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PEDIATRIC RHEUMATOLOGY (S OZEN, SECTION EDITOR)

Importance of Adherence in the Outcome of Juvenile Idiopathic Arthritis

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Abstract Medical treatment of juvenile idiopathic arthritis (JIA) has advanced in the last decade, and improved prognosis is a reality in daily clinical practice. Despite this improvement in the quality of treatment, the outcome can still be compromised by modifiable factors, including delayed referral to a specialist, delayed drug treatment, poor adherence to treatment, and early interruption of drug treatment. In this review we discuss the most relevant aspects related to adherence to treatment in JIA, with emphasis on: factors that affect adherence to treatment; effect of poor adherence to treatment on JIA prognosis; when to suspect and how to assess poor adherence to treatment; and strategies to promote adherence to treatment, with an emphasis on information-reinforcement education. Besides presenting the findings of other authors, we also try to report our experience of this subject, which is still a challenge for health professionals.

Keywords Juvenile idiopathic arthritis · Adherence · Treatment · Outcome · Medication · Physical disability · Chronic disease · Rheumatic diseases · Self management · Questionnaire · Health-related quality of life

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood, causing physical disability and reduced quality of life. JIA has a variable prognosis, and is characterized by periods of activity and remission. Approximately 70–90 % of children with JIA achieve a good clinical outcome without physical disability if appropriate treatment is received. However, the disease is recurrent in approximately 5 % of cases, and 10 to 30 % of patients reach adulthood with moderate or severe functional disabilities [1, 2, 3•].

Fortunately, the medical treatment of rheumatic disease has advanced, especially in the last decade, and improved prognosis for JIA is a reality in daily clinical practice. Favorable outcomes reported in controlled clinical trials involving the use of adequate doses of subcutaneous methotrexate and biological drugs, regardless of the disease subtype at onset, and the maintenance of clinical inactivity for prolonged periods, reinforce the urgent need for early initiation and prolonged maintenance of treatment [4–9]. Despite this improvement in the quality of treatment, disease outcome can still be compromised by modifiable factors, including delayed referral to a specialist, delayed drug treatment, poor adherence to treatment, and early interruption of drug treatment [10–12].

The use of more effective drugs, with more comfortable dosages for the patient (weekly, biweekly, or monthly administration), results in a significant reduction in the daily use of nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. This development has resulted in a partial improvement of adherence, but there is still a large difference between treatment prescription and the certainty of administration. Knowledge about adherence to treatment is still based largely on the experience of experts and on studies reporting the experience of some reference centers.

The most relevant aspects related to adherence to treatment in JIA will be discussed in this review, which intends to

improve our knowledge of this subject, provide updates from the literature, and inspire new approaches to the subject.

Methods

A literature review was conducted by searching PubMed and SciELO using the keywords: "compliance" or "adherence" and "juvenile arthritis" or "chronic disease". The most relevant articles for discussion of the topic were selected. Some classic studies were included, and the opinion of experts with over 20 years of experience in pediatric rheumatology was valued.

Definition of Adherence to Treatment

According to the World Health Organization, adherence to treatment is defined as the extent of agreement between the patient's behavior in taking medications, following a diet, or implementing lifestyle changes, and the treatment regimen recommended by the health care provider [12, 13]. Although there is no standard for what should be regarded as poor adherence to drug and non-drug treatments, a patient is regarded as non-adherent when they omit more than 20 % of the recommended amount of prescribed drugs and/or of non-drug treatments [12, 14–16, 17••].

Factors that Affect Adherence to Treatment

Studies evaluating adherence to treatment in chronic disease report several factors related to poor adherence, and different levels of association among them. Some of those factors are related to patients and their caregivers, and others are related to the health system, which includes physicians and other healthcare professionals [12, 13, 18–20, 21••].

Socioeconomic Factors

Studies of adherence of patients with JIA reveal higher adherence among patients whose families have higher socioeconomic status [15, 17••, 18]. In addition, good adherence to treatment in environments with a better family structure (stable union) is observed in several studies of patients with chronic diseases, which suggests that greater family support facilitates patients' adherence to treatment [12, 18, 21••, 22, 23].

