Title: The Duality of Economic Issues with Medication Non-Adherence in Patients with Inflammatory Arthritis

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ABSTRACT

Purpose of Review: In this review, we synthesize current data on non-adherence across inflammatory arthritides and explore 1) the effects of economic factors on non-adherence and 2) the impacts of non-adherence on economic outcomes.

Recent findings: Recent evidence demonstrates medication non-adherence rates as high as 74% in ankylosing spondylitis (AS), 90% in gout, 50% in psoriatic arthritis (PsA), 75% in systemic lupus erythematosus (SLE), and 82% in rheumatoid arthritis (RA).

Summary: The effects of socioeconomic factors have been studied most in RA and SLE but with inconsistent findings. Nonetheless, the evidence points to having prescription coverage and costs of treatment as important factors in RA and education as an important factor in SLE. Limited data in AS and gout, and no studies of the effects of socioeconomic factors in PsA, show knowledge gaps for future research. Finally, there is a dearth of data with respect to the impacts of non-adherence on economic outcomes.

Introduction

For many patients living with lifelong diseases, managing conditions and taking medications as prescribed ("adherence") is a challenge. Because patients rely on medications to relieve symptoms, continue participation in daily life activities and prevent the worsening of disease, medication non-adherence is especially problematic in inflammatory arthritis – a group of conditions that includes ankylosing spondylitis (AS), gout, psoriatic arthritis (PsA), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA). Evidence synthesis including those in gout (1), SLE (2), and RA (3-7) show that adherence is sub-optimal across many of these conditions. Also alarming is the impact of non-adherence on patient outcomes, such as increased hospitalizations and emergency department visits in SLE (8, 9), elevated serum uric acid levels in gout (10), and disease flares in RA (11).

Given the growing epidemic of non-adherence in inflammatory arthritides and the high costs of medications used to treat many of these conditions, particularly biologics, it is important to have a better understanding of associated economic issues. In our view, there is a duality of these issues as: 1) the effects of economic factors on non-adherence; and 2) the impacts of non-adherence on economic outcomes. Specifically, as one of the World Health Organization's 5 Dimensions of Adherence, soecioeconomic factors may have an effect on non-adherence through various mechanisms including affordability (e.g., cost of medications), access (e.g., having prescription coverage), or understanding of the medications and their use (e.g. low education level) (12). In 2013, Kardas et al. compiled findings across 51 systematic reviews on determinants of non-adherence to develop a taxonomy of factors for each of the World Health Organization's 5 dimensions (13). According to this taxonomy, socioeconomic factors include family support (e.g., family support in executing medication), family/caregiver factors (e.g., number of people in the household), social support, and social stigma of a disease, as well as those that are of particular relevance to our review –

costs of drug and/or treatment, prescription coverage, socioeconomic status, education, and employment status (13).

The other side of the issue is the economic consequences of non-adherence. In their 2014 review, Iuga and McGuire described a conceptual mechanism of how non-adherence compromises the effectiveness of treatment, leads to adverse health outcomes, thus increasing healthcare utilization and costs (12, 14). As such, there is potential economic impact of non-adherence on the health care sector, patient and family, as well as other sectors. **Figure 1** provides a conceptual framework of the duality of economic issues when considering non-adherence. Guided by this framework, our objective is to provide a synthesis of the current research on the burden of non-adherence in inflammatory arthritides as well as associated economic issues. While we focused our review on literature published in the past 5 years, in cases of limited data, we extended beyond this period.

Understanding Medication Non-Adherence

In keeping with calls in the literature to standardize the nomenclature of medication non-adherence (15-17), we outline the relevant definitions. Specifically, the term 'medication non-adherence' can refer to either: 1) *poor execution* or *implementation* of the prescribed treatment recommendation, leading to omitted or delayed doses which may interrupt drug action; and 2) stopping or *discontinuation* of the prescribed treatment, leading to transient or permanent interruption of drug action (18, 19). Medication *persistence* refers to the act of continuing treatment for the prescribed duration, and is reciprocal to discontinuation (15).

