The Rate of Adherence to Antiarthritis Medications and Associated Factors among Patients with Rheumatoid Arthritis: A Systematic Literature Review and Metaanalysis

Anat Scheiman-Elazary, Lewei Duan, Courtney Shourt, Harsh Agrawal, David Ellashof, M. Cameron-Hay, and Daniel E. Furst

ABSTRACT. ***Objective.*** Reported adherence in rheumatoid arthritis (RA) varies widely (10.5–98.5%). Variability may result in part from different methods used to measure adherence. Our aims were to quantify adherence to antiarthritis medications for each method and to identify variability and associated factors.

Methods. The systematic literature review examined PubMed, the Cochrane central database, and article reference lists from 1970 to November 2014. Papers with medication adherence data (disease-modifying antirheumatic drugs, steroids, and nonsteroidal antiinflammatory drugs) in adult patients with RA or data on associated factors were included. Adherence rate was recorded for each method. Random-effect metaanalysis estimated adherence for different evaluation methods.

Results. Adherence rate was 66% (95% CI 0.58–0.75). There were no differences in adherence among different measurement methods (interview, questionnaires, etc.). Regression analysis showed that adherence decreases during followup. Among 100 possible factors potentially effecting adherence, 7 adherence-associated factors were found in at least 2 different studies. These were the use of infliximab compared with etanercept or methotrexate (MTX), use of MTX compared to sulfasalazine or to etanercept, belief in the necessity of the medications, older age, and white race.

Conclusion. Overall adherence rate was 66%. We suggest that readers appraise adherence studies according to the medications evaluated, the validity of the method, and the scales and cutpoints. (First Release February 15 2016; J Rheumatol 2016;43:512–23; doi:10.3899/jrheum.141371)

Key Indexing Terms:
RHEUMATOID ARTHRITIS RISK FACTORS ADHERENCE
METAANALYSIS MEDICATIONS

Adherence was defined by the World Health Organization (WHO) 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 healthcare provider[1]. As the WHO report stated, "Poor adherence to long-term therapies severely compromises the effectiveness of treatment...[1]" Therefore, it is important to have a firm understanding of measurement and determinants of adherence in rheumatoid arthritis (RA). The exact prevalence of adherence to medications in patients with RA is unknown. Variability exists regarding apparent adherence among literature reports, and results vary from 10.5% to 98.5%[2] across studies. This variability may result in part from different methods used to measure adherence[2]. Definition of adherence, type of medication, etc., may be involved as well. Further, little is known about predictors for adherence in RA[3]. Our primary aim was to determine, in RA, the rate of adherence to antiarthritis medications according to the different methods used to measure adherence. We hypothesized that adherence rate is influenced by the method used to measure it.

Our secondary aims were to identify the variability among studies and predictors for adherence.

This is, to the best of our knowledge, the first attempt to estimate adherence rate in RA, both cumulative and

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separately, for different methods used to measure adherence, including the influence of duration of followup. We also demonstrate the variability of the cutpoints used in different studies to define adherence. Finally, we update the previous review[3] that summarized the literature on risk factors for adherence up to 2011.

MATERIALS AND METHODS

Information sources. The systematic literature review (SLR) examined the Medline, Scopus, Cochrane central, and CINAHL databases from 1970 to November 2014 (Supplementary Data 1 available online at jrheum.org) to identify adherence studies to medications in adult patients with RA. Associated reference lists were searched. Only English literature was included. Reviews, case reports, letters, and editorials were not included as primary data. Reviews were used to identify relevant articles and to test the search strategy. Both observational data and data from control groups of randomized controlled trials (RCT) were included.

Study selection and data extraction. All abstracts or titles were screened for potential inclusion by 2 authors independently (Table 1). There was a 93% agreement by the primary readers. After screening of titles and abstracts, eligible papers were fully read and evaluated independently by 2 investigators for further eligibility using standardized data extraction forms (Table 1). Discrepancies not resolved by consensus were adjudicated by a third author (DEF). Data were sought for type of RA population, country, study design, timepoint when adherence was assessed, outcome (percent of adherent/compliant patients), and factors associated with adherence. As a result of careful extraction of the articles as well as reviews[6,7], variability within studies was identified according to 5 domains: type of medications, length of drug use, cutpoints defining adherence, ways of defining adherence, and method used to measure adherence.

Table 1A. Inclusion criteria.

1. Patients: with RA (either defined by the American College of Rheumatology criteria or as defined in the articles), aged ≥ 18 years of age.
2. Intervention: Not applicable.
3. Comparator: Not applicable.
4. Outcome: papers that reported adherence/compliance data with disease-modifying antirheumatic drugs or other antiarthritis medications*, such as nonsteroidal antiinflammatory drugs and steroids, or factors associated with adherence.
5. Study design: observational studies and controlled clinical trials (only the control group).

* As per author. RA: rheumatoid arthritis.

Table 1B. Exclusion criteria.

1. Studies on adherence to nonmedication therapy or general recommendations (e.g., appointments, exercise, splints, or non-antiarthritic medications (e.g., antihypertensive)[4].
2. Articles on persistence, discontinuation, switching, treatment gap, or retention rate*.
3. Reviews, case reports, letters, and editorials were excluded from the analysis, but used to search references lists.
4. Articles that used the term "adherence," but actually measured persistence or retention rate or treatment gaps.
5. Articles from which specific information on RA could not be extracted (e.g., papers contained data on a mix of systemic lupus erythematosus or RA, but there was not a breakdown of adherence or factors by diseases)[5].
6. Duplicates.
7. Papers from which neither adherence nor associated factors could be extracted[5].
8. When adherence was defined only according to physician evaluation [level of compliance was determined by physician ratings of patients, but no corroborating method(s) such as questionnaires, pill counts, etc.][4].
9. A cutpoint to define adherence was not used.
10. Articles not in English.

* Persistence represents the time over which a patient continues to fill a prescription. Discontinuation is a measure of persistence that includes number of days to discontinue the medication. RA: rheumatoid arthritis.

Variability across studies was evaluated according to 3 domains: the method used to measure adherence (questionnaire, etc.), the type of questionnaires used, and the cutpoints to define adherence. An attempt to contact authors was made if further data were needed.

