# Pediatric rheumatology

# Psychological side effects of MTX treatment in juvenile idiopathic arthritis: a pilot study

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## Abstract

### Objective

*To document the psychological side effects of methotrexate (MTX) treatment in children with juvenile idiopathic arthritis (JIA) and to explore the usefulness of psychological therapy to ameliorate these side effects.*

### Methods

*The patients included in this study consisted of 29 patients with JIA using MTX. Of these, ten were referred to a pediatric psychologist because of MTX side effects, and had behavioural therapy to cope with these side effects with a strong behavioural component (anticipatory nausea, anxiety). The behavioural therapy was adapted to age and used systemic desensitization (distraction in a positive atmosphere) or cognitive behavioural therapy (relaxation and overruling negative thoughts by positive ones). The parents of the 29 children were interviewed about MTX treatment and the side effects their child had developed. Parents of children referred to the psychologist were also interviewed for their impression of the results of the behavioural therapy.*

### Results

*Prior to the behavioural therapy, nine out of 10 children reported MTX related nausea. Six of these ten were nauseous even before the administration and developed anticipatory nausea. Nine out of ten patients also showed some sign of distress in anticipation of MTX treatment, either orally of via injections. The behavioural therapy they had fully abolished side effects in five children and decreased the severity of nausea and distress in two children. Of the remaining nineteen children, not referred to the pediatric psychologist, 11 reported nausea after MTX treatment and four of these developed anticipatory nausea. In addition, eight of these 18 developed behavioural distress in anticipation of the treatment.*

### Conclusion

*This study showed that children with JIA who receive MTX treatment frequently develop psychological side effects, such as anticipatory nausea and behavioural distress in anticipation of treatment. This is true for patients selected for reported MTX side effects, as well as for randomly chosen JIA patients using MTX. As MTX is still the first choice in the treatment of severe JIA, more attention should be given to the treatment and prevention of side effects. Psychological intervention can be of help, but further studies are needed on the nature of the side effects, as well as on the prerequisites and efficacy of behavioural therapy.*

**Key words**

Juvenile rheumatoid arthritis, adverse effects, methotrexate, behavioural therapy.

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## Introduction

Juvenile idiopathic arthritis (JIA) is one of the most common rheumatic diseases in children. JIA plays a major role in the everyday functioning of an affected child. JIA includes multiple types of arthritis in children, all resulting in joint inflammation. This disease affects approximately 1 in 1,000 children under sixteen (1). Overall, JIA is more common in girls than in boys.

In some children with JIA, the disease can be treated with non-steroidal anti-inflammatory drugs (NSAID) and physiotherapy. However, in other children this treatment is not fully effective, prompting treatment with a second line so-called disease modifying antirheumatic drug (DMARD). Methotrexate (MTX) has become first choice DMARD in the treatment of juvenile idiopathic arthritis, especially in the extended oligoarticular, polyarticular and systemic onset subsets (2, 3). The efficacy and safety has been well studied and reviewed (3-7). The physical side effects of MTX in children are the same as in adults, though children generally tolerate MTX well. The most common side effects involve the gastrointestinal tract, including nausea and vomiting. Folic acid is given after the MTX dose in order to reduce the side effects (3-8). Some children experience so-called 'anticipatory' nausea. This means that symptoms occur before the dose is taken (e.g. as soon as the parent takes the lid off the medication bottle). Sometimes this results in reluctance or refusal to take the medication (9). By then it is no longer only a physical side effect but it becomes a psychological side effect as well. 'Anticipatory' nausea is a term that is used frequently in relation to cancer treatment. In that context, it has been conceptualized as the result of classical conditioning principles. Therefore, treatment with behavioural interventions may be useful (10-14). If treatment includes weekly intramuscular injections with MTX, children may develop fear of needles. These psychological effects in children treated repetitively with either oral medication or injections are clinically relevant as they add to a feeling of aversion against therapy and may contribute to patient non-compliance and eventually termination of treatment (11).

We questioned to what extent children with JIA who have to take a weekly dose of MTX, either orally or parenterally, show psychological side effects and to what extent they might benefit from a behavioural intervention. No studies have been published on the psychological effects of MTX treatment in this patient group. The main purposes of this study were to document the psychological side effects of MTX treatment in children with JIA and to explore the effects of behavioural intervention.

