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## Predictors of Medication Adherence in Patients with Rheumatoid Arthritis

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### Abstract

Medication adherence is a significant problem in patients with rheumatoid arthritis (RA), a prevalent autoimmune disease. Due to the equivocal results reported in the research, consistent predictors of medication adherence in patients with RA are undetermined. A cross-sectional descriptive, predictive study of 108 patients with RA was used to: 1) describe self-reported medication adherence to disease modifying anti-rheumatic drugs (DMARDs); 2) compare demographic (age, residence, marital status, employment status, years of education, and ethnicity) and clinical (duration of disease and number of medications) factors of adherent and non-adherent individuals; and 3) determine the predictive power of demographic and clinical factors for DMARD adherence using various cut-points (research-based, mean, and median) on a validated, self-report scale measuring medication adherence. Independent samples t-tests, Chi square analyses, and logistic regression modeling were used to analyze these data. Approximately 90% of the individuals with RA reported adherence with their prescribed DMARD prescriptions. The only demographic and clinical difference between the adherent and non-adherent group was ethnicity ( $p=0.04$ ); nonwhite individuals reported significantly less adherence with their prescribed DMARDs when compared to white individuals. Logistic regression models identified ethnicity (OR= 3.34-10.1;  $p< 0.05$ ) and the number of medications taken (OR=1.7;  $p< 0.05$ ) as predictors of medication non-adherence. These data provide evidence that ethnicity and taking an increased number of prescribed medications are independent predictors of medication adherence in patients with RA. These findings confirm the presence of a health disparity and an area where further research is needed to optimize patient outcomes.

### Keywords

medication adherence; predictors; rheumatoid arthritis

### INTRODUCTION

Rheumatoid arthritis (RA), an autoimmune disease characterized by an erosive synovitis, has been diagnosed in approximately 1% of the U.S. population [American College of Rheumatology (ACR) Subcommittee, 2002; Helmick et al., 2008], and is twice as prevalent in women as men [Gabriel et al., 1999; Helmick et al., 2008]. Individuals with RA are twice as likely to die at the same age when compared to a person in the general population without the disorder (standardized mortality ratio 2.26) [Wolfe et al., 1994]. The yearly direct costs from RA or treatment-related costs are nearly twice that of osteoarthritis; the indirect costs or the costs due to decreased productivity are five times that of osteoarthritis [Maetzel et al., 2004]. The initiation of pharmacologic therapy with disease-modifying anti-rheumatic drugs

(DMARDs) within three months of diagnosis is currently recommended to prevent the potential effects of untreated synovitis which includes joint destruction, loss of joint function, and pain [ACR Subcommittee, 2002]. Adherence to pharmacologic therapy is vital to meet these therapeutic goals and improve patient outcomes.

Unfortunately, adherence to pharmacologic therapy in the RA population is a major issue with reported medication adherence ranging from 30% -107% [de Klerk et al., 2003; Doyle et al., 1993; Park et al., 1999; Tuncay et al., 2007; Viller et al., 1999]. Adherence greater than 100% indicates that the individuals were taking more medication than was prescribed. The majority of medication adherence studies that included patients with RA have defined adherence as taking 80% or more of the prescribed medication over the duration of the study time [de Klerk et al., 2003; Dunbar-Jacob et al., 2004]. However, these studies used a number of measures of medication adherence and a variety of research designs that produced widely varying ranges of medication adherence and did not identify consistent risk factors for medication nonadherence.

### Background and Significance

Medication adherence to DMARDs is serious clinical issue with previous investigators describing significant proportions (30% to 107%) of individuals with RA as non-adherent to prescriptions [de Klerk et al., 2003; Doyle et al., 1993; Park et al., 1999; Tuncay et al., 2007; Viller et al., 1999]. A number of investigators have attempted to identify consistent risk factors for medication non-adherence in the RA population. Demographic variables like age and ethnicity have been described as factors affecting medication adherence in patients with RA [Garcia-Gonzalez et al., 2008; Park et al., 1999; Viller et al., 1999]. Older age was found to be associated with higher rates of medication adherence in patients with RA [Park et al., 1999; Viller et al., 1999] and Garcia-Gonzalez and colleagues [2007] suggested that Hispanic and African American patients with RA have significantly reduced medication adherence when compared to Caucasians. Other investigators have found that demographic factors such as age did not significantly influence medication adherence [Owen et al., 1985; Treharne et al., 2004; Wong and Mulherin, 2007]. Other demographic variables like marital status have been found to have equivocal effects on medication adherence [Owen et al., 1985; Treharne et al., 2004; Wong and Mulherin, 2007].

