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## Original article

# Medication adherence in patients with juvenile idiopathic arthritis



Liana Silveira Adriano<sup>a,b,\*</sup>, Marta Maria de França Fonteles<sup>a</sup>,  
Maria de Fátima Menezes Azevedo<sup>b</sup>, Milena Pontes Portela Beserra<sup>a</sup>,  
Nirla Rodrigues Romero<sup>a</sup>

<sup>a</sup> Universidade Federal do Ceará (UFC), Fortaleza, CE, Brazil

<sup>b</sup> Hospital Infantil Albert Sabin (HIAS), Fortaleza, CE, Brazil

### ARTICLE INFO

#### Article history:

Received 27 January 2015

Accepted 24 November 2015

Available online 30 May 2016

#### Keywords:

Medication adherence

Juvenile idiopathic arthritis

Pharmaceutical care

### ABSTRACT

**Objective:** The aim of this study was to investigate pharmacological treatment adherence of patients with juvenile idiopathic arthritis, attended in an outpatient pharmacy at a tertiary hospital in northeastern Brazil.

**Methods:** The analysis of adherence was performed along with caregivers, through a structured questionnaire based on Morisky, Green and Levine, which enabled the categorization of adherence in “highest”, “moderate” or “low” grades, and through evaluating medication dispensing registers, which classified the act of getting medications at the pharmacy as “regular” or “irregular”. Drug Related Problems (DRP) were identified through the narrative of caregivers and classified according to the Second Granada Consensus. Then, a pharmaceutical orientation chart with information about the therapeutic regimen was applied, in order to function as a guide for issues that influenced adherence.

**Results:** A total of 43 patients was included, with a mean age of 11.12 years, and 65.1% ( $n = 28$ ) were female. Applying the questionnaire, it was found “highest” adherence in 46.5% ( $n = 20$ ) patients, “moderate” adherence in 48.8% ( $n = 21$ ), and “low” adherence in 4.7% ( $n = 2$ ). Through an analysis of the medication dispensing registers, a lower level of adherence was observed: only 25.6% ( $n = 11$ ) of the participants received “regularly” the medications. Twenty-six DRP was identified, and 84.6% ( $n = 22$ ) were classified as real. There were no significant associations between socio-demographic variables and adherence, although some caregivers have reported difficulty in accessing the medicines and in understanding the treatment.

**Conclusion:** Our findings showed problems in the adherence process related to inattention, forgetfulness and irregularity in getting medicines, reinforcing the need for the development of strategies to facilitate a better understanding of treatment and to ensure adherence.

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\* Corresponding author.

E-mail: [lianasilveira93@hotmail.com](mailto:lianasilveira93@hotmail.com) (L.S. Adriano).

<http://dx.doi.org/10.1016/j.rbre.2016.05.004>

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## Adesão ao tratamento farmacológico em pacientes com artrite idiopática juvenil por meio de questionários

### R E S U M O

#### Palavras-chave:

Adesão ao tratamento farmacológico  
Artrite juvenil idiopática  
Atenção farmacêutica

**Objetivo:** Investigar a adesão ao tratamento farmacológico de pacientes com artrite idiopática juvenil, atendidos na farmácia ambulatorial de hospital terciário do Nordeste do Brasil.

**Métodos:** A análise da adesão foi feita junto aos cuidadores, por meio de questionário estruturado com base no teste de Morisky, Green e Levine, que viabilizou a categorização da adesão em “máxima”, “moderada” ou “baixa”, e da avaliação dos registros de dispensação dos medicamentos, que classificou a retirada de medicamentos na farmácia como “regular” ou “irregular”. Os problemas relacionados com medicamentos (PRM) foram identificados por meio da narrativa dos cuidadores e classificados conforme o Segundo Consenso de Granada. Em seguida, aplicou-se uma tabela de orientação farmacêutica, que contém informações sobre o esquema terapêutico, de forma a esclarecer questões que influenciavam a adesão.

