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1 **TITLE PAGE**

2 **The experience of taking methotrexate for juvenile idiopathic arthritis: results of a**
3 **cross-sectional survey with children and young people.**

4

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16

17 Abstract18 **Background:**

19 Children and young people (CYP) with juvenile idiopathic arthritis (JIA) are known to have
20 impaired health-related quality of life (HRQoL), which is improved significantly for many by
21 treatment with methotrexate (MTX). However, a significant proportion of CYP experience
22 difficulties in taking MTX, which may reduce its potential benefits for HRQoL. The aim of
23 this research was to examine how CYP with JIA perceive MTX treatment and how this
24 relates to HRQoL.

25 **Methods:** CYP aged 8-16 years taking MTX for JIA completed an adapted Parent Adherence
26 Report Questionnaire, which contains 100mm visual analogue scales, to assess difficulty
27 taking MTX, adherence, frequency of negative reactions and helpfulness of MTX. They also
28 completed the Pediatric Quality of Life Inventory (PedsQL) Generic and Rheumatology
29 scales. We collected data on age, gender, JIA course, disease duration, MTX duration of use,
30 route and dose. Number of inflamed and limited joints were indicators of disease severity.

31 **Results:** 116 CYP participated. Most considered MTX helpful (median 87; interquartile
32 range (IQR) 50.75–98) and reported adherence was high (median 98; IQR 90–100). There
33 was greater variability on scores for difficulty (median 22; IQR 2–69) and frequency of
34 negative reactions (median 14.5; IQR 1.25–80). Mean (S.D.) scores on the PedsQL Physical
35 and Psychosocial subscales were 71.63 (24.02) and 71.78 (19.59) respectively, indicating
36 poorer HRQoL than that reported by healthy children. After controlling for demographic
37 and disease variables, poorer physical HRQoL was significantly accounted for by greater
38 difficulty in taking MTX. Poorer psychosocial HRQoL was significantly accounted for by
39 subcutaneous MTX administration, a lower rating of MTX helpfulness and a greater reported
40 difficulty in taking MTX.

41 **Conclusions:** Taking MTX for JIA was viewed as helpful by most CYP but HRQoL was
42 poorer in those who reported greater difficulty in taking MTX.

43

44 **Keywords:** Juvenile idiopathic arthritis, methotrexate, quality of life

45 BACKGROUND:

46 Children and young people (CYP) with juvenile idiopathic arthritis (JIA) are known to have
47 impaired health-related quality of life (HRQoL), particularly on measures of the physical
48 domain [1,2]. Although this is improved significantly for many CYP by treatment with
49 methotrexate (MTX) [3] and biologic therapies [4], HRQoL can remain suboptimal [5].
50 Higher pain scores and poorer physical function are important predictors of poorer HRQoL in
51 JIA [6] but variability in HRQoL is not explained purely by these factors [7]. For example,
52 Seid et al [5] found that many CYP with no or mild symptoms still report impaired HRQoL.

53

54 A factor that may influence HRQoL in JIA is how CYP experience their treatment. Although
55 MTX has been found to improve HRQoL in JIA [3], CYP may experience side effects such
56 as nausea and vomiting and procedural distress [8,9]. Approximately half of CYP who take
57 MTX for JIA are reported to experience difficulties. We have previously reported proxy data
58 from mothers of CYP with JIA which found that feeling sick after taking MTX and anxiety
59 about injections were related to poorer HRQoL [9]. Such proxy reports are essential in child
60 health, particularly in relation to younger children, but given the differences found between
61 patient and proxy reports on other measures [10-12], CYP's own reports of their experiences
62 of taking medication for JIA are also needed.

