SYSTEMATIC REVIEW

Comparative Efficacy and Safety of Non-Steroidal Anti-Inflammatory Drugs in Patients With Juvenile Idiopathic Arthritis: *A Systematic Review and Network Meta-analysis*

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Objective: We conducted a systematic review and network meta-analysis to compare the efficacy and safety of nine non-steroidal anti-inflammatory drugs (NSAIDs) in treating patients with juvenile idiopathic arthritis (JIA). **Methods**: Randomized controlled trials (RCTs) of NSAIDs for the treatment in children with JIA were searched systematically by using MEDLINE, EMBASE, and the Cochrane Library for available literature up to January 1, 2019. Bayesian network meta-analysis was used to combine direct and indirect evidence on treatment effectiveness and safety. **Results**: Eight eligible RCTs involving 1112 patients with JIA were identified, addressing 9 interventions. The ranking probability plot based on the surface under the cumulative ranking curve (SUCRA) indicated that celecoxib (6 mg/kg twice-a-day) had the highest probability of being most effective (SUCRA = 76.4%) among four NSAIDs (celecoxib, rofecoxib, meloxicam, and naproxen). Also, rofecoxib (0.3 mg/kg once-a-day) and piroxicam demonstrated a higher probability of safety in treating children with JIA (SUCRA = 33.0% and 35.5%, respectively), compared with other interventions. **Conclusions**: The quality of available evidence limits the formation of powerful conclusions regarding the comparative efficacy or safety of NSAIDs used to treat JIA.

Keywords: *Drugs, Juvenile chronic arthritis, Management, Pain, Rheumatoid arthritis, Side-effects.*

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood and one of the leading causes of pediatric acquired disability. It encompasses a heterogeneous group of disorders characterized by chronic arthritis, of unknown etiology, lasting for 6 weeks or more, with disease onset before 16 years of age having excluded arthritis caused by other diseases [1]. Treatment is aimed to achieve disease remission, prevent or halt joint damage, and foster normal growth and development. Currently, early diagnosis and treatment of JIA with conventional and biologic disease-modifying anti-rheumatic drugs (DMARDs) have vastly improved outcomes for children with these diseases.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended as an adjunct therapy for symptomatic management, particularly during initiation or escalation of therapy with DMARDs or biologic agents [2]. NSAIDs exert their analgesic and anti-inflammatory effects by blocking prostaglandin formation *via* inhibition of cyclo-oxygenase (COX) isoenzymes, a rate-limiting enzyme in the prostaglandin biosynthetic pathway. Both non-selective (which suppress both COX-1 and COX-2 enzymes) and selective (suppress COX-2 only) NSAIDs have been used in JIA [3].

Previous comparative studies of NSAIDs were mostly performed to evaluate the efficacy and safety of two NSAIDs or one NSAID versus placebo [4,5]. However, the preferred NSAID in the treatment with JIA still remains unclear. To comprehensively compare and rank different NSAIDs in the treatment of children and adolescents with JIA, we conducted a systematic review and network meta-analysis [6,7].

METHODS

This systematic review with meta-analysis was conducted and reported according to the Preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines [8].

Eligibility criteria and search strategy: Randomized controlled trials (RCTs) were included if they met the following criteria: (*i*) the study compared any NSAID with placebo or another NSAID in the treatment of JIA; (*ii*) the study provided endpoints for the efficacy or adverse events; and (*iii*) the study included patients diagnosed with JIA. The details of eligibility criteria are provided in ***Web Table***

1. For this network meta-analysis, MEDLINE (via PubMed), EMBASE, and the Cochrane Library were searched for RCTs published from January 1, 1965, to January 1, 2019, comparing the efficacy and (or) safety of NSAIDs in the treatment of JIA. The following search terms were used: "#1 "Juvenile Idiopathic Arthritis" OR "Arthritis" OR "Still Disease" OR "Rheumatoid" AND #2 "NSAIDs" OR "Agents" OR "Non-Steroidal Anti-Inflammatory Drugs" OR "Analgesics" OR "indomethacin" OR "naproxen" OR "Naprosyn" OR "aspirin" OR "acetylsalicylic acid" OR "celecoxib" OR "Celebrex" OR "rofecoxib" OR "piroxicam" OR "ibuprofen" OR "meloxicam" OR "tolmetin" OR "diclofenac" OR "Voltaren" OR "voltarol" AND #3 "randomized controlled trial" OR "controlled clinical trial" OR "placebo" OR "drug therapy" OR "groups". In order to ensure the authenticity of data, we also searched the list of references included in the articles.

