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# Title: Parent-Reported Medication Side-Effects and Their Impact on Health-Related Quality of Life in Children with Juvenile Idiopathic Arthritis

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**Conflicts of interest**

NJS has > $10,000 Abbvie stock and <$10,000 Mylan, AstraZeneca, Sanofi, Novartis, Iovance, Galapagos, and Gilead stock. Other authors declare no conflicts of interest.

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**ABSTRACT**

**Objective:** To describe frequency and severity of parent-reported medication side effects (SE) in children with Juvenile Idiopathic Arthritis (JIA), relative to physician-reported actionable adverse events (AAE); and to assess their impact on health-related quality of life (HRQoL).

**Methods:** Newly diagnosed JIA patients recruited between 2017 and 2019 to the Canadian Alliance of Pediatric Rheumatology Investigators (CAPRI) Registry were included. Parents reported presence and severity (0=no problem, 10=very severe) of medication SE at every clinic visit. Physicians were asked to report any AAE. HRQoL was assessed using the Quality of My Life (QoML) questionnaire (0=the worst, 10=the best) and parent's global assessment (0=very well, 10=very poor). Analyses included proportion of visits with SE or AAE, cumulative incidence by Kaplan-Meier methods, and HRQoL impact measured with longitudinal mixed effects models.

**Results:** SE were reported at 371/884 (42%) visits (95% CI 39-45%) in 249 patients with a median of 2 SE per visit (IQR 1,3), and median severity of 3 (IQR 1.5,5). Most SE were gastrointestinal (32.5% of visits) or behavioral/psychiatric (22.4%). SE frequency was lowest with NSAID alone (34.7%) and highest with prednisone and methotrexate combinations (66%). SE cumulative incidence was 67% (95% CI 59-75) within 1y of diagnosis, and 36% (95% CI 28-44) for AAE. Parent global and QoML scores were worse with SE present, the impact persisted after adjusting for pain and number of active joints.

**Conclusion:** Parents report 2/3 children with JIA experience SE impacting their HRQoL within 1y of diagnosis. SE mitigation strategies are needed in managing JIA.

**Significance:**

1. Physician-reported adverse events are commonly captured in clinical trials and drug registries, but adherence and quality of life are likely directly influenced by parents' perceptions of medication side-effects.
2. Parent-reported medication side effects were present in 2/3 of children with JIA within 1 year of diagnosis.
3. Most side effects were gastrointestinal or behavioral and of mild to moderate severity.
4. Reported side effects were associated with decreased quality of life, independent of pain scores and the number of active joints.

Juvenile Idiopathic Arthritis (JIA) is the most common chronic rheumatic disease of childhood and affects approximately 1 in 1000 children (1). One or more medications are often necessary to control disease symptoms and prevent long-term damage. Medication side effects (SE) are a concern for parents and physicians and may impact adherence to treatment and health-related quality of life (HRQoL) (2).

While physician-reported adverse events (AE) are commonly captured in clinical trials and drug registries, there has been little systematic study of parent perceptions of the frequency and severity of SE in JIA and their impact on quality of life (3), with the exception of the well-known methotrexate (MTX)-associated nausea and vomiting (4). Recently, the parent/patient perspective has been emphasized with the development of patient-reported outcomes (PROs); experience with medications is included among the different domains that are assessed (5-7). Two well-known juvenile arthritis questionnaires, the Juvenile Arthritis Quality of Life Questionnaire (JAQQ) (8) and the Juvenile Arthritis Multidimensional Assessment Report (JAMAR) (9) include lists of SE reported by patients and parents, but to date no systematic analysis of reported SE has been published.

The aim of this study was to describe parent-perceived SE associated with all anti-rheumatic treatments prescribed in a Canadian inception cohort of children with JIA, with two specific objectives: 1) to describe the frequency and severity of parent-reported medication SE relative to physician-reported actionable adverse events (AAE); and 2) to assess the association of parent-reported SE with HRQoL.

## METHODS

Data from the Canadian Alliance of Pediatric Rheumatology Investigators (CAPRI) JIA Registry were used in this study (10). Recruitment into the registry began in February 2017. Children were enrolled within 3 months of JIA diagnosis at one of 14 participating sites, each of which obtained local ethics board approval.