Papers with lower cutpoints compared with most other papers were excluded to reduce variability[8,9,10]. Nevertheless, they were evaluated for associated factors if they included relevant data. Some studies used verbal and not a numerical scale, such as "taking medications none/some/most/all of the time". Since most papers used the general concept that adherent patients take their medications most of the time, we considered "taking medication most or all of the time" as relatively high cutpoints.

We used the cutpoints suggested by the authors in their articles for any dichotomizations.

Papers were assigned to subgroups according to the method used to measure adherence. When intrastudy variability was found, we chose the result most congruent with the other studies in each subgroup. In studies that measured adherence at multiple timepoints, we used only the first measurement.

If studies reported the percent of nonadherent patients, we used the formula:

$$100 - \%\ \text{nonadherent patients} = \%\ \text{adherent patients}$$

We used the terms reported by the original authors for describing compliance or adherence, as suggested in the WHO report[1].

Methodological process for exploring the factors associated with adherence. A list of factors that were examined for possible association with adherence was produced through a literature search. These included age, sex, disease outcomes, etc. Risk factors were categorized as either associated (positively or negatively) or not associated with adherence. All factors were listed in a table that summarized which study examined each factor. Identical factors from different studies were collapsed. Positive association with adherence was considered as negatively associated with nonadherence only if the factor was a dichotomous variable (for example, male/female). Factors were categorized into 5 groups according to the 2003 WHO report[1].

Quality assessment. After reviewing several systems for quality assessments [Newcastle-Ottawa quality assessment scale, the UK National Institute for Health and Care Excellence (NICE) guidelines, the Grading of Recommendations Assessment, Development, and Evaluation], we chose the one for observational studies designed specifically for adherence[3]. Studies were high quality if at least 4 of 5 essential questions regarding participation rate (≥ 80%), reproducibility of method, reduction of recall bias, and selection bias (using consecutive or representative samples) were affirmatively answered, and the total score was at least 7 out of 10. The NICE guidelines were used for RCT, examining for selection bias, performance bias, attrition bias, and detection bias. RCT were considered high quality if at least 3 criteria were fulfilled.

Statistical analysis. Data were collected and reported based on the recommendations for the Meta-analysis by Observational Studies in Epidemiology, because most of the studies were observational, and we did not examine studies evaluating healthcare interventions.

Qualitative assessment of heterogeneity. The included trials were heterogeneous in population, methods to measure adherence, scale, and cutpoints used. Statistical heterogeneity was examined using the I^2 statistic. A value > 50% represented substantial heterogeneity.

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Between-study heterogeneity was assessed by the Q-statistic test and statistic. P values < 0.1 were considered statistically significant.

The included studies were detailed according to design, populations, quality assessment, and method used to measure adherence (Table 2 and Table 3).

Within each method of measurement, if heterogeneity was low, we planned to apply the fixed-effects model. Otherwise, random-effect model using the restricted maximum likelihood methods was applied to estimate percentage of adherence. Forest plots were generated to summarize the overall estimated proportion and the estimated proportion stratified by measurement method based on their fitted model. Influential case diagnostics were performed to test outlying cases. We had planned to perform sensitivity analyses by implementing the leave-one-out diagnostics for each study. We had planned to perform a weighted linear regression using sample size as

Table 2. Baseline characteristics.

Studies	n	Population, Country	Age, Yrs, Mean (SD)	Disease Duration, Yrs, Mean (SD)	Followup	Design	Medications	Quality
Borah, *et al*[11]	2537*	Medical database, USA	49.18 (13.25)[&]	NS	NA	Retrospective	ADA, ETN	High
Cannon, *et al*[12]	455	VARA registry Veterans cohort, USA	64 (11)[^^^]	9.4 (10.3)	NA	Retrospective	MTX	High
Li, *et al*[13]	2638	Non-institutionalized Medicaid patients, USA	54.9 (16.6)[&]	NS	NA	Retrospective	ANA, ETN, IFX	High
Harley, *et al*[14]	2662	Medicare or commercial enrollees, USA	47.4 (12.6)[&]	NS	NA	Retrospective	MTX, ETN, IFX	High
Contreras-Yanez, *et al*[15]	93	Early RA, Mexico	40.8 (13.9)	Early	6 mos	Prospective	DMARD[@]	Low
Salt and Frazier[16]	108	University clinic, USA	52 (13)	9.7 (9.8)	NA	Cross	Oral DMARD, biologics, steroids[@]	Low
van den Bemt, *et al*[2]	228	Outpatients, Netherlands	56.2 (12.2)	4.6 (3.3)	NA	Cross	DMARD	High
Neame and Hammond[17]	331	Outpatients, UK	NS[##]	NS	NA	Cross	NS[@]	Low
Treharne, *et al*[18]	85	Outpatients, UK	58.8 (12.64)	10.29 (9.93)	NA	Cross	DMARD, NSAID, steroid[@]	Low
Tuncay, *et al*[19]	86	Outpatients, Turkey	49.3 (± 11.8)	9.2 (± 7.1)	12 mos	Prospective	NSAID, CS, DMARD	Low
Owen, *et al*[20]	178	Community-based population, Australia	60 (51.8–70)[###]	NS	NA	Cross	NSAID, CS, SAARD	Low
Lee and Tan[21]	108	Hospital outpatient clinic, New Zealand	NS	9.6 (8.5)[$]	NA	Cross	Antirheumatic tablets	Low
Lorish, *et al*[22]	200	Outpatients, USA	51 (27)	9.5 (6.2)	NA	Cross	Arthritis medications	Low
Viller, *et al*[23]	556	Early disease, France, Norway, Netherlands	NS	2.1 (1.4)	36 mos	Prospective	Steroids, NSAID	Low
Pullar, *et al*[24]	26	Active RA, UK	59 (26–73)***	NS	NA	Cross	D-Pen	Low
Brus, *et al*[25]	33	Outpatient, Netherlands	58.7 (9.2), in the control	Diagnosis ≤ 3 yrs	6 mos	RCT prospective	SSZ	Low
Park, *et al*[**26]	121	Community dwelling, USA	Range 34–84 (Mean NS)	3.8	1 mos	Prospective	Arthritis medications, other**	High
Hill, *et al*[27]	49	Outpatient clinic, UK	62[$$$]	12 (0.33–45)[$$$]	6 mos	RCT	D-Pen	Low
Tkacz, *et al*[28]	3892, 2099 for ETN	Database of insured individuals, USA	51.1	NS	NA	Retrospective	ADA, ETN, golimumab	High
Jinnett and Parry[29]	695[!!!!]	Research database, USA	52.3 (9.5)***	NS	NA	Retrospective	Oral DMARD, Biologics	Low
Esposti, *et al*[30]	438	Administrative database, Italy	NS	NS	NA	Retrospective	ADA, ETN, IFX	Low
Bluett, *et al*[31]	286	Outpatient clinic, UK	58 (50.2–64.5)****	7 (3–15)****	6 mos	Prospective	ETN, ADA, certolizumab, golimumab	Low
Waimann, *et al* [32]	111	Outpatient clinic, USA	107	8 (6)	2 yrs	Prospective	MTX, LEF, HCQ, SSZ, prednisone	Low
van den Bemt, *et al*[33]	50	Outpatient clinic, Netherlands	55.2 (12.4)	4.6 (3.5)	NS	Prospective interventional	Oral DMARD	Low
Grijalva, *et al*[34]	6018	TennCare database, USA	NS	NS	NA	Retrospective	DMARD	High
Grijalva, *et al*[35]	14,586	TennCare database, USA	55 (45–64)***	NS	NA	Retrospective	DMARD, CS	Low
De Klerk, *et al*[36]	81	Outpatient clinic, Netherlands	60 (14)	NS	NA	Cohort study	NSAID, SSZ, MTX	High
Curkendall, *et al*[37]	2285	MEDSTAT database, USA	54 (± 12)	NS	NA	Retrospective	ETN, ADA	High
Doyle, *et al*[8]	59	Outpatient clinic, UK	62.1 (37–80)[&&&]	NS	NA	Cross	D-Pen	Low
de Thurah, *et al*[9]	85	National database, Denmark	63 (32–80)***	NS	9 mos	Prospective	MTX	High
Beck, *et al*[10]	63	Outpatient clinic, USA	Mean 57	Mean 10.4	68 days	Prospective	Salicylate	Low