63

64 We are aware of two studies in JIA that have examined the relationship between CYP's
65 views about their treatment and their HRQoL. Seid et al [7] found a relationship between
66 greater self-reported treatment problems assessed with the PedsQL Rheumatology Module
67 [2] and poorer physical and psychosocial HRQoL. A study which examined HRQoL in JIA
68 using self-reports from CYP aged 8 years and over, identified 'subjective burden of
69 medication use' as a predictor of psychosocial HRQoL in JIA [13]. Neither of these studies

70 asked specifically about MTX and we are not aware of any research that has examined CYP's
71 own reports of taking MTX and how this impacts on their HRQoL. The aim of this study
72 was to examine how CYP with JIA perceive their MTX treatment and how this relates to
73 their HRQoL.

74

75

76 **METHODS**

77 **Design**

78 A cross-sectional design was used. Data were collected as part of the Childhood Arthritis
79 Response to Medication Study (CHARMS), which investigates factors that influence
80 response to MTX or anti-TNF treatment for JIA. This study examines genetic, immunological
81 and psychological aspects of response to medication and recruits CYP who are about to start
82 taking methotrexate (MTX) or anti-TNF, are taking MTX at the time of recruitment or have
83 taken MTX in the past. The study methodology has been described in detail elsewhere [9].

84

85 **Participants**

86 Participants were recruited from Great Ormond Street Hospital for Children and the
87 Adolescent Rheumatology service at University College Hospital, London, UK between May
88 2006 and May 2008. Patients were eligible to take part in the CHARMS study if they had a
89 diagnosis of JIA defined by International League of Associations for Rheumatology (ILAR)
90 criteria [14]. Although CHARMS recruits patients of any age, only patients aged 8 years and
91 over completed questionnaires about their experience of MTX. Not all CYP in the study
92 were still taking MTX at the time the study questionnaires were completed. As some CYP
93 may have ceased taking MTX because they were well but others may have ceased due to

94 intolerance, this analysis is restricted to those CYP who were taking MTX at the time of
95 questionnaire completion to help ensure a more homogeneous sample.

96

97 **Procedures**

98 Parents were approached to take part in the CHARMS study at a routine out-patient
99 appointment. Written informed consent was obtained from at least one parent and age-
100 appropriate written assent was obtained from the patient. CYP completed the questionnaires
101 described below during waiting time in the clinic. They were given the option to complete the
102 questionnaires independently or for the researcher to read through the questions for them. The
103 researcher was also available to answer any queries from CYP who chose to complete the
104 questionnaires independently. Parents did not assist CYP with questionnaire completion.

105

106 **Ethics, consent and permissions**

107 The study had full ethical approval from the Institute of Child Health/GOSH Local Research
108 Ethics Committee, reference 05/Q0508/95. All participants gave full, informed written
109 consent (parental consent and age appropriate child/young person assent). The study
110 conforms to the principles outlined in the Declaration of Helsinki.

111

112 **Measures**

113 Participants completed the following questionnaires:

- 114 • Views about MTX were assessed by adapting the Parent Adherence Report
115 Questionnaire (PARQ)[15] so that the questions were addressed to the CYP instead of
116 the parent. CYP indicated on a 100mm horizontal VAS i) their level of difficulty in
117 taking MTX with endpoints very easy/very hard; ii) how often they take MTX as
118 prescribed with endpoints never/always; iii) negative reactions such as crying in response

119 to taking MTX with endpoints never/always and iv) their opinion of the helpfulness of
120 MTX for their arthritis with endpoints not helpful/very helpful. A mean of questions i) –
121 iii) is calculated to provide an ‘ability to take’ score. Higher scores represent greater
122 perceived ability to take and greater perceived helpfulness.

- 123 • HRQoL was assessed using the Pediatric Quality of Life Inventory (PedsQL) Generic
124 and Rheumatology scales [2]. The generic scale provides physical and psychosocial
125 composite scores. The rheumatology scale has 5 subscales: pain and hurt; daily activities;
126 treatment; worry; communication. The composite and subscale scores are each
127 transformed to 0–100 scores as specified by Varni et al (2002)[2], where a higher score
128 represents better HRQoL.
- 129 • We also collected data on the child's age, gender, JIA type according to ILAR criteria
130 [14] (systemic, oligoarticular persistent, oligoarticular extended, polyarticular RF-,
131 polyarticular RF+, psoriatic, enthesitis-related arthritis (ERA), undifferentiated) disease
132 duration, MTX duration of use, route and dose. The number of inflamed/active and
133 limited joints was recorded as indicators of current disease activity.