Core data are collected for the Registry at *every clinic visit* by parents, patients and physicians, including information on disease activity, treatments, physician-reported AAE, parent-reported medication SE, disease outcomes, and quality of life (10). There are no arbitrarily fixed study visit intervals to enter the information in the Registry. For the purpose of this study, data were extracted in May 2019 and focused on questions related to medications and HRQoL.

### Side effects

*At every visit*, parents were asked: 1) Is your child taking any medication for his/her arthritis? 2) If yes, is your child having any SE from medications taken for his/her arthritis? 3) If yes, parents selected SE from a 17-item list and could add any additional SE that were not listed (see Appendix). This list was created based on the questions about SE from two validated questionnaires (JAQQ and JAMAR) (8, 11) plus 2 additional items often raised by parents in clinic (infections and poor attention).

Parents were also asked to rate on a 21-point horizontal numerical scale 4) How difficult or bothersome is it for your child to take their arthritis medication (by mouth or injection)? 0=no problem to 10=very bothersome; and 5) Overall, what is the severity of the SE your child has from medication taken for arthritis? 0=no problem to 10=very severe.

### Adverse events

At every visit, physicians were asked if the patient had any AAE since their last visit. An AAE was defined as any untoward medical occurrence that requires additional medical visits, investigations, treatments or a change in arthritis medications, *irrespective of its cause*. If yes, AAE were selected

from an 18-item list and any not listed could be added (see Appendix). The AAE items listed incorporated those from the German Biologics in Pediatric Rheumatology (BIKER) registry (12), and the Childhood Arthritis and Rheumatology Research Alliance (CARRA registry) (13). The physician was also asked to report what actions were taken and if the AAE was serious, defined as any AAE that resulted in death, was life threatening, required hospitalization (admission for overnight stay), or resulted in a significant disability or a congenital anomaly; or, an AAE that required medical or surgical intervention to prevent death, significant disability or a congenital anomaly. The CAPRI Registry does not collect information on adverse events that are not actionable.

**Quality of life**

HRQoL was assessed by the child at every visit using the Quality of My Life questionnaire (QoML) (14), if the child was old enough to answer the questions according to the parent, usually 6 years and older. The question of interest was "Considering my HEALTH, my life is", the answer was rated on a 21-point horizontal numerical scale from 0=the worst to 10=the best. We also used the parent's global assessment (15) as a measure of the parent's perception of the child's HRQoL: "Considering all the ways that arthritis affects your child, please rate how your child is doing over the PAST WEEK", response was noted on a 21-point horizontal numerical rating scale from 0=very well to 10=very poor.

**Statistical analysis**

All analyses were done with STATA, version 12 (STATA Corp, College Station, TX, USA). Descriptive statistics included the median, interquartile range, and proportions. The frequency of SE was calculated as the number of visits where SE were reported, divided by the total number of visits observed in the cohort. Using this global denominator provides a measure of the overall burden of side effects in the cohort, and comparable metrics across all SE. It also avoids ambiguity, since in some visits physicians and parents disagreed as to whether the child was receiving anti-rheumatic medications (perhaps the patient was not taking prescribed treatments, or the parents were providing treatments they considered anti-rheumatic but were not prescribed by their rheumatologist). For

comparisons of frequency of SE across different medication regimens, the denominator was the total number of visits where that regimen was reported by the rheumatologist, and p values were calculated with the chi square test. Calculation of SE incidence as SE per 100 patient years of observation was not done because SE often persisted from one visit to the next and some patients reported multiple side effects. Instead, Kaplan-Meier survival methods were used to estimate the cumulative incidence of parent-reported SE and physician-reported AAE. Longitudinal mixed effects models were used to assess the impact of SE severity on QoML and parent global scores before and after adjusting for pain severity and the number of active joints. All variables were modelled as time-varying and models included a quadratic term for time, as recommended by Rabe-Hesketh and Skrondal (16).

## RESULTS

As of May 2019, 975 visits in 275 newly diagnosed patients were available in the CAPRI Registry. Eleven visits (1.1%) were excluded due to missing diagnosis date, 14 visits (1.4%) due to missing physician data and 66 visits (6.8%) due to missing parent data. The remaining 884 visits (90.5%) from 249 patients were included in the analysis. The characteristics of included patients are shown in Table 1.