* N for ETN was 2537, total n was 3829. ** Separate analysis showed no difference across type of medications. [@] Did not specify which medications in the Q. [$] 9.6 (8.5) for compliant patients, 9.9 (9.9) for noncompliant. [^^^] 64 (11) for adherent patients, 62 (12) for nonadherent. [&] For ETN. [##] 49.5% were over 65 years. [###] 60 (51.8–70) for compliant, 65 (55.8–70.3) for noncompliant patients, median (interquartile range). [$$$] Median for control group. *** Median (range). **** Median (interquartile range). [&&&] Mean (range). [!!!!] N = 447 for the first year. RA: rheumatoid arthritis; NS: not stated; NA: not applicable; RCT: randomized controlled trials; ADA: adalimumab; ETN: etanercept; MTX: methotrexate; ANA: anakinra; IFX: infliximab; DMARD: disease-modifying antirheumatic drugs; NSAID: nonsteroidal antiinflammatory drugs; CS: corticosteroids; SAARD: slow-acting antirheumatic drugs; D-Pen: D-penicillamine; SSZ: sulfasalazine; LEF: leflunomide; HCQ: hydroxychloroquine; cross: cross-sectional.

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Table 3. Definitions, cutpoints, and percent adherence/compliance across studies. Percent of adherent patients across studies that were included in the metaanalysis. Studies were placed into subgroups according to the method used to measure adherence. Scale and cutpoints used to rate adherence are also shown.

Study	Outcome	Definition/scale	Cutpoint for Adherence/compliance	Adherence, %
Prescription claims				
Borah, *et al*[11]	Adherence	MPR defined as the total days during followup period that the patient had a supply of the index medication/365 × 100.	MPR ≥ 80%	48.6 for ETN
Cannon, *et al*[12]	Adherence	MPR defined as the number of prescribed days of MTX during a course divided by total duration of days of the course.	MPR ≥ 80%	84 full cohort
Li, *et al*[13]	Adherence	PDC defined as the number of days covered with biologic/365 days.	PDC ≥ 80%	32 for ETN
Harley, *et al*[14]	Compliance	Compliance ratio-number of therapy administrations or filled prescriptions divided by the expected number.	Compliance ratio ≥ 80%	68 for ETN
Tkacz, *et al*[28]	Adherence	MPR defined as the sum of the days' supply of the index treatment divided by the duration of treatment; PDC was also calculated, adjusted for double-counting of covered days.	MPR ≥ 80%	61.8 for ETN
Jinnett and Parry[29]	Adherence	The ratio of days in possession of a DMARD in a given year (no. days supplied with DMARD) divided by the no. days in the reference year, for individuals with at least 1 DMARD prescription fill in that year.	MPR ≥ 75%	52.1
Esposti, *et al*[30]	Adherence	PDC = total mg of the drug prescribed/defined daily dose; total coverage (%) = sum of prescription coverage (days)/duration of the followup period (365 days) × 100.	> 80% of the followup period was covered by drug dispensation	31 for ETN
Questionnaires				
van den Bemt, *et al*[33]	Adherence	Questions on taking medications and missing doses (4-point scale, do not agree at all–agree very much).	CQR score ≥ 80%	70
Contreras-Yanez, *et al*[15]	Adherence	Adherent was defined when either boxes 3 (almost always) or 4 (always) were filled for items 10, 11, and 12 (in the past 2 mos, I took my medication exactly at the days/day times/the precise amount indicated by my rheumatologist).	NA	80.6
Salt and Frazier[16]	Adherence	Forgot to take, alter dose, stop taking, miss a dose, etc. Five-point scale; never to very often.	MARS-9RA scale ≥ 86%	90.7 previous cutpoint
van den Bemt, *et al*[2]*	Adherence	Questions regarding taking medications and missing doses (4-point scale, 0 = strongly disagree, 3 = strongly agree).	CQR score ≥ 80%	68 for CQR
Neame and Hammond[17]	Adherence	I often do not take my medicines as directed (5-item scale: strongly disagree, disagree, neither agree nor disagree, agree, strongly, agree). Adherence was defined as strongly disagree or disagree.	NA	91.8
Treharne, *et al*[18]	Adherence	How often they forget to take medications/miss/adjust a dose (5-point scale from very often to never). Adherent patient was defined as rarely or never miss a dose.	NA	90.6, 80% cutpoint
Bluett, *et al*[31]	Adherence	A classification of adherence was given if the injection was administered by the patient on the day agreed with the healthcare professional.	NA	84.7
Interview				
Tuncay, *et al*[19]	Compliance	Questions regarding dose and timing (4-item scale: strictly, quite, not really, not at all). Compliant patients were defined as strictly or quite.	NA	52.3
Owen, *et al*[20]	Compliance	Compliant patient claimed that they did not alter the dose of their medication from their prescriber instructions.	NA	63.5
Lee and Tan[21]	Compliance	Did you take your antirheumatic tablets all of the time, most of the time, some of the time, or never? Adherence was defined as most or all of the time.	NA	61.1
Lorish, *et al*[22]	Adherence	Missed at least 1 dose during the last mo (dose not taken within 4 h of the prescribed time).	NA	77.5
Viller, *et al*[23]	Compliance	Do you always take your drugs exactly on time and at the dosage recommended? Four-point scale: not at all, not exactly, fairly exactly, exactly. Patients who answered yes, exactly to both questions were classified as compliant.	NA	57
Pullar, *et al* [24]^	Compliance	Noncompliance was defined as admission in interview.	NA	96
Pill count				
Brus, *et al*[25]	Compliance	No. tablets taken divided by the no. tablets prescribed.	≥ 80% was defined as high compliance	87
Pullar, *et al*^[24]	Compliance	Pill count: compliant patients were defined as "returned tablet count indicating that more than 85% of the prescribed dose had been taken."	Pill count ≥ 85%	76
MEM				
Park, *et al*[26]^	Adherence	If a subject took an accurate no. doses on any given day, they were considered adherent.	NA	95.4