**Resultados:** Participaram 43 pacientes, com média de 11,12 anos, 65,1%, (n=28) do sexo feminino. Por meio do questionário, verificou-se adesão “máxima” em 46,5% (n=20) dos pacientes, “moderada” em 48,8% (n=21) e “baixa” em 4,7% (n=2). Pelo registro de dispensação, observou-se um nível de adesão menor: apenas 25,6% (n=11) dos participantes receberam os medicamentos “regularmente”. Identificaram-se 26 PRM, 84,6% (n=22) classificados como “reais”. Não foram observadas associações significativas entre as variáveis sociodemográficas e a adesão, embora alguns cuidadores tenham relatado dificuldade de acesso ao medicamento e de compreensão do tratamento.

**Conclusão:** Nossos achados demonstraram falhas no processo de adesão, relacionadas ao descuido, esquecimento e à irregularidade para receber os medicamentos, o que reforça a necessidade de estratégias para facilitar a compreensão do tratamento e garantir a adesão.

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## Introduction

Juvenile idiopathic arthritis (JIA) refers to a clinically heterogeneous group of patients with arthritis of unknown cause, with more than six weeks duration that starts up to 16 years old.<sup>1</sup> The treatment of arthritis includes education of the patient and his family, drug therapy, physiotherapy, psychosocial support, occupational therapy and surgical approaches. In drug therapies, generally anti-inflammatory non-steroidal drugs, corticosteroids, synthetic and biological disease-modifying antirheumatic drugs, and immunosuppressants are used,<sup>2</sup> in order to control pain and to achieve clinical inactivity or remission.<sup>3</sup>

However, as the complete resolution of the disease is of uncommon occurrence, most children and adolescents need to use multiple medications for a long period of time, especially in polyarticular forms of arthritis.<sup>4</sup> This aspect, along with other factors, contributes to a poor adherence to treatment of children and adolescents with chronic rheumatic diseases.<sup>5</sup>

The World Health Organization considers that inadequate adherence to treatment of chronic diseases is a worldwide problem of great magnitude and defines that adherence to treatment comprises a phenomenon subject to the influence of multiple factors that directly affect the patient and determine the behavior with respect to the recommendations for the treatment of disease and that, moreover, they are related

to socio-demographic conditions, the disease, the treatment, the relationship of health professionals with the patient and also to the patient him/herself.<sup>6</sup>

Crespo et al. suggested that physicians and pharmacists who follow the patient with arthritis should perform integrated actions in an effort to identify the emergence of problems related to prescription drugs, including non-adherence to treatment and, from this point, carry out interventions to reduce and prevent these problems.<sup>7</sup>

In this sense, the present study aimed to analyze the adherence to pharmacological treatment of patients with Juvenile Idiopathic Arthritis under outpatient monitoring in a pediatric hospital in Northeastern Brazil, and identify drug-related problems that can influence in this process.

## Patients and methods

The study was conducted in an outpatient pharmacy of a public hospital in northeastern Brazil, considered as a reference in tertiary care in pediatric area, where, in 2012, 130 patients with JIA were followed. Inclusion criteria were: child or adolescent (17 years and 11 months), with a confirmed diagnosis of JIA through clinical and laboratory tests, considering: onset before age of 16, duration of symptoms less than six weeks, with exclusion of the possibility of other causes.<sup>1</sup> The patient should be registered in the Specialized Component for Pharmaceutical Assistance and the primary

caregiver should attend the outpatient pharmacy of the hospital during the study period in order to receive medicines. We considered as primary caregiver that person who administers the medicine and/or monitors the treatment together with the pediatric patient, to obtain a sample by convenience. Exclusion criteria were: patients with caregivers showing any limitations that prevented answering the questionnaire, or whose companions were not the caregivers responsible by the therapy.

The caregiver of each patient with JIA was asked to answer the questionnaire on adherence, composed of two blocks: the first block approached sociodemographic data, where variables related to the patient (gender and age) and to the caregiver (education, origin, current working status and family income), as well as the degree of relationship between the caregiver and the patient were obtained; the second block dealt with the evaluation of adherence, with an initial question that identified if the responsible for the administration of the drug was the caregiver or the child himself, followed by four questions related to the adherence according to Morisky, Green and Levine test (adapted),<sup>8</sup> with questions directed to the caregiver. Thus, each positive response was assigned a value of 1 point. A final score of zero indicated 'high' adherence, 1-2 indicated 'moderate' adherence, 3-4, 'low' adherence. An analysis of the number of affirmative answers to each question was performed, in order to identify which parameter was more related to non-adherence.