134

135 **Statistical analysis**

136 Statistical analysis was performed in IBM SPSS Statistics 22.

137 Medians and interquartile ranges (IQR) were calculated for scores on the PARQ. To examine
138 the hypothesis that CYP's views of MTX would account for some of the variance in HRQoL
139 measured with the PedsQL, the relationship between variables was examined initially by
140 correlations (Pearson r correlations for continuous variables, Spearman's rho (r_s) for ordinal
141 variables). In the case of categorical independent variables (e.g. gender), differences in
142 HRQoL between categories were examined by t-test or analysis of variance (ANOVA), as
143 applicable. As expected, we recruited small numbers of CYP with the lower prevalence JIA

144 types (psoriatic = 6; ERA = 7; undifferentiated = 2); therefore we classified participants into
145 whether they had an oligoarticular or polyarticular course, that is the number of joints that
146 had been involved up to the time of the study (4 or less, more than 4 respectively).

147 To examine which variables accounted for most variance in HRQoL, all significant variables
148 identified from the univariate analyses were included in hierarchical multiple regressions
149 using enter method and a level of $p < .05$ as an entry criterion.

150

151 Two regression analyses were performed, one for the Physical and one for the Psychosocial
152 summary scales of the Generic PedsQL. The independent variables were entered into the
153 regression in blocks in the following order: 1. Demographic variables; 2. Disease variables; 3.
154 MTX-related variables. This order was used because it enables examination to be made as to
155 whether experience of MTX added to the explanation of quality of life once disease severity
156 had been taken into account.

157

158 **RESULTS**

159 116 CYP who were taking MTX at the time of study recruitment completed the study
160 questionnaires. Sample characteristics are shown in Table 1. As expected in JIA, the majority
161 of CYP were female, and for most, their JIA had taken a polyarticular course, affecting 5 or
162 more joints. A small majority of CYP (54.3%) were taking MTX subcutaneously at time of
163 assessment.

164

165 CYP's views about MTX are shown in Figure 1, which reports the median and inter quartile
166 range (IQR) scores on the PARQ. Self-reported adherence was very high among most CYP,
167 with a median (IQR) of 98 (90 - 100) on the 100mm scale, however 20 (17.4%) scored below
168 80, and of these, 9 (7.8%) scored below 50. Scores on the other items of the PARQ showed

169 greater variability. A quarter of CYP scored 69 or above on the 100mm scale for level of
170 difficulty in taking MTX and 80 or above on the 100mm scale for frequency of negative
171 reactions to MTX. Most CYP rated MTX as helpful with half scoring 87 or above on level of
172 helpfulness however a quarter scored on or below the midpoint of the scale.

173

174 Scores on the PedsQL Generic Scale and Rheumatology Module are shown in Table 2. Mean
175 scores on the Rheumatology Module and Physical and Psychosocial subscales were similar to
176 those recorded by the scale's developers in children with JIA [2]. Scores were poorer than
177 those reported by a healthy UK sample, aged 8-18 years, of 88.51 (11.62) and 81.84 (13.21)
178 respectively [16].

179

180 In univariate analysis, the independent variables that were associated with better Physical
181 HRQoL were: male gender ($t=2.12$, $df=114$, $p<0.05$); fewer active joints ($r_s = -0.22$, $p<0.05$);
182 greater perceived ability to take MTX ($r=0.38$, $p<0.005$) and greater perceived helpfulness of
183 MTX ($r=0.30$, $p=0.001$). The independent variables that were associated with better
184 Psychosocial HRQoL were: fewer active joints ($r_s = -0.23$, $p<0.05$); oral administration of
185 MTX ($t=2.27$, $df=113$, $p<0.05$), greater perceived ability to take MTX ($r=0.38$, $p<0.005$) and
186 greater perceived helpfulness of MTX ($r=0.27$, $p<0.005$).