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Table 3. Continued

Study	Outcome	Definition/scale	Cutpoint for Adherence/compliance	Adherence, %
Waimann, *et al*[32]	Adherence	The total no. days or weeks with the correct no. doses divided by the total no. monitored days, multiplied by 100.	Took DMARD as prescribed at least 80% of the time	21 DMARD
Drug level				
Pullar, *et al*[24]^	Compliance^	Compliance was defined by phenobarbitone LDR = PB concentration divided by daily PB dose.	PB LDR ≥ 85% of the age-adjusted lowest value found in a group of 40 volunteers	58
Hill, *et al*[27]	Adherence	Poor adherence was defined as PB LDR (the ratio of phenobarbitone blood levels to prescribed dose) less than 85% of that prescribed.	PB LDR ≥ 85%	84 analysis 1[#]

[#] Analysis 1 included any patient who stopped taking the medication regardless of the reason. Analysis 2 included patients who stopped medication because of adverse events according to medical advice. We excluded analysis 2 because other studies included any patient as in analysis 1. [@] Participants used a 5-point scale (from very often to never) to answer the RAM scale questionnaire (how often they forget to take their medications). "Never" was considered as equivalent to a cutpoint of 100% and rarely to ≥ 75%. ^ Results were given as percent of nonadherent/compliant patients. * This article used an interview and questionnaires to measure adherence. The interview included the following question: Do you sometimes decide to skip a dose or do you sometimes forget a dose? The possible answers were 1 (never), 2 (once a month), 3 (3 times a month), 4 (once a week), 5 (several times a week), and 6 (I never take this medicine). Response 4 (missed dose a week) was defined as the cutoff for nonadherence. Because this is an absolute and not a relative scale, this result was not used in the metaanalysis; rather, we used the result obtained by the questionnaire. MEM: medication and event monitors; MPR: medication possession ratio; MTX: methotrexate; PDC: proportion of days covered; DMARD: disease-modifying antirheumatic drug; LDR: level to dose ratio; PB: phenobarbitone; CQR: Compliance Questionnaires in Rheumatology; NA: not applicable; MARS: Medication Adherence Report Scale; RA: rheumatoid arthritis; ETN: etanercept; RAM: Reported Adherence to Medication.

weights to test the difference among methods used to measure percentages of adherence. We had planned to perform funnel plots and Egger test to investigate the influence of publication bias. All analyses were performed using R3.1.2[38]. The metaanalysis was conducted using the metafor package[39]. The statistical significance level was 0.05, except for the test of between-study heterogeneity.

RESULTS

Study selection. The search strategy yielded 320 citations (Figure 1). Perusal of the reference lists yielded an additional 5 articles[8,14,17,22,23]. After applying inclusion/exclusion criteria, 53 articles remained. Following detailed extraction, a further 22 articles were excluded (Figure 1), leaving 31 articles examined for either metaanalysis on percent adherence (n = 24) or associated factors (n = 30; Table 2). The 7 articles included in the associated factors analysis but not the adherence analysis were excluded because they did not have definable cutpoints for adherence[34,35,36,37] or because the cutpoints were much lower than the rest of the studies[8,9,10]. Dichotomization of the scale used to measure adherence was necessary to quantitate adherent patients. Papers that only reported the absolute mean score for all patients but did not use a cutpoint to define which patients were considered adherent were excluded from our metaanalysis because it was not possible to extract the percentage of adherent patients.

Among the 31 included papers, 1 was excluded from the analysis for associated factors because data were lacking[33]. Overall, 13,921 patients were included in the metaanalysis for rate of adherence and 67,216 patients were included in the associated-factors analysis.

Quality of studies. Eleven studies were of high quality (Table 2). Seven studies that used prescription claims[11,12,13,14,34,35,37] had high scores of 9 out of 10, but had a potential selection bias (not inviting/reporting consecutive patients or a representative sample; Supplementary Table 1 and Supplementary Table 2 available online at jrheum.org).

Variability across studies. Variability across studies was observed in 2 categories: measurement methods and cutpoints.

Among measurement methods, 7 studies used prescription claims[11,12,13,14,28,29,30], 6 used interview[19,20,21,22,23,24], 7 used questionnaires[2,15,16,17,18,31,33], 2 used electronic medication and event monitors (MEMS)[26,32], 2 used drug levels[24,27], and 2 used pill count[24,25]. Variability arose within questionnaire studies because questionnaires varied. Three studies used the Compliance Questionnaires in Rheumatology[2,18,33], 1 used the Rheumatology Attitudes Index, and 1 used the Drug Record Registry, and all are specific to antiarthritis drugs. The rest used nonspecific questionnaires.