### Side effects and actionable adverse events

Parents reported at least one medication SE in 371 of 884 visits (42%) (95%CI 39-45) with a median of two SE per visit (IQR 1,3). Table 2 reports the frequency of different types of SE and the frequency of physician-reported AAE. The most frequent SE were gastrointestinal (GI) (32.5% of 884 visits) and behavioral/psychiatric symptoms (22.4% of 884 visits). Physicians reported at least one AAE at 112 of 884 visits (12.7%). Eighty-nine visits had both a physician-reported AAE and a parent-reported SE. In total, 9 AAE were considered serious: 3 infections with hospitalization and one each of nausea/vomiting, adrenal suppression, inflammatory bowel disease, GI bleed, facial edema and epistaxis.

Figure 1 contrasts the cumulative incidence of SE and AAE. Within the first year of diagnosis, the proportion of parents reporting at least one SE was 67% (95%CI 59-75), and the proportion of physicians reporting at least one AAE was 36% (95%CI 28-44). Cumulative incidence of gastrointestinal and behavioral effects is shown in Figure 2. For behavioral/psychiatric symptoms, the cumulative incidence was 51% for SE, and only 4% for AAE.

Table 3 reports the frequency and severity of SE and difficulty in taking medications according to the drug regimen prescribed. The median severity of all reported SE was 3 (IQR 1.5, 5). At more than half of the visits (58.4%), the severity of SE was rated $\leq 3$ and in 83.8% was rated $\leq 5$. Of note, in 15 visits the SE had negligible severity, rated as 0. The frequency of SE was 35% with NSAID monotherapy, 59% with MTX monotherapy and 66% with prednisone and methotrexate combinations ($p < 0.001$ by chi square for differences across regimens). However, the median severity was similar

across regimens. There was no significant difference in frequency of SE according to the route of MTX (oral vs sub-cutaneous) (Table 3).

The overall median difficulty in taking medications was 2 (IQR 0, 5); 2.5 (IQR 0, 6) in the presence of SE and 1.0 (IQR 0, 3.5) if no SE was present. It varied across medication regimens from 1 in patients taking NSAID only, to 6 in patients taking biologics and MTX. Regimens including medications given by injection had higher difficulty scores (Table 3).

**Quality of life**

HRQoL was evaluated by parents using the parent global assessment and by children using the QoML. The median parent global assessment was 2.0 (IQR 0.5, 5) in the presence of SE and 0.5 (IQR 0, 2) if no SE was present. The parent global was higher (worse) with more severe SE, median of 4 (IQR 1.5, 6.5) if SE severity was > 3, compared to 1.5 (IQ 0, 3) if SE severity was ≤3. The median QoML score was 7 (IQR 5, 8.5) when SE were present and 8 (IQR 6.5, 9.5) if no SE was present. QoML was lower (worse) in the presence of more severe SE, with a median of 6 (IQR 4.7, 8.2) if SE severity was >3, compared to 7.5 (IQR 5.5, 9) if severity was ≤3.

Longitudinal mixed effects models showed that SE severity had a measurable impact on HRQoL even after adjusting for pain scores and the number of active joints (Table 4). Pain had the largest impact on HRQoL in adjusted analyses with a beta coefficient of 0.577 for the parent global assessment, and of -0.284 for QoML. In other words, a 1-unit increment in the 0-10 pain scale corresponded to a 0.577 unit increase in the parent global and a 0.284 unit decrease in the QoML score. SE severity had a beta coefficient for the parent global of 0.185 and for QoML of -0.087, numerically larger than the impact of the number of active joints (0.051 and -0.064, respectively) (Table 4).

**DISCUSSION**

In this study, we report the perspective of parents concerning SE of anti-rheumatic medications taken by their children for the treatment of JIA. In 2/3 of children with JIA, parents reported at least one SE within one year of diagnosis. Children reported to have SE by parents had impaired quality of life, independent of JIA related pain scores or the number of active joints. While most pediatric rheumatologists are aware of difficulties parents face giving medications, we believe this is the first systematic study of parent-reported SE associated with all anti-rheumatic medications used in a modern inception cohort of children with JIA.

We found a high frequency of parent-reported medication SE (42% of visits), and the risk of developing at least one SE during the first year after diagnosis was 67%.These frequency and incidence estimates cannot be directly compared to the rates of physician reported AAE, but their side-by-side analysis helps put SE in perspective and offers interesting insights. Parents and physicians were provided different lists to choose from (see Appendix), with the parent's list emphasizing symptoms using lay language and recording all levels of severity, while physicians were instructed to only report AAE selected from the list that required an action to be taken. Some of the SE were mild and may have been deemed not to require action by both parents and physicians and therefore would have been recorded by the parent as a SE but not by the physician as an AAE. Other SE may have been unknown to the physician, even though we encouraged sharing of the parents' list. There was a higher frequency of SE while receiving MTX, which reflects the well-known SE of this medication (2, 4). It is important to underline that NSAID monotherapy also had a high frequency of SE.

