybe you could comment on that. - What was the mean duration of this pilot study for the first 100 patients? Only data on the individual end of the study - when SUA was consecutively achieved in two measurements in a time frame of 2 months - is mentioned. Figure? - There are no data provided on the diet of patients and the course of BMI. Did patients lose weight during the study? This would/could have an impact on the sUA levels. - Was a dietary advice given concerning sUA and appropriate food? - Please provide the distinct percentage of patients with tophaceous gout. And please comment if in these patients the target level of <5mg/dl sUA was aimed at / achieved. - on page 14, line 6 an m is missing : long-term - For this is a longitudinal study, the course of mean GFR would be

	of interest. If the duration of this pilot was quite long, a deterioration of GFR due to the natural course of CKD has to be assumed which would result in an elevation of sUA. - Please provide data on the co-medication used and explicitely data on changes in this medication. 46% of patients are suffering of 2 or more co-morbidities; please provide data on the use of ASS, diuretics etc having an impact on sUA. - Measurement of gGT was not part of the protocol. Did the pharmacist ask about alcohol consumption? - on page 13, line 48 it is said that many cases of medication non-adherence were encountered. Please specify.

REVIEWER	Harrold, Leslie University of Massachusetts
REVIEW RETURNED	19-Sep-2013

THE STUDY	Overall comments: The authors describe a new gout management clinic staffed by pharmacists with supervision by rheumatologists to increase the likelihood that patients will achieve the target serum urate level. This is an interesting study and an important problem since adherence in gout is poor and there is substantial morbidity associated with undertreated gout. Overall comments: It's not clear to me why the researchers created this program—meaning what deficit in the literature did they identify by which they structured this program. For example, they touch upon medication adherence being an issue, yet there is no mention of patient education or motivational interviewing to address patient nonadherence. It seems implicit, based on the description of the intervention, that the problem is that physicians do not appropriately escalate therapy and monitor patients given the pharmacists are purely checking levels and adjusting medication dosages. I think the introduction should be revised to focus on the goals of the intervention and how the research team designed the intervention to meet those goals. For readers to understand whether a program such as this would work in their clinical setting, they need to understand the patients who participated. Since the clinic was based on referrals, it is not clear which patients were referred and why. I am assuming the "tough" cases were cared for by rheumatology and thus these were the patients with more mild disease. But it is unknown. For Table 1, readers will want to know about the prevalence of tophi, duration of gout, associated medications that influence ULT therapy like diuretics. Also it would be nice if there was a clear description of these patients and how they compare to the usual gout patient population. Since this work is coming from an integrated health system, is it possible to understand the characteristics of these patients as compared to other gout patients seen during the same time period in terms of diagnoses, health care encounters for gout, and medication utilization (use of and monthly adherence to a ULT

	prior to enrollment in the clinic based on NDC codes and dispensing data)? Were any of the results examined for relevant subgroups? Adherence has been shown to be worse in younger, healthier patients. Was that examined? The discussion touches upon the broad categories of challenges faced by gout patients and their providers but doesn't address specifically how this program does or does not address these challenges. I would want to know what "worked" and what didn't "work" for the intervention. Others have published upon a nurse driven effort that includes patient education and treatment acceleration as described here. It would be nice if the discussion discussed the pros and cons of the 2 approaches. Also it would be very helpful if the authors would describe specifically how this program addresses the challenges of adherence and achieving a target serum urate level. It would be helpful to assess the impact of the program in terms of health care utilization. Not clear how a program like this would be implemented in a nonintegrated health care system. Specific comments: 1. It would be helpful to know the % of patients with tophi since their total body burden of urate may be higher and thus would require more extensive treatment with ULTs.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Dr Frédéric Lioté, MD, PhD

Goldfien et al raised an important issue: how to enhance ULT monitoring in gout. They have designed a smart flow chart and methodology including one clinical pharmacist and one rheumatologist. They report results from a pilot study raising interesting questions in terms of feasibility.

Patient description should be improved (table 1), including
- % of patients with at least one clinical tophus,
- with chronic arthropathy
- CKD should be clarified giving the number of patients in each CKD class.

Response: The nature of this program was such that the gout patients we managed were never seen by the supervising rheumatologist. As such, we could only rely on the electronic medical record to ascertain whether an individual patient had tophaceous gout. As the reviewer might imagine, such chart-based ascertainment is quite unreliable and therefore we did not attempt to classify our patients based on the presence of clinical tophi. We admit this would be interesting information but we are not able to comment on this.
We have clarified the stage of CKD in the results section. We only included patients with stages 2-4 (patients with CKD stage 5 or on dialysis were not eligible for referral)

It is unclear from the methodology section which ULT was first chosen (allopurinol in all?), at which

INITIAL dosage; similarly it appears that a few number received febuxostat: reason in unclear.
Response: In the Methods section “Pharmacological treatments” we state that “ULT wa initiated with allopurinol…” and “The starting dose for allopurinol-naïve patients was 100 mg daily...” “…unless the patient had a known ADR or allergy to allopurinol”. Subsequently, we have stated that “Patients who developed a significant ADR or symptoms of allergy to allopurinol were switched to either febuxostat 40 mg daily or probenecid 500 mg daily…” the decision about which agent was used as a second line drug was at the discretion of the supervising rheumatologist as noted in the methods section.