Psychological and clinical factors that have been studied as potential risk factors for medication non-adherence in patients with RA include level of self-efficacy, degree of social support, functional ability, individual pain rating, duration of disease, and beliefs about medications use and adverse medication effects [Brus et al., 1999; Lorish et al., 1989]. Greater degrees of self-efficacy and social support improved medication adherence in patients with RA [Brus et al., 1999; de Klerk et al., 2003; Lorish et al., 1989; Taal et al., 1993]. Improved medication adherence has also been associated with: 1) the use of corticosteroids, 2) a strong belief about the necessity and over-use of medications, 3) having no children at home, and 4) having a greater number of prescribed medications [Treharne et al., 2004; Viller et al., 1999]. In contrast, the presence of medication adverse effects, lower levels of education and income, higher medication costs, and a more positive perception of health at baseline were associated with poorer medication adherence [de Klerk et al., 2003; Lorish et al., 1989]. Although these demographic, psychological, and clinical factors have been suggested to be risk factors for medication non-adherence, none have been found consistently and none are powerful independent predictors.

Geographic residence has not been specifically studied as a risk factor for medication adherence in patients with RA. However, RA is a prevalent disease in rural populations and those diagnosed with RA living in rural communities do have significant disability [Center for Disease Control, 2007; Hakala et al., 1994; Wang et al., 2000]. Barriers to treatment for

those residing in rural communities included lack of rheumatology services, delay of evidence-based treatment, and lack of reliable transportation to health care [Lu et al., 2007; Saag et al., 1998; Potter et al., 2002]. Hakala and Nieminen [1996] found that those patients with RA living in a rural community in Finland had greater impairment when compared to urban dwellers with similar time from diagnosis. Although residence in a rural area can clearly influence access to specialty providers and delay of treatment [Lu et al., 2007; Saag et al., 1998; Potter et al., 2002], there are no studies that investigated the influence of rural residence on medication adherence in patients with RA.

Currently there is limited understanding about the factors that influence medication adherence in patients with RA. In addition, the lack of an established cut-point to indicate non-adherence on self-report measures of medication adherence limits the ability to compare findings across studies. Thus, the purpose of this study was to evaluate the predictive ability of demographic (age, rural residence, marital status, employment status, years of education, and ethnicity) and clinical factors (duration of disease and number of medications) for medication adherence in a sample of patients with RA using various cut-points on a self-report scale measuring medication adherence. The specific aims of the study were: 1) to describe self-reported medication adherence to DMARDs in a group of adults with RA; 2) to compare demographic (age, rural residence, marital status, employment status, years of education, and ethnicity) and clinical (duration of disease and number of medications) factors of adherent and non-adherent individuals; and 3) to determine the predictive power of demographic (age, rural residence, marital status, employment status, years of education, and ethnicity) and clinical (duration of disease and number of medications) factors for DMARD adherence using various cut-points for a validated self-report scale measuring medication adherence.

## METHODS AND MATERIALS

### Design and Sample

This was a cross sectional, descriptive predictive study that included 108 adults with RA. This convenience sample was recruited from a university rheumatology clinic between February and March 2008. Inclusion criteria were: (1) 18 years of age or older; (2) current diagnosis of RA per the 1987 ACR Diagnostic Criteria [Arnett et al., 1988] determined by a health care provider who specialized in rheumatology; (3) taking a prescribed DMARD for arthritis; and (4) English-speaking. Individuals who were less than 18 years of age or Non-English speaking and those with obvious cognitive impairments were excluded.

