

Improving adherence to gout therapy: an expert review

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Abstract: Gout is the most common form of inflammatory arthritis and is a considerable burden to patients and health care systems worldwide. Despite its clinical, economic, and social impact, patient persistence and adherence to prescribed urate-lowering therapies (ULT), ranging from 20% to 70%, is considered to be among the poorest of all chronic conditions. The majority of gout patients consequently receive suboptimal benefits of their prescribed pharmacotherapies. As gout is associated with several comorbidities along with an increased risk of premature mortality, achieving improved outcomes through adherence to ULT is crucial. Adherence to medication is complex and multidimensional and includes a combination of treatment-, patient-, and physician-related factors. This review explores the factors related to ULT adherence with the overall aim of helping health care providers better understand the barriers to adherence. Several interventions targeting pharmacists, nurses, and patients are being investigated to improve adherence. Furthermore, enhanced awareness and understanding of the need to treat-to-target in order to improve patient outcomes is needed among health care professionals. Greater understanding of the multidimensional nature of non-adherence can help physicians to treat gout more effectively and empower patients to improve self-management of this long-term disease.

Keywords: treatment, gout suppressants, persistence, monitoring

Introduction

Gout is the most common form of inflammatory arthritis in the general population and is a considerable burden for both the patient and health care system.^{1,2} Unfortunately, this burden is likely to worsen due to the increasing prevalence of gout in Western countries. For example, a UK-based study in which the prevalence and incidence of gout was estimated for each calendar year from 1997 to 2012 registered a 63.9% increase in prevalence and a 29.6% increase in incidence over the 15-year period.³ Furthermore, data from the USA show that the prevalence of gout has risen in the recent decades in individuals over the age of 65 years, while it is relatively stable among younger age groups. The increase in prevalence is highest among those over the age of 75 years, where it has increased from ~20 per 1,000 to around 65 per 1,000.¹

Gout can be considered to be a systemic disease caused by the accumulation of monosodium urate crystals in tissues that induce inflammation.⁴ Effective treatment of gout is important, not only to improve the negative impact it has on patient quality of life and use of health care resources,^{5,6} but also because gout is associated with an increased risk of premature mortality.^{7,8} The presence of tophi in gout patients has been associated with a greater risk of mortality, largely due to cardiovascular (CV) causes.⁷ A 2017 study showed that even patients with a duration of gout <10 years are at increased risk of death from both non-CV and CV causes.⁸ Monosodium urate deposition can occur

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in tissues when serum urate (sUA) levels exceed 6.8 mg/dL ($>405 \mu\text{mol/L}$) or even lower in the presence of favorable conditions,⁹ and may result in gout flares, tophi formation, and structural damage to joints.¹⁰ Long-term management of gout is based on maintaining sUA below a target level of 6 mg/dL ($<360 \mu\text{mol/L}$) to enhance crystal dissolution.^{11,12}

Adherence to prescribed medication is important to the management of chronic diseases, including gout, as obviously long-term drug effectiveness is substantially compromised by patient non-adherence.¹³ For gout, achieving the optimal therapeutic target of sUA requires concerted efforts to increase adherence to urate-lowering therapies (ULT). However, most studies on the matter have reported very low rates of adherence to ULT among patients with gout. The provision of effective therapy is further limited by the fact that only ~50% of patients with gout are either being consulted for gout or under treatment with ULT.³ Consequently, there is considerable interest in optimizing treatment and management of gout at the patient, community, and national levels. One key intervention is to actively advocating better adherence to ULT.

Defining adherence to therapy

The World Health Organization defines adherence to long-term therapy as “the extent to which a person’s behavior—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider” (Figure 1).¹⁴ Such a definition places strong emphasis on the patient’s agreement to prescriber recommendations and that patients need to be active partners with health care professionals.¹⁵ Non-adherence includes “failing to fill

prescriptions, delaying prescription fills, reducing the strength of the dose taken, and reducing the frequency of administration. It can also include the failure to keep appointments or to follow recommended lifestyle or dietary changes.”¹⁵

Factors affecting adherence

Measuring adherence to therapy is not necessarily straightforward, and a number of methods, including both indirect and direct approaches, have been proposed (Table 1). A common indirect approach involves subjective rating of adherence using patient and prescriber questionnaires. However, such methods are often inaccurate as patients may not report their actions or behavior in relation to adherence objectively, consistently, or correctly.^{16,17}

The 8-item Morisky Medication Adherence Scale has recently been used to monitor medication adherence, but was found to not be useful in discriminating patients who were or were not achieving the recommended target of sUA; nevertheless, it was able to identify patients who failed to comprehend the need for long-term ULT.¹⁸ In such patients, targeted education and support to improve coping mechanisms may be beneficial.