187

188 Multivariate analyses of the relation between experiences of MTX and physical and
189 psychosocial HRQoL are shown in Table 3. CYP's perceptions of MTX made a small but
190 statistically significant contribution to explaining variability in HRQoL. MTX-related
191 variables explained an additional 9% and 16% respectively in physical and psychosocial
192 HRQoL after controlling for gender and disease activity, as shown by the change in
193 cumulative adjusted R^2 in Table 3. After controlling for demographic and disease variables,

194 poorer physical HRQoL was significantly accounted for by greater reported difficulty in
195 taking MTX. Poorer psychosocial HRQoL was significantly accounted for by subcutaneous
196 MTX administration, a lower rating of MTX helpfulness and a greater reported difficulty in
197 taking MTX.

198

199

200 **DISCUSSION**

201 This is the first study of which we are aware that has reported CYP's views about taking
202 MTX for JIA in relation to their HRQoL. In the multiple regression analyses MTX-related
203 variables made an independent contribution to explaining variance in physical and
204 psychosocial HRQoL after controlling for demographic and disease-related variables.
205 Physical HRQoL was poorer in those who reported greater difficulty in taking MTX.
206 Psychosocial HRQoL was poorer in those who: took MTX subcutaneously rather than orally;
207 reported a greater level of difficulty in taking MTX and reported a lower level of helpfulness
208 of MTX. Our findings concur with those of Seid et al 2014 [7] and Haverman et al 2012 [13],
209 which found that self-reported problems with treatment were related to poorer HRQoL. The
210 current study found that MTX-related factors were important in explaining both physical and
211 psychological HRQoL as measured by the PedsQL.

212

213 We have previously reported findings from the mothers of CYP in the CHARMS study [9].
214 Approximately half of CYP were reported by their mothers to have experienced MTX side
215 effects and/or procedural anxiety regarding injections or blood tests. The child assessment we
216 report in this paper used a simpler, less detailed measure of MTX-related difficulties, so the
217 results are not directly comparable but the finding of a relationship between problems taking
218 MTX and poorer HRQoL is consistent across the respondents.

219

220 Receiving MTX to treat JIA has been shown to have a beneficial effect on CYP's HRQoL
221 [3], however those CYP who experience difficulty in taking MTX may not gain the full
222 benefit. This study has shown that although most CYP rated MTX as helpful and reported
223 high adherence, a significant minority report difficulties taking MTX and these difficulties
224 were associated with poorer HRQoL. Clinicians who ask directly about CYPs' experiences of
225 taking MTX may be able to further enhance the HRQoL of their patients by offering
226 treatments to help address these difficulties.

227

228 Psychosocial HRQoL was poorer in CYP taking MTX by subcutaneous rather than oral route.
229 The data for this study were collected before the introduction of the Metoject pen. It would
230 be of interest to examine whether use of the pen has an impact on pain and/or anxiety and any
231 consequent impact on HRQoL.

232

233 The study has several limitations. As the study is cross-sectional, the direction of causation is
234 unclear therefore it is possible that those children with poorer HRQoL have a generally more
235 negative outlook and perceive MTX more negatively. We have however controlled for
236 disease activity in the analysis (see Table 3) which indicates that experience of MTX is an
237 independent predictor of HRQoL after taking disease activity into account i.e. it is not the
238 case that the findings are explained simply by CYP with more active joints perceiving MTX
239 more negatively.

240

241 The study reports HRQoL at a single time-point in those CYP currently taking MTX.
242 Although the CHARMS study included CYP who were no longer taking MTX, the study was
243 not examining reasons for stopping MTX and therefore this information was not recorded. It

244 is possible that HRQoL would have varied in those CYP who stopped MTX due to
245 intolerance or remission but we were unable to examine these differences. We therefore
246 limited the analyses in this paper to CYP currently taking MTX. It would be informative to
247 examine CYPs' experiences of taking MTX and HRQoL over time from when they first take
248 the medication.