Access to medication is another aspect to be considered, and its relevance has increased as the cost of treatment has increased. Pelajo et al. assessed adherence to methotrexate of 76 children from two centers in locations with different socioeconomic levels (Rio de Janeiro, lower level; and Boston, higher level), and revealed poor adherence in 18 % of patients. In that study, the difficulty in obtaining medication was the main cause of poor adherence in Rio de Janeiro, whereas the refusal by the child to take the medication was the main cause in Boston [17••]. In a study performed at our outpatient clinic, non-use of medications because of their unavailability was a main cause of poor adherence to treatment for patients with chronic rheumatic diseases [21••].

Individual and Family Factors

The emotional stress experienced by caregivers is related to lower health-related quality of life among newly diagnosed patients with JIA [24•]. Iwamoto et al. assessed the psychological stress and quality of life of 40 caregivers of JIA patients, and found that caregivers who are female, single, and care for polyarticular JIA patients are the most affected by stress [25]. Haverman et al. studied the predictor factors of impaired health-related quality of life (HRQOL) in JIA. That study revealed a relationship between impaired HRQOL and impaired physical function, pain, school absenteeism, and a feeling of burden by the caregiver related to medication use [26].

Not all caregivers are fully able to manage the treatment of children with chronic diseases, which is complex and includes administering several medications every day and carrying out non-drug treatments that are time-consuming and require an organized schedule. Adolescents and young adults with JIA also have difficulties with self-management, particularly during the transition to adulthood, resulting in a worse prognosis for this period because of the lack of training in organizational skills and the reduced adherence to treatment [27•]. The lack of self-management ability of patients and caregivers reduces adherence because, for example, patients forget to take medication and to attend examinations and medical appointments [12, 14, 17••, 18, 21••].

Factors Related to the Healthcare Team and System

Iwamoto et al. observed that a hostile health environment, with a lack of structure related to healthcare, difficulty in obtaining medication, and architectural barriers in public places, can be a major cause of psychological stress for caregivers of patients with JIA [25]. Studies evaluating the main factors associated with satisfaction or dissatisfaction with healthcare services found a significant correlation between patient satisfaction with their healthcare team, and improved adherence to treatment and lower probability of changing service providers [28, 29].

Factors Related to Treatment Regimens and Disease Knowledge

The complexity of the therapeutic regimen can affect adherence to drug treatment [16, 18, 19, 22]. A recent study conducted in our service revealed poor adherence to drug treatment when the regimen consisted of more than three daily drugs. Lower adherence to immunosuppressive drugs and disease modifiers was also observed [21••].

Some drugs used in the treatment of JIA, particularly NSAIDs, methotrexate, leflunomide, corticosteroids, and biological drugs, are associated with unwanted adverse events (AEs) that compromise adherence. The presence of AEs may lead the patient to refuse to take the drug or the caregiver not to administer the drug because of a fear of worsening the patient's condition [17••, 26].

The lack of knowledge about the mechanisms of the disease is also an important factor that can cause poor adherence to treatment. It leads patients to refuse to take drugs, or to stop non-drug treatments including physiotherapy and the use of orthoses [12, 17••, 21••, 30, 31].

Effect of Poor Adherence to Treatment on JIA Prognosis

Medication adherence rates in chronic rheumatic disease in children and adolescents range from 38 to 96 %, being lower for adolescents (50–55 %) [12, 15, 17••, 18, 20, 21••, 23, 30, 31]. Regarding non-drug treatment, the adherence rate ranges from 40 to 86 % for physical exercises and is approximately 50 % for the use of orthoses [12, 17••, 20, 30, 31]. Patients with poor adherence to drug treatment usually have poor adherence to other therapeutic aspects, for example attendance at outpatient consultations and examinations [32•].

Studies of adherence to treatment in children and adolescents with chronic diseases reveal that patients who do not properly follow treatment have increased symptomatology, more visits to emergency units, and a higher hospitalization rate, thus overburdening the healthcare system [13, 17••, 18, 19, 22, 30, 33]. Unnecessary changes to treatment and false outcomes in therapeutic efficacy studies can also be cited as consequences associated with poor adherence. No studies have directly evaluated the effect of not taking medications on the articular prognosis of JIA.