Objective methods, such as counting remaining dosage units, pill counts, and electronic monitoring systems (pharmacy data, medical records, and medication event monitoring system), attempt to overcome some of the limitations of subjective methods, but may be either too expensive for routine use, or may capture incomplete information.¹⁹ In this regard, the medication possession ratio, that is, the number of doses filled by the pharmacist divided by the number of days in a predefined period, has been used to quantify adherence to gout therapy.²⁰ Biochemical measurements using nontoxic biological markers is a direct approach to assess adherence behaviors as it can provide more objective evidence that a patient has taken a dose of the medication.²¹ However, the feasibility of such an approach may limit its practical utility

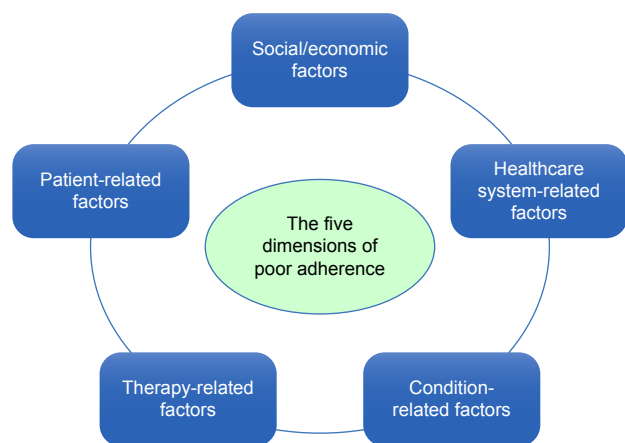


Figure 1 The five dimensions of poor adherence.

Notes: Adapted from World Health Organization. Adherence to long-term therapies. Evidence for action. Available from: http://www.who.int/chp/knowledge/publications/adherence_report/en/.¹⁴

Abbreviation: WHO, World Health Organization.

Table 1 Methods used to measure adherence to gout therapy

Indirect methods

- Patient questionnaires
- Physician questionnaires
- Morisky Medication Adherence Scale

Direct methods

- Counting dosage units
- Pill counts
- Pharmacy data
- Medical records
- Medication event monitoring system
- Biochemical measurements

due to variability in diet, absorption, and rate of excretion. Regardless of how adherence to therapy is measured, it is clear that non-adherence remains a major problem to be overcome in the long-term management of many chronic conditions.

Social/economic factors

Social support, including from family, friends, or caregivers, can be an important factor in assisting patients to adhere to medication regimens. Patients with social support often show improved adherence to prescribed treatments. In contrast, negative social/economic factors, such as unstable living environments, lack of adequate access to health care, limited financial resources, high costs of medication, and difficult schedules at work, have been associated with poor adherence.¹⁴

The economic costs of increased urate and gout are significant; for 1 year following diagnosis of gout in patients aged >65 years, direct cost associated with either gout or increased sUA levels was US\$876 (5.9%) of the total health costs registered in the period (2005); this was mainly related to inpatient care (57.6%). A very high sUA level (≥ 9 mg/dL) was associated with an additional US\$3,103 in regression-adjusted total 12 months all-cause health care costs and US\$276 in regression-adjusted 12 months gout-related costs, compared with a low sUA level (< 6 mg/dL).^{6,22} A recent Canadian study of patients with incident gout aged ≥ 66 years examined their 5-year total health care costs. It reported that patients with gout (CA\$44,297) incurred a significantly higher average health care cost compared with gout-free patients (CA\$33,965), for an incremental cost of CA\$10,332 (95% CI: CA\$9,617–CA\$11,039; $p < 0.01$).²³

Health care system-related factors

The physician–patient relationship is an important aspect related to the health care system that can greatly affect adherence to therapy. It is obvious that empathy between the prescriber and the patient can encourage the patient, aiding increased adherence to treatment. At the same time, lack of communication on the benefits and need for treatment, as well as precise instructions on taking the medication and its adverse events, can negatively influence adherence. It is also clear that costs, reimbursement issues or lack thereof, as well as prescriber incentives in some settings may greatly impact adherence.¹⁴

