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# Medication adherence to disease-modifying anti-rheumatic drugs among patients with rheumatoid arthritis at Assiut University Hospital, Egypt

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## Abstract

**Background:** Rheumatoid arthritis is a chronic disabling autoimmune disease with predilection to synovial joints and many extraarticular manifestations. Disease-modifying anti-rheumatic drugs are the cornerstone and initial therapy in rheumatoid arthritis. Although medication adherence is crucial for successful therapy, non-adherence is a substantial problem in some. This study aimed to determine the adherence rate of treatment with disease-modifying anti-rheumatic drugs among patients with rheumatoid arthritis in an Egyptian university hospital. In this study, seventy-three adult rheumatoid arthritis patients who are on disease-modifying anti-rheumatic drugs treatment for at least 6 months were included in this study. After full history and clinical examination, assessment of the adherence rate to disease-modifying anti-rheumatic drugs was done using the Clinician Rating Scale. Measuring the quality of life using the Health Assessment Questionnaire Disability Index and screening for depression and anxiety using the Hospital Anxiety and Depression Scale were done. The socio-economic level of the patients was assessed by socio-economic status scale.

**Results:** In the current study, 65.1% of the patients were highly adherent to their disease-modifying anti-rheumatic drug (DMARD) medications, while 26% showed middle level of adherence. There was a significant difference between medication adherence and anxiety, but not with other demographic data, clinical data, disease activity, or socio-economic level.

**Conclusion:** In this study, no significant difference was found between medication adherence and demographic, clinical, or socio-economic data. However, anxiety was significantly related to DMARD adherence in the studied group. Age and HAQ-DI were found to be strong predictors to medication adherence in our RA patients. Further studies should be conducted on a large number of patients with rheumatoid arthritis to become generalizable to a broader population.

**Keywords:** Adherence/compliance, Quantitative, Rheumatoid arthritis

## Background

Rheumatoid arthritis (RA) is a chronic progressive autoimmune disease that causes inflammation and destruction of synovial joints. It has a strong impact on people's everyday lives. Patients with RA suffer from pain, limited

mobility, and disability besides experiencing a decreased quality of life [1].

Despite the great advances in the treatment of RA with biological therapy, disease-modifying anti-rheumatic drugs (DMARDs) remain the cornerstone and initial therapy in this disease [2]. These drugs have shown to retard disease progression including joint destruction.

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Early application of DMARDs has revealed significant benefit when compared with their use later in the course of the disease although even early DMARD therapy does not fully prevent disease progression in the majority of the patients [3].

It is believed that adherence to treatment is crucial for successful therapy; however, non-adherence is a substantial problem in patients with chronic rheumatic conditions, including RA [4].

Medication adherence refers to the patient's act of conforming to the recommendations made by health care providers with respect to timing, dosage, and frequency of medication-taking [5].

Medication adherence can be divided into three major components: (a) initiation when the patient takes the first dose of a prescribed medication, (b) persistence defined as the length of time a patient fills prescriptions without permissible gaps, and (c) execution adherence defined as the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken [6].

Adherence to treatment improves the outcome and affects several widely used indices [Disease Activity Score (DAS28) and Clinical Disease Activity Index (CDAI)] [7].

Previous studies have reported that DMARD non-adherence results in more disease activity, loss of function, and a lower quality of life [8, 9].

## Method

### Aim of the study

The study aimed to determine the adherence rate of treatment with DMARDs among patients with RA.

### Study design

This observational clinical study was conducted in the outpatient clinic of the Rheumatology and Rehabilitation Department at our University Hospital. Seventy-three adult RA patients (68 females and 5 males) who fulfilled the 2010 ACR/EULAR classification criteria for RA [10] and selected by quota sample were included in the study. The researchers started to collect data from January to June 2019; each interview took 20–30 min.

### Inclusion criteria

This study included RA patients aged  $\geq 18$  years, on current treatment with one or more of DMARDs of at least 6 months duration and with cognitive level enabling them to interact actively in the study. Patients with other rheumatic diseases, end-stage organ failure, and cognitive impairment were excluded from the study.