The second category was the cutpoints used. Most studies defined good adherence at the 80% cutpoint (Table 3). Ten studies used categorical scales or a yes/no scale, defined by words to evaluate adherence[12,15,17,19,20,21,22,23,24,26].

Variability within studies and selection of relevant data.

(1) Type of medications: Three studies (all used prescription claims) measured adherence to several medications[11,13,14]. Because etanercept (ETN) was the most frequently used medication, ETN was used as our benchmark for the prescription claims group (Table 3).

(2) Length of drug use: Two papers (both used prescription claims) measured adherence in naive versus longterm users[11,12]. Because most studies did not report these data, we used total adherence data.

(3) Different cutpoints: If multiple cutpoints were recorded, we used the one closest to 80%[16,18] (Table 3).

(4) Defining adherence: Including adverse events as a

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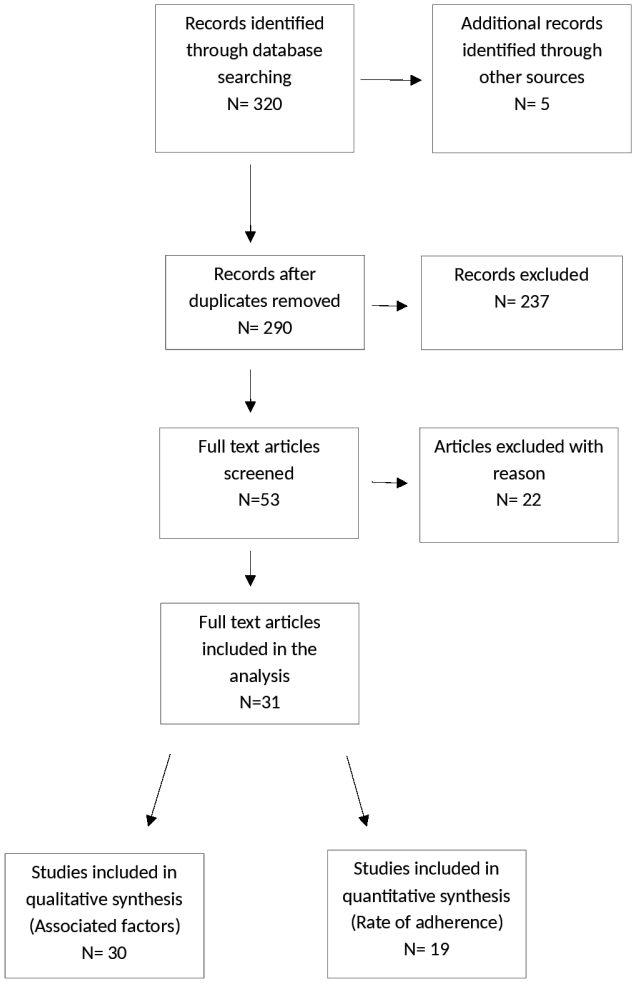

Figure 1. Article selection. The search strategy yielded a total of 31 articles, 24 articles for the metaanalysis of adherence rate, and 30 articles for a qualitative analysis of associated factors.

source of nonadherence is less accurate than is desirable because including adverse events confounds the adherence percentages. Nevertheless, we used that definition because most papers did not differentiate among reasons for non-adherence[27] (Table 3).

(5) Type of questionnaires: When more than 1 questionnaire was available[2,15,21], the one most commonly used or where cutpoints were available[18] was used.

Results of metaanalysis. Overall, 66% of patients were adherent to medications (95% CI 0.58–0.75; Figure 2). Weighted linear regression revealed no statistically significant difference among methods used to measure percentage of adherence ($p = 0.2$). Statistically significant large ($I^2 = 95.31\%$) heterogeneity [$Q (df = 25) = 466.15$, $p < 0.001$] was observed for overall adherence. Statistically significant heterogeneity was also present in some measuring methods: prescriptions claims [$Q (df = 1) = 31.43$, $p < 0.001$, $I^2 = 96.82\%$], MEMS [$Q (df = 6) = 282.79$, $p < 0.001$, $I^2 = 98.41\%$], and interview [$Q (df = 5) = 10.03$, $p < 0.074$, $I^2 = 45.27\%$]. Random-effects models were applied to these methods, while fixed-effects models were applied to questionnaires, pill count, and drug level.

Sensitivity analysis. We computed various outlier and influential case diagnostics, such as DFFITS and Cook distance, which indicate the influence of deleting 1 study at a time on the model fit and the fitted values. The summary percentages of adherence remained stable, indicating that our results were not driven by any single study. Influential case diagnostics suggested that several studies[2,13,17,31] introduced some additional residual heterogeneity into the model (Supplementary Figure 1 available online at jrheum.org).

Publication bias. Asymmetry was observed in the funnel plot (Supplementary Figure 2 available online at jrheum.org); however, the evidence of publication bias detected using Egger test was not statistically significant ($p = 0.06$).

The cumulative metaanalysis revealed that the summary percentage of adherence converged to the final estimate when more studies were included in the analysis.

Adherence during followup. Seven longitudinal studies measured adherence across time[15,19,23,25,26,27,31] (Table 2) with a mean followup of 10.4 months (range 1–36 mos). Most studies included outpatients and 2 studies included patients with early RA. Quality was low in 6 studies and high in 1. Regression analysis of pooled data calculated that percent of adherent patients decreased nearly 1% per month of followup (Supplementary Figure 3 available online at jrheum.org).

Associated factors. One hundred associated factors were identified. Using the WHO categories reported in 2003, we identified 19 patient-related factors, 34 treatment-related factors, 17 condition-related factors, 9 health system factors, and 21 sociodemographic/economic factors. Seven factors were found in at least 2 different studies as having a significant association with adherence with no studies to the contrary (Table 4). Three studies found that better adherence was associated with a belief that the drug was necessary, while 1 study found no association[2,9,17,18].

Older age was associated with better adherence in 5 studies, but no association with age was found in 10 studies. An association of age with adherence was also found in human immunodeficiency virus (HIV)[40], lending some support to this association.

White compared with African American/black ethnicity was associated with adherence in 2 studies, while 1 study did not find this association. A statin study supported the finding of a lower adherence rate among non-whites[39]. Conflicting findings were found regarding sex[2,9,12,13,15,18,19,20,21,23,25,28,37].