In our study, the most frequent GI SE reported by parents were abdominal pain, poor appetite and nausea. With MTX, it is well-known that parent-reported nausea, vomiting and behavioral difficulties occur in about half of children and impact quality of life (4, 17). A 'MTX Intolerance Severity Score" to measure MTX intolerance has been validated (18), and models to predict intolerance have been published (19). A more general questionnaire, Gastrointestinal Symptom Scale for Kids (GISSK), was developed by Brunner et al. in a convenience sample of children with JIA receiving second line

agents (20). It includes a visual analogue scale to assess severity similar to the one used in our study, but with a different anchor (severe stomach problems). Although 58% of parents in their study reported some GI symptoms, the median severity was low (6/100). Several randomized trials of NSAIDs have reported GI AE in children with JIA. Foeldvari et al. reported a 36.1% frequency of GI AE with naproxen at 7.5 mg/kg bid for 12 weeks (21), Ruperto et al. reported 32% with naproxen at 5 mg/kg bid in a one-year trial (22), and Lovell et al. reported 37% with different doses of naproxen/esomeprazole combinations for up to 6 months (23). These rates are comparable to our 34.7% frequency of parent-perceived GI SE with NSAID monotherapy (mostly naproxen).

Behavioral/psychiatric SE in children with JIA have not been well characterized in the literature but had a remarkably high incidence in our study, with an estimated 50% of parents reporting symptoms of mood change, sleep problems or headache in their children at least once during the first year after diagnosis. Headaches have been reported by physicians in 6-15% of children with JIA receiving naproxen in the above-mentioned trials (18-20) and were reported by parents in 6% of visits in our study. Without a control group of age and sex-matched children as a comparison, it is difficult to know what the general background report for these symptoms might be, but parents in our study clearly attributed them to the anti-rheumatic medications.

Some of these GI and behavioral SE could be the result of nocebo effects (24, 25). As an example, in placebo-controlled trials of NSAIDs for the control of migraine, patients receiving placebo often reported GI and behavioral symptoms and furthermore, studies that use structured lists to elicit SE also report higher frequencies of SE (26). On the other hand, we should be cautious of dismissing parent reports as nocebo effects without further evidence. Even if the nocebo effect plays a role in these reports, we can see that parent perceived SE in their children clearly impacted HRQoL, likely influencing parents' choices about treatment and adherence to treatment.

Strategies to mitigate SE are needed but it is not clear what those strategies should be. Trials with Cox-2 inhibitors and combinations of NSAID with proton pump inhibitors (PPI) have not been very encouraging to date (18-20), and these drugs (PPI) are unlikely to have much impact on

behavioral/psychiatric symptoms. As for MTX, possibilities such as adding ondansetron and cognitive behavioral therapies have been reported with mixed results (17).

HRQoL is an important outcome of the care we provide to our patients with JIA. When looking at the presence of SE and their severity, we can note a clear impact on the HRQoL. The lowered HRQoL of JIA patients has been previously established (2, 27, 28) and our study suggests that SE play a role in this lowered HRQoL. Brunner et al. showed that patients with a GISSK score ≥2 had a significantly lower HRQoL than others without GI symptoms but similar disease activity (20). In their cohort of JIA patients, Weitzman et al enrolled 180 parent-patient dyads to complete PROs during routine care. They reported that measures of disease and treatment burden were independently negatively associated with HRQOL (2). These data, connecting medication issues to low HRQoL, are important information for physicians treating children with JIA, if we want to improve the lives of our patients. The trade-off between pain control and improved function, versus SE is a well-known struggle for physicians and parents alike and we should continue to study patients' perceptions to include this vital data in our decision-making. In concordance with our finding that pain has the largest effect on patient's quality of life, a study by Burnett et al. suggested that parents value a medication's effectiveness at controlling pain and improving function more highly than the possibility of negative SE (29).