Condition-related factors

These are factors associated with illness-related burdens that the patient must face. In many conditions, adherence

to treatment often decreases over the long term. This is especially true of conditions, such as well-controlled gout where the patient has few or no symptoms. This reinforces the need for the patient to have adequate knowledge of their condition and the possible consequences if adequate treatment is not provided.¹⁴

Therapy-related factors

The most prominent therapy-related factors are linked to the difficulty in adhering to the prescribed treatment regimen and its duration. In addition, failure of previous treatment, as well as repeated changes in the treatment regimen, may be associated with low adherence. Moreover, the possible side effects of therapy must not be overlooked as they cause patients to discontinue their medication or take it in a manner that is not in accordance with that prescribed.¹⁴

Patient-related factors

Such factors include knowledge, attitudes, beliefs, and expectations that the patient has toward a particular therapy. If patients lack knowledge about the disease and why adequate treatment is needed, they may have poor medication adherence.²⁴ Similarly, a perceived lack of interest in treatment of the condition and substance abuse may be related to reduced adherence to therapy.²⁵ Forgetfulness, psychological anxiety, possible adverse effects of medication, and negative concerns about the perceived efficacy of treatment can also influence treatment adherence.¹⁴

Patient-related non-adherence may be non-intentional or intentional. The UK National Institute for Health and Care Excellence defines these as follows: “Unintentional non-adherence occurs when the patient wants to follow the agreed treatment but is prevented from doing so by barriers that are beyond their control. Intentional non-adherence occurs when the patient decides not to follow the treatment recommendations.”²⁶ Unintentional non-adherence involves aspects, such as the lack of capacity or resources, for example, when patients have not understood prescribing instructions and/or the consequences of not taking their medication, when they cannot afford co-payment costs, or whenever they find it difficult to schedule, administer, or remember to take their treatment. Intentional non-adherence involves an unwillingness to take a medication based on the person’s perceptions of that treatment and their lack of motivation or desire to initiate and continue it. In some patients, psychiatric issues, such as depression, cognitive restraints, low or lacking office visits, and a poor relationship with the prescriber, may also contribute to greater non-adherence to

therapy. Prescribers thus need to have a better understanding of patient-related factors that can dispose to either intentional or unintentional non-adherence and attempt to overcome these barrier to adherence.

Adherence in other chronic diseases

Good adherence is most commonly defined as the percentage of patients who take at least 80% of their prescribed medication, although this cutoff value may be up to 90% in some investigations.²⁷ Unfortunately, poor adherence is a primary reason for the suboptimal clinical benefits of pharmacotherapy in many diseases.²⁸ In general, adherence is believed to be highest in the management of human immunodeficiency virus infection and cancer, indicating that disease seriousness is a major motivating factor for patients to take their medication as prescribed.²⁹ While it is sensible to presume that more seriously ill patients would be more adherent to medication, at least 1 study has reported that patients with cancer on long-term oral treatment exhibit non-adherence comparable with that of the general patient population.³⁰ Treatment adherence rates and related issues in several diseases are briefly overviewed below by way of example.

Non-adherence to treatment for hypertension is a well-documented cause of poor control of blood pressure and development of “pseudo-resistant” hypertension. Published estimates of the prevalence to antihypertensive therapy vary widely, with rates of non-adherence ranging from 3% to up to 65%,³¹ using biochemical screening, 25% of patients are either totally or partially non-adherent to treatment.³² Unsurprisingly, the highest prevalence of partial and total non-adherence was among patients who had inadequate control of hypertension.³³

In type 2 diabetes, despite the well-known benefits of targeted antihyperglycemic therapy on organ damage and mortality, recommended targets are achieved by <50% of patients and are frequently associated with suboptimal adherence.^{27,34} As for other pathologies, the reasons for non-adherence are multifactorial and include patient age, perception and duration of disease, complexity of therapeutic regimen, psychological comorbidities and tolerability, and cost of treatment.²⁷

In rheumatoid arthritis (RA), adherence ranges from 50% to 80%.¹⁹ Patients appear to be more adherent to biologic disease-modifying anti-rheumatic drugs (DMARDs) and par-enteral administration, in contrast to oral and nonbiological DMARDs. Patient education programs (eg, self-efficacy strategies, information about RA therapy, and strategies for coping) have been shown to increase adherence to therapy.²⁵