Indeed at that methodology section and in the result section, it is essential to associate allopurinol dosages AND CKD levels. (maximal dosage ..)

Prophylaxis should be precised with respect to counter indication.

In the abstract a short sentence or in brackets should explain why patients did not complete the study.
Response: We have added a comment to this effect in the abstract.

This study provides an elegant way to monitor ULT dosage and compliance, at least in part. It seems to contribute to reduce therapeutic inertia (Lioté F & Choi HK, ARD 2013). This point should be discussed
Response: A comment was added in the discussion and the ARD citation was added (reference 24)

However the reviewer is not convinced that two SUA<6.0 mg/dL 3 months apart are sufficient to insure good compliance. A formal one year SUA after beginning the study for each patient would have been more appropriate. Please add if available. Or update the SUA follow-up.
Response: Because the program was a feasibility project and patients were referred back to their primary physician after completing the study, there was no requirement to do a follow up sUA. Even so, we examined the records of all the patients who completed the program successfully (78 patients) and looked for the most recent sUA measurement. We have put this data into the results section. We were able to document a repeat sUA test in 63 of the patients and the sUA was at goal in 53 of these (80%) at a mean follow up of 36 weeks from clinic discharge. Clearly, in an ideal system, long term follow up is required to assure continued treatment.

Total follow up duration before discharge is missing. Also titration period duration is missing.
Response: This data is available in our database and we agree this if of significant interest in interpreting the efficacy of the program. We have therefore summarized this data in the results section and commented on it in our discussion

Another pitfall is to discharge patients after achieving these 2 "good SUA levels"... what is the results of further F/Up? Please comment and add data.

Response: Please also see above and below. We have provided follow up sUA levels in those patients where this was available.

Prophylaxis details should be added: please refer to the Ree's study in which few patients received colchicine. Should be added the number of patients under colchicine, duration and maximal dose, combination with NSAID's? number of flares?

Response: Flare prophylaxis was used in all patients as described in the “Pharmacological Treatments” section of the methods. NSAIDS were used only in a very small number of patients, and essentially, colchicine was used in the doses described in more than 90% of patients. Because we discharged patients once the sUA was maintained at target for 3 months, all patients used flare

prophylaxis during the entire study period.

This elegant structured treat to target protocol does not take into account other key aspects of gout management, namely patient education, life style changes including diet. Please acknowledge these points in the discussion section
Response: We agree strongly that patient education and lifestyle counseling are an indispensable part of optimal management of gout. We did in fact provide written educational materials and lifestyle counseling to each patient at the time of entry into the clinic, but omitted this information in the original submission. We have now amended this.

Reviewer: Judith Sautner, MD,

The paper is definitely of interest and reads well. The goal to improve the management of gout eg to more effective lowering of sUA to the target level is very well understandable.

- The chosen setting with pharmacists being involved and even in a decisive position in the therapeutic process as such is quite unusual in Europe and would not be possible in our understanding. But I assume this was done due to local customs and in order to leverage physician time - as mentioned in the discussion of the manuscript. In my opinion this is definitely a limitation of the study because the setting is not freely transferable to other countries and would not pass the Ethics committee in Austria.
Response: Although we were not aware that pharmacists could not perform this function in Europe, we believe another trained health care professional (for example an clinical nurse specialist) could substitute for this role and provide the same quality of care and leveraging function.

- page 7, line 15: it is mentioned that Allopurinol is used up to 300mg and in some patients up to 450 mg. on page 10, line 51 it is mentioned that 2 patients even required a dosage of 600mg. Please correct.

Response: This has been clarified and corrected on page 7.

- Albeit flare prophylaxis in 100% of patients, which is described as sufficient, a flare rate of 34% is pretty high. Maybe you could comment on that.
Response: We found that a significant number of gout flares actually occurred during periods of medication non-adherence. We added a comment explaining this on page 13 in the discussion. We suspect that such a high rate might not be seen in a formal prospective drug study.

- What was the mean duration of this pilot study for the first 100 patients? Only data on the individual end of the study - when SUA was consecutively achieved in two measurements in a time frame of 2 months - is mentioned. Figure?

Response: We have now included this data in the results section along with some comments. The mean was 47.8 weeks with a range of 14.9 weeks to 109.6 weeks.