Data extraction: The following information was extracted from each study: *i*) study characteristics (author, year, study design); *ii*) patient characteristics (sample size, race, age, sex, duration of JIA, subtype); *iii*) interventions: any NSAID, dosage, concomitant therapy, follow-up time when outcomes were evaluated; and, *iv*) outcomes (efficacy, and adverse events). Data were extracted from original studies by two independent investigators, and any discrepancy between the investigators was resolved by after discussions along with a third investigator.

The primary outcomes were efficacy (the number of patients who had improvement in symptoms of arthritis) and safety (the number of patients who experienced adverse events).

Quality assessment: The risk of bias was assessed using Cochrane risk of bias tool [9], evaluating for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias like sample size, [10] (labeling them as low risk of bias with 200 participants or more per treatment group, unclear risk with 50 to 199 participants per treatment group, or high risk with fewer than 50 participants per treatment group), multiple publications, financial declara-tions, and participants with conflicts of interest.

Statistical analyses: First, we divided the three-arm or more-than-three-arm tests into combinations of any two arms, and performed the evidence network diagram for the comparison of each treatment. We assessed the inconsistency or extent of disagreement between direct and indirect evidence. For closed loops, we tested the transitivity assumption by examining loop-specific consistency between direct and indirect effects using network side splits and global consistency by comparing a model assuming consistency with an inconsistent model. When the global Wald test indicated no significant differences between the consistency and inconsistency models [11] and no significant differences in estimates based on side splits, we presented consistency model estimates. The Markov chain Monte Carlo (MCMC) method was used to obtain pooled effect sizes [6]. We calculated the risk ratio (RR) with 95% credible interval (CI; or Bayesian confidence interval). The efficacy and safety of NSAIDs in different arms were ordered according to the probability of being ranked as the best performing regimen. We did a network meta-analysis within a Bayesian framework with WinBUGS (version 1.4.3) and further analysis with Stata (version 15.1). Information on relative effects and safety was converted to a probability that a treatment is the best, second best, etc., or to the ranking of each treatment, called the surface under the cumulative ranking curve (SUCRA) [12]. The SUCRA value was 100% when a treatment is certain to be the best for efficacy but the worst for safety.

RESULTS

The selection of studies is shown in the flowchart (**Fig. 1**). Overall, 8 studies provided data of 1112 individual JIA patients receiving the following NSAIDs: celecoxib,

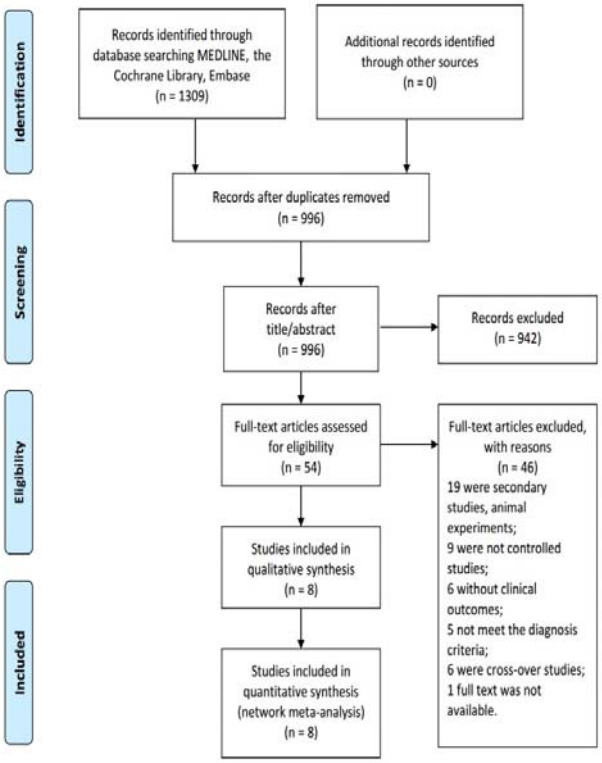

Fig. 1 PRISMA 2009 flow diagram.