When to Suspect and How to Assess Poor Adherence to Treatment

Detecting a case of poor treatment adherence is not a simple task in daily clinical practice. Many parents do not assume that medication is administered irregularly, and the children do not have the ability to express this problem. Therefore, this possibility should be considered in all cases of inadequate response to prescribed treatment. A detailed clinical interview about the number of daily pills, possible failures, and number of remaining pills is always valuable. A direct question, for example "How many pills did you forget to give to your child in the last month?" has a higher chance of revealing a failure than an open question, for example "Did you forget to give some drug to your child in the last month?" We should also suspect caregivers who repeatedly miss medical and multidisciplinary team appointments.

In addition to a careful interview, we have some tools that can assist qualitatively and quantitatively in this task: self-applied questionnaires, structured interviews with patients and caregivers, electronic monitoring devices for medication adherence, prescription history, and assessment of serum medication levels [15, 32•, 34, 35]. Although useful, these tools have advantages and disadvantages that make use of multiple tools the best form of evaluation [16, 36].

De Civita et al. developed questionnaires to evaluate adherence to JIA treatment that are validated in English and French [14]. Among them, the Parent Adherence Report Questionnaire (PARQ) evaluates adherence from a caregiver's viewpoint. It is composed of four repeated questions for each component of the treatment, including the use of medications and orthoses and the performance of physical exercises, and specific questions related to adherence, for example about difficulties in following the treatment, the frequency of associated adverse reactions, and the level of efficacy attributed to treatment. The questions are scored separately on a 100 mm visual analogue scale for each type of treatment. An adjustment of the Child Adherence Report Questionnaire (CARQ) was performed for children over nine years of age [14, 37].

Recently we developed a specific questionnaire to identify factors related to poor adherence to the treatment of rheumatic diseases, the Pediatric Rheumatology Adherence Questionnaire (PRAQ). PRAQ consists of 46 questions that assess the patient's socioeconomic factors, their relationship with the healthcare team and system, their health conditions and treatment, and the caregiver–patient relationship. This questionnaire was administered to a group of caregivers responsible for patients who recently started treatment at our clinic. After six months, a questionnaire to quantify the adherence of patients was administered, and the cases where caregivers and/or patients followed less than 80 % of the proposed treatment were regarded as having poor treatment adherence. Our preliminary results reveal that PRAQ identified the greatest association between poor adherence and socioeconomic variables, and that it can be a useful tool for early detection of patients at risk of low adherence to treatment [38•].

Strategies to Promote Adherence to Treatment

Rapoff and Lindsley wrote an excellent review about strategies to improve adherence to treatment for children with JIA that lead to satisfactory results. These strategies mainly work by using positive reinforcement, for example points and/or poker chips. These authors conclude that behavioral strategies, either alone or combined with educational strategies, have the best results for patients with chronic rheumatic diseases. Moreover, they suggest that patients with poor adherence should be closely monitored by their healthcare team, including nurses and psychologists. In addition, healthcare professionals should reinforce educational strategies about the disease and treatment, simplify treatment regimens, strive to reduce adverse events, and guide adolescents during their transition to adulthood [35].

Winnick et al. also wrote a comprehensive review about strategies to improve adherence in children, and concluded that the doctor–patient relationship is critical to the success of treatment. The experience and the sensitivity of the physician are crucial for identifying adherence problems. Some simple actions, for example asking about difficulties with the administration of medication and considering the lifestyle of the family, usually help [39].

Our pediatric rheumatology unit trains residents in pediatrics and pediatric rheumatology. We routinely advise these residents to carefully consider treatment adherence during the anamnesis. Patel and Davis evaluated the attitudes and practices of physicians regarding adherence to treatment regimens of patients with chronic diseases, and found that 96 % believe that the caregiver or patient is responsible for adherence and, despite the fact that adherence assessment and management are reported by experienced physicians or physicians with previous training in those aspects, most physicians do not investigate the factors related to adherence in clinical practice [40]. It is crucial that factors related to adherence be addressed in the daily practice of healthcare professionals, because otherwise the problem will not be identified.

Below, we have listed some strategies to promote better adherence, and we also discuss future prospects related to this subject.