### Ethical considerations

This study has been approved by the local ethics committee of our Faculty of Medicine and conforms to the

guidelines of the Declaration of Helsinki. Clinical trial registration number of the study is NCT03316027. Written consent was obtained from each studied subject.

### Process

Full history and clinical examination of all patients were done with calculation of the disease activity using DAS-28 ESR scoring [11, 12]. A DAS-28 of greater than 5.1 = high active disease, 3.2 to 5.1 = moderate activity, 2.6 to 3.2 = low activity, and less than 2.6 = remission.

All patients were reviewed for completing 4 standardized interview-questionnaires as follows:

1. *Clinician Rating Scale (CRS)*

It is an ordinal scale of 1–7 to quantify the clinician's assessment of the level of adherence shown by the patient. Higher numbers represent greater adherence [13, 14].

2. *Health Assessment Questionnaire Disability Index (HAQ-DI)*

Functional disability was evaluated by the HAQ-DI, which included 20 questions in 8 sub-dimensions: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. The response alternatives were 0 grade, able without any difficulty; 1 grade, able with some difficulty; 2 grades, able with much difficulty; and 3 grades, unable. *Scoring system:* The 8 scores of the 8 sub-dimensions are summed and divided by 8. In the event that one sub-dimension is not completed by a subject, the summed score would be divided by 7. The HAQ-DI score is not calculated when the patient provides answers in fewer than six sub-dimensions. The HAQ-DI score ranged from 0 to 3, with higher scores indicating more disability. Functional disability was defined as the HAQ-DI score  $\geq 1$  according to a previous study [15].

3. *Hospital Anxiety and Depression Scale (HADS)*

A 14-item questionnaire was used to detect anxiety (7 items) and depression (7 items). Each item had a 4-point Likert scale and was scored between 0 and 3 grades, e.g., "I can sit at ease and feel relaxed", with responses of 0 = definitely, 1 = usually, 2 = not often, and 3 = not at all; each sub-scale was constructed by summation. *Scoring system:* The HADS ranged from 0 to 21, a score between 0 and 7 suggests "no case," 8 to 10 represent a "borderline case," and 11 to 21 indicate a "case of anxiety/depression." These cutoff points have been validated against clinical interviews with sensitivity and specificity approximately 0.80. Recent studies have reported good internal consistency for both anxiety (0.89) and

depression (0.86) sub-scales [16, 17]. The Arabic version of the questionnaire was used [18].

#### 4. Socio-economic status scale

Designed by Abd-El-Tawab [19] to assess socio-economic status of the family and included the following:

- Personal characteristics of the patients such as age, sex, residence, and marital status
- Patient's and his wife/her husband level of education
- Patient's and his wife/her husband occupation
- Total family monthly income
- Lifestyle of the family

**Scoring system:** The scores for these items were fed into a mathematical formula to produce the socio-economic score. The total score was divided into 3 scales as high, moderate, and low [20].

#### Validity and reliability

The evaluation of data collection tools was done by three experts from the Rheumatology and Rehabilitation Department at our University Hospital to measure the validity of the tools. Reliability was analyzed by Cronbach's alpha the value was 0.87.

#### Methods of data collection

A pilot was carried out before starting data collection on 10% (7 patients) who excluded from sample. It is aimed to test the clarity of tools and to estimate the time required to fill questionnaires. The necessary modification was done according to result of pilot study.

#### Statistical analysis

Date entry and data analysis were done using Statistical Package for Social Science (SPSS) version 20. Data were presented as number, percentage, mean, and standard deviation. Also, Kruskal-Wallis test was used for comparing the differences between more than 2 groups. Multivariate linear regression modeling was used for prediction studying. *P* value was considered statistically significant when *P* < 0.05.