249

250 As the study respondents are CYP, it is limited to those aged eight years and over. However,
251 a strength of the CHARMS study is that we collected data from both parents and CYP so our
252 related publication reporting mothers' views was able to include proxy reports for younger
253 children. A limitation of using a VAS to measure participants' views about MTX is that it is
254 not clear what cut-off scores on the 100mm scales should be considered to signify, for
255 example, mild, moderate and severe problems in taking MTX and therefore what percentage
256 of CYP would fall into each category. The CYP in this study were already being treated with
257 MTX for varying durations when they were recruited therefore it was not possible to control
258 for level of response to MTX in our analysis. We did, however, include an indicator of
259 disease severity in the number of active and limited joints.

260

261 CONCLUSIONS

262 In conclusion, this analysis of CYP's views about and experience of taking MTX supports the
263 findings from our reports of mothers of CYP with JIA that MTX is viewed as helpful by most
264 CYP but HRQoL is poorer in those who report greater difficulty in taking MTX.

265

266

267 COMPETING INTERESTS

268 The author(s) declare(s) that they have no competing interests.

269

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281 AUTHORS' CONTRIBUTIONS

282 LRW and SN - study conception and design, analysis and interpretation of data and drafting

283 of the manuscript. KM - acquisition, analysis and interpretation of data and drafting of the

284 manuscript. All authors read and approved the final manuscript.

285

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296

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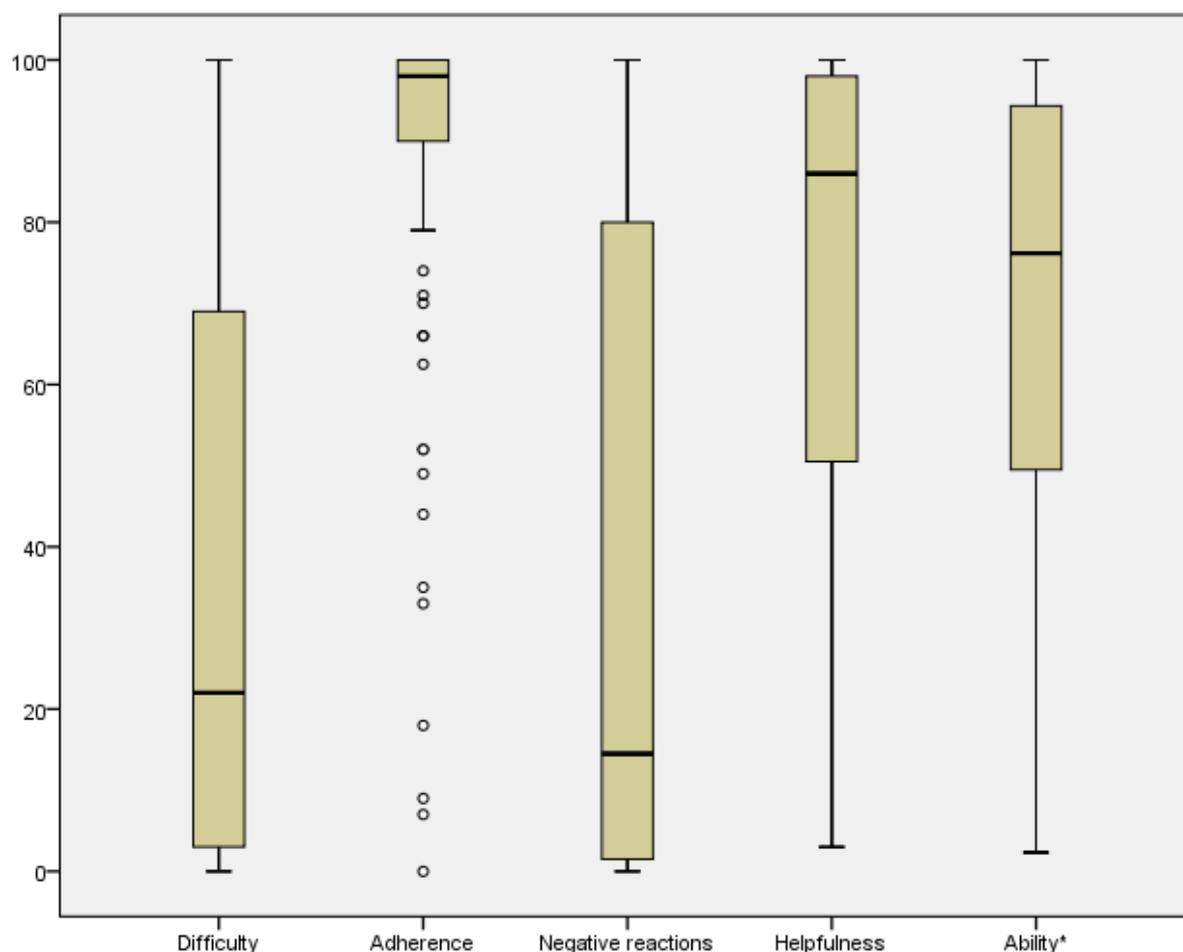
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- 359
360
361