Also relevant to our review is *drug survival* – defined as the length of time from initiation to discontinuation of a particular treatment (20) – as it has been used to describe patterns of use of biologics in RA over the past several years and more recently in AS and PsA. In this context, drug

survival (as well as related terms, *treatment retention, treatment continuation*) is an alternative way to describe persistence and could therefore be considered as another measure of adherence (21). However, some scholars argue that the term drug survival excludes additional factors encompassing the complexity of adherence – such as the determinants of adherence and patient attitudes and beliefs (22). However, many argue that drug survival can be used as a general marker of treatment success which encompasses various components of patient adherence, side effects and drug efficacy (23). A final consideration is the directionality of reporting, that is, whether studies centered on 'adherence' (i.e., having 'good' behavior or outcome) or 'non-adherence', which has implications for consistency. For our purposes, we centered our review on 'non-adherence', and when feasible, converted and/or translated findings from included studies that have centered on 'adherence.'

Ankylosing Spondylitis

Affecting 0.1 to 1.4% of the population (24, 25), AS is characterized by inflammatory back pain, progressive bony fusion of the vertebrae, and arthritis in the hips, shoulders, or peripheral joints (24). 80% of cases present before 30 years of age and less than 5% after 45 years (26). According to recommendations of the Assessments in Ankylosing Spondylitis International Society and European League Against Rheumatism (EULAR), the primary goal of AS treatment is to maximize health-related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, and normalisation of function (27). Non-steroidal anti-inflammatory drugs (NSAIDs) as first-line therapy for pain and stiffness and physical therapy are mainstay treatment approaches in AS (28). Recently, treatment recommendations from the American College of Rheumatology (ACR) include the use of tumour necrosis factor (TNF) inhibitors (29).

Few studies have evaluated the burden of non-adherence to medication in AS. The earliest study was in 1996 by De Klerk et al. in the Netherlands which revealed low rates of NSAID non-adherence in 65 AS patients (20%) using electronic monitoring devices (30). The introduction of biologics led to studies of non-adherence with these agents in AS, including a 2006 Spanish study (31), a 2008 Norwegian study (32), and a 2009 Czech study (33). In 2013, a study from Argentina by Arturi et al. showed that non-adherence to pharmacological treatments (including NSAIDs, DMARDs, and biologics) in 59 AS patients was 25.4% based on self-reported questionnaires (34). However, more recent reports have reported higher non-adherence rates among AS patients. Betegnie's 2016 study from France used a questionnaire to understand why AS patients decide to discontinue biologic treatment. In this study, 74% of 351 AS patients discontinued their biologics at least once (35). Among these, 20% of discontinuations were the patients' decision with reasons including low level of pain, self-administration of biologics, negative beliefs about treatment, and lack of medical and social support. Finally, Lyu's 2016 study from Germany used electronic medical records to study persistence to subcutaneous biologic therapies among patients with rheumatic disease including 108 patients with AS (36). They reported 1-year discontinuation of 51.9% with mean treatment duration of 228.5 days (36).

As with the burden of non-adherence, data on the economics of non-adherence in AS is very limited. We identified a single 2013 study by Arturi et al. on the effects of economic factors on non-adherence, which primarily used self-reported questionnaires including the Compliance Questionnaire Rheumatology (CQR) to identify factors associated with non-adherence among 59 patients with AS in Argentina (34). While they observed lower number of years of education among non-adherent patients compared to adherent patients, this was not statistically significant (11.4 ± 4 vs. 12.4 ± 4 years, p-value >0.05) (34). Interestingly, a higher proportion of non-adherent patients reported

having health insurance compared to adherent patients, however this was also not statistically significant (72.7% vs. 53.5%, p-value >0.05) (34). Finally, there were no studies that have directly evaluated the economic impacts of treatment non-adherence in AS. Nonetheless, a 2009 cohort study of 310 AS patients in Argentina by Pavelka et al. reported that the proportion of fully employed patients increased from 48% at baseline to 63% after 1-year of therapy with anti-TNF agents (33).