rofecoxib, meloxicam, diclofenac, ibuprofen, naproxen, piroxicam, and tolmetin. The study sample size ranged from 26 to 310. The duration of treatments was from 2 weeks to 24 weeks. It was reported that there was no significant difference in age, sex, course of disease between the groups. The subtype of JIA contained polyarticular JIA, oligoarticular JIA, and systemic JIA. The details of each included trial were listed in **Table I**. Risk of bias within individual studies was assessed (**Fig. 2**).

Network meta-analysis for efficacy: Network meta-analysis was only performed when studies were sufficiently homogeneous regarding outcome criteria. Thus, for efficacy, three studies [14-16] with the efficacy criteria of achieving an American College of Rheumatology Pediatric-30 (ACR Pedi 30) response [22-23] were eligible. Four NSAIDs (celecoxib, rofecoxib, meloxicam, and naproxen) were compared with at least one other active drug directly and indirectly. There were no significant differences between any two NSAIDs regarding efficacy (**Fig. 3**). The ranking of treatments based on cumulative probability plots and SUCRAs is shown in **Web Fig. 1**. In terms of efficacy, celecoxib (6 mg/kg bid) had the highest probability of being most effective (SUCRA = 76.4%), while two doses of meloxicam ranked last.

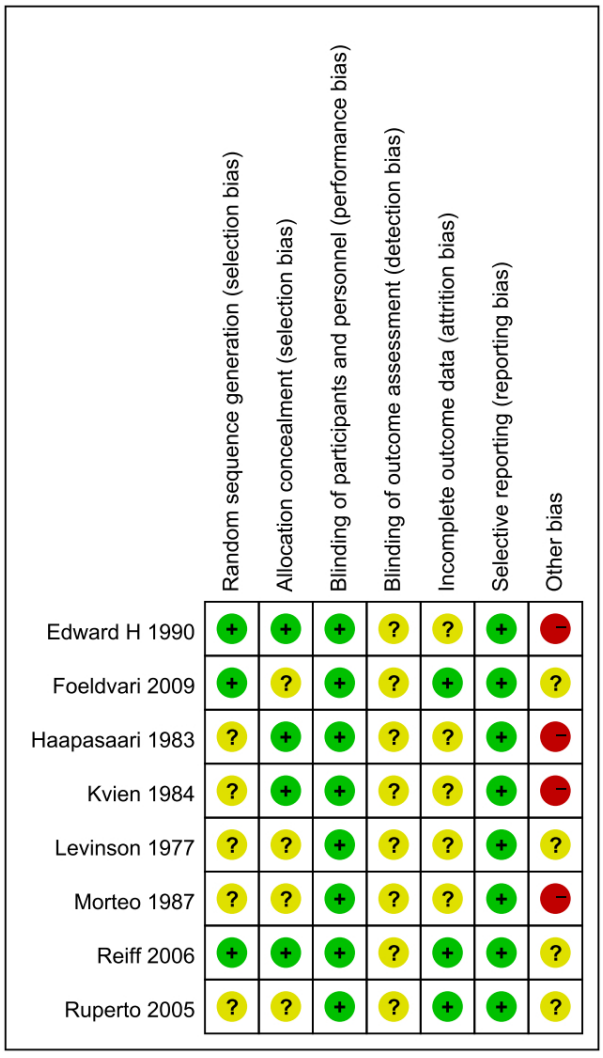

Fig. 2 Risk of bias assessment.