Reinforcement in the Educational Strategies for Patients and Caregivers

According to Rapoff and Lindsley, one of the most important aspects of improving adherence to treatment is to provide information about treatment objectives, minimization of adverse events, and self-management to both patients and educators [35]. We must invest in the improvement of self-management treatment skills, i.e., enable patients and caregivers to improve their ability to manage the symptoms, treatment, physical and psychosocial consequences, and lifestyle changes inherent in living with a chronic condition. Thus, patients and caregivers should begin to work actively on JIA treatment, becoming the partners of the healthcare professionals in making therapeutic decisions. This ability may improve adherence to treatment and facilitate the transition of the patients into adulthood [27•].

In our opinion, patients and caregivers should be fully informed about all aspects of the disease at the end of the appointment. However, we know that the duration of a medical appointment can be limited. A method of improving the educational strategy is distributing material explaining JIA, for example brochures, or mentioning the availability of explanatory material on the internet. Examples of quality internet-based information for families can be found at the Arthritis Foundation (www.arthritis.org), Kids Get Arthritis Too (www.kidsgetarthritistoo.org), and the Pediatric Rheumatology International Trials Organization websites (www.printo.it).

Control of Adherence by the Multidisciplinary Team

Usually, inadequate use of medication is a consequence of non-attendance of routine appointments for different reasons. Many caregivers believe that their children are doing well because they are asymptomatic, but clinical examination and laboratory tests are essential to confirm that the patient is really doing well. Many physicians do not keep track of whether patients miss medical appointments, and so do not intercede in these cases. In an attempt to minimize this problem, we have in our outpatient clinic a dedicated social worker who contacts the patient and family by telephone after the second consecutive absence and then monitors their follow-up and the performance of examinations.

Social Support for Adherence in Cases of Difficulty in Obtaining Medications

Although effective, biological drugs are more expensive than those conventionally used, for example methotrexate. Healthcare providers should consider this problem, and families should have support to obtain the prescribed treatment. Another point to be emphasized is the support required for the patient to commute to specialized pediatric rheumatology centers, because not all cities have such specialist centers. This is a worldwide challenge, but certainly the populations of the poorest countries are the most vulnerable.

Change in the Treatment Regimen

The presence of some relatively common AEs caused by drugs used in clinical practice may compromise treatment

Table 1 Drugs commonly associated with poor adherence to treatment because of unwanted adverse effects, and strategies used to minimize this

Drug	Unwanted adverse effects	Strategies
Nonsteroidal anti-inflammatory	Nausea, epigastric pain	Administer after meals; use gastric protectors, for example omeprazole or ranitidine
Methotrexate (oral)	Nausea, vomiting, abdominal pain, weakness, dizziness[a]	Change subcutaneous regimen; avoid the administration of nonsteroidal anti-inflammatory drugs on that day; use antiemetic drugs one hour before; use folic acid
Methotrexate (subcutaneous)	Nausea, vomiting, weakness, dizziness[a]	Avoid the administration of nonsteroidal anti-inflammatory drugs on that day; use antiemetic drugs one hour before; use folic acid
Leflunomide	Nausea, vomiting, diarrhea	Avoid the administration of nonsteroidal anti-inflammatory drugs on that day; use antiemetic drugs one hour before
Corticosteroids	Weight gain, Cushing's syndrome, acne	Administer once a day; monthly pulse therapy with faster reduction in daily dose; early use of immunosuppressive drugs; careful dietary guidance
Biological (subcutaneous)	Pain and hyperemia at the application site	Alternate the application site; supervised medication administration at room temperature; use topical corticosteroids in delayed reactions

[a] Many patients have these symptoms even before the administration of methotrexate, suggesting that the fear initiates the reaction. In these cases a psychological approach may be necessary

adherence [17••]. Table 1 lists some AEs of these drugs, and the strategies used to manage this situation.

The availability of simpler treatment regimens facilitates adherence [21••, 35]. However, some caregivers have difficulty following the treatment regimen, especially for oral medications given daily. Failures are more common in cases of multiple daily medications, so we have medications that can be administered subcutaneously or intravenously, in extended-dosing intervals (weekly, biweekly, and monthly) at the day hospital, including some immunosuppressive and/or biological drugs. In these cases, we can change the dosage and monitor the patients during their visit for the proper drug administration under the supervision of nurses and the social worker.