Gout

Gout is the most common inflammatory arthritis that affects up to 3.8% of adults (37) and develops due to an excess of serum uric acid (SUA) levels which results in the formation of monosodium urate crystals (38) and, if left untreated, can cause severe inflammatory response leading to joint destruction (1). In addition, the disease is complicated by substantial cardiovascular, metabolic, and renal comorbidities (39). Both acute and chronic manifestations of gout are caused by deposition of monosodium urate crystals (38), and as such eliminating urate crystals by reducing urate levels essentially 'cures' the disease. The ACR (40) and EULAR (41) recommend the use of urate lowering therapies (such as allopurinol) as well as uricosuric agents for the management of gout.

Medication non-adherence in gout has been well described. In 2013, we published a systematic review investigating the burden, predictors, and impacts of non-adherence in gout (1). We identified 16 studies which used various methods of measuring non-adherence. Overal, the proportion of non-adherent gout patients ranged from 54 to 90%, highlighting that non-adherence is a significant problem in gout. Among included studies, older age, as well as having comorbid hypertension, was consistently shown to be positively associated with better adherence (1). In 2016, a retrospective study using a national administrative pharmacy claims database in Ireland demonstrated that, for all gout

patients initiating urate lowering therapies, 54.2% of patients discontinued treatment within 6 months (42). Indeed, these consistent reports of suboptimal treatment adherence in gout is alarming especially given the contribution of non-adherence to disease outcomes (43).

Despite the number of studies on the burden of non-adherence in gout, very few have reported on the effects of economic factors on non-adherence in gout or the economic impacts of non-adherence in gout. With respect to the former, in 2013, Zandman-Goddard et al. used administrative data from a health maintenance organization in Israel to identify predictors of non-adherence with allopurinol (44). Among these factors was socioeconomic status which was categorized into quintiles according to a poverty index that was based on household income, educational qualifications, crowding, material conditions, and car ownership (44). Compared to the reference category or the 3rd quintile, individuals in the 1st quintile (lowest SES) had a 21% higher odds of being non-adherent (OR, 1.21; 95% CI, 1.03-1.42) and those in the 5th quintile (highest SES) had a 61% lower odds of being non-adherent (OR, 0.39; 95% CI, 0.32-0.46) (44). Finally, we could not identify any study that has directly evaluated the economic impacts of treatment non-adherence in gout. Nonetheless, a study that has shown an indirect relationship is one by Halpern et al.'s 2009 cohort study which used administrative databases for a managed health care plan in the US (45). Specifically, authors first showed the relationship of a lower proportion of individuals non-adherent to allopurinol therapy (having medication possession ratio <0.80) achieving target serum uric acid level (<6.0 mg/dL) across three time periods – 27.8% non-adherent vs. 49.3% adherent in period 1, 22.5% vs. 51.8% in period 2, and 23.8% vs. 56.8% in period 3 (45). Afterwards, in both unadjusted and adjusted analyses, authors showed the relationship between lower serum uric acid levels and gout-related healthcare (including medical claims for office visits, outpatient hospital visits, emergency department visits, and inpatient hospitalizations) costs (45). Specifically, median costs for corresponding serum uric acid levels were

$167, $196, and $222 for <6.0 mg/dL, between 6.0 and 9.0 mg/dL, and ≥9.0 mg/dL, respectively. Multivariable models show that compared to individuals at the lowest serum uric acid level, gout-related healthcare costs for those at the highest serum uric acid level were 1.6 times higher (exponentiated coefficient, 1.576; 95% CI, 1.02-2.46) (45).

Psoriatic Arthritis

PsA is a chronic, seronegative inflammatory arthritis associated with psoriasis, a chronic autoimmune inflammatory skin disease (46). Estimated prevalence rates of PsA range from 0.04% to 0.1% (47). According the recommendations for the pharmacological management of PsA by EULAR, the goals of treatment are to maximize quality of life through control of symptoms, as well as prevention of structural damage and normalization of function and social participation through control of inflammation (48). Recommendations include use of traditional DMARDs as initial therapy followed, if necessary, with biologics (48).