Adherence in gout

A number of methods have been used to assess adherence in gout, including electronic prescription records, self-reporting measures, and laboratory results.³⁵ However, regardless of the method used to measure adherence, it is unequivocal that medication adherence is suboptimal and remains a therapeutic challenge. Overall, adherence rates vary widely, from 20% to 70%,¹⁹ and are possibly among the worst for any medication for chronic disease. Adherence during the first year of drug therapy in seven chronic conditions, including hypertension (72.3%), hypothyroidism (68.4%), diabetes mellitus (65.4%), seizure disorders (60.8%), hypercholesterolemia (54.6%), and osteoporosis (51.2%), were all better than for gout (36.8%).¹²

A systematic review showed that less than half of patients (10%–46%) appeared adherent to ULT.³⁵ In a large study of 4,166 patients initiating ULT, over half (56%) were non-adherent; predictors for non-adherence included age <45 years, fewer comorbidities, no previous office visits for gout before ULT initiation, and prior administration of non-steroidal anti-inflammatory agents within the last year.³⁶

Studies worldwide have confirmed that adherence to ULT is low (Table 2). A study using a large primary care database in the UK (the Clinical Practice Research Datalink [CPRD]) with health information on ~8% of the general population, 61% of patients were found to be either non-adherent (18%) or partially adherent (43%) to ULT.¹⁴ Similar results have been reported using a pharmacy claims database in Ireland, where 45.5% and 35.3% of patients initiating ULT were adherent at 6 and 12 months, respectively.²⁰ In addition, a large retrospective study in Israel showed that only 17% were adherent to allopurinol,³⁷ while in Italy, only 3.2% of patients remained adherent to allopurinol after 1 year.³⁸ In a gout-oriented rheumatology practice in Australia, failing to reach target sUA was almost always due to non-adherence.³⁹ Finally, a recent population-based cohort study from Sweden of 7,709 gout patients confirmed that long-term adherence was poor.⁴⁰ Within 1 year after first diagnosis of gout, only 32% of patients had received ULT. Moreover, of those initiating ULT, 75% did not persist with the treatment during the first 2 years. The study also reported that age <50 years and lack of comorbidities were associated with non-persistence to ULT.

Barriers to adherence in gout

Improving adherence to ULT requires overcoming treatment-, patient-, and physician-related barriers. These are depicted in Figure 2.