Similar to what we observed in our JIA population, Cooper et al. reported a high prevalence of patient reported SE, contrasting with low clinician estimates of SE in a cross-sectional study of adults with asthma (30). They also noted that a greater number of SE were associated with non-adherence to oral steroids, which we did not specifically assess in our study. Similar findings were also reported for adults with rheumatic diseases enrolled in the German RABBIT (Rheumatoide Arthritis: Beobachtung der Biologika-Therapie) registry (31). There was good agreement for easily observable, objective medication SE between patients and physicians, but the agreement was low for more subjective SE that could have an impact on QoL.

When evaluating the negative experiences of JIA patients with medications in clinical trials or registries, it is likely not sufficient to consider physician-reported AE alone as the frequency of negative events appears to be underestimated when compared to parent-reported SE. Over the past years, the importance of including PROs has been increasingly recognized, and these measures are now part of most registries, however SE reported by parents are not routinely included in clinical trials (3). Our study highlights the importance of adding these measures in future trials to better understand how families cope with medication SE and the impact of these SE on compliance. Our CAPRI registry is ongoing and pragmatic trials that include PROs to better address parent/patients' concerns and voice about their care are underway. We believe it is very important to evaluate treatment experiences with disease burden when measuring outcomes, particularly given the high frequency of potentially distressing SE observed in our study.

Our study has several limitations. The parent perceptions of medication SE were not verified, nor was their attribution to any specific medication. Furthermore, physicians may have known about these parental concerns but did not report them because they were not AAE. We did not ask parents if they were willing to accept the described SE without intervention (i.e. non-actionable) because the medication was perceived as being beneficial in other ways. Therefore, no direct comparison is possible between parent reported SE and physician reported AAE. We did not ask patients themselves to report SE; discrepancies between patients and parents have been reported for some PROs (5). Additionally, there are limitations in comparing our AAE rates to the rates reported in pharmaceutical trials because physicians were specifically instructed to only report events that required a medical action.

**Conclusion**

In this modern JIA inception cohort, parents of children with JIA reported a very high frequency of medication SE that had a measurable effect on the parent's global assessment of wellbeing and on the patient's assessment of HRQoL. Most common SE were GI and behavioral/psychiatric symptoms. Addressing medication SE reported by patients and parents may improve the HRQoL of children with

JIA. Good communication with families is key to avoid dismissing medication SE that they feel are important. Studies developing and testing effective strategies to mitigate these SE are needed.

**Data availability statement**

The data underlying this article are available by contacting the authors. Access to unpublished CAPRI JIA Registry data may be granted to other investigators provided that (1) they collaborate in a team that includes at least one CAPRI JIA Registry investigator, and (2) their research protocol is approved by the Canadian Alliance of Pediatric Rheumatology Investigators Scientific Protocol Evaluating Committee. For more details, contact Dr. Jaime Guzman at jguzman@cw.bc.ca.

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**Author contributions**

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr Chédeville, McGuire and Guzman had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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**Table 1:** Characteristics of patients included in the study

| | |
|---|---|
| Number of patients | 249 |
| Age in years | 7.9 (3.4, 12.6) * |
| Female | 60% |
| Weeks from diagnosis to enrolment | 4 (0, 8.6) |
| Disease duration at baseline in weeks | 22.6 (12.9, 39.4) |
| JIA category, n (%) | |
| Oligoarthritis | 108 (43.4) |
| Polyarthritis rheumatoid factor negative | 46 (18.5) |
| Enthesitis related arthritis | 40 (16.1) |
| Psoriatic arthritis | 14 (5.6) |
| Systemic arthritis | 14 (5.6) |
| Undifferentiated arthritis | 14 (5.6) |
| Polyarthritis rheumatoid factor positive | 7 (2.8) |
| Missing | 6 (2.4) |
| Physician global assessment at baseline | 3 (1.5, 4.25) |
| Active joint count at baseline | 2 (1, 4) |
| Parent global assessment at baseline | 1.5 (0, 4) |
| QoML score at baseline (n=160) ** | 7.5 (5, 9) |
| Medications, calculated per visit, n (%) | |
| Total visits | 884 (100) |
| No medications | 132 (14.9) |
| Naproxen | 453 (51.2) |
| Other NSAID | 102 (11.5) |
| Methotrexate PO | 187 (21.2) |
| Methotrexate SC | 176 (19.9) |
| Other DMARDs | 21 (2.4) |
| Prednisone | 94 (10.6) |
| Other corticosteroid | 4 (0.5) |

| | |
|---|---|
| Biologic | 104 (11.8) |
| Ocular corticosteroid | 24 (2.7) |

* Numbers are median ($25^{th}$, $75^{th}$ centiles), or number (%).