- There are no data provided on the diet of patients and the course of BMI. Did patients lose we
- Was a dietary advice given concerning sUA and appropriate food? ight during the study? This would/could have an impact on the sUA levels.

Response: We did not ask our patients to report weight or details of any dietary changes and because there were no clinic visits required as part of the protocol, we cannot comment on BMI changes.

However, we did provide written dietary advice to patients at the initiation of the program (We can provide the written materials if desired as an attachment.)

- Please provide the distinct percentage of patients with tophaceous gout. And please comment if in these patients the target level of <5mg/dl sUA was aimed at / achieved.
Response: As noted above in our response to Dr. Liote, we did not examine the patients and do not feel the documentation in the medical record was of sufficient reliability to use in reporting the prevalence of tophaceous gout. Although we might have chosen to use a lower sUA target in patients with tophaceous gout, our algorithm and approach to ULT would otherwise not have been influenced by the presence of tophi.

- on page 14, line 6 an m is missing : long-term
Response: Corrected

- For this is a longitudinal study, the course of mean GFR would be of interest. If the duration of this pilot was quite long, a deterioration of GFR due to the natural course of CKD has to be assumed which would result in an elevation of sUA.

- Please provide data on the co-medication used and explicitly data on changes in this medication. 46% of patients are suffering of 2 or more co-morbidities; please provide data on the use of ASS, diuretics etc having an impact on sUA.
Response: Although we measured serum creatinine routinely in our patients, we saw no significant trend towards increasing creatinine in our patients. Also, though we have medication data available, we decided for the purposes of this study that we would not ask the referring physicians to stop either ASA or diuretics in their patients. Our reasoning was that we would be able to control sUA without interfering with other treatments our patients were being given to manage serious comorbidities. Though one could argue that such changes might be helpful, our results seemed to confirm that we could indeed control sUA without stopping these medications.

- Measurement of gGT was not part of the protocol. Did the pharmacist ask about alcohol consumption?
Alcohol consumption was not addressed in this protocol.
Response: This is correct: alcohol consumption was not specifically addressed by the protocol, though we did provide dietary advice to limit alcohol consumption.

- on page 13, line 48 it is said that many cases of medication non-adherence were encountered. Please specify.

Response: We have added a comment to clarify this. The fact that the protocol required repeating the sUA until at goal for at least 2 consecutive measures means that in a significant number of patients, the second sUA had risen. This was almost inevitably due to discontinuation (or sometimes self adjustment) of ULT and at those times, therapy was reinstituted. Patients were also instructed to call if a gout flare occurred, and in several cases, it was concomitantly recognized that the patient had stopped the ULT. As noted in the discussion, this was anticipated and an important reason for using a structured program.

Reviewer: Leslie R Harrold, MD, MPH

Overall comments:

The authors describe a new gout management clinic staffed by pharmacists with supervision by rheumatologists to increase the likelihood that patients will achieve the target serum urate level. This is an interesting study and an important problem since adherence in gout is poor and there is substantial morbidity associated with undertreated gout.

Overall comments:

It's not clear to me why the researchers created this program—meaning what deficit in the literature did they identify by which they structured this program. For example, they touch upon medication adherence being an issue, yet there is no mention of patient education or motivational interviewing to address patient nonadherence. It seems implicit, based on the description of the intervention, that the problem is that physicians do not appropriately escalate therapy and monitor patients given the pharmacists are purely checking levels and adjusting medication dosages. I think the introduction should be revised to focus on the goals of the intervention and how the research team designed the intervention to meet those goals.

Response: We have added some comments in the introduction to try to make more clear the gaps in gout care that we hoped to address using our program. Although we accept the potential benefit of motivational interviewing, it was not used in our program. As for educational material and dietary guidance, we did in fact provide this, but neglected to state this in the methods section. This has been corrected.

For readers to understand whether a program such as this would work in their clinical setting, they need to understand the patients who participated. Since the clinic was based on referrals, it is not clear which patients were referred and why. I am assuming the "tough" cases were cared for by rheumatology and thus these were the patients with more mild disease. But it is unknown. For Table 1, readers will want to know about the prevalence of tophi, duration of gout, associated medications that influence ULT therapy like diuretics. Also it would be nice if there was a clear description of these patients and how they compare to the usual gout patient population. Since this work is coming from an integrated health system, is it possible to understand the characteristics of these patients as compared to other gout patients seen during the same time period in terms of diagnoses, health care encounters for gout, and medication utilization (use of and monthly adherence to a ULT prior to enrollment in the clinic based on NDC codes and dispensing data)?