#### Results

The vast majority (93.2%) of patients were females and less than one third of them (31.5%) had age ranged from 50 to < 60 years old. Most of the studied patients were from rural areas and they were housewives (90.4%) for both. While (71.2%) of them were married and most of them (84.9%) were illiterate (Table 1)

It was clear that 82.19% of patients received hydroxychloroquine as a current medication followed by 61.64%

**Table 1** Demographic characteristics of the studied patients (No. = 73)

Demographic characteristics	No.	Percent
<b>Sex</b>		
Male	5	6.8
Female	68	93.2
<b>Age (years)</b>		
< 40	12	16.4
40–< 50	18	24.7
50–< 60	23	31.5
≥ 60	20	27.4
Mean ± SD (range)	50.81 ± 11.94	(25.0–85.0)
<b>Residence</b>		
Rural	66	90.4
Urban	7	9.6
<b>Occupation</b>		
Housewife	66	90.4
Retired	1	1.4
Free business	2	2.7
Unemployed	4	5.5
<b>Marital status</b>		
Married	52	71.2
Not married	21	28.8
<b>Educational level</b>		
Illiterate	62	84.9
Literate	11	15.1

No. number, SD standard deviation

who received leflunomide, while only 15.06% of patients received sulphasalazine. Fifty-four patients received combined DMARDS and none of the study patients received biologic treatment. It was found that 41.1% of studied patients had disease duration of less than 10 years and 46.6% of them had treatment duration of less than 10 years (Table 2).

Table 3 describes the Clinician Rating Scale (CRS) among studied patients. About one quarter of patients (24.7%) partially refused or only accepted minimum dose, while 13.7% of patients were occasionally reluctant and 20.5% of them were active participants and showed some responsibility for regimen following.

Figure 1 illustrates the medication adherence level among studied patients. We considered that the first two statements of the CRS were indicators of low adherence, the next 2 statements were denoting middle-level adherence, while the last 3 statements as indicators of high-level adherence. Depending on this assumption, it was observed that 42.5% of patients had a high level of adherence, while 31.5% of them had a low level, and 26.0% of them had middle level.

**Table 2** Distribution of studied patients according to their disease duration, current medication, and treatment duration (No. = 73)

Items	No.	Percent
<b>Disease duration (years)</b>		
< 10	30	41.1
10–20	28	38.4
> 20	15	20.5
Mean ± SD	11.79 ± 7.84	
Median (range)	10.0 (1.0–35.0)	
<b>Current medications*</b>		
Hydroxychloroquine	60	82.19
Methotrexate	27	36.98
Leflunomide	45	61.64
Sulphasalazine	11	15.06
Corticosteroid	15	20.54
<b>Treatment duration (years)</b>		
< 10	34	46.6
10–20	25	34.2
> 20	14	19.2
Mean ± SD	11.06 ± 7.95	
Median (range)	10.0 (0.5–35.0)	

No. number, SD standard deviation

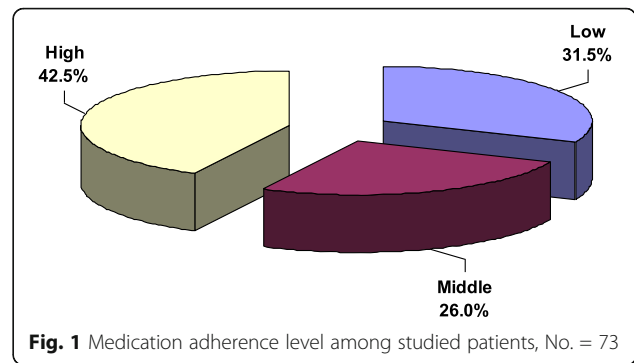
\*More than one medication was allowed

The clinical data of the studied patients are shown in Table 4 where 45.2% of the patients had moderate disease activity while 26.0% of them had high disease activity. Only 8.2% were in remission. As regards the health assessment of disability index level among studied patients, it was clear that 47.9% of patients had mild level of disability (0–< 1) and 27.4% of them had severe level (2–3), while 24.7% of them had moderate (1–< 2) level