## Patient and methods

*Setting and Subjects*

The study contains a retrospective chart review performed in the pediatric immunology and pediatric psychology departments of the University Medical Center Utrecht. Ten JIA patients were referred to the pediatric psychologist because of psychological side effects of MTX. They had behavioural therapy to cope with these side effects with a strong behavioural component (anticipatory nausea, anxiety) between May 2002 and August 2004. To further assess the frequency of MTX related gastrointestinal side effects, nineteen consecutive patients who were using MTX and who visited the outpatient clinic from April until June 2005 were included. These patients were under the age of sixteen years and used, or had been using MTX. Exclusion criteria were age above sixteen and a systemic type of JIA, as systemic symptoms may interfere with possible side effects of MTX. Nineteen patients met these criteria and all of them were willing to participate. All of these children fulfilled the revised International League of Associations for Rheumatology (ILAR) criteria for oligo-, extended oligo-, or poly-articular JIA (12).

*Measures*

Medical data were obtained from the patient's medical records. These data included year of diagnosis and date of starting MTX. In what way there were changes in dosage of the MTX and/or

changes in the way of administering and the reasons for doing so.

A structured interview for the parents was designed to collect information about the MTX treatment in their children. Questions pertained to side effects, changes in way of administering the MTX (e.g. from oral to injections) and supportive measures for possible problems with the administration of the tablets or injections.

The parents of the children who received behavioural therapy were asked additional questions about the behavioural therapy, the effect of the therapy, whether the acquired coping strategies were still used and whether they would have liked to receive the therapy earlier during the MTX treatment.

Parental answers, confirmed the existence of three different psychological side effects. The first side effect was nausea; defined as the child feeling nauseous after MTX treatment. The second side effect was 'anticipatory' nausea, which was defined as the child feeling nauseous before the MTX dose. The third side effect was behavioural distress; defined as the child showing panic and distress in anticipation of the treatment e.g. the child needs to be forcefully held down to administer the MTX tablets or injection.

*Behavioural therapy*

The behavioural therapy has been adapted to age. The younger children are treated with the so-called 'Magic Box' method, based upon systematic desensitization by distraction. The magic box contains attractive toys. In a few sessions the child learns, with the distraction of the magic box, that the injection is necessary, but that you do not need to be afraid of it. Cognitive behavioural therapy (relaxation, overruling negative connotations, by positive thoughts) is used for children above nine years. Furthermore, an injection protocol was made for the children who received MTX injections. This protocol is meant for the general practitioner or his/her assistant. The protocol stresses to avoid delay in the waiting room before the time of the injection, to just administer the injection and to let the parent distract the child with the magic box, or in case of an older child, let the child be able to rehearse the learned thoughts.

The effect of the behavioural therapy was divided into three groups. The therapy was considered to be effective when the specific behavioural side effects, for which the child was referred to the psychologist, were no longer present. The injections or the tablets could, after the therapy, be administered without any resistance from the child. A therapy was considered moderately effective when the side effects, for which the child was treated, were still present but decreased in severity. A therapy was defined as non-effective when the therapy had no effect on the side effect(s).

*Procedure*

Parents of eligible patients were sent a letter in which the purpose of the study was explained. Oral consent from a parent was obtained at the beginning of the interview by phone. The interviews were mostly conducted right after oral consent was given. Sometimes an appointment was made for a later moment that was more convenient for the parent.

**Results**

Ten patients with behavioural therapy and an additional 19 patients also using MTX were included in this study, in total 8 males and 21 females. Characteristics including diagnostic disease type and side effects are summarized in Table I. All of the children received low doses MTX treatment and folic acid 24-48 hours after MTX administration. All but one child also used a NSAID besides the MTX. One girl from the behavioural therapy group did not use a NSAID because of allergic (skin) reactions on different types of NSAIDs.