Similar to AS, data on medication adherence in PsA is still emerging. However, the development of biologics, particularly anti-TNF therapies, has dramatically improved the management PsA, and several reports have examined non-adherence – largely, discontinuation of these therapies among patients. Prior studies including a Spanish study in 2006 (31), a Norwegian study in 2008 (32), and a UK study in 2009 (49) reported discontinuation rates ranging from 12% to 24.5% at 1-year with the most cited reasons for discontinuation as lack of efficacy and adverse events. In 2012, Chastek et al. used administrative data in the US and reported that among 346 PsA patients, approximately half discontinued their index anti-TNF therapy within 1 year. Pauses in therapy and therapy discontinuation were common, but more than 40% of patients restarted their index anti-TNF after

discontinuation (50). Finally, Lyu's 2016 study in Germany using an electronic medical record database including 197 PsA patients found that 42.1% of patients discontinued their anti-TNF therapies within 1 year with mean treatment duration of 264.1 days (36).

We could not identify any studies on the effects of economic factors on non-adherence in PsA or the economic impacts of non-adherence in PsA.

Systemic Lupus Erythematosus

SLE is a chronic systemic autoimmune rheumatic disease that specifically attacks collagen and results in multifarious clinical manifestations including joint pain, photosensitivity, malar rash, and clinical nephritis (51, 52). It occurs predominantly in women (approximately 9:1 female to male) during their childbearing years (53), with reported prevalence of 143.7 per 100,000 and incidence of 23.2 per 100,000 person-years (54). As there is no cure for SLE, the goals of treatment include decreasing autoimmunity to slow down disease progression and prevent damage to other organ systems from the downstream effects of SLE (53). The conventional option to achieve these goals among patients with SLE with minimal organ involvement is the long-term use of antimalarials, namely hydroxychloroquine and chloroquine (55, 56). It is recommended that SLE patients with multiple organ systems involved should additionally be taking other immunosuppressive medications (azathioprine, cyclophosphamide, methotrexate, chlorambucil, and cyclosporine) (55, 56).

Similar to gout, medication non-adherence has been well described in SLE. In 2008, Harrold et al. published a systemic review of medication non-adherence in selected rheumatic diseases which included four papers in SLE (57). However, reported non-adherence rates were largely inconsistent.

Updating this data, in 2017 we published a systematic review to investigate the burden and predictors of non-adherence in SLE and identified 11 studies which used various methods of measuring adherence. The percentage of non-adherent SLE patients ranged from 43% to 75%, studies consistently reporting that over half of patients are non-adherent (2). Furthermore, in this systematic review, we identified determinants of non-adherence including having depression and polypharmacy (2).

There are a few studies on the effects of economic factors on non-adherence in SLE and as such, we have included both earlier and more current studies in our review. Four studies including 2 in the US (58, 59) , 1 in Brazil (60), and 1 in Egypt (61) reported on the effect of education, albeit operationalized differently. For example, in a cross-sectional study of 32 patients with SLE in the US, Garcia-Gonzalez et al. reported a positive correlation between education (categorized as less than high school, high school, college, Bachelor's degree, advanced degree) and adherence as measured by the CQR ($r = 0.31$; $p<0.01$) (58). Using a combination of self-report questionnaire, chart review, and patient interviews, Oliveira-Santos et al., evaluated a variety of factors associated with medication non-adherence among 246 women with SLE in Brazil (62). In this sample, 37.8% had completed secondary education and the variable "schooling" was shown to have a negative association with adherence to SLE treatment (OR, 0.46; 95% CI, 0.21-1.00) in the final multivariable model, however authors did not indicate the reference category, limiting interpretation (62). Interestingly, a finding of this study were reasons individuals cited for having difficulty in "taking their medicines" which for our purposes may signal non-adherence, which include lack of money to purchase the medicine (52.4% of patients) and failure to receive the medicine free of cost from the Unified National Health System (6.4% of patients) (62). In Egypt, Koneru et al. evaluated determinants of non-adherence in 80 patients with SLE and reported that compared to individuals with >12 years of education, those with

≤12 years had a 4-fold odds (OR, 4.2; 95% CI, 1.6-8.4) of being non-adherent as measured by the CQR (63). In this study, authors also assessed socioeconomic status using a validated scale for health research in Egypt and showed that compared to patients at moderate and high status, those with very low and low socioeconomic status had 3.5 times the odds of being non-adherent (OR, 3.5; 95% CI, 1.6-7.9) (63). Finally in a recent study (2016) of 92 patients with SLE in Brazil, Prudente et al. showed that acquisition of medications at a high-cost pharmacy are more likely to be adherent (OR, 5.95; 95% CI, 1.02-34.69) (64).