### Instruments

**Medication Adherence Report Scale (MARS)**—The MARS [Horne and Weinman, 2002] is a 9-item scale with each item rated on a 5-point Likert-type scale with 5 = *never*, 4 = *rarely*, 3 = *sometimes*, 2 = *often*, and 1 = *very often* [Horne and Weinman, 2002]. Items include: forgot to take, alter the dose, stop taking it, decide to miss a dose, and take it less than instructed, I avoid using it, I only use it when I feel pain, I use it regularly every day (reverse scored), and I use it only as a reserve if my other medications don't work. In this study, two items were modified to address the medications and symptoms specific to individuals with RA. The modified scale is referred to in this text as the MARS-9RA. Modifications included changing the word sick to pain, and changing the phrase if my other inhaler doesn't work to if my other medications don't work. The MARS-9RA was scored by summing patient responses to all items. Total scores can range from 9 to 45; higher scores indicate more adherent behavior. Scale developers have not provided a standard cut-point to define adherent versus not adherent medication taking behaviors.

In this sample of 108 patients with RA, the Cronbach's alpha for the MARS-9RA was .77, and the test-retest reliability was .60 ( $p = .01$ ,  $n = 59$ ). The MARS-9RA had significant correlations with two other validated self-report measures of medication adherence providing evidence of concurrent validity [Salt et al., 2009].

**Demographic and Clinical Data**—Participants were requested to provide information that included age, marital status, employment status, years of education, ethnicity, duration of disease, and medications prescribed for RA. Rural/urban residence was determined by the rural/urban continuum codes [United States Department of Agriculture, 2010].

### Procedure

This study was approved by the University of Kentucky Medical Institutional Review Board. Individuals were recruited following a regularly scheduled office visit. Potential participants were asked by their rheumatology health care provider if they were interested in participating in the study. For those interested, the principal investigator determined eligibility via interviews. Once informed consent was obtained, patients were asked to complete the MARS-9RA [Horne and Weinman, 2002] with the two modified items and a demographic and clinical data form.

### Data Analysis

Descriptive statistics were used to characterize participants. Total MARS-9RA score was calculated for each participant and determined to be adherent or non-adherent based on various cut-points including: a score used in a prior research study [Clatworthy et al., 2009] ( $\leq 38$ = non-adherent;  $>39$ = adherent), the mean score ( $\leq 42$  non-adherent;  $> 43$ = adherent), and the median score ( $< 43$ = non-adherent;  $\geq 44$ = adherent). Using the cut-point used in a prior research study, the proportion of participants who were adherent was calculated and the adherent and non-adherent groups were compared using independent sample t-tests or Chi square analyses based on the level of measurement. Adherence was determined using three cut-points and logistic regression models were used to determine whether age, rural/urban residence, duration of disease, marital status, employment, number of medications taken, years of education, and ethnicity were independent predictors of medication adherence. No covariates were included as there are no factors consistently identified as predictive in the literature. All statistical analyses were performed using Statistical Package the Social Science [SPSS, version 18.0, Chicago, IL]. An a priori significance level of 0.05 was used to determine significance for all analyses.

## RESULTS

### Characteristics of the Sample

The participants in this study ( $n = 108$ ) were primarily married (57%), female (76%), and Caucasian (83%) with an average age of  $52 \pm 13$  years (Table 1). Only one fourth (36%) of participants were employed full-time; those unemployed (9%) or disabled (33%) comprised the majority of the sample. Participants had been diagnosed with RA for an average of  $9.7 \pm 9.8$  years and the majority of individuals were prescribed methotrexate (71%). One third of participants (33%) were prescribed newer biologic drugs that inhibit the actions of pro-inflammatory molecules like TNF $\alpha$ . Other common DMARDs prescribed for these participants included hydroxychloroquine (29%) and prednisone (38%) (Table 2).

### Medication Adherence

Scores on the MARS-9RA ranged from 16 to 45 with a mean score of  $44 \pm 4.3$ . Using the cut-point from a prior research study, 90.7% of these participants were considered adherent

to medication prescriptions and the remainder (9.3%) were non-adherent. Using the mean cut-point, 38% were adherent; the remaining 62% were non-adherent. Using the median split, 49% were non-adherent and 51% were adherent.

### Comparison of Adherent and Nonadherent Participants

Using the cut-point from a prior research study [Clatworthy et al., 2009], demographic and clinical characteristics of adherent ( $n = 97$ ) and non-adherent ( $n = 10$ ) participants were compared using independent samples t-tests for continuous variables and Chi square analyses for categorical variables (Table I). There were no significant difference in clinical (duration of disease and number of medications) or demographic (age, rural residence, marital status, employment status, years of education, and ethnicity) factors between groups except for ethnicity. Ethnicity was significantly different; 84 (86%) of the adherent participants were Caucasian, while only 5 (56%) of the non-adherent participants were Caucasian ( $p = 0.04$ ). Prescription of DMARDs was not different between adherent and non-adherent participants (Table 2).

