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Medication Adherence of Patients with Selected Rheumatic Conditions: A Systematic Review of the Literature

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Abstract

Objective—Nonadherence with medication treatment has been found to occur in large proportions of patients with a broad range of chronic conditions. Our aim was to perform a systematic review of the literature examining adherence with treatments for inflammatory rheumatic conditions to assess the magnitude of the problem in this patient population.

Methods—A MEDLINE search of English language literature was performed to identify studies published between January 1, 1985 and November 30, 2007 that evaluated adherence with chronic medications needed in the treatment of rheumatic conditions.

Results—A total of 20 articles met the criteria for evaluation, the majority of which focused on the treatment of rheumatoid arthritis. Most of the studies examined the use of nonsteroidal anti-inflammatory medications and disease modifying anti-rheumatic drugs. Adherence was assessed based on self-report, pill counts, pharmacy dispensings, openings of pill containers using electronic devices, laboratory assays, and physician assessment. Adherence varied greatly based on the adherence measure used, arthritic condition evaluated and medication under study. Overall, the highest rates of adherence were based on self-reports for a wide variety of medications and conditions (range of persons reporting adherence was 30 to 99%), while the lowest adherence rates were for allopurinol based on pharmacy dispensings (18–26%).

Conclusions—Adherence has not been widely examined for most chronic inflammatory rheumatic conditions and the few studies that exist used different definitions and populations, thus limiting any conclusions. However, the current literature does suggest that nonadherence is a substantial problem.

Keywords

adherence; arthritis

Introduction

Estimates suggest that at least 50% of adults prescribed pharmacological therapy for chronic conditions will have difficulty adhering to their regimen after six months.^{1, 2} Adherence (or compliance) with a medication regimen generally refers to whether a patient takes a prescribed medication according to the provider's instructions.³ Poor adherence contributes to worse

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clinical outcomes and increased health care utilization and cost.^{4, 5} While providers assume patients with rheumatic conditions take their medications since nonadherence may result in increased joint pain and functional impairment, this in fact is not necessarily the case.^{6, 7} While the magnitude and determinants of adherence have been well examined in patients with a variety of conditions, such as cardiovascular disease and hypertension, it has not been greatly explored in arthritis and musculoskeletal conditions.⁸

The last reviews of arthritis medication adherence were performed approximately 20 years ago and focused solely on the treatment of rheumatoid arthritis.^{6, 9} Therefore we undertook a comprehensive critical appraisal of the literature regarding adherence as it related to the treatment of selected chronic rheumatic conditions since that last review.

Methods

Identification and selection of articles

A MEDLINE search of English language literature was performed to identify studies published between January 1, 1985 and November 30, 2007 that evaluated adherence, compliance, or persistence of medications for the treatment of rheumatic conditions. The following key words were used as search terms: (patient compliance or adherence or persistence or discontinuation or switching) and (ankylosing spondylitis, or arthritis, or gout, or psoriatic arthritis, or polymyalgia rheumatica, or rheumatoid arthritis, or systemic lupus erythematosus, or vasculitis, or anti-inflammatory agents, or etanercept, or infliximab, or adalimumab, or prednisone, or methotrexate, or hydroxychloroquine, or azathioprine, or sulfasalazine, or antirheumatic agents, or allopurinol, or uricosuric agents, or probenecid, or gold sodium thiomalate, or gold compounds, or gold sodium thiosulfate, or cyclophosphamide). We then limited the search to those articles published in English and work involving humans. A total of 2916 articles were identified. Each article abstract was reviewed to identify potentially relevant articles for retrieval, selecting studies that included original data and examined adherence or persistence with medications in the treatment of chronic inflammatory rheumatic conditions. We excluded studies that examined the use of medications for the treatment of osteoarthritis (n=3), as patients may not require chronic therapy, meaning they only take their medications as needed when they have pain, and thus adherence is difficult to assess. We also excluded studies when the type of arthritis was not specified (n=4), since some forms of arthritis do not require continuous therapy with medications (for example infrequent gout attacks). The majority of manuscripts were unrelated to adherence or the treatment of chronic rheumatic conditions.