Among treatment-related factors[13,14,30,34,36], although there were only a few studies, the results were consistent (Table 4). Adherence was better when taking either ETN or infliximab (IFX) than methotrexate (MTX)[14,34]. Adherence was also better when taking MTX compared with

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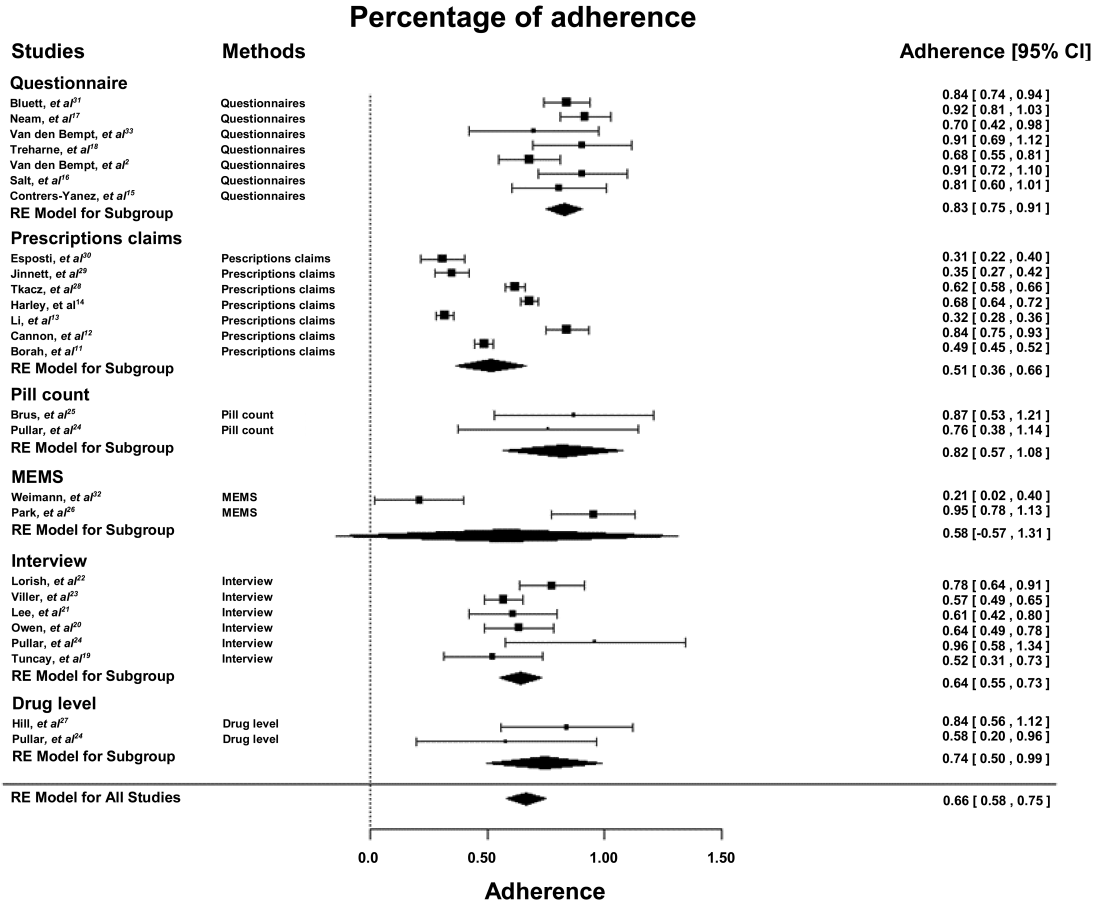

Figure 2. Metaanalysis of percent of adherent patients by method used to measure adherence. RE: random-effects; MEMS: medication and event monitors.

sulfasalazine (SSZ)[34,36] and finally, adherence to IFX was better than to ETN[13,14,30].

Higher weekly out-of-pocket cost was negatively associated with adherence in 1 study[37]. On the other hand, higher total healthcare cost[11], financial status[22], and health maintenance organization insurance[37] were positively associated with adherence.

DISCUSSION

Our metaanalysis is the first, to our knowledge, to evaluate adherence quantitatively and to seek a relationship between adherence and the method used to measure it.

Overall, 66% of patients were adherent to antiarthritic medications. Although previous literature suggested that interviews overestimated adherence rate[2], our analysis found no statistical differences among the different methods (Figure 2). We also showed that adherence decreases during followup.

A previous SLR[3] included 11 studies and 64 associated factors. We identified an additional 15 studies[8,12,14,16,24,25,27,28,29,30,31,32,34,35,36] and analyzed 100 factors.

Importantly, the previous SLR[3] did not quantify adherence. In our metaanalysis, all patients were considered adherent because they fulfilled the cutpoint as defined by the authors. Most studies used a cutpoint of > 80% to define adherent patients. We excluded data on persistence, discontinuation, switching, treatment gap or retention rate, and adherence to nonmedical therapy[7] (Table 1), as well as 1 study[4] that merely used physician opinion to evaluate adherence, which could increase variability. We included 2 RCT because we did not seek to evaluate differences among interventions but sought overall quantitation. We took only the control group, because these patients were not subjected to intervention. Further, we both included and removed the 2 RCT from our analysis and found that it made no significant difference in the results (data not shown).

Associated factors. Age, sex, education, Health Assessment Questionnaire, and disease duration were the most studied risk factors (Table 4). It was not possible to calculate a reliable estimate of the magnitude of the associations from the available data because of the heterogeneity of the methods used and the low quality of most studies. We can only point to trends and interesting findings that may represent targets for further studies. Three studies[13,14,30] found IFX to be associated with a higher adherence than ETN. These data

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Table 4. Associated factors. Includes all the factors that were examined for possible association with adherence or nonadherence. The table shows the number of studies that found either positive or negative association with adherence. The total number of studies that looked for an association is given and includes studies that did not find any association. Values are n unless otherwise specified.