After the questionnaire, the caregiver was asked to relate how the medicines were being used. The caregiver was free to express their perceptions regarding the treatment in private and in a comfortable manner. From the reports, it was possible to identify Drug Related Problems (DRP), which were classified, according to the Second Consensus of Granada, in problems of need, effectiveness or safety.<sup>9</sup> DRP rating was still considered as 'real', when there was a manifestation, or 'potential', in the face of the possibility of occurrence.<sup>10</sup>

In the face of the main difficulties of the caregiver regarding treatment, a pharmaceutical orientation table was drawn up, filled with information on the treatment regimen (dose, schedule, recommendations for intake with food, conservation), based on the medical prescription. At the time of dispensing the drug, both the caregiver and the patient received the table as well as the relevant guidelines.

Adherence to treatment was evaluated by analyzing the drug dispensing registers of the outpatient pharmacy that provides the following medications for patients with JIA: chloroquine, azathioprine, leflunomide, cyclosporine, methotrexate, etanercept and adalimumab. During four months, the books and annotations of the outpatient pharmacy dispensing register were evaluated monthly for each study participant, in order to verify the occurrence of delays in obtaining the medicines by the caregiver. The analysis of the drug dispensing registers was based on the method used by Gomes et al., which ranked the obtaining of medicines in the pharmacy as 'regular' or 'irregular'.<sup>11</sup>

An adjustment of the criteria used was carried out with the purpose of its adaptation to the particular medications used for JIA, given that the dosage varies, namely, chloroquine, azathioprine, leflunomide and cyclosporine are

daily agents; methotrexate and etanercept, weekly agents; and adalimumab, every other week agent. In the outpatient pharmacy of the hospital, medications are received in sufficient quantity for one month. Thus, for patients users of daily agents, it was considered as 'irregular' the delay of more than one day; for patients users of weekly agents, it was considered as 'irregular' the delay of more than eight days; and finally, for patients users of every two weeks agents, it was considered as 'irregular' the delay of more than two weeks.

Finally, we established a statistical relationship between the level of adherence to treatment and socio-demographic variables, using the Statistic Package for Social Sciences (SPSS) version 16.0, and applying the chi-squared test with a significance criterion for  $p < 0.05$ .

The project was approved by the Hospital Research Ethics Committee, within the regulations governing research on human beings under registration number 097/2011. The informed consent was signed by caregivers.

## Results

### Socio-demographic profile of patients and caregivers

A total of 43 patients participated in the study, of whom 65.1% ( $n = 28$ ) were female. The mean age of the patients was 11.12 years; 23.2% ( $n = 10$ ) of patients were aged under 8 years, 51.2% ( $n = 22$ ) were aged between 8 and 14 years, and 25.6% ( $n = 11$ ) between 15 and 17 years.

Regarding the profile of caregivers, none showed limitation to answering the questionnaire. The mean age of the participants was 41.07 years, and 90.7% ( $n = 39$ ) were female. Among these caregivers, 76.8% ( $n = 33$ ) were mothers of patients, 9.3% ( $n = 4$ ) were fathers and 13.9% ( $n = 6$ ) had another relationship. 72.1% ( $n = 31$ ) lived in the country and, with respect to working status, 55.8% ( $n = 24$ ) were employed, but generally had low income: 44.2% ( $n = 19$ ) earned less than the minimum wage, 51.2% ( $n = 22$ ) earned one to two minimum wages and 4.6% ( $n = 2$ ) earned more than three times the minimum wage. Only 32.6% ( $n = 14$ ) of the caregivers had education above elementary school.