Only two studies evaluated the economic impacts of non-adherence in SLE. In a 2009 cohort study of 834 patients with SLE in the US, Julian et al. showed that those with self-reported unintentional adherence had increased numbers of rheumatology visits, primary care visits, emergency department visits, and hospitalizations (**Table 2**) and were more likely to visit the emergency department (OR, 1.45; 95% CI, 1.04-2.04) as compared to patients who did not report adherence difficulties (9). Using US Medicaid data in 2015, Feldman et al. showed that among SLE patients on hydroxychloroquine, those who were classified as non-adherent (based on medication possession ratio [MPR] <80%) had higher incidence of SLE-related emergency department visits (incidence rate ratio [IRR] 1.60; 95% CI, 1.43-1.80) and SLE-related hospitalizations (IRR, 1.30; 95% CI, 1.18-1.44) compared to those classified as adherent (8). Similarly, among SLE patients on immunosuppressive medications, those who were classified as non-adherent had higher incidence of SLE-related emergency department visits (IRR, 1.69; 95% CI, 1.38-2.05) and SLE-related hospitalizations (IRR, 1.60; 95% CI, 1.34-1.91) (8).

Rheumatoid Arthritis

RA is a chronic autoimmune disease characterized by joint inflammation with pain, swelling, damage and disability. RA affects approximately 1% of the population with an increased prevalence in women and the elderly (65). Current guidelines recommend treating the majority of RA patients with disease-modifying anti-rheumatic drugs (DMARDs) in order to control symptoms, induce disease remission and to prevent disability (66, 67). Adherence to these prescribed drugs is essential in order to prevent irreversible joint damage (68-73). For patients with high disease activity or a suboptimal response to DMARDs, better disease control may be achieved by switching or adding a biologic agent to their therapeutic regimen (66, 67).

Amongst inflammatory arthritides, the burden of therapy non-adherence has been best described in RA with earlier syntheses including a systematic review in 2009 by Harrold and Andrade (74) and two reviews in 2010 by De Achaval and Suarez-Almazor (75) and Salt and Frazier (3) – all based on DMARDs. Various adherence measures were used across studies but nonetheless, reported non-adherence rates as high as 70% signals an important therapeutic challenge in RA. With respect to biologics, prior systematic reviews by Koncz in 2010 (21) and Blum in 2011 (76) similarly concluded that non-adherence to biologic therapies in RA is a problem. More recently, in 2012 van den Bemt et al. published a critical appraisal of the literature on non-adherence to both DMARDs and biologics, reporting rates ranging from 20% to 70% (6). In 2014, we published a review of the economics of non-adherence to biologics in patients with RA which included a synthesis of non-adherence rates which ranged from 13% to 76% among studies that explicitly evaluated adherence (n = 7) and 20% to 82% among studies that evaluated drug survival (n=16) (5). In this synthesis of the evidence, we observed that etanercept had the highest persistence rates, in general, compared to infliximab and adalimumab (5).

As with the burden of non-adherence, the effect of various economic factors on non-adherence in RA has been evaluated in a number of studies and synthesized in aforementioned reviews (4-6, 75). We tabulated findings from these prior reviews as the number of studies that have reported lack of an association or an association with various socioeconomic factors and non-adherence (**Table 3**). Data on socioeconomic status, employment status, and education are inconsistent; for example, in their 2012 review, van dem Bent et al. identified 5 studies that have reported a lack of association of education with non-adherence but also 3 studies that have reported an association (6). Having prescription coverage was the only factor that was consistently shown to have an association with non-adherence across reviews.