**Table 3** Clinician Rating Scale (CRS) among studied patients (No. = 73)

CRS	No.	Percent
Complete refusal	5	6.8
Partial refusal or only accepts minimum dose	18	24.7
Accepts only because compulsory, very reluctant/requires persuasion, or questions the need for medication often (e.g., every 2 days)	9	12.3
Occasional reluctance (e.g., questions the need for medication once a week)	10	13.7
Passive acceptance	6	8.3
Moderate participation, some knowledge and interest in medication and no prompting required	10	13.7
Active participation, readily accepts, and shows some responsibility for regimen	15	20.5

No. number



with mean ± SD (1.28 ± 0.98). Depression was found in 31.5% of cases, while borderline depression was found in 19.2% of patients. On the other hand, 21.9% of the patients had anxiety and 16.4% were having borderline anxiety.

Table 5 showed no statistically significant relation between medication adherence level and demographic characteristics,

**Table 4** Clinical data of the studied patients (No. = 73)

Clinical Item	No.	Percent
<b>DAS-28 level</b>		
Remission < 2.6	6	8.2
Low (2.6–< 3.2)	15	20.6
Moderate (3.2–5.1)	33	45.2
High > 5.1	19	26.0
Mean ± SD	4.29 ± 1.40	
Median (range)	4.1 (2.0–7.5)	
<b>HAQ-DI level</b>		
Mild (0–< 1)	35	47.9
Moderate (1–< 2)	18	24.7
Severe (2–3)	20	27.4
Mean ± SD	1.28 ± 0.98	
Median (range)	1.1 (0.0–3.0)	
<b>Depression (score)</b>		
No case (0–7)	36	49.3
Borderline (8–10)	14	19.2
Case (11–21)	23	31.5
Mean ± SD	8.14 ± 5.74	
Median (range)	8.0 (0.0–20.0)	
<b>Anxiety (score)</b>		
No case (0–7)	45	61.7
Borderline (8–10)	12	16.4
Case (11–21)	16	21.9
Mean ± SD	6.25 ± 5.75	
Median (range)	5.0 (0.0–21.0)	

DAS Disease Activity Index, HAQ-DI Health Assessment Questionnaire Disability Index, No. number, SD standard deviation

**Table 5** Relation between medication adherence score and some demographic and clinical data, HAQ-DI level, depression score, anxiety score, DAS-28 level, and socio-economic class among studied patients (No. = 73)

Items	Medication adherence score		P value
	No.	Mean rank	
<b>Demographic characteristics</b>			
<b>Age (years)</b>			
< 40	12	33.17	0.7
40–< 50	18	41.58	
50–< 60	23	35.91	
≥ 60	20	36.42	
<b>Occupation</b>			
Housewife	66	37.12	0.74
Retired	1	16.00	
Free business	2	43.00	
Unemployed	4	37.25	
<b>Disease duration (years)</b>			
< 10	30	34.32	0.18
10–20	28	35.23	
> 20	15	45.67	
<b>HAQ-DI level</b>			
Mild (0–< 1)	35	32.80	0.22
Moderate (1–< 2)	18	42.31	
Severe (2–3)	20	39.58	
<b>Depression score</b>			
No case (0–7)	36	36.83	0.95
Borderline (8–10)	14	38.50	
Case (11–21)	23	36.35	
<b>Anxiety score</b>			
No case (0–7)	45	36.21	0.05*
Borderline (8–10)	12	48.96	
Case (11–21)	16	30.25	
<b>DAS-28 level</b>			
Remission < 2.6	6	46.50	0.6
Low (2.6–< 3.2)	15	36.77	
Moderate (3.2–5.1)	33	34.89	
High > 5.1	19	37.84	
<b>Socio-economic class</b>			
Low	15	35.50	0.82
Middle	45	38.17	
High	13	34.69	

No. number, HAQ-DI Health Assessment Questionnaire Disability Index, DAS Disease Activity Index

Kruskal-Wallis (non-parametric) test was used

\*Statistically significant difference ( $P < 0.05$ )

clinical data, HAQ-DI level, DAS-28 level depression, and socio-economic class among studied patients. However, anxiety was significantly related to adherence rate ( $P = 0.05$ ).