Variables	Positive	Negative	Total	References
Treatment-related factors				
ETN compared to MTX	2	0	2	14, 34
IFX compared to ETN	3	0	3	13, 14, 30
IFX compared to MTX	2	0	2	14, 34
SSZ compared to MTX	0	2	2	34, 36
Type of DMARD/type of medications	0	0	3	16, 20, 23
ADA compared to ETN	0	1	1	11
ANA compared to IFX	0	1	1	13
ANA compared to ETN	0	1	1	13
ANA compared to MTX	0	1	1	34
Golimumab compared to ETN	1	0	1	28
Golimumab compared to ADA	1	0	1	28
New users of LEF, IFX, ETN, and ADA alone compared to new users of MTX	1	0	1	34
Patients receiving DMARD or MTX specifically	0	0	1	18
No. doses per day	0	0	1	20
1–4 daily regimen	0	0	1	20
Total no. all tablets taken per day	0	0	2	19, 21
Increased total no. medications for RA/antirheumatic drugs	0	1	3	16, 20, 21
Total no. medications	1	0	3	2, 18, 26
No. antirheumatic tablets taken per day	0	0	2	19, 21
Combined DMARD therapies[##]	0	1	1	34
Combinations^^	0	1	1	15
Therapeutic regimens of more than 3 DMARD compared to MTX monotherapy	0	1	1	15
Concurrent therapy with MTX^^^	0	0	1	12
Use of steroids	1	1	5	13, 15, 16, 18, 35
Use of NSAID	0	0	2	2, 18
MTX dose or prescribed MTX dose	0	0	2	9, 12
Prescribed dose of D-Pen	0	0	1	24
Use of DMARD prior to anti-TNF therapy initiation	1	0	1	37
Oral DMARD use in the 12-mo preindex period to their index biologic	1	0	1	13
Folic acid use	1	0	1	9
Medication type, symptomatic/disease-modifying/combination	0	0	1	20
Observed weekly MTX dose	1	0	1	12
Duration of use of MTX	1	0	1	12
Adverse event/physical effect of treatment, pain, discomfort	1	0	2	2, 20
Patient-related factors				
Necessity BMQ, higher score	3	0	4	2, 9, 17, 18
Attitude to medications[#]	1	0	1	20
Perceived effectiveness of medications	0	0	1	20
Overuse BMQ	0	1	1	18
Lower concern score BMQ	1	0	4	2, 9, 17, 18
Higher necessity concern differential	1	0	1	17
Harm belief of medications	0	1	1	18
Reason to take medication[$$]	0	1	1	20
Coping*	0	0	2	2, 36
Coping with arthritis-related mood	1	0	1	26
Optimism	0	0	1	18
Belief about ability to control pain	0	0	1	26
Belief about ability to control disease activity	0	0	1	26
Belief about ability to control negative moods related to arthritis	1	0	1	26
Outcome expectation[&]	0	0	1	25
Self-efficacy expectation[&&]	1	0	1	25
Perceived barriers for taking SSZ**	0	0	1	25
Knowledge score, knowledge of disease	0	0	2	17, 26
Use of an organizer	0	0	1	26
Sociodemographic and economic-related factors				
Residence: Netherlands compared to France or Norway	0	1	1	23
Residence location northeastern compared to north central, south, west USA	1	0	3	16, 20, 37
Ethnicity: white vs African American or black[&&&]	2	0	3	12, 13, 16
Older age	5	0	15	2, 9, 10, 12, 15, 16, 18, 19, 20, 21, 23, 24, 25, 26, 28

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Table 4. Continued.

Variables	Positive	Negative	Total	References
Higher education~	1	0	9	2, 9, 10, 15, 16, 20, 22, 23, 25
Age 55–64 yrs compared to younger or older	1	0	1	13
Male sex	4	1	13	2, 9, 12, 13, 15, 18, 19, 20, 21, 23, 25, 28, 37
Higher socioeconomic status/higher income	0	0	4	15, 18, 20, 22
Employment, working full-time compared to not working full-time	0	1	1	22
Employment status/occupation	0	0	3	15, 16, 18
Marital status, divorced	1	0	6	2, 13, 15, 16, 18, 22
Living alone with no help	0	1	1	22, 32
Ever tobacco user/smoking	0	0	2	2, 12
No. children	0	0	1	18
Children at home	1	0	1	18
Financial status	1	0	1	22
Perceived social attitude^	0	0	1	12
Perceived social support[!]	0	0	1	25
Social support[$]	0	0	2	18, 26
Busy lifestyle	0	0	1	26
Cognition deficit, speed of processing, memory, reasoning	0	1	1	26
Health system–related factors				
Regularity of health insurance	0	0	1	19
SIMS adverse event effect score	0	0	1	2
Satisfaction from consultation[@@]	1	0	1	18
Medicaid patients in Florida compared to New York or California, USA[@]	0	1	1	13
Health maintenance organization insurance	1	0	0	37
Higher weekly out-of-pocket cost	0	1	1	37
Satisfaction with social support	0	0	1	18
Satisfaction about medication information[###]	0	0	1	2
Higher total healthcare cost	1	0	1	11
Condition-related factors				
DAS28 higher	1	3	5	12, 15, 25, 31, 32
ESR higher	1	2	5	12, 15, 19, 20, 23
Morning stiffness	1	0	3	19, 20, 27
Quality of life 0, RAQol score	0	0	1	36
Disease severity	0	0	1	26
Higher CRP	0	0	3	15, 19, 27
Disease flare	0	1	1	15
Higher disability/HAQ	0	2	10	2, 8, 9, 12, 19, 20, 23, 25, 32, 36
Antibody status***	0	0	2	12, 21
Patient global	0	0	1	12
Pain lower severity	1	0	6	12, 20, 21, 25, 26, 27
Comorbidity/health status	0	0	4	9, 15, 18, 28
Longer disease duration	0	1	10	2, 9, 16, 18, 19, 20, 21, 23, 24, 26
Chronicity	0	0	1	21
Erosions	0	0	1	21
Lower joint count/articular index	1	1	4	12, 19, 21, 27
Functional status AIM2, mobility tasks, 0/1	0	0	1	26