Because a large number of medications are prescribed, parents may get confused or even forget to administer a particular pill. Such medication failings may also be explained by life circumstances—for example, longer hours at work, working night shifts, and even sharing child custody in the case of divorced parents. In the latter case, much more attention to adherence is required, and enough medication should be stocked in both the mother's and the father's homes. The school should be aware of the disease and treatment, because medication may be required during school hours.

Optimization of Multidisciplinary Monitoring

Specific instruments for the pediatric age group, which can be used in daily clinical practice, are available to measure the level of satisfaction with the healthcare system and team [41, 42]. The Healthcare Satisfaction Generic Module version 3.0 of the Pediatric Quality of Life Inventory (HS-PedsQL) is a simple and concise questionnaire that assesses information, family inclusion, communication, management techniques, emotional needs, and overall satisfaction. Questions and lack of information are a cause of poor adherence to treatment, and poor communication between healthcare providers, patients, and their families leads to dissatisfaction, insecurity, anxiety, and stress [41, 43, 44]. The HS-PedsQL is valid for use on children with oncological, renal, or rheumatic diseases [42].

Attention to Patients and/or Caregivers with a Continuous Pattern of Non-adherence

All these strategies seem to be ineffective in some particular cases of continuous poor adherence to treatment, with patients

Table 2 Strategies recommended for patients diagnosed with poor adherence to treatment

Medical appointments and evaluation by a multidisciplinary team

1. Always schedule appointments with the same professional, preferably the one with greater experience.
2. A nurse and social worker should call the caregivers to notify them of missed appointments and review therapeutic procedures in case of two consecutive absences.
3. Call the judicial authorities in case of failure to reach the absentee by telephone.

Drug treatment and procedures

1. Remind them during all medical appointments that nonadherence may worsen the disease, and that the caregivers will face social and judicial consequences in the case of a preventable adverse outcome.
2. Count the remaining medications and vials of injectable medications during medical appointments with patients and caregivers.
3. When possible, prescribe parenteral medications and medications with longer half-lives
4. Teach adolescents to be responsible for their treatment earlier if their parents are unable to conduct the treatment.

remaining at the mercy of the disease's natural course. In such cases, treatment regimens based on weekly or monthly parenteral administration of medication, including corticosteroids (methylprednisolone), subcutaneous methotrexate, and biological drugs with longer half-lives, are preferred. Medications requiring daily administration should be avoided, even when the healthcare provider is reasonably sure they would be administered without problems in adherent families. Table 2 lists the strategies used for these cases.

Conclusions and Future Prospects

Poor adherence to treatment is a problem experienced by all professionals involved in the treatment of children and adolescents with JIA. However, its actual effect on the outcome is still unknown. The use of instruments that measure adherence may help with data collection in specialized services, enabling the provider to understand in greater detail the reasons why a family does not administer medications as prescribed.

The multifactorial nature of poor adherence requires the adoption of multiple strategies to obtain more significant results, with an emphasis on strategies targeted at patients and caregivers, including information-reinforcement education, social and psychological support for families with problems, changes in the treatment regimen (when possible), and special attention to patients and/or caregivers with a continuous pattern of non-adherence, including active intervention by the multidisciplinary team.

In this review we noted that more studies are needed that focus on the prevention of poor adherence and on understanding the features of the patients and/or caregivers. In our outpatient clinic, we have initiated a procedure that includes analysis of the correlation between the psychological and cognitive aspects of these caregivers and treatment adherence. Attention, memory, verbal comprehension, non-verbal comprehension, intelligence quotient (IQ), and the presence of psychological disorders including anxiety, depression, and other disorders in caregivers are being evaluated in this analysis. We believe that many caregivers report that they understand the guidelines at the end of the medical appointment, but are not fully able to follow these guidelines at home.

Compliance with Ethics Guidelines

Conflict of Interest Claudio A. Len, Vanessa B. Miotto e Silva, and Maria Teresa R. A. Terreri declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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