### Evaluation of adherence by a structured questionnaire

Initially, in 81.4% ( $n = 35$ ) of cases, the caregiver was identified as the main responsible for the process of taking medicine at home. However, caregivers reported that patients used to be participatory, reminding the caregiver that it was time to take the medicine, which shows the co-participation of children/adolescents in the process of completing the treatment.

By analyzing the questionnaire, adherence was classified as 'high' in 46.5% ( $n = 20$ ), 'moderate' in 48.8% ( $n = 21$ ) and 'low' in 4.7% ( $n = 2$ ) of cases. We noted that the question with the highest number of positive responses (39.5%,  $n = 17$ ) was on the 'neglect with medication administration schedule,' followed by the question of 'forgetting to administer the medicine' (25.6%,  $n = 11$ ) (Table 1).

**Table 1 – Profile of affirmative responses of caregivers (n = 43) to the adapted questionnaire of Morisky, Green and Levine.**

Parameters evaluated	Yes n (%)
1. Forgetting to administer the medicine	11 (25.6)
2. Careless at times about taking the medicine	17 (39.5)
3. Discontinuing the medicine when feeling better	2 (4.7)
4. Discontinuing the medicine when feeling worse	4 (9.3)

### Analysis of adherence using the medication dispensing register

In the analysis of adherence using the medication dispensing register, it was observed that during the four-month period of the study, only 25.6% (n = 11) of participants received the agents regularly in the outpatient pharmacy. 27.9% (n = 12) of participants had an 'irregular' dispensation (a delay in one of the study months), 30.2% (n = 13) had two 'irregular' dispensations and 16.3% (n = 7) had three 'irregular' dispensations.

### Relationship between level of adherence and socio-demographic variables

The relationship between adherence verified by the structured questionnaire and socio-demographic variables of patients and caregivers (Table 2) was evaluated. Concerning statistical analysis, patients with 'low' or 'moderate' adherence were allocated in the same group.

The relationship of the variables with the adherence assessed by an analysis of medications dispensing registers was also established (Table 3). In this case, for statistical analysis, patients with at least one drug dispensation considered as 'irregular' were placed in the same group.

In both cases, no statistically significant relationship between socio-demographic variables and adherence was found, although caregivers not living in the state capital and with low education level have reported greater difficulty in accessing and understanding of the treatment, respectively.

### Analysis of Drug Related Problems and implementation of the intervention model

Based on medication dispensing registers, the profile of medicines' use from Specialized Component of Pharmaceutical Assistance for treatment of JIA was checked; it was observed that 46.5% of the participating patients were taking only methotrexate; 18.6% methotrexate + etanercept; 13.9% methotrexate + leflunomide; 4.7% adalimumab; 4.7% azathioprine; 4.7% azathioprine + chloroquine; 2.3% cyclosporine; 2.3% leflunomide; and 2.3% methotrexate + adalimumab.

In the analysis of Drug Related Problems, based on the reports of caregivers themselves about the treatment, it was observed that, of the 43 respondents, 18 did some account in which it was possible to identify one or more DRP. As a whole, 26 DRP were identified and in most cases (38.5%, n = 10), the problem was related to the lack of use of a necessary drug; followed by a non-quantitative uncertainty with respect to the drug (26.9%, n = 7); quantitative ineffectiveness of the drug

(19.2%, n = 5); problems arising from the use of an unnecessary drug (11.5%, n = 3) and non-quantitative ineffectiveness of the drug (3.9%, n = 1). Of the total 26 DRP, 84.6% (n = 22) were classified as 'real' and 15.4% (n = 4) as 'potential'.

From the identification of DRP, it was possible to direct the implementation of the intervention model in order to clarify the caregiver on the main issues that negatively influenced the treatment. The pharmaceutical orientation table has been used as a strategy to facilitate the understanding of the treatment, minimizing forgetfulness and, therefore, improving adhesion.