Table 2 Summary of studies worldwide on adherence to ULT

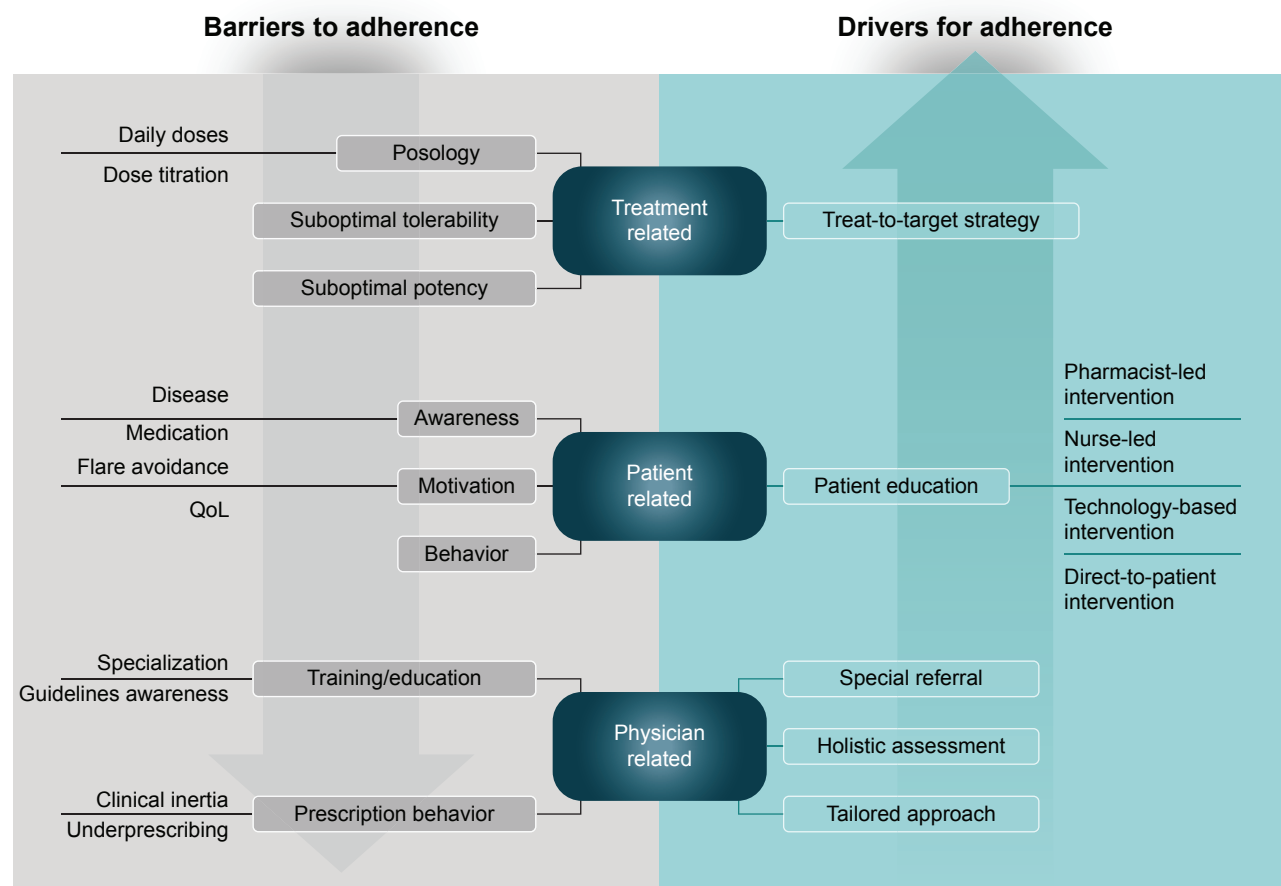
Author (reference)	Country	No of patients	Notes	Main finding
Kuo et al, ³ 2015	UK	115,608	Reference year 2012	40% of patients were found to be adherent or partially adherent to ULT
McGowan et al, ²⁰ 2016	Ireland	34,634	Adherence was defined as continued use of therapy with no periods exceeding a refill gap of >63 days	45.8% and 22.6% of patients were adherent at 6 and 12 months, respectively
Zandman-Goddard et al, ³⁷ 2013	Israel	7,644	Drug adherence >80%	17% were adherent to allopurinol over a 2-year period
Mantarro et al, ³⁸ 2015	Italy	3,727	≥80% days covered considered adherent	3.2% of patients remained adherent to allopurinol after 1 year
Dehlin et al, ⁴⁰ 2017	Sweden	7,709	Age <50 years, lack of comorbidities, and "normal kidney function" or "end-stage kidney failure" were associated with non-adherence with ULT	Of patients starting ULT, only 25% were adherent within 2 years

Abbreviation: ULT, urate-lowering therapies.

Treatment-related factors

There are several treatment-related factors that affect adherence, including posology, tolerability, and potency. With regard to posology, once-daily ULT (such as febuxostat, benzbromarone, or lesinurad) would likely be favored by

patients over those that require multiple daily doses as in the case of probenecid and allopurinol (if prescribed at >300 mg/day), which may thus promote greater adherence. In addition, continual dose adjustment required for some ULT to achieve the desired clinical effect may be a painstaking

**Figure 2** Barriers and facilitators of adherence to chronic gout medications.

Abbreviation: QoL, quality of life.

process that discourages adherence. It is clear that ULT that are better tolerated will likely be associated with improved adherence to therapy.

Physicians should also consider that the relative potency of ULT may be a risk of inducing gout flares, which may represent a limitation in terms of adherence. This is relevant since some studies have suggested that poor adherence to ULT may be associated with the risk of acute gout flares when initiating therapy, as well as with poor response, continued attacks of acute gout, suboptimal dosing, and intolerance to allopurinol.²⁰ Accordingly, education and information on the risk of initial flares and implementation of adequate measures, such as prophylaxis and early control of acute inflammation, may be useful to avoid discontinuation of ULT.

Adherence to ULT, considering both allopurinol and febuxostat, has been studied in the large, real-life observational study, CACTUS, involving 3,079 patients with gout.⁴¹ Appropriate adherence was observed in 92% and 82% of patients on febuxostat and allopurinol, respectively. Intervention was likely associated with the increase in adherence, which can be considered adequate with both medications.