Response: The reviewer brings up some excellent points which merit clarification and responses. Unfortunately we do not have data on such things as presence of tophi, or duration of gout.
Given the high prevalence of gout and the limited number of rheumatologists, our pilot program was set up to test whether it would be possible to use a structured but highly leveraged program in lieu of a formal rheumatology referral in a real world setting where primary care physicians were attempting treat gout patients. For any given patient, a referral to a rheumatologist (RG is the sole rheumatologist at the Richmond facility) remained an option. Indeed, because the referral process used was actually incorporated into the usual rheumatology referral process, the great majority of patients referred would otherwise have been referred to the rheumatologist were it not for the program. Therefore, we offered the program to our primary care colleagues as an alternative to a rheumatology consultation. But the referring physicians knew that the same rheumatologist would be managing the program. We can't really know, but it is our belief that the patients referred were representative of gout patients in other settings who are now cared for by rheumatologists or primary care physicians. This has been clarified in the methods section to help the reader understand how patients entered the program.
The only inclusion criteria for the program were the presence of recurrent or chronic gout and the decision of the primary care physician that the patient was a candidate for ULT. This approach has some advantages and disadvantages. An advantage is that we were able to assess our program in a setting that represents a common clinical problem: a gout patient not doing well and being managed

by their primary physician and not by a rheumatologist. A limitation is that the cohort we treated was not as well characterized as would be the case in a formal study.

Were any of the results examined for relevant subgroups? Adherence has been shown to be worse in younger, healthier patients. Was that examined?
Response: We did not do a subgroup analysis, but agree it could be helpful and we hope to examine this in future studies.

The discussion touches upon the broad categories of challenges faced by gout patients and their providers but doesn't address specifically how this program does or does not address these challenges. I would want to know what "worked" and what didn't "work" for the intervention. Others have published upon a nurse driven effort that includes patient education and treatment acceleration as described here. It would be nice if the discussion discussed the pros and cons of the 2 approaches. Also it would be very helpful if the authors would describe specifically how this program addresses the challenges of adherence and achieving a target serum urate level.

Response: In the discussion we call attention to the success of the clinic protocol in achieving a target sUA in the great majority of patients, thus addressing the well-recognized issue of treating to target. We also addressed the issue of follow up monitoring to assure continued effective ULT. Though our program was by design time-limited, the fact that we were able to detect medication non-adherence in many patients and rectify that is another problem the discussion addresses. A third area we addressed is the persistent problem of withholding adequate doses of allopurinol in patients with CKD. We were able to show that standard doses were safe and effective in this population.

It would be helpful to assess the impact of the program in terms of health care utilization.
Response: This is a very important issue and we are actively pursuing this avenue, but the time frame required to see a significant effect was significantly longer than we were able to look at in this study. Indeed, because of this delay, few studies have been carried on long enough to document a reduction in utilization that we hope would result from improved management.

Not clear how a program like this would be implemented in a nonintegrated health care system.

Response: This is another potential limitation of our study. Nevertheless, in countries other than the US and perhaps in the US with the adoption of accountable care organizations, integrated systems such as ours should be more common in the future.

Specific comments:

1. It would be helpful to know the % of patients with tophi since their total body burden of urate may be higher and thus would require more extensive treatment with ULTs.

Response: We agree this is an interesting question and likely to be true (at least it may well take longer to see a cessation of gout flares). We could not get reliable data on the prevalence of tophaceous gout in our patients however.

VERSION 2 – REVIEW

REVIEWER	Sautner, Judith State Hospital Stockerau
REVIEW RETURNED	07-Nov-2013

GENERAL COMMENTS	1) The authors have definitively improved the manuscript and have

	added essential data. 2) There are data on BMI in Table 1 and it is mentioned that information has been given on gout specific diet at the beginning of the study, but I still have not found data on the trend of weight and BMI respectively during the entire study period. Please comment if there are data concerning this topic or if these data are lacking. 3) page 32, table 1 and line six respectively: in table 1 the number of 75% of patients suffering from hypertension is given, in line 6 seventy-eight % is written. Please correct for the correct number - either in table 1 or in the text. On the whole, the manuscript has been improved and after the clarification of the points raised above I find it considerable and ready for publication in your journal.

VERSION 2 – AUTHOR RESPONSE

In response to reviewer 2 we have made the following changes:

2) There are data on BMI in Table 1 and it is mentioned that information has been given on gout specific diet at the beginning of the study, but I still have not found data on the trend of weight and BMI respectively during the entire study period. Please comment if there are data concerning this topic or if these data are lacking.

We were not able to track weight or BMI due to the design of the protocol. This was a telephone intervention and thus not all patients had their weight documented in the record at a visit and we did not ask patients to self-report weight. Consequently, BMI could not be measured as a variable and analyzed.

Thank you for your assistance in reviewing and improving our manuscript.

Sincerely,

Robert Goldfien MD

3) page 32, table 1 and line six respectively: in table 1 the number of 75% of patients suffering from hypertension is given, in line 6 seventy-eight % is written. Please correct for the correct number - either in table 1 or in the text.

This has been corrected in the text.