Network meta-analysis of the safety: Nine NSAIDs (celecoxib, rofecoxib, meloxicam, naproxen, ibuprofen, aspirin, diclofenac, piroxicam, and tolmetin) were directly compared with at least one other active drug. There were no significant differences between any two NSAIDs regarding safety (**Fig. 4**). Ranking probability based on SUCRA values indicated that rofecoxib (0.3 mg/kg/d) had the highest probability of being the safest treatment (SUCRA=33.0%), followed by piroxicam (SUCRA =35.5%). Tolmetin and aspirin appeared to have the worst safety probability (SUCRA=82.3% and 82.0%, respectively) (**Web Fig. 2**).

Inconsistency plots assessing network inconsistencies between direct and indirect estimates showed a low possibility of inconsistencies that might significantly affect the results. In addition, the results of the random and fixed-effects models yielded the same interpretation, indicating that the results were robust.

DISCUSSION

We conducted a network meta-analysis of currently available literature regarding NSAIDs for children and adolescents with JIA. Unlike previous meta-analyses, we were able to generate a ranking order for the relative efficacy and safety of NSAIDs in patients with JIA. We found that the rate of efficacy observed in all treatment groups in our study were above the pooled composite placebo response rate (28.9%) reported in a meta-analysis of six placebo-controlled trials [25]. However, no statistically significant differences were observed between NSAIDs in terms of efficacy or safety. The findings are similar to the previous meta-analysis on NSAIDs for osteoarthritis in adults [26,27]. The SUCRA ranking suggests that celecoxib had better efficacy, while piroxicam and rofecoxib have higher safety probabilities, compared to other NSAIDs.

The most common adverse effects across all treatment groups were gastrointestinal side effects, rash, headache, and pyrexia. These side effects occurred more frequently within the aspirin, tolmetin, and ibuprofen groups, resulting in more non-compliance. Estimates of NSAIDs-associated gastropathy range from 0.7-75%, depending on different study designs [28-32]. Most of the gastrointestinal

Table I Randomized Controlled Trials Included in the Systematic Review and Network Meta-analysis of Efficacy and Safety of Non-steroidal Anti-inflammatory Drugs in Juvenile Idiopathic Arthritis

Study, year	*Size of sample (t1/t2/t3)*	*Mean age (y) (t1/t2/t3)*	*Subtype*	*Mean duration (y) t1/t2/t3 (wk)*	*Treatment*			*Concomitant therapy*			*Treatment duration (wk)*
					t1	*t2*	*t3*	*DMARDs (%)*	*Biologic agents (%)*	*CS (%)*	
Foeldvari, *et al.* [14], 2009	77/82/83	10.4/10.2/10.4	pJIA, oJIA	2.71 (2.8)/ 3.77 (3.4)/ 3.41 (3.2)	Celecoxib 3 mg/kg bid	Celecoxib 6 mg/kg bid	Naproxen 7.5 mg/kg	50.6/47.6/51.8	0/3.7/3.6	NA	12
Reiff, *et al.* [15], 2006	109/100/101	9.7/9.4/10.7	pJIA, oJIA	4.0 (3.6)/ 3.4 (3.0)/ 3.7 (3.3)	Rofecoxib 0.3 mg/kg qd	Rofecoxib 0.6 mg/kg	Naproxen 7.5mg/kg	53.2/51.0/45.5	NA	19.3/22/14.9	12
Ruperto, *et al.* [16], 2005	73/74/78	8.9/9.0/7.5	pJIA, oJIA	3.47 (3.4)/ 2.5 (2.8)/ 2.31 (2.1)	Meloxicam 0.125 qd	Meloxicam 0.25 mg/kg	Naproxen 5 kg	24.7/28.4/37.2	NA	NA	12
Edward, *et al.* [17], 1990	92,1:1	7.7	pJIA, oJIA, sJIA	NA	Ibuprofen 30-40 mg/kg/d	Aspirin 60-80 mg/kg/d	——	0	0	NA	12
Haapasaari, *et al.* [18], 1983	45,1:1:1	N/A	pJIA, oJIA, sJIA	NA	Diclofenac 2-3 mg/kg/d	Aspirin 50-100 mg/kg/d	Placebo	NA	NA	NA	2
Morteo, *et al