A total of 70 original studies were identified as well as 9 review articles^{9–17} and 6 editorials and/or commentaries,^{18–23} which were retrieved for full text review. The references lists for all the articles were reviewed for additional relevant studies. There were eleven additional articles identified from the reference lists, four of which were review articles and thus not included. After review of the full-text papers, an additional 57 articles were excluded for the following reasons:

1. discontinuation of medications due to ineffectiveness and/or adverse effects (n=25)
2. interventions to improve adherence (n=10)
3. patient beliefs and attitudes regarding medications (n=5)
4. development or validation of instruments to measure adherence (n=7)
5. treatment guideline adherence (n=3)
6. case reports of individual patients (n=1)

7. physician prescribing patterns (n=4)
8. adherence is evaluated for the same study population as an earlier study by the same investigator (n=2)

Based upon the results of this final stage of assessment, 20 articles are included in this review (16 identified from the original MEDLINE search and 4 identified from the review of reference lists).

Results

Characteristics of the studies

The majority of studies focused on the treatment of rheumatoid arthritis (Table 1). There were four or fewer studies examining adherence in conditions including juvenile idiopathic arthritis, 14, 24 polymyalgia rheumatica,²⁵ systemic lupus erythematosus,^{26–29} and gout.^{7, 25, 30} The most common medications studied were nonsteroidal anti-inflammatory drugs (NSAIDs) and disease modifying antirheumatic agents (DMARDs). These studies employed a variety of study designs to assess adherence including chart review, analysis of pharmacy records, patient interviews, self-administered questionnaires, pill counts, electronic devices to measure openings of pill containers, laboratory assays to measure metabolites, and assessments by treating physicians. Sample sizes ranged from 12 to almost 5600.

Measures of adherence described in the studies

Due to the varying study designs, differing measures of adherence were utilized. Self-reported adherence was often assessed based on responses to questions probing difficulties adhering to the medication regimen or altering the dose. In one study, two physicians involved in the patient's care independently assessed adherence to treatment. Using pharmacy records adherence was defined in various ways including the actual number of therapy administrations or the number of filled prescriptions divided by the expected number, the medication possession ratio (the actual medication supply received divided by the maximum medication supply that could have been received during the time period), and filling a days supply that would cover at least 80% of the time period evaluated. The electronic devices measured the number of openings of the pill container. Some authors defined adherence as opening the bottle at least 80% of the expected number while others used 100% as the comparison. Consumption of 85% of pills was used to assess adherence in one study that utilized pill counts.

Adherence results

Polymyalgia rheumatica, juvenile idiopathic arthritis, and inflammatory arthropathies—One article each assessed adherence in polymyalgia rheumatica and inflammatory arthropathies, while two articles explored adherence among patients with juvenile idiopathic arthritis (Table 2). Berry and colleagues surveyed 37 new patients and 44 existing patients with inflammatory arthropathies (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, polymyalgia rheumatica and systemic lupus erythematosus) regarding their use of medications.³¹ Among new patients, who were treated with anti-inflammatories and painkillers, 47% reported they took their medications always as prescribed, and 25% reported taking their medications most of the time. In comparison, 89% of existing patients (almost half of whom were treated with methotrexate) reported always taking the medications as prescribed and a further 10% reported taking the medications most of the time. De Klerk used electronic monitoring devices, which signal opening of pill bottles, to assess adherence in 17 patients with polymyalgia rheumatica starting prednisolone followed over 6 months.²⁵ In that population, 88% of doses were presumed to be taken as prescribed based on the opening of the pill bottles. Rapoff and coworkers similarly used electronic devices to assess adherence with NSAIDs in 48 patients with newly diagnosed juvenile idiopathic arthritis.³² Over the 28

day period only 52% of patients were felt to have taken 80% of the prescribed doses based on the opening of pill bottles. Feldman and colleagues surveyed parents of 175 juvenile idiopathic arthritis patients every 3 months over a 12 month period and found adherence to medications averaging between 86–92 on a 100mm visual analog scale.²⁴

Systemic lupus erythematosus—Two articles focused on adherence to the treatment of systemic lupus erythematosus using self-report (Table 2). Moseley-Williams and colleagues asked 65 African Americans and 47 white women to report the frequency that they failed to take their lupus medications during the past year, on a 5-point scale (1=never, 2=rarely, 3=sometimes, 4=often, 5=all the time).²⁷ The mean score was 2.3 (standard deviation 1.2) in African Americans and 2.5 (standard deviation 1.3) in whites, with 31% of African American patients and 23% of white patients reporting they never fail to take their medications. Rojas-Serrano and Cardiel interviewed 180 lupus patients who presented to the emergency unit and used a scale from 0 (takes none of their medications) to 10 (excellent adherence) to assess adherence. The median score was 8.3 (standard deviation 2.2) for every 10 pills the patient had to take. Wang and colleagues examined discontinuation of antimalarials in 156 patients with systemic lupus erythematosus based on chart review. There were 13 patients (8%) who refused or failed to take the medication. In contrast, Adler and colleagues assessed adherence to medications based on the independent judgments of two physicians in charge of the patients' care.²⁶ Nonadherence was agreed to be a poor in 11 of 21 patients with end stage renal failure.