### Predictors of Medication Nonadherence

Logistic regression was used to determine if clinical (duration of disease and number of medications) or demographic (age, rural residence, marital status, employment status, years of education, and ethnicity) factors were independent predictors of medication adherence (Table 3). Ethnicity (Caucasian versus non-Caucasian), residence (rural versus urban), duration of disease, years of education, number of medications taken, marital status (married or living as though married versus non-married), employment (employed full-time or part-time versus not employed), and age were entered into the model in one block using three cut-points (value used in a prior research study, mean, and median). Using the prior research cut-point, ethnicity was found to be an independent predictor of medication adherence. Caucasians were 10 times more likely to be adherent to medication prescriptions ( $p = .012$ ; CI: 1.66 to 61.40); Using the mean value as a cut-point, Caucasians were 3.3 times more likely to be adherent to medication prescription ( $p = .05$ ; CI: 1.02 to 10.95). Thus, non-Caucasians patients were approximately 3-10 times more likely to report non-adherent medication taking behaviors than Caucasian patients. Using the median as a cut-point, ethnicity was not a significant predictor, but the total number of medications taken independently predicted medication adherence. Those patients taking an increased number of medications were 1.7 times more likely to be non-adherent to medication prescriptions ( $p = .02$ ; CI: 1.09 to 2.63).

## DISCUSSION

Using the cut-point on the MARS-9RA from a prior research study, 91% of the participants in our study self-reported being adherent when taking medication prescriptions for RA. Only 9% reported some degree of non-adherence using a self-report scale. Using the cut-point from a prior research study and the mean score of the MARS-9RA as a cut-point, ethnicity was the only significant independent predictor of medication adherence. Caucasians were more likely to be adherent to medication prescriptions; non-Caucasians were significantly more likely to be non-adherent. Using the median value as a cut-point, the only variable found to be an independent predictor of medication adherence was the number of medications taken. Those patients taking an increased number of medications were 1.7 times more likely to be non-adherent to medication prescriptions.

A high rate of adherence to DMARDs (90.7%) was self-reported in this study. This is within the range reported in prior research (30 to 107%) [de Klerk et al., 2003; Doyle et al., 1993; Park et al., 1999; Tuncay et al., 2007; Viller et al., 1999]. The high adherence rate



reported in this study may be attributed to the self-report measure used to measure adherence. Although self-report scales have been reported to have adequate concordance with objective measures, they are not considered a “gold standard” measurement [Garber et al., 2004]. Another possible explanation for the high adherence rate found in this study is that those patients that consented to participate in this study were more likely to be adherent individuals.

When patients were categorized as adherent and non-adherent based on the cut-point used in a prior research study, ethnicity was the only factor that was significantly different between these groups. Our findings are similar to the only other known study investigating ethnicity as a risk factor for medication non-adherence also using a self-report measure of medication adherence [Garcia-Gonzalez et al., 2008]. Those investigators reported that African-American and Hispanic patients with RA had poorer medication adherence when compared to Caucasian patients with RA [Garcia-Gonzalez et al., 2008]. Their sample included a higher proportion of African American (32%) and Hispanic (43%) patients diagnosed with both RA and systemic lupus erythematosus ( $N = 102$ ) compared with our sample. Even so, ethnicity has been found to be different in those who are adherent and those who are not in two different samples from varied geographic regions (Texas and Kentucky).

Because there is not standard cut-point for the MARS-9, we used three separate cut-points for our logistic regression analyses. Using the cut-point from a published research study and using the sample mean for the MARS-9RA produced similar results; ethnicity was an independent predictor of medication adherence. When the median split was used as a cut-point, the total number of prescriptions was the only independent predictor. This difference was surprising as the median was very close to the mean (44 versus 43). Clearly, the choice of a cut-point is important, as we demonstrated that it can produce very different results with only a change of 1 unit. However, we do have strong evidence that ethnicity is likely an independent predictor of medication adherence in the RA population in Kentucky, as two of our models identified odds ratios of 3.4 to 10 ( $p < 0.05$ ). Our small sample size ( $n = 108$ ) with the number of variables entered into the models also reduced the power. Thus, investigation of the predictive power of ethnicity and total number of medications should be a focus of continued research with larger samples.