Studies exploring the relationship between economic outcomes and medication non-adherence in RA are limited. A 2009 study by Tang et al. compared treatment persistence in patients taking anti-TNF therapies (adalimumab, etanercept, or infliximab) in combination with methotrexate and the effects of persistence on overall healthcare costs (77). Across patients, those with treatment persistence greater than 80% (persistent) had higher mean total health care costs compared with those with treatment persistence less than 80% (non-persistent), largely driven by pharmacy costs. However, nonpharmacy costs including inpatient, other outpatient, and laboratory services were lower in the first cohort. Importantly, emergency department costs and inpatient services were reduced by over 60% among persistent patients. Finally, persistence with medication was associated with lower healthcare costs, lower comorbidity levels and lower disease stage score. Also in the US, Borah et al. found that total health care costs were higher among RA patients who were adherent to their subcutaneous anti-TNFs compared to those who were non-adherent; however, adherent patients had fewer ambulatory, emergency room, and inpatient visits compared to non-adherent patients (78). Finally, a 2017 report from the Netherlands by Pasma et al. explored the relation

between non-adherence to DMARDs and healthcare costs in a group of 206 patients, 74.2% of which had RA, 20.9% PsA and 4.9% undifferentiated arthritis (79). Their study demonstrated that as the percentage of adherent patients decreased from 100% to 60% (40% of the amount of medication not taken), the mean healthcare costs (including costs for comorbidities, referrals, anti-TNF therapies, synthetic DMARDs and rheumatology outpatient clinic as measured by hospital files) increased. Furthermore, in multivariable models, authors showed the statistically significant associations between non-adherence and rheumatology outpatient clinic costs, rheumatology-related costs, and total hospital costs. This was the first study of its kind to demonstrate that that non-adherence is associated with hospital healthcare costs in the first year of treatment for arthritis patients. Beyond hospital files, however, economic impacts excluded from the study encompass medical costs made outside the hospital, travel costs and costs of productivity loss.

Discussion

In this review, we synthesized current data on non-adherence across inflammatory arthritides – confirming that non-adherence is indeed sub-optimal in gout, SLE, and RA - diseases where it has been well described and highlight emerging evidence for less studied diseases of AS and PsA. The effects of socioeconomic factors have been studied most in RA and SLE but with inconsistent findings. Nonetheless, the evidence points to having prescription coverage and costs of drug/treatment as important factors in RA and education as an important factor in SLE. Limited data in AS and gout, with only 1 study identified for each, and no studies of the effects of socioeconomic factors in PsA show knowledge gaps for future research. Perhaps one of the key findings of our review is limited data across inflammatory arthritides on the impacts of non-adherence on economic outcomes. Indeed, a comprehensive understanding of the burden of non-

adherence in inflammatory arthritis also needs to consider its impacts particularly on costs to the patient, the health care system, and society.

Conflict of Interest

Natasha Campbell, Khalid Saadeldin, and Mary A. De Vera declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Table 1. Studies of Effects of Socioeconomic Factors on Non-Adherence in Inflammatory Arthritides

Study	Country	Design	N	Drug	Economic Factor	Outcome
AS						
Arturi 2013	Argentina	cross-sectional	59	NSAIDs DMARDs anti-TNFs	a. education (years) b. health insurance (% yes)	**non-adherent vs adherent** a. 11± 4 vs 12.4 ± 4 yrs, p >0.05 b. 72.7% vs 53.3 %, p >0.05
Gout						
Zandman-Goddard 2013	Israel	cohort	7,644	allopurinol	SES (quintiles)	**non-adherent** 1st (<8): OR, 1.21; 95% CI: 1.03-1.42 2nd (9-11): OR, 1.12; 95% CI: 0.95-1.31 3rd (12-13): Ref 4th (14-16): OR, 0.57; 95% CI: 0.48-0.68 5th (17-20): OR, 0.39; 95% CI: 0.32-0.46
PsA – No studies						
SLE						
Garcia-Gonzalez 2008	US	cross-sectional	32	NS	education	**adherence** r=0.31, p <0.01
Koneru 2008	US	cross-sectional	63	NS	high school diploma (vs. no)	**non-adherence** a. prednisone (less likely) b. HCQ (no difference)
Oliveira-Santos 2011	Brazil	cross-sectional	246	NS	a. schooling	**adherence** OR, 0.46; 95% CI, 0.21-1.00 **reasons for difficulty taking medicines** lack of money (52.4%) failure to receive free of cost (6.4%)
Abdul-Sattar 2015	Egypt	cross-sectional	80	NS	a. SES scale for health research b. education level	**non-adherence** a. very low/low: OR: 3.5 (1.6-7.9) moderate/high: OR: 1.0 b. ≤12 yrs: OR: 4.2 (1.6-8.4) >12 yrs: OR: 1.0
Prudente 2016	Brazil	cross-sectional	37	NS	high-cost pharmacy	**non-adherence** PR: 5.95; 95% CI: 1.02-34.69