Gout—Three articles evaluated adherence in the treatment of gout (Table 2). De Klerk and colleagues examined adherence in 12 patients starting colchicine and 17 initiating urate lowering agents.²⁵ Using electronic monitoring devices, over 12 months only 44% of colchicine doses and 74% of urate lowering agent doses were estimated to have been taken as prescribed based on opening of pill bottles. Using a managed care database, Sarawate and colleagues found that approximately 26% percent of 2405 allopurinol users over a two-year period had a medication possession ratio of $\geq 80\%$ (actual days supply received divided by the maximum possible medication supply) and the median length of continuous treatment was only three months.³⁰ Riedel and coworkers similarly used an administrative dataset to examine adherence with allopurinol over a 24 month period.⁷ Among 5597 patients who filled at least 2 prescriptions for allopurinol, only 18% were adherent with therapy (≥ 0.80). Most users were adherent only 56% of the time.

Rheumatoid arthritis—Rheumatoid arthritis has been the most studied rheumatic condition to date with 11 studies evaluating adherence (Table 2). Four studies examined adherence to overall medications. Taal and colleagues interviewed 71 patients of whom 66 (93%) responded they had no difficulty adhering to medications.³³ Similarly, Owen and coworkers interviewed 178 patients of whom 113 (63%) claimed they did not alter the dose of their medication from the prescriber's directions.³⁴ Park et al. used electronic devices to measure openings of pill bottles over a month's time in 121 patients.³⁵ In this sample, 38% had presumably perfect adherence (no missed doses and no extra doses) based on openings of pill bottles. Tuncay and colleagues obtained detailed drug histories in 100 patients using NSAIDs, prednisone and DMARDs during three assessments over a 12-month period. They found 26 (30%) patients who stated at all assessments that they were "strictly" or "quite" adherent to both the dose and timing of the prescribed medications.³⁶

Beck et al. assessed adherence to salicylates in 63 patients over a mean length of 68 days.³⁷ Using a serum assay to measure salicylate levels, 31 of the subjects (49%) were considered adherent. In a multinational study in which 556 patients from Norway, the Netherlands, and France were surveyed over three years, mean adherence to NSAIDs, steroids and DMARDs was observed in 56, 65 and 59% of patients respectively.³⁸ Using electronic monitoring devices, De Klerk and colleagues found the percentage of doses taken as prescribed based on

openings of pill bottles in 13 patients taking diclofenac, 20 patients taking naproxen, 25 patients on sulfasalazine, and 23 patients taking methotrexate was 67%, 68%, 55% and 81% respectively.²⁵ Adherence with methotrexate was also examined by Harley, Frytak and Tandon using pharmacy records.³⁹ Among the 1668 patients receiving methotrexate followed for one year, 64% achieved at least 80% adherence.

Adherence with D-penicillamine in the treatment of rheumatoid arthritis was examined in two articles. Doyle and coworkers found good adherence based on urine samples in 61% of the 49 patients studied.⁴⁰ Pullar and colleagues assessed adherence in 26 patients by three methods. Poor adherence was identified in one patient based on an interview, in 6 patients based on pill counts and 11 patients based on blood tests.⁴¹ Only two studies have focused on biologic therapy. Adherence in 853 etanercept users and 141 infliximab users was assessed over a one year time period based on pharmacy dispensings with adherence $\geq 80\%$ occurring in 68 and 81% of users, respectively.³⁹ Wendling et al. reported nonadherence in only one of 41 infliximab users over a mean follow-up period of 15.3 months.⁴²

Discussion

This systematic review of the literature is the first to examine the current state of knowledge regarding the use of medications for the treatment of selected chronic inflammatory rheumatic conditions. Overall there were 20 studies that fulfilled criteria to be included in the review, the majority of which were focused on the treatment of rheumatoid arthritis. Many of the studies focused on treatments that are not commonly used today, including D-penicillamine and chronic high-dose salicylates. The studies used a variety of methodologies and populations. Overall, the highest rates of adherence were based on self-reports for a wide variety of medications, while the lowest adherence rates were for allopurinol based on pharmacy dispensings.