Using the median as a cut-point, the number of prescribed medication was an independent predictor of medication adherence. Our patients took a mean of  $2.3 \pm 1.1$  medications and prescriptions ranged from 0 to 5. Taking an increased number of prescribed medications increased the likelihood of medication nonadherence ( $OR = 1.7$ ;  $p < 0.05$ ). Thus, those patients taking more medication were significantly more likely to have poorer medication adherence. This is contrary to Treharne and colleagues [2004] who reported that an increased number of prescription medications was associated with better medication adherence. Other researchers found no effect from the number of medication prescribed [Owen et al., 1985; Wong & Mulherin, 2007]. Thus, this variable requires more investigation in a larger sample of patients, while ensuring that there is adequate variability in the number of medications prescribed.

The power of rural living as a predictor of medication adherence has not been previously studied, but could be an important factor in medication adherence. Patients living in rural areas frequently have limited health care resources, particularly for the management of relatively rare, chronic disease like RA. There are also limited educational opportunities, transportation to tertiary centers may be lacking and those familiar with signs, symptoms, and management of RA may be few and far between. Although rural versus urban residence was not a significant predictor in our study and was not significantly different between the adherent and nonadherent groups, this was likely due to a lack of statistical power due to the

small sample size. This potentially important risk factor requires further investigation in a larger sample of participants.

### Limitations

This study was conducted in a primarily white, female population in one university clinic; however the demographics of these participants reflect the epidemiology of RA. The small sample size may not have provided sufficient statistical power to determine the influence of these variables on medication adherence. However, there were more than 10 cases per variable- which is suggested for regression analyses. An additional limitation is the use of a self-report scale without a clearly defined cut-point defining adherence and non-adherence to measure medication adherence. There is some evidence that self report can be a valid measure of adherence and we use several cut-points in our analyses to compare the significant risk factors we identified. Future multi-center studies with a larger, more diverse sample, using objective electronic devices to measure medication adherence should be conducted to evaluate these potential risk factors for medication non-adherence.

### Conclusions

Medication adherence is necessary for optimal management of RA. In our study, ethnicity was the only significant demographic predictive factor for medication non-adherence in this group of patients with RA. Non-Caucasian patients were three to ten times more likely to be non-adherent than Caucasian patients, and those patients taking an increased number of medications were 1.7 times more likely to be non-adherent to their medication prescriptions. Other previously identified risk factors for medication non-adherence like lower levels of education and older age were not found to be significant in these patients.

We have evidence that ethnicity and number of medication are independent predictors of medication adherence. These factors should be considered in the management of this patient population, so that optimal outcomes can be achieved. Future research is necessary to determine the nuances of ethnicity producing health disparity in patients with RA, to determine other independent predictors of medication nonadherence in these patients and to develop and test evidenced-based interventions to improve medication adherence.

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**Table 1**

## Characteristics of Participants.

Variable	Total sample (n = 108)	Adherent group (n = 98)	Non-adherent group (n = 10)	p value
Age in years	52 ± 13	52 ± 14	53 ± 9	0.77
Gender female	82 (76%)	75 (76%)	6 (68%)	0.69
Ethnicity				
Caucasian	89 (83%)	84 (86%)	5 (56%)	0.04
African American/	14 (13%)	11 (11%)	3 (33%)	
Other	4 (4%)	3 (3%)	1 (11%)	
Education in years	13 ± 3	13 ± 3	12 ± 3	0.81
Marital status				
Married/cohabit	62 (58%)	56 (57%)	6 (67%)	0.74
Widowed	7 (7%)	7 (7%)	0	
Divorced/Separated	20 (19%)	19 (19%)	1 (11%)	
Single/ Never Married	18 (17%)	16 (16%)	2 (22%)	
Employment				
Employed full-time	27 (26%)	25 (26%)	2 (22%)	0.72
Employed part-time	7 (7%)	7 (7%)	1 (11%)	
Unemployed	10 (9%)	10 (10%)	0	
Sick leave/disability	35 (33%)	33 (34%)	2 (22%)	
Homemaker	7 (7%)	6 (6%)	1 (11%)	
Retired	20 (19%)	17 (17%)	3 (33%)	
Residence location				
Urban	55 (51%)	48 (53%)	7 (78%)	0.18
Rural	45 (42%)	43 (47%)	2 (22%)	
Years since diagnosis	10 ± 10	10 ± 10	11 ± 8	0.73
Total number of RA medications	2 ± 1	2 ± 1	3 ± 2	0.43