*Side effects before start of behavioural therapy*

All of the children from this group developed at least one side effect. Side effects and other characteristics are shown in Table I. Nine out of ten children developed nausea after MTX treatment. In most children this nauseous feeling started right after taking the tablets or getting the injection and sometimes this resulted in throwing up. Six out them developed 'anticipatory' nausea as they already were nauseous before they had to take the medication. Some children became nauseous when they saw the tablet or injection, heard the word MTX, and sometimes even when they saw the color yellow (because the MTX tablets and injection fluid are yellow). Other children became nauseous as soon as they entered the practitioner's office. Also 9 children showed some form of behavioural distress (such as showing panic or resistance at the sight of the medication) in anticipation of the treatment. This was not only present in children who were treated with injections, but also in children who received the MTX orally. Some of the children did not want to go to the general practitioner office and were already upset if they had to go into the car to get there. Others needed to be held down while the injection was administered. Most children simply refused to take the medication.

*Side effects in the remaining 19 JIA children using MTX*

Only 4 children from this group did not experience any side effect of the MTX treatment, either orally or via injections, 3 of them were boys. Eleven children developed nausea after MTX treatment, which consisted of MTX tablets. One child with MTX injections became nauseous after the injection was given. One-third of the children with nausea developed 'anticipatory' nausea. All of these children used MTX tablets. At first they became nauseous after taking the tablets and after a while they were already nauseous before they had to take the MTX. Eight children developed behavioural distress in anticipation of the treatment. These children showed the same signs as the children treated with behavioural therapy, such as resistance at taking the tablets or showing panic at the sight of an injection.

No differences were found in side effects between children of different ages. There was no relation between duration of MTX treatment and the amount or type of side effects.

**Table I.** Characteristics of each patient with MTX treatment orally and/or via injections and its side effects.

| Age | Male/ Female | Type JIA | Age at diagnosis | Age MTX | Duration MTX | Nausea | Anticipatory nausea | Behavioral distress |
|---|---|---|---|---|---|---|---|---|
| 19 children without behavioral therapy | | | | | | | | |
| 3.7 | M | ext. oligo | 1.0 | 1.3 | 2.3 | | | x |
| 7.1 | M | ext. oligo | 1.0 | 4.9 | 1.7 | | | |
| 7.3 | F | ext. oligo | 1.8 | 2.3 | 4.1 | x | | |
| 7.7 | F | oligo | 2.1 | 7.1 | 0.6 | x | x | |
| 9.1 | F | ext. oligo | 3.7 | 5.2 | 3.9 | x | | |
| 9.2 | M | oligo | 2.8 | 4.7 | 1.6 | | | |
| 9.3 | M | oligo | 2.0 | 7.6 | 1.7 | x | x | x |
| 9.9 | F | ext. oligo | 1.8 | 4.1 | 4.3 | | | x |
| 10.5 | F | poly | 1.9 | 6.3 | 3.3 | x | | x |
| 10.5 | M | poly | 9.0 | 9.5 | 1.0 | | | |
| 12.3 | M | poly | 9.3 | 10.3 | 2.0 | | | x |
| 12.4 | F | ext. oligo | 3.3 | 6.5 | 5.5 | x | x | |
| 12.7 | F | poly | 7.8 | 9.0 | 3.5 | x | | |
| 12.8 | F | poly | 4.1 | 6.8 | 5.9 | | | x |
| 12.8 | F | poly | 7.1 | 7.6 | 2.5 | | | |
| 13.6 | F | ext. oligo | 2.0 | 7.8 | 5.8 | x | x | x |
| 14.1 | M | oligo | 11.0 | 12.3 | 1.8 | x | | |
| 15.2 | F | poly | 12.9 | 13.4 | 1.8 | x | | |
| 15.5 | F | poly | 6.4 | 11.6 | 1.3 | x | | x |
| 10 children with behavioral therapy | | | | | | | | |
| 5.9 | F | poly | 2.6 | 2.8 | 3.2 | | | x |
| 7.0 | F | oligo | 1.7 | 5.9 | 1.1 | x | | x |
| 7.2 | F | poly | 4.1 | 4.3 | 2.8 | x | x | x |
| 7.9 | F | poly | 1.2 | 5.0 | 2.9 | x | | x |
| 9.1 | F | poly | 5.6 | 6.0 | 3.1 | x | x | x |
| 12.8 | F | oligo | 1.5 | 7.2 | 4.3 | x | x | x |
| 13.3 | F | oligo | 5.8 | 10.0 | 3.3 | x | | |
| 13.6 | F | poly | 8.0 | 9.8 | 3.9 | x | x | x |
| 14.8 | F | ext. oligo | 1.6 | 3.3 | 11.4 | x | x | x |
| 15.6 | M | oligo | 10.8 | 12.9 | 2.6 | x | x | x |

ext. oligo: extended oligo; x: side effect present; : no side effects at all.