Patient-related factors

One of the most important patient-related factors is the lack of understanding by health care providers, and as a consequence, gout can become chronic in patients if left untreated/undertreated.⁴² Some patients may view gout attacks as being only inconvenient and that they have no adverse effects on their overall health, and thus seek only pain relief and dietary control.⁴² However, taking a medication requires patients to fill prescriptions for a prescribed medication and to understand how to take the medication; they also need the knowledge of how the medication fits into overall disease management.⁴³

Additional barriers include concerns about cost and side effects of therapy, forgetfulness, the belief that gout did not warrant any long-term treatment and doubts about its effectiveness, pill size and difficulty in swallowing, and a lack of adequate information.⁴⁴⁻⁴⁶ Undoubtedly, at least in some settings, financial concerns may be related to non-adherence as patients must obviously have the resources to pay for their medication, in addition to the motivation and self-management skills to take it on a regular basis.

Prescription of ULT from a nonspecialist, compared with rheumatologists or nephrologists, is also a predictor of poor adherence.⁴⁷ It may be that if patients are not made aware of the risk of gout flares, a subsequent flare may lead to greater non-adherence. Patients should thus be clearly instructed that

lowering sUA levels to target is the only means of avoiding future risk of gout flares, which may, therefore, be a major motivating factor to adhere to therapy.

Overcoming patient-related barriers to better adherence also requires identification of motivators for persisting on therapy, including the prevention of both gout flares and pain.⁴⁵ Furthermore, patients may report that ULT gives them the opportunity to eat certain preferred foods in moderation without flares, and that integrating ULT into their everyday routine was a successful approach.⁴⁵ The latter is important as it would help to minimize non-intentional adherence. Accordingly, improving patient self-management skills while providing patient education would appear to be two critical areas of intervention.

Physician-related factors

The CPRD link study in the UK demonstrated that not only was patient adherence to therapy low, but ULT agents were also underprescribed.³ Among prevalent gout patients, only 49% were being consulted explicitly for gout or treated with ULT; of these, 38% received ULT. In addition, only 18.6% of incident gout patients were receiving ULT within 6 months of diagnosis, which increased to 27.3% at 12 months. Nevertheless, it is worthwhile highlighting that even in the UK, the prescription rate for ULT is highly variable in different settings, ranging from 0% to 100%.⁴⁸ This failure to initiate or intensify therapy according to evidence-based guidelines is increasingly being acknowledged as a phenomenon that contributes to inadequate management of chronic conditions and is referred to as clinical inertia.

Physicians often complain that they are unfamiliar with both current guidelines and management of gout;⁴⁹ they do not usually aim for a specific sUA target or regularly monitor levels of sUA,⁵⁰ and prescribe standard doses of medication instead of tailored prescriptions, which may not be adequate for a number of patients.⁵¹

Quality of care indicators are the important quality improvement initiatives for guiding physicians in the clinical care and management of patients with gout.⁵² However, in a UK-based study of physician adherence, one-quarter to one-half of all patients eligible for at least one of the validated quality of care indicators were subject to possible prescribing error, suggesting that inappropriate prescribing practices are widespread in patients with gout.⁵³ A study undertaken in general practitioners identified specific knowledge gaps and discrepancies between illness perceptions and stated clinical practice behavior that may compromise patient management in primary health care.⁵⁴ Accordingly,

both holistic assessment and patient education are fundamental to addressing individual risk factors that can help to improve adherence to therapy. Undoubtedly, greater physician education is needed to reach this goal. It must be realized that in some settings, due to cost considerations, physicians may have prescribing limitations in terms of choice of drug and that patients have difficulty in accessing health care, limiting the ability of prescribers to treat patients.

Overcoming the barriers to better adherence to ULT

Several types of interventions have been investigated for their potential to improve adherence to ULT. It should be emphasized that both a treat-to-target strategy and the European League Against Rheumatism have considered patient education to be an overarching principle of gout therapy.^{11,12} It is thus crucial that health care providers inform and properly educate patients to enhance adherence. Figure 3 outlines the factors identified as associated with good adherence in patients using ULT for gout.