Bold face indicates factors that were found in at least 2 different studies as having a significant association with adherence with no studies to the contrary. * Active attitude, palliative reaction, avoidance, seeking social support, passive reaction pattern, expression of emotions, comforting thoughts. ** Afraid of adverse events, doubt about exact prescription, forgetfulness, use of other meds simultaneously. [^] Influence from the environment regarding use of SSZ, attitude of family and friends to use of medications. [^^] MTX + SSZ + plaquanil + LEF or therapeutic regimens with > 3 DMARD compared with MTX monotherapy. [&] Expected improvement of the disease activity and expected limitation of destruction in joints. [&&] Regarding use of DMARD exactly according to the prescription of the physician. [$] Size of support network — who can you count on. [$$] Pain relief versus treat RA/spouse pressure/doctors order. [#] No objection/resistance to take medications. [##] MTX + plaquanil/IFX/ADA/ANA compared with MTX. [@] No difference in copayments and policies. [@@] Affective, cognitive, and behavioral aspects. [!] Support from family and friends in taking medication. *** Anticyclic citrullinated peptide, rheumatoid factor. [^^^] Traditional DMARD/anti-TNF/other biologics. ~ Beck, *et al*[10] did not show direction of the association. [###] SIMS action score (how to use the medication). [&&&] Other studies examined white versus other than black, Hispanic, and white[18], white versus other than African Americans, white[21], white versus other than white, African Americans, Hispanic[11]. ETN: etanercept; MTX: methotrexate; IFX; infliximab; SSZ: sulfasalazine; ANA: anakinra; DMARD: disease-modifying antirheumatic drug; ADA: adalimumab; LEF: leflunomide; RA: rheumatoid arthritis; NSAID: nonsteroidal antiinflammatory drug; D-Pen: D-penicillamine; anti-TNF: antitumor necrosis factor; BMQ: beliefs about medicines; SIMS: Satisfaction with Information about Medicines Scale; DAS28: Disease Activity Score at 28 joints; ESR: erythrocyte sedimentation rate; RAQoL: RA quality of life; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; AIM: Arthritis Impact Measurement Scale.

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suggest that administration under supervision versus self-management promotes adherence. One potential intervention that could be driven from these results is to enhance administration under supervision in patients at risk for nonadherence. Adherence was better when taking either ETN or IFX than when taking MTX[14,34]. Adherence was better when taking MTX than when taking SSZ[34,36]. If this association is true, it may be related to the number and size of tablets. One may conclude that complex treatment regimens reduce adherence in RA. Indeed, complex treatment regimens have been associated with nonadherence in cancer[41], diabetes[42], epilepsy[43], hypertension[44], and HIV[45]. However, in RA the data are inconsistent. One study[33] found neither an association with the number of doses per day nor with 1–4 daily regimens. Two other studies found no association with the total number of all tablets taken per day[10,18]. On the other hand, 1 study found a negative association with adherence when using > 3 disease-modifying antirheumatic drugs (DMARD) versus MTX monotherapy[12]. Another study found negative association with the increased total number of RA medications or the number of antirheumatic tablets taken per day[13], while 2 studies did not find such association[18,33]. Overall, no conclusion can be drawn from the literature regarding regimen complexity and adherence in RA (Table 4).

Patient-related factors represent the resources, knowledge, attitudes, beliefs, perceptions, and expectations of the patient[2]. In this category, we found beliefs in the efficacy of treatment to be a consistent predictive factor for adherence[2,9,17,18]. This is in concert with literature in RA[3], HIV, and tuberculosis therapy[1], contrary to most demographic factors that vary between studies.

Older age was the most examined risk factor, being tested in 15 different RA studies. Again the data are inconsistent. There was a positive association in 5 studies and no association in 10, which is not a robust finding. Yet, older age was also associated with adherence in epilepsy[46], diabetes[47], bipolar disease[48,49], HIV[15], and for statin use[16].

Data regarding ethnicity may be incomplete because the number of non-white patients recruited into research studies is very low and this may cause a potential lack of power. Overall, sociodemographic predictors of adherence may be of limited value because they are not modifiable, although they may be of some use for risk screening and targeted interventions.

There is uncertainty about the association of nonadherence with disease activity. Three studies found an association between nonadherence and various aspects of higher disease activity such as the Disease Activity Score at 28 joints (DAS28), flare, disability, and swollen joint count[12,15,32] or its inverse (better adherence with less pain)[21]. Conversely, longer duration of morning stiffness was associated with better adherence[20] and no association or negative associations with DAS28 were found twice[25,31]. Conflicting findings were found regarding associations with erythrocyte sedimentation rate[12,15,19,20,23] and joint count[12,19,21,27]. Thus, they do not allow a conclusion regarding an association of disease activity with adherence, much less allow conclusions regarding cause and effect because these studies were not designed to answer this question.

Disease duration was negatively associated with adherence in the study by van den Bemt, *et al*[2], as was found in diabetes[50]. None of the health system–related factors was repeatedly associated with adherence in more than 1 study.

Quality of evidence and limitations. Variability across and within studies was prominent. Most of the variability could be explained by heterogeneity. Yet heterogeneity was lower than 50% among studies that used questionnaires as well as among studies that used interviews. Among studies that used drug level, MEMS, and pill count, there were few studies and ranges within categories were very wide, and thus the analysis of these studies is of limited power. Further, the quality of studies was generally low. Our search did not include the EMBASE database and the search was limited to the English literature, which could bias the findings.

Many studies referred to antiarthritis medications and did not specify the drugs. In fact, some of the questionnaires and interviews were not specific to antiarthritis medications in any way[15,16,18,20], although the questions were asked in the context of a rheumatology clinic.

The potential effect that recruitment has on our metaanalysis results could not be measured because even in studies that recruited consecutive patients, those who are nonadherent to medications are also more likely to miss outpatient appointments and potentially miss being recruited.

Our SLR and metaanalysis found an overall adherence rate to antiarthritis medications (DMARD, nonsteroidal antiinflammatory drugs, and steroids) in RA of 0.66, using cutpoints of ≥ 75% to define adherence. However, heterogeneity was large. Adherence decreased during followup. Seven factors were associated with better adherence (IFX compared with ETN or MTX, use of MTX compared to SSZ or to ETN, belief in the necessity of the medications, older age, and white race compared with African American).

To better interpret existing data, we suggest that readers consider the following: (1) which type of medications were evaluated?; (2) the method used to measure adherence — is it valid?; and (3) was a cutpoint used, and if so, at which level?

Future studies should use valid methods to measure adherence and use of cutpoints on the higher end of the scale. We also suggest moving away from the focus on static predictors and toward modifiable variables such as treatment regimen and psychosocial predictors to develop effective interventions.

ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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