Abbreviations: SES – socioeconomic status

Table 2. Studies of Economic Impacts of Non-Adherence in Inflammatory Arthrides

Study	Country	Design	N	Drug	Economic Outcome	Results
AS						
Pavelka 2009**	Argentina	cohort	310	anti-TNF	ability to work	baseline 48%, 1-year (on anti-TNF) 63%
Gout						
Halpern 2009***	US	cohort	18,243	allopurinol	gout-related health costs	SUA<6.0: median $167 6.0≤SUA<9.0: median: $196 SUA≥9.0: median: $222
PsA – No studies						
SLE						
Julian 2009	US	cohort	834	NS	healthcare utilization a. rheumatology visits b. primary care visits c. ED visits d. hospitalizations	adherent/non-adherent a. 3.24 ± 3.19/ 4.34 ± 6.93; p=0.005 b. 3.80 ± 6.43/ 4.78 ± 6.24; p=0.03 c. 0.74 ± 3.68/ 1.31 ± 3.04; p=0.02 d. 1.53 ± 1.04/ 1.77 ± 2.20; p=0.33
Feldman 2015	US	cohort	a. 9600 b. 3,829	a. hydroxychloroquine b. ISM	healthcare utilization a1. ED visits a2. hospitalizations b1. ED visits b2. hospitalizations	adherent (ref) a1. IRR: 1.60; 95% CI: 1.43-1.80 a2. IRR: 1.30; 95% CI: 1.18-1.44 b1. IRR: 1.69; 95% CI: 1.38-2.05 b2: IRR: 1.60; 95% CI: 1.34-1.91
RA						
Tang 2008	US	cohort	1,242	adalimumab etanercept infliximab	costs a. total healthcare b. pharmacy c. inpatient d. physician visit e. ED visit f. laboratory	adherent/non-adherent a. $19,271.53/$15,598.46; p<0.001 b. $16,180.61/$10,997.49; p<0.001 c. **$600.96/ $1,740.18; p=0.03** d. $998.63/ $1,220.38; p=0.022 e. $23.21/ $72.94; p=0.041 f. $55.14/ $74.20; p=0.015
Borah 2009	US	cohort	3,829	a. etanercept b. adalimumab	total health care costs	adherent/ non-adherent a. $24,783/ $20,476; p=0.0001 b. $25,667/ $20,080; p<0.0001
Pasma 2017	Netherlands	cohort	206	methotrexate prednisone sulfasalazine hydroxychloroquine leflunomide	costs a. rheumatology outpatient clinic b. rheumatology-related c. total hospital	non-adherence a. β = 0.253; p= 0.001 b. β = 0.181; p = 0.020 c. β = 0.188; p = 0.006

*: Centered on 'non-adherence' for purposes of this review and as such, any studies reporting on adherence were converted/translated; **not a direct study of economic impact of non-adherence and not feasible to convert/translate but nonetheless included given limited data; ***not a direct study of economic impact of non-adherence but in same paper, authors showed relationship between adherence and SUA levels which could then be extrapolated to SUA levels and gout-related health costs;

Table 3. Number of Studies Reporting Association Between Socioeconomic Factors and Non-Adherence in Rheumatoid Arthritis from Prior Reviews

Socioeconomic Factor	De Achaval 2010		van dem Bent 2012		Pasma 2013		De Vera 2014	
	no association (n)	association (n)	no association (n)	association (n)	no association (n)	association (n)	no association (n)	association (n)
cost of drug/treatment		1	1	1		1		2
prescription coverage		**1**		**1**		**1**		**1**
socioeconomic status		1	3		3	1		-
employment status	-	-	1	1	3		1	
education		1	5	3	5	2		-