Pharmacist-based interventions

Goldfien et al presented the results of a pilot study examining the efficacy of a pharmacist-based, telephone-driven program, including educational materials in which sUA of

at least 6 mg/dL was achieved and maintained in >80% of subjects.⁵⁵ The benefits of pharmacist-led care are being further investigated in the Randomized Evaluation of an Ambulatory Care Pharmacist-Led Intervention to Optimize Urate Lowering Pathways study, wherein gout patients newly initiating allopurinol are being randomized to either pharmacist-led intervention or usual care.⁵⁶

Nurse-based interventions

Nurse-delivered intervention has also been successfully used to show that patients can successfully meet treatment goals.⁵⁷ After showing a positive effect (ie, >90% of patients at sUA target) in a proof of concept study,⁵⁷ the effectiveness of nurse-led intervention in the long term was further confirmed by Abhishek et al.²⁴ The study investigators evaluated the persistence and adherence to ULT in primary care at 5 years after an initial nurse-led treatment of gout in 100 patients. In the 75 patients who returned completed questionnaires, the 5-year persistence to ULT was 90.7%; of those with sUA measurements available, the mean level was 292.8 $\mu\text{mol/L}$ (4.93 mg/dL). These results suggest that initial treatment combined with individualized patient education and involvement in treatment decisions results in excellent adherence to ULT.

Patient-targeted interventions

In 2013, an analysis of gout patient education resources concluded that critical information on prophylaxis of acute flares during ULT initiation and titration, and treating sUA to target, was not present in at least 60% of patient-targeted materials.⁵⁸ Moreover, about one-third of materials were above the average reading level of rheumatology patients. Fields et al published the results of a multidisciplinary patient education and monitoring program for gout patients.⁵⁹ After 12 months, on a scale of 1 (most) to 5 (least), scores of ≤ 3 were given by 84.6% of subjects with regard to the usefulness of the overall program in understanding and managing gout. Thus, patient education programs can be considered to be effective in increasing patients' knowledge of the disease. However, much work remains to provide patients with adequate resources that can positively influence adherence to therapy.

Technology-based interventions

Given the increasing reliance and utilization of mobile devices and the Internet, a self-management eTool has recently been proposed with a number of potentially useful characteristics, such as education, monitoring sUA,

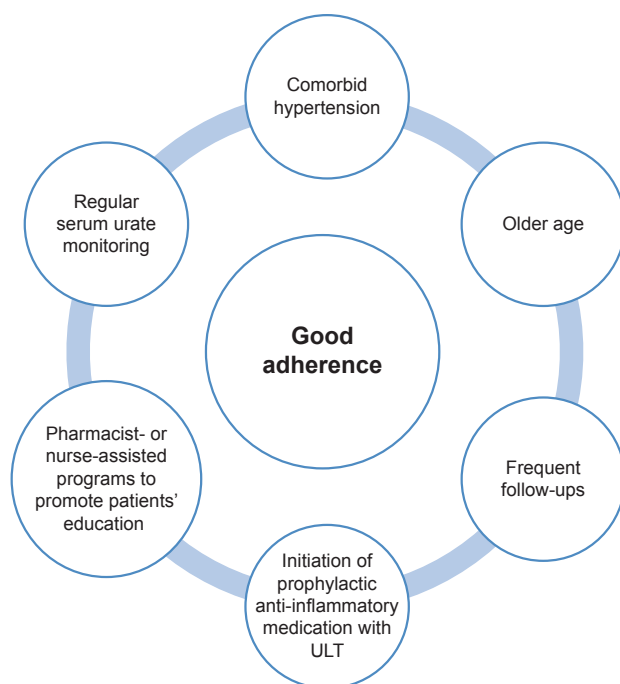


Figure 3 Factors identified as associated with good adherence in patients using ULT for gout.

Abbreviation: ULT, urate-lowering therapies.

and reminders for medication.⁶⁰ Such tools will certainly provide valuable resources for a selected group of patients. Finally, a number of mobile applications are available that may aid in the management of gout.⁶¹ However, at present, there is only one app that includes all current recommendations to assist in patient self-management, even if some features must be activated manually.⁶¹ The development of specific mobile apps, therefore, represents another area that can help to empower successful self-management of gout, even if underdeveloped at present.

Conclusion

Gout is becoming more prevalent and is associated with an increased number of comorbidities and risk of premature mortality. Given that well-tolerated and highly effective treatments are available, they should be properly prescribed. ULT are currently underprescribed and are associated with poor patient adherence, which is considered to be predominantly due to lack of patient education by the prescribing physician,⁵¹ as well as misconceptions about treatment expectations, targets, and outcomes. While many efforts to improve adherence have been centered on patient education and support using a variety of approaches,⁶² health care professionals also need to be aware that both patient and physician education are needed to bridge existing gaps and improve patient outcomes through better adherence to treatment.

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Author contributions

Both authors have substantially contributed to conception and design of the paper, drafted and revised it critically for important intellectual content, approved the final version for submission, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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