*Countering strategies*

Half of the parents of the children who were not referred for behavioural therapy, did not feel a need for supportive measures as to the administration of MTX, because the side effects were not that severe, or because they did not believe psychological intervention could help. In five cases the oral treatment was switched to intramuscular injections because of nausea. All but one of these children were still nauseous after the MTX injections. Three children changed from tablets to injection fluid orally, which relieved the side effects in one child.

*Behavioural therapy*

Of the ten children who had behavioural therapy, seven children received therapy because of behavioural distress after some time of MTX treatment with injections. Mean duration of MTX injection until therapy was 1.1 years ± 0.6 SD. In five children, the therapy was found to be fully effective. The effectiveness of the behavioural therapy is summarized in Figure 1. Of these five children, all but one experienced behavioural distress in anticipation of the MTX treatment with injections or MTX tablets. The therapy was moderately effective in two children who both had developed nausea, anticipatory nausea and behavioural distress because of MTX injections. In both children, all three side effects were still present after therapy, but anticipatory nausea and behavioural distress decreased in severity. In three children, the therapy was found to be of no effect. One child was not motivated for the therapy. For the other two the side effects they experienced before therapy were still present after therapy.

## Discussion

This is to our knowledge the first study on the psychological side effects of MTX treatment in children with JIA. In our study not only patients who were referred to the child psychologist showed side effects, but also fifteen out of nineteen (79%) consecutive patients at the outpatient clinic developed one or more side effect. All but one child from the behavioural therapy group and almost two-thirds of the patients from the outpatient clinic group developed nausea during MTX treatment, underscoring that this problem is contributing to treatment related distress in a large number of JIA patients.