362 **Figure 1. Views about methotrexate**



363

364 **Figure Description:**

365 Figure 1 shows boxplots of scores on the adapted PARQ measure.

366

367 **Figure Legend:**

368 Scale 0 – 100, higher score = greater perceived difficulty/ adherence/ negative reactions/
 369 helpfulness/ability to take.

370 The dark lines in the middle of boxes show the median. The bottom and top of the boxes
 371 show the 25th and 75th percentile respectively. The T-bars show the minimum and maximum
 372 scores. Circles show outliers.

373 *The Ability score is a combination of the Difficulty (reversed), Adherence and Negative
 374 reactions (reversed) scores.

375 **Table 1. Sample characteristics**

n	116
Gender, n (%) female	77 (66.4)
Age in years when questionnaire data completed, mean (S.D.)	11.9 (2.2)
JIA course, n (%)	
<i>systemic</i>	14 (12.1)
<i>oligoarticular</i>	11 (9.5)
<i>polyarticular</i>	91 (78.4)
Disease duration in years, mean (S.D.)	5.5 (3.4)
Current disease severity, median, range, (IQR)	
Number of active joints (data for n = 111)	0, 0-10, (0-2)
Number of limited joints (data for n = 108)	1, 0-32, (0-3)
Duration of MTX use in years, median (IQR)	2 (1-5)
MTX current route	
<i>Oral, n (%)</i>	53 (45.7)
<i>Subcutaneous, n (%)</i>	63 (54.3)
Current MTX dose in mg/m²/week, median (IQR)	15 (12.5 – 20.0)

376

377 **Table 2. Participant scores on the Generic Core Scales and Rheumatology Module of**
 378 **the Pediatric Quality of Life Inventory (PedsQL)**

PedsQL, Generic Scale, mean (S.D.) *

Physical	71.63 (24.02)
Psychosocial	71.78 (19.59)

PedsQL, Rheumatology Module, mean (S.D.) *

Pain and hurt	65.80 (25.94)
Daily activities	85.91 (19.77)
Treatment	69.51 (21.65)
Worry	67.17 (24.16)
Communication	64.51 (28.97)

379 * scale 0 – 100, higher score = better HRQoL

380 **Table 3. Multiple regression analyses of variables related to health-related quality of life**

Variables	PedsQL Physical			PedsQL Psychosocial		
	β	t	Cumulative Adjusted R ²	β	t	Cumulative Adjusted R ²
Demographics:			0.03			
Gender	-0.149	-1.645		-	-	
Disease activity:			0.05			0.03
Active joints	-0.110	-1.195		-0.126	-1.422	
MTX:			0.14			0.19
Subcutaneous route	-	-		-0.197	-2.216*	
PARQ Ability to take	0.256	2.688**		0.270	2.912**	
PARQ Helpfulness	0.159	1.732		0.217	2.408*	

381 *p<0.05, **p<0.01

382

383