Values are mean + SD or frequency (%), May not total to 100% due to some missing data points

Variables compared with independent t tests or Chi square analyses based on level of measurement

For those variables with no cases in a cell, categories were collapsed to ensure the assumptions of Chi square were met prior to analysis

**Table 2**

Medications taken by the patients with RA (N = 108)

Variable	Total sample (n = 108)	Adherent group (n = 98)	Non-adherent group (n = 10)	p value
Methotrexate	76 (70%)	70 (71%)	6 (60%)	0.34
Prednisone	41 (38%)	36 (37%)	5 (50%)	0.50
Hydroxychloroquine	31 (29%)	29 (30%)	2 (20%)	
Sulfasalazine	16 (15%)	13 (13%)	4 (40%)	
Etanercept	12 (11%)	9 (9%)	3 (30%)	
Adalimumab	11 (10%)	10 (10%)	1 (10%)	
Abatacept	6 (6%)	5 (5%)	1 (10%)	
Infliximab	5 (5%)	5 (5%)	0	
Leflunomide	4 (4%)	4 (4%)	0	
Rituximab	1 (1%)	1 (1%)	0	
Cytosan	1 (1%)	1 (1%)	0	

Proportions if adherent and nonadherent groups were compared with Chi square analyses.

Chi square analyses were not performed when there were less than 5 cases per cell.

Totals may be equal 100% due to rounding.

**Table 3**

Predictors of adherence to DMARDs.

<b>Using the cut point from a prior research study</b>				
<b>Factor</b>	<b>Odds Ratio</b>	<b>Significance</b>	<b>95% Confidence Interval</b>	
			<b>lower</b>	<b>upper</b>
Ethnicity (white versus nonwhite)	10.10	0.01	1.66	61.40
Residence (rural versus urban)	7.52	0.10	83.33	0.70
Duration of disease	1.00	0.83	1.01	1.00
Years of education	1.09	0.61	1.50	0.79
Total number of medications taken for RA	1.26	0.51	2.53	0.63
Marital status (married versus not married)	1.44	0.75	0.151	13.68
Employment (full time versus not full-time)	2.19	0.52	21.3	0.21
Age	1.01	0.80	0.94	1.08
<b>Using the median cut point</b>				
<b>Factor</b>	<b>Odds Ratio</b>	<b>Significance</b>	<b>95% Confidence Interval</b>	
			<b>lower</b>	<b>upper</b>
Ethnicity (white versus nonwhite)	2.67	0.12	0.78	9.17
Residence (rural versus urban)	1.54	0.38	0.58	4.08
Duration of disease	1.00	0.18	1.01	0.99
Years of education	1.03	0.73	0.89	1.19
Total number of medications taken for RA	1.69	0.02	2.63	1.09
Marital status (married versus not married)	2.76	0.17	11.63	0.66
Employment (full time versus not full-time)	2.71	0.20	0.59	12.40
Age	0.99	0.71	1.04	0.97
<b>Using the mean cut point</b>				
<b>Factor</b>	<b>Odds Ratio</b>	<b>Significance</b>	<b>95% Confidence Interval</b>	
			<b>lower</b>	<b>upper</b>
Ethnicity (white versus nonwhite)	3.34	0.05	1.02	10.95
Residence (rural versus urban)	1.87	0.22	0.70	5.05
Duration of disease	1.00	0.11	1.01	0.99
Years of education	1.04	0.59	1.21	0.89
Total number of medications taken for RA	1.37	0.16	2.11	0.89
Marital status (married versus not married)	2.11	0.30	8.62	0.51
Employment (full time versus not full-time)	2.62	0.21	0.58	11.79
Age	1.00	0.88	1.04	0.97