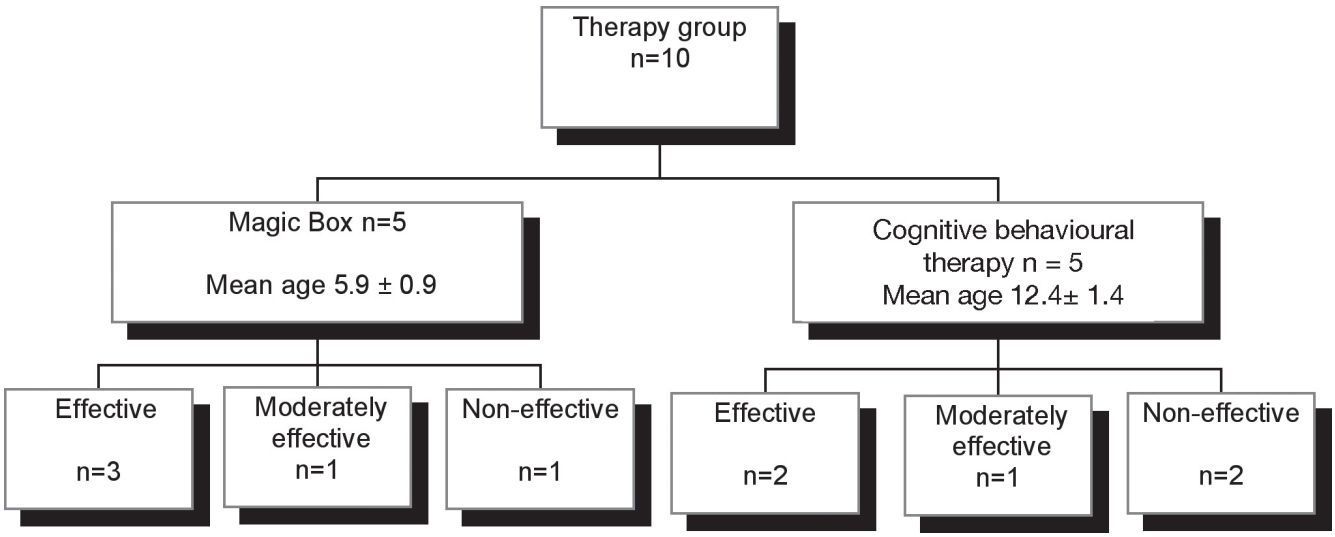


**Fig 1.** Effectiveness of behavioural therapy.

In previous studies, nausea has been frequently described as a side effect, but without numbers indicating its frequency of occurrence. In 2002 Murray *et al*. (9) reported that a number of JIA patients show 'anticipatory nausea', while Ramanan *et al*. (5) reported that psychological support should be considered for children with JIA, who show habitual nausea after MTX. Approximately 50% of the patients in the behaviourally treated group and 20% of the patients in the non-treated group developed anticipatory nausea, a number that is comparable to findings in pediatric cancer patients. Dolgin *et al*. (11) documented anticipatory nausea in 28% of pediatric patients with cancer who were receiving outpatient chemotherapy. Although this is another patient group, the psychological mechanism of conditioning to (several aspects of) MTX medication that causes anticipatory nausea is identical. Both cancer patients and JIA patients became nauseous after treatment, which is a physical effect. After a while, it became psychological as these children showed nausea in anticipation of the treatment.

The Figure reported in our study may overestimate the overall prevalence of anticipatory nausea, because the patients who received behavioural therapy were not randomly chosen from the total group of JIA patients. In the group of nineteen patients who did not receive behavioural therapy, 20% developed anticipatory nausea. However, it is also possible that with a longer duration more patients will develop this side effect. Besides anticipatory nausea, parents also reported 'behavioural distress' in anticipation of the MTX injections or tablets. Most research on needle fear in children includes hospitalized children who encounter venipunctures, intravenous cannulation, capillary sticks, port-a-cath access or intra-muscular injections. In a study on emotional responses in children prior to or during needle insertion Duff (13) concluded that what is seen clinically is neither fear nor phobia of needles per se, but anticipatory fear and distress. This phenomenon was also seen in our study, with a prevalence rate of respectively 90% and 42% in our study groups with or without behavioural therapy. The behavioural distress was not only present in children who received injections, but also in children who used MTX tablets. This suggests that not only the fear of pain in case of an injection plays a role, but also fear of the medicine (the small yellow tablets) and its weekly administration itself. Several studies (10, 14-16) reported possible treatment options for these psychological side effects, such as topical anesthetics, comfort by parents (verbal reassurance and distraction) and no delay in needle insertion. Behavioural interventions for anticipatory nausea have only been studied in adult and pediatric cancer patients undergoing chemotherapy. In these patient groups behavioural interventions (e.g., hypnosis, emotive imagery, distraction, relaxation and cognitive restructuring) could effectively control anticipatory nausea and vomiting. In our study behavioural therapy, using distraction, was fully effective in half of the patients receiving behavioural intervention. One explanation why only half of these children responded to their treatment, could be that these patients had longer existing problems concerning the MTX, while also other factors could have played a role in maintaining the side effects. Within this pilot study, only a few variables were included. Other factors, such as parent's interaction, parental management of children in stressful situations and temperament of the child may also contribute to the development and/or maintenance of anticipatory nausea and behavioural distress in anticipation of administration.

As MTX is still the first choice in the treatment of severe JIA, more attention should be given to the treatment and prevention of side effects. The alternatives for MTX, such as etanercept and leflunomide should be given in cases of inefficacy or intolerance of MTX. Reducing the MTX intolerance in JIA will enable a better choice of second line drugs, taking into account possible adverse events and financial consequences. Moreover, pediatric rheumatologists should be aware of the psychological

side effects. They can provide patients and their parents with more information concerning the medicine and its possible (psychological) side effects. Furthermore, in case of changing the MTX from tablets to injections, they can provide a protocol for the administration of the injection, which minimizes behavioural distress.

In summary, it is clear from our results that children with JIA frequently develop psychological side effects because of MTX treatment. This is true for patients selected for reported MTX side effects, as well as a randomly chosen group using MTX. This pilot study left questions unanswered as to the prevalence of these psychological side effects in the total group of JIA patients and whether psychological intervention could be effective in more children and what would be the right time to start a behavioural therapy. Further research is needed in a larger cohort of patients, with more detailed questionnaires.

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