It is difficult to draw conclusions about medication adherence in the treatment of rheumatic conditions based on the studies evaluated. Studies varied in terms of study design, study populations, and definitions of adherence. For example the subjects in the studies could be new users, chronic users or all current users of the medications. Some patients were enrolled in clinical trials while other study populations were identified based on pharmacy dispensings and thus are more heterogeneous. Only a few studies evaluated whether there were differences in adherence based on gender, age and ethnicity of the population.^{27, 35} None of the studies evaluated the impact of patient costs on adherence. In addition, it is difficult to control for severity of disease, duration of disease and complexity of the treatment regimens in these patients.³⁹

There are advantages and disadvantages to the study designs employed. Patient interviews or self-administered questionnaire, which are relatively easy to obtain, may overestimate adherence.^{27, 31} Similarly, pill counts may also overestimate adherence if patients are aware it is being assessed.¹² Laboratory assays are influenced by individual variations in absorption, metabolism and excretion.³⁸ Participants in some of the studies that employed electronic devices to identify the openings of pill bottles were notified on how the devices worked which may have influenced the behavior of the patient.^{25, 35} In addition, opening the pill container does not guarantee the medication was ingested. Pharmacy records provide information on whether the medications were purchased but this does not necessarily equate with use. For example, patients may share medications, lose tablets or buy over the counter medications.¹² The challenges of evaluating adherence are exemplified in the work by Pullar and colleagues.⁴¹ Among a cohort of 26 rheumatoid arthritis patients over a 4 week period, adherence was reported as 96% based on self-report, 77% based on pill counts and 58% based on a laboratory assay measuring a metabolite of D-penicillamine. More recently Koneru and

colleagues observed differences in adherence measures in patients with systemic lupus erythematosus.⁴³ Among 41 patients prescribed prednisone, physicians rated 16 (39%) patients as adherent, patient self-report estimated 20 (49%) as adherent, and pharmacy data supported adherence in only 11 (27%).

Many of the studies evaluated adherence to one drug over a short period of time. Most patients with rheumatic conditions are on chronic therapy with multiple medications. In fact, increasing the number of medications and duration of therapy has been shown to decrease adherence.^{25, 41} The complexity of a treatment regimen also correlated with adherence with patients being less adherent to more complex treatment plans.⁴⁴ Unfortunately many inflammatory rheumatic conditions require complex treatment regimens. For example, consider the treatment of tophaceous gout in which patients take a chronic urate lowering medication (ULD) as well as prophylactic colchicine or an NSAID to prevent a flare when initiating the ULD. As sometimes happens, when the patients in this situation have a flare, they need to either increase the doses of their prophylactic medication or potentially add a corticosteroid as well as continue the ULD which most likely triggered the flare. Many patients may find it hard to follow the treatment due to both the complexity of the regimen and the realization that the medication used to treat the gout (the ULD) caused the disease flare.

Risk of side effects from medications is a common problem for patients with chronic rheumatic conditions. While not examined in the articles selected for this review, the occurrence of side effects is also likely to influence adherence.⁴⁴ For example, initiating high doses of corticosteroids for lupus nephritis is standard of care, yet it is highly likely that young women with the condition will purposefully be nonadherent with the regimen due to the visible effects of the medications. Few of the studies examined adherence with biologic therapy; however, route of administration may influence adherence with patients being reluctant to administer subcutaneous medications.³⁹

In summary, adherence with medical treatment has not been well examined in the chronic rheumatic conditions. The available evidence does suggest that nonadherence is a substantial problem. Clinicians should routinely address adherence issues during clinic visits. Providers need to negotiate with patients and tailor therapy to treatments patients are likely to adhere to. Given the cost and toxicity associated with the newer treatments for rheumatic disease, is it essential to assess whether patients truly failed adequate trials of standard therapy. In addition, more research is needed to investigate how to assess, predict and improve adherence. Standardized definitions of adherence as well as practical and valid methods for assessing adherence need to be generated. The prevalence and types of nonadherence and risk factors for nonadherence should be explored in more diverse populations. This will lay the foundation for randomized controlled clinical trials to validate strategies for improving adherence.¹⁴

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Table 1

Characteristics of the studies (N=20) evaluating drug adherence in rheumatic conditions.