Disease activity was significantly correlated with functional disability index, depression, and anxiety with  $P$  value of 0.000, 0.017, and 0.002, respectively, while it showed no significant association with the socio-economic level (not shown in tables).

Table 6 shows the results of the linear regression analysis of some clinical data with the medication adherence. It shows that both the age and HAQ-DI were significant predictors of the medication adherence with  $P$  value of 0.024 and 0.43, respectively.

## Discussion

Rheumatoid arthritis (RA) is an autoimmune systemic disease that primarily causes inflammation of the synovial joints [21]. If left untreated, chronic inflammation of the joints causes articular destruction and bone erosions, leading to functional disabilities [22].

Disease-modifying anti-rheumatic drugs (DMARDs) remain the first treatment line of RA as they can retard the joint damage and deformities [23].

Noncompliance to the medications leads to poor disease control, increased morbidity, and recurrent hospital admission with consecutive increased utilization of health resources [24–28].

Several interacting factors can influence patients' non-adherent behavior including disease-related factors, patient-related factors, health professional/health service-related factors, and therapy-related factors [29].

This study aimed for determining adherence rate to DMARDs among sample of Egyptian patients with RA.

In the current study, 42.5% of the studied patients were highly adherent to their DMARDs medications, while 26% were moderately adherent with a sum of 68.5%.

High adherence rate was also reported by Ragab et al. who found that 62.5% of RA patients were adherence

**Table 6** Multiple regression between medication adherence and some clinical data (No. = 73)

	Ordered clinical data	Beta	Significance
1	Age (years)	.350	.024*
2	HAQ-DI score	.271	.043*
3	Anxiety score	.183	.157
4	Disease duration (years)	.165	.192
5	Educational level	.154	.214
6	Marital status	.107	.398
7	Co-morbidities	.088	.481

Linear regression analysis test was used

No number, HAQ-DI Health Assessment Questionnaire Disability Index

\*Statistically significant difference ( $P < 0.05$ )



DMARDs [30]. On the other hand, Prudente et al. found that (16.4%) of RA patients were adherent to treatment [31]. Suggested explanation of the recorded adherence rate in the current study is the close, monthly follow-up of RA patients in the outpatient clinic. During the follow-up visits, physicians perform medication reconciliation and emphasize the importance of medication adherence and rise patients' awareness of the destructive nature of rheumatoid arthritis, so they have become keen to adhere to anti-rheumatic drugs to avoid deformities and disabilities. Another factor could be that some of the included patients received their medications through the government-funded public health system while others received it through the health insurance system. Therefore, the medication cost did not have a negative impact on their medication adherence.

In the current study, age seems to lack an influence on treatment adherence in RA patients. Similar results were reported by some investigators [29, 32], while others found a better adherence rate among older patients than in younger ones [23, 33].

Xia et al. found no statistically significant differences between age, employment, disease duration, and DAS28 score in association with adherence rate, while monthly per capita income was found to have a significant correlation with adherence rate [34]. Moreover, Sharma et al. [35] found that low income and was statistically significant responsible for the non-adherence to the treatment ( $P < 0.0001$ ) [31]. Other investigators have reported that age and disease duration were associated with medication adherence, and disease activity [36–39].

In the present study, and in line with several studies, no significant association was found between the disease duration and treatment adherence to anti-rheumatic drugs in RA patients [30, 32, 33]. Moreover, no statistically significant relation could be detected between medication adherence and disease activity expressed as DAS28-ESR and socio-economic class.

In concordance with these findings, Li et al. [40] found no significant difference between medication adherence and disease activity among RA patient [34], and Lorish et al. [41] reported that socio-economic level was not associated with adherence. However, Ragab et al. reported that DAS28 was found to correlate significantly with adherence ( $P = 0.001$ ) [30].

As regards psychological abnormalities (depression and anxiety) among studied patients, the current study revealed that 31.5% and 21.9% of patients had depression and anxiety, respectively.