## Discussion

The results found showed that most patients had 'moderate' or 'low' adherence, which is related to compliance failure in at least one of the asked items. It was noticed that the main questions associated with non-adherence were a carelessness with the medication administration schedule and forgetfulness, which justifies the relevance of interventions, for example, the table with the therapeutic regimen used, which organizes the schedules of medication taken and prevents forgetfulness, given that clinical improvement with JIA is related to an appropriate fulfillment of any suitable treatment.<sup>12</sup>

The socio-demographic profile of the participating patients was similar to that observed in other studies. We found a predominance of female patients, which was expected, considering that JIA affects about three times more women than men.<sup>13</sup>

The highest frequency of patients aged 8–14 was also found both in other national (such as the study by Santos et al., who reviewed the medical records of patients with JIA and followed up at the Rheumatology Department of the Hospital das Clínicas, Universidade Federal do Estado de Minas Gerais from 2003 to 2005, whose patients had a mean age of 13.7 years<sup>14</sup>) and international studies, such as that by Feldman et al., conducted in two hospitals in Vancouver, with 175 children with JIA, where the mean age was 10.2 years.<sup>15</sup>

Regarding the profile of caregivers, it was observed that this task has been performed mainly by the patient's mother – a point already observed in another study of patients with JIA.<sup>16</sup>

The identification of variables related to socio-demographic profile of caregivers was considered relevant for the application of the questionnaire and also for implementing the intervention model, because this information allows an initial inference of possible factors that can influence adherence. The information on education level is relevant, so that one can communicate the explanations adequately for a clear understanding of the caregiver. The information of the caregiver's origin (most of caregivers in this study did not live in the state capital) allows the identification of a possible difficulty of access to medicines that were dispensed by the public health system only in the state capital. The low income of many caregivers may hinder the displacement of such people from the municipalities where they live to the capital, as well as the access to the medication through purchase, if necessary. The working status (it was reported that most caregivers were employed) may be related to the difficulty to take time off work to receive the medicine. However, the study

**Table 2 – Association between adherence to therapy assessed by the structured questionnaire and socio-demographic variables of patients and caregivers (n = 43).**

Variables	Adherence to therapy, n (%)		p-Value <sup>a</sup> p < 0.05
	Low/moderate	High	
Total	23 (53.5)	20 (46.5)	
Patient's gender			
Female	16 (68.2)	12 (61.9)	p = 0.666
Patient's age (years)			
<8	5 (22.7)	5 (23.8)	p = 0.226
8–14	10 (40.9)	12 (61.9)	
15–17	8 (36.4)	3 (14.3)	
Caregiver's age (years)			
<37	5 (22.7)	5 (23.8)	p = 0.967
37–47	12 (50.0)	10 (52.4)	
>47	6 (27.3)	5 (23.8)	
Caregiver's gender			
Female	20 (86.4)	19 (95.2)	p = 0.607
Education			
Elementary school	16 (68.2)	13 (66.7)	p = 0.916
Origin			
Capital	5 (22.7)	7 (33.3)	p = 0.438
Countryside	18 (77.3)	13 (66.7)	
Working			
Yes	13 (54.5)	11 (57.1)	p = 0.864
Income (MW)			
< 1	11 (47.8)	8 (38.1)	p = 0.432

MW, minimum wage.  
<sup>a</sup> Significant if  $p < 0.05$ , chi-squared test.

did not find a statistically significant relationship between these variables and adherence, possibly because the profile of the population served by the hospital is very homogeneous, not allowing the observation of differences between more or less adherent groups.

Considering the mean age of patients participating in the study, one can see that even in adolescence, the caregiver participates with the patient in the drug-taking process, as recommended in the literature, which highlights the importance of children to participate with their families in making decisions about their own treatment, in a manner appropriate to their stage of development and to the nature of the health problem at hand.<sup>17</sup>

Regarding the assessment of the drug dispensing register, this method is considered as suitable for detecting patients at risk of not effectively taking the medication correctly or even of abandoning treatment.<sup>18</sup> In the present study, through the analysis of drug dispensing registers, it was possible to show a lower level of adhesion than that observed with the analysis of the questionnaires. However, we cannot state in all cases that the irregularity in obtaining the medication in the outpatient pharmacy is associated with non-adherence, because in some situations the caregiver, living mainly in the interior, chose to buy the medicines (if they were available for sale directly to the consumer, such as cyclosporine and azathioprine) or used drug leftovers from a change in dosing regimen.