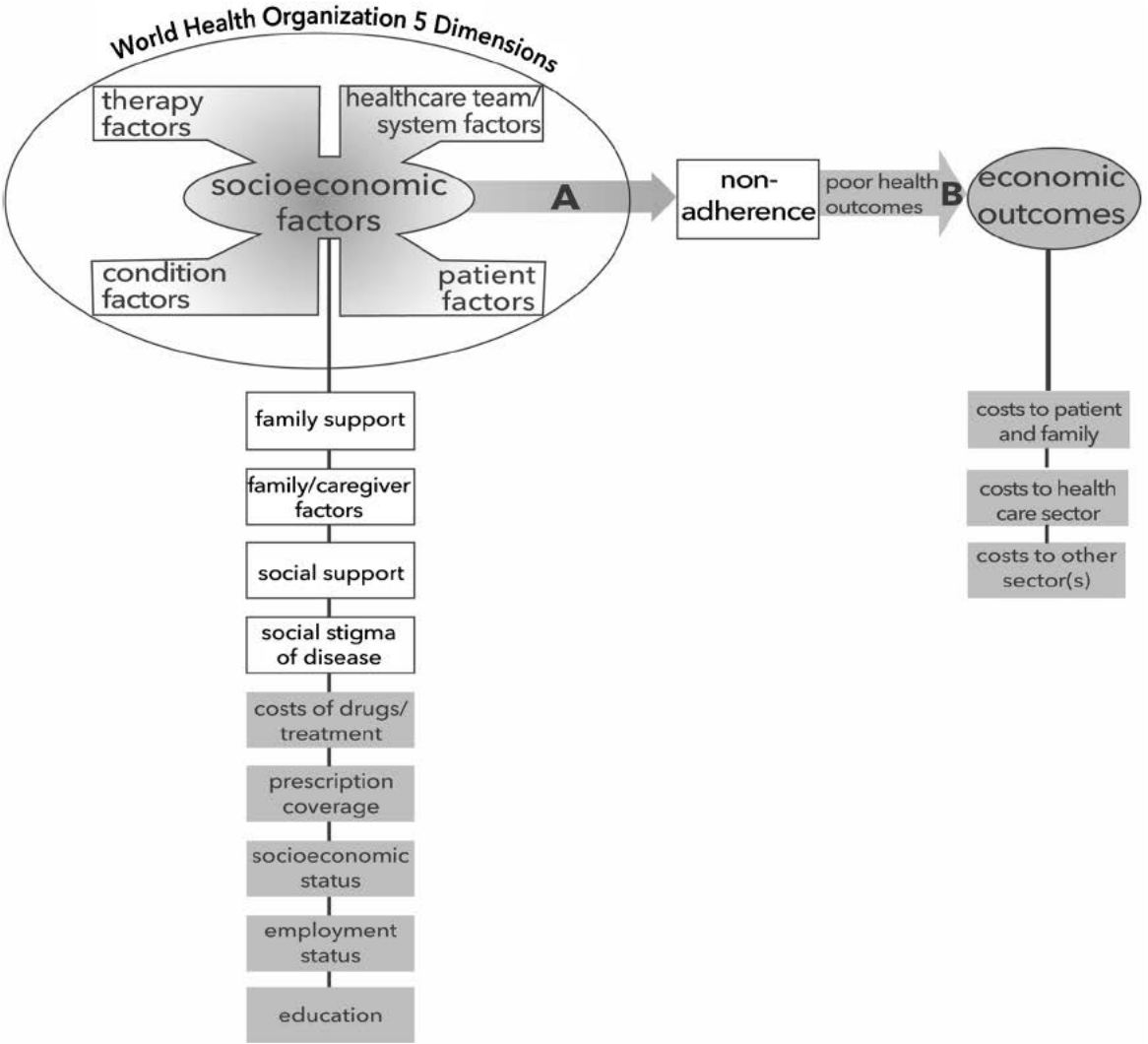

Fig. 1 Conceptual framework showing **a** the effects of socioeconomic factors on non-adherence and **b** the impacts of non-adherence on economic outcomes (in developing this framework, we integrated the World Health Organization's five dimensions of adherence with Kardas' taxonomy of factors; socioeconomic factors relevant to our review are shaded in light gray)