Zhang et al. found that 27.5% and 30.6% of his RA patients had depression and anxiety, respectively [42], whereas Xia et al. found higher percentage of depression and anxiety in RA patients (69% and 70%, respectively) [34].

A possible explanation of the low prevalence of depression/anxiety among studied patients could be attributed to the religious background that Egyptian patients have in the face of their illness, it can be also explained by the emotional support of the patients' partners and families as most of the patients are married. Although several studies had reported the negative effect of depression on medication adherence [43–45], in this study, a statistically significant relation was found between medication adherence and anxiety ( $P = 0.05$ ) but not with depression.

Although no significant relation was found between the demographic and clinical data in this study with the medication adherence, regression analysis was done between some of these data which was found to have significant impact on the medication adherence in previous literatures [46–48].

A large number of factors have been reported to influence medication adherence in RA patients but no consistent non-adherence risk profile was agreed upon by the researchers [49].

In this study, age and HAQ-DI were found to be predictors of medication adherence. This is consistent with the results reported by Cohen et al. who reported that older patients were more adherent to their medications. This could be explained by the relative more time the older people have to take care of their health, the relative more cooperation and interaction with the health-care system, following with the physician appointments, and better belief in the importance of proper disease management [50]. Similar finding was reported by Park et al. [23].

We found that HAQ-DI was a significant predictor of medication adherence. Likewise, Hromadkova reported low drug compliance in patients with good QOL. A possible explanation is that low QOL may trigger the patient's attention towards his health care system including compliance to clinic appointment and medication regimen [51].

We found non-significant influence of other factors like anxiety, disease duration, educational level, comorbidities, and marital status on the medication adherence. This may be due to the small sample size ( $n = 73$ ) and the multiple variables entered into the model that has reduced the statistical power.

## Conclusion

Based on the results of the current study, it was concluded that more than two thirds of the studied patients had moderate to high adherence rate to their DMARDs medications and there is no statistically significant difference between medication adherence and demographic, clinical, or socio-economic data, while there is a significant relation between anxiety and medication adherence.

Age and HAQ-DI were found to be strong predictors to medication adherence in our RA patients.

### Recommendations

The current study recommended that the rheumatologist should build an open and trustworthy relationship with the patient, in which non-adherence can be openly discussed. When the rheumatologist has a trusting relation with the patient, they will be able to know if non-adherence is hampering the treatment goal. The effect of cumulative doses of corticosteroids on the psychological status of the patients should be considered. Investigation of other factors that could influence the medication adherence in different age groups such as the polypharmacy and nonintentional lack of adherence due to cognitive causes in elderly patients and drug availability and patients' knowledge about the medication should be considered in future studies.

Lastly, further studies on a larger number of patients with rheumatoid arthritis are recommended to improve the statistical power, so that the results would be generalizable to a broader population.

### Abbreviations

RA: Rheumatoid arthritis; DMARDs: Disease-modifying anti-rheumatic drugs; DAS28: Disease Activity Score; CDAI: Clinical Disease Activity Index; CRS: Clinician Rating Scale; HAQ-DI: Health Assessment Questionnaire Disability Index; HADS: Hospital Anxiety and Depression Scale; SPSS: Statistical Package for Social Science

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### Authors' contributions

SM: Conception and design, critical revision of the submitted protocol for important intellectual content, and writing the manuscript. TK: Administrative, technical or material support, and supervision. EM: Acquisition of data, analysis and interpretation of data, and statistical analysis. EE: Drafting of the submitted protocol and critical revision of the submitted protocol for important intellectual content. All authors read and approved the final manuscript.

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### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Ethics approval and consent to participate

This study has been approved by the local ethics committee of the Faculty of Medicine and conforms to the guidelines of the Declaration of Helsinki. Date of approval, 19 November 2017. Clinical trial registration number of the study is NCT03728231. All studied subjects gave written consent to participate in the study.

### Consent for publication

Not applicable

### Competing interests

The authors declare that they have no competing interests.

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