Condition	Frequency of articles
Rheumatoid arthritis	11
Systemic lupus erythematosus	4
Gout	3
Juvenile idiopathic arthritis	2
Polymyalgia Rheumatic	1
Multiple inflammatory arthropathies	1
Medications	
DMARDs	9
NSAIDs and salicylates	7
Arthritis medications or medications in general	6
Glucocorticoids	4
Urate lowering medications	3
Biologic agents	2
Colchicine	1
Adherence evaluation	
Patient interview/questionnaire	9
Pharmacy records	4
Electronic device	3
Laboratory assay	3
Chart review	2
Pill counts	1
Physician assessment	1
Population size	
<50	7
50 to 200	10
200 to 1000	2
>1,000	3
Duration of monitoring	
≤1 month	3
1 to 6 months	1
6 months to 1 year	3
> 1year	6

Table 2
Adherence to treatments in a variety of inflammatory rheumatic conditions.

Reference	Medication *	Study size (n=)	Duration of observation	Adherence evaluation	Adherence (score or %)
Inflammatory arthritis					
Berry **31	NSAIDs and painkillers	37	N/A	Self-report	72
Berry **31	MTX, HCO, Prednisolone, SSZ, NSAIDs and painkillers	44	N/A	Self-report	99
Polymyalgia rheumatica					
De Klerk ²⁵	Prednisolone	17	6 months	Electronic device	88
Juvenile idiopathic arthritis					
Rapoff ³²	NSAIDs	48	28 days	Electronic device	52
Feldman ²⁴	Medications	175	12 months	Self-report	86-92 (range 0-100; 100 is perfect adherence)
Systemic lupus erythematosus					
Mosley-Williams ^{**27}	Lupus medications	112	N/A	Self-report	2.3-2.5 (range is 1-5; 1 is perfect adherence)
Adler ^{**26}	Medications	21	N/A	Physician assessment	48
Rojas-Serrano ^{**28}	Medications	180	N/A	Self-report	8.3 (range 0-10; 10 is perfect adherence)
Wang ²⁹	Antimalarials	156	Mean 6.9 years	Chart review	92
Gout					
De Klerk ²⁵	Colchicine	12	12 months	Electronic device	44
De Klerk ²⁵	Urate lowering therapy	17	12 month	Electronic device	74
Reidel ⁷	Allopurinol	5597	24 months	Pharmacy records	18
Sarawate ³⁰	Allopurinol	2405	24 months	Pharmacy records	26
Rheumatoid arthritis					
Taal ³³	Any medication	71	N/A	Self-report	93
Park ³⁵	Any medication	121	4 weeks	Electronic device	38
Tuncay ^{**36}	NSAIDs, prednisone, DMARDS	100	12 months	Self-report	30
Owen ^{**34}	NSAIDs and DMARDS	178	N/A	Self-report	64
Beck ³⁷	Salicylates	63	N/A	Laboratory assay	49

Reference	Medication *	Study size (n=)	Duration of observation	Adherence evaluation	Adherence (score or %)
Viller ³⁸	NSAIDs	429	3 years	Self-report	56
Viller ³⁸	Steroids	429	3 years	Self-report	65
Viller ³⁸	DMARDs	429	3 years	Self-report	59
De Klerk ²⁵	Diclofenac	13	6 months	Electronic device	68
De Klerk ²⁵	Naproxen	20	6 months	Electronic device	67
De Klerk ²⁵	SSZ	25	6 months	Electronic device	81
De Klerk ²⁵	MTX	23	6 months	Electronic device	55
Harley ³⁹	MTX	1668	1 year	Pharmacy records	64
Pullar ⁴¹	D-penicillamine	26	4 weeks	Self-report	96
Pullar ⁴¹	D-penicillamine	26	4 weeks	Pill count	77
Pullar ⁴¹	D-penicillamine	26	N/A	Laboratory assay	58
Doyle ⁴⁰	D-penicillamine	49	N/A	Laboratory assay	61
Harley ³⁹	Etanercept	853	1 year	Pharmacy records	68
Harley ³⁹	Infliximab	141	1 year	Pharmacy records	81
Wendling ⁴²	Biologic	41	15.3 months (mean)	Chart review and pharmacy records	98

* NSAIDs= nonsteroidal anti-inflammatory drugs; MTX: methotrexate; HCQ: hydroxychloroquine; SSZ: sulfasalazine; lupus medications were not specified in the manuscript; antimalarials included hydroxychloroquine and chloroquine.

** analyses were not stratified by medication