** The Quality of My Life (QoML) score was available for children who were old enough to complete the questionnaire at the parent's discretion, usually 6y and older.

**Table 2:** Frequency of parent-reported side effects (SE) and physician-reported actionable adverse events (AAE)

| Side effects grouped by system | Parent-reported medication SE, n (% of total visits) | Physician-reported AAE, n (% of total visits) |
|---|---|---|
| **At least one gastrointestinal symptom** | **287 (32.5)** | **69 (7.8)** |
| Abdominal pain | 117 (13.2) | 15 (1.7) |
| Loss of appetite | 106 (12.0) | 2 (0.2) |
| Nausea | 93 (10.5) | 45 (5.1) |
| Constipation | 55 (6.2) | 1 (0.1) |
| Mouth sores | 46 (5.2) | 2 (0.2) |
| Weight gain | 43 (4.9) | - |
| Diarrhea | 34 (3.8) | 2 (0.1) |
| Heartburn | 27 (3.1) | - |
| Blood in stool | 6 (0.7) | 6 (0.7) |
| Increase of appetite | 1 (0.1) | - |
| Weight loss | 1 (0.1) | - |
| IBD | - | 1 (0.1) |
| **At least one behavioural symptom** | **198 (22.4)** | **7 (0.8)** |
| Mood changes | 108 (12.2) | 1 (0.1) |
| Sleep problems | 73 (8.3) | - |
| Headaches | 54 (6.1) | - |
| Tired, fatigue | 24 (2.7) | 1 (0.1) |
| Poor attention | 16 (1.8) | - |
| Lightheaded or dizzy | 3 (0.3) | 3 (0.3) |
| Anxiety | 2 (0.2) | - |
| Depression | 1 (0.1) | 1 (0.1) |
| Fidgeting | 1 (0.1) | - |
| Irritable | 1 (0.1) | 1 (0.1) |
| **At least one skin disorder** | **70 (7.9)** | **17 (1.9)** |

| | | |
|---|---|---|
| Rash or hives | 33 (3.7) | 10 (1.1) |
| Injection reaction | 25 (2.8) | 3 (0.3) |
| Facial oedema | 5 (0.6) | 2 (0.2) |
| Dry skin | 4 (0.5) | - |
| Hair loss | 4 (0.5) | 1 (0.1) |
| Excess hair growth | 3 (0.3) | - |
| Stretch mark | 1 (0.1) | - |
| Photosensitivity | 1 (0.1) | - |
| Acne | 1 (0.1) | - |
| Ecchymosis | 1 (0.1) | - |
| Pseudoporphyria | - | 1 (0.1) |
| Subcutaneous atrophy after joint injection | - | 1 (0.1) |
| **Infections** | **14 (1.5)** | **6 (0.7)** |
| **Other** | **8 (0.9) *** | **21 (2.4) **** |

* Other side effects included dark or blood-tinged urine in 2 visits, and 1 each of: aches, heavy periods, nose bleeds, urinary incontinence, hand tremors, and excessive salivation.

**Other adverse events included 12 abnormal bloodwork results, 4 infusion reactions, 2 dyspnea episodes, 1 adrenal suppression episode after corticosteroid joint injection, 1 epistaxis, and 1 joint surgery.

**Table 3:** Frequency and severity of parent-reported side effects (SE) for the most common drug regimens

| Medication regimen * | Number of visits/patients** | SE frequency, n (% of visits) | SE severity, median (IQR) | Difficulty taking medication, median (IQR) |
|---|---|---|---|---|
| NSAID only | 314/148 | 109 (34.7) | 2.5 (1.5, 4) | 1 (0, 5) |
| MTX only | 98/54 | 58 (59.2) | 2 (1,4) | 2 (0, 5) |
| NSAID + MTX | 147/75 | 79 (53.7) | 3 (2, 5) | 3.75 (2, 6.5) |
| Prednisone + MTX +/- other | 50/27 | 33 (66) | 3.5 (1, 5) | 4 (0.5, 7.5) |
| Biologic only | 10/6 | 3 (30) | 2 (0.5, 3) | 2 (1, 8) |
| Biologic + NSAID | 6/3 | 4 (66.7) | 3.75 (2, 5.25) | 5.25 (1, 7) |
| Biologic + MTX | 31/15 | 11 (35.5) | 3 (1, 5) | 4.5 (2.5, 6) |
| Biologic + MTX +/- other | 72/26 | 35 (48.6) | 3.5 (1, 5) | 6 (3, 7.5) |
| | MTX oral versus subcutaneous | | | |
| NSAID + po MTX | 82/45 | 39 (49) | 3 (2, 4) | 3 (0.5, 5) |
| NSAID + sc MTX | 65/37 | 39 (60) | 3.5 (1.5, 5) | 5 (3, 7) |
| po MTX | 50/29 | 28 (56) | 2.75 (1.5, 4.2) | 1.7 (0, 6) |
| sc MTX | 48/28 | 30 (63) | 2 (1, 4) | 2 (0,5) |