As for the relationship between socio-demographic variables and adherence, and in a similar way with our findings, the study by Feldman et al. found no association between socioeconomic status and adherence to treatment in patients with JIA. This same study found higher therapeutic compliance reported by caregivers, who considered the high benefit of drug treatment in patients with JIA, that is, who understood the usefulness of treatment, as well as among patients with less severe disease, observed by counting functional joints.<sup>12</sup> However, these parameters were not assessed in our study.

The results related to DRP reveal a more frequent occurrence of necessity problems where the patient does not use a drug that he/she needs, followed by security problems, where the patient shows a non-quantitative uncertainty with the use of the medication, which may be, for instance, an adverse reaction. The risk of adverse events is a common problem in patients with chronic rheumatic conditions with direct influence on adherence, together with the high number of medications and the duration and complexity of treatment.<sup>18</sup>

The study of Silva et al. reports that the implementation of pharmaceutical interventions, from the identification of the DRP (seeking to provide clear and organized information in relation to the therapeutic regimen) is an effective way to optimize treatment. The pharmaceutical care in pediatrics has promoted the streamlining of regulations and the reduction of medication errors and of adverse events, as well as an increased adherence to treatment.<sup>17</sup>



**Table 3 – Association between adherence to therapy assessed with the medication dispensing register and socio-demographic variables of patients and caregivers (n = 43).**

Variables	Dispensing register (%)		p-Value <sup>a</sup> p < 0.05
	Irregular	Regular	
Total	32 (74.4)	11 (25.6)	
Patient's gender			
Female	20 (62.5)	8 (72.7)	p = 0.719
Patient's age (years)			
< 8	9 (28.1)	1 (9.1)	p = 0.230
8–14	14 (43.8)	8 (72.7)	
15–17	9 (28.1)	2 (18.2)	
Caregiver's age (years)			
<37	9 (28.1)	1 (9.1)	p = 0.560
37–47	18 (56.3)	4 (36.4)	
>47	5 (15.6)	6 (54.5)	
Caregiver's gender			
Female	30 (93.7)	9 (81.8)	p = 0.267
Education			
Elementary School	20 (62.5)	9 (81.8)	p = 0.291
Origin			
Capital	10 (31.3)	2 (18.2)	p = 0.698
Countryside	22 (68.7)	9 (81.8)	
Working			
Yes	16 (50.0)	8 (72.7)	p = 0.294
Income (MW)			
<1	15 (46.9)	4 (36.4)	p = 0.728

MW, minimum wage.  
<sup>a</sup> Significant if p < 0.05, chi-squared test.

Our study has some methodological limitations, also perceived in other studies assessing the adherence in pediatric patients with JIA, as the work of Feldman et al. These authors argue that the application of questionnaires may be biased to the extent that caregivers can report that to them is socially correct, overestimating patient compliance.<sup>12</sup> Evaluation of the drug dispensing register, while providing relevant information, has its limitations, given that some medications could be bought in private pharmacies; and bearing in mind that this situation was not always reported by caregivers, we cannot state how often this actually happened; in addition, the fact that the drug is received by the caregiver does not make it possible to state that the patient will actually take it. Direct methods of assessment of adherence methods, such as the determination of serum levels of drugs, would allow us to obtain more accurate results. In this study it was not possible to assess the impact of the intervention model. It is suggested that further studies to evaluate the treatment in patients with JIA take into account the realization of a pharmacotherapeutic follow-up program, which will identify different variables that were not addressed in this study, but which are of great importance for the adherence to the pharmacological treatment.

Our findings allow us to identify and understand different aspects related to the current scenario of adherence to pharmacological treatment for JIA in the study population, and flaws were observed in the adherence process, mainly related

to negligence with the medication administration schedule, forgetfulness and irregularity in receiving the drugs, which reinforces the need for strategies that facilitate understanding about the treatment and ensure adherence.

### Conflicts of interest

The authors declare no conflicts of interest.

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