* Any of these regimens could be accompanied by intraarticular corticosteroid injections. MTX: methotrexate.

** The number of patients adds to more than the total number of patients in the cohort because patients can have one medication regimen at one visit and another at a subsequent visit.

**Table 4:** Selected factors influencing HRQoL according to mixed effects models *

| Variable | Impact on parent global assessment | | Impact on Quality of My Life scale | |
|---|---|---|---|---|
| | Unadjusted beta coefficient (95% CI) | Adjusted beta coefficient (95% CI) n=817 | Unadjusted beta coefficient (95% CI) | Adjusted beta coefficient (95% CI) n=534 |
| **Severity of SE** | **0.356** (0.280, 0.431) p<0.001 | **0.185** (0.125, 0.245) p<0.001 | **-0.186** (-0.269, -0.102) p<0.001 | **-0.087** (-0.164, -0.010) P=0.03 |
| **Pain** | **0.635** (0.587, 0.684) p<0.001 | **0.577** (0.526, 0.627) p<0.001 | **-0.327** (-0.387, -0.268) p<0.001 | **-0.284** (-0.345, -0.222) p<0.001 |
| **Number of active joints** | **0.141** (0.107, 0.175) p<0.001 | **0.051** (0.025, 0.078) p<0.001 | **-0.106** (-0.140, -0.073) p<0.001 | **-0.064** (-0.096, -0.032) p<0.001 |

* Unadjusted beta coefficients are from models including only the variable of interest. Adjusted beta coefficients are from models including all three variables at once.

**Figure 1:** Cumulative incidence of parent-reported side effects and physician-reported actionable adverse events calculated with Kaplan Meier methods. The shaded area is the 95% confidence interval.

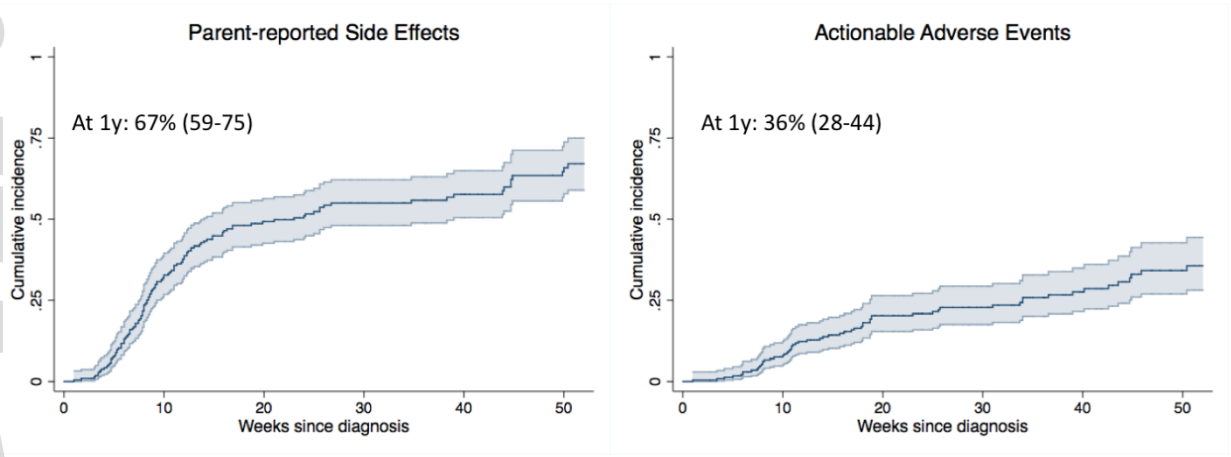

**Figure 2:** Cumulative incidence of gastrointestinal and behavioral effects reported by parents and physicians calculated with Kaplan Meier methods. The shaded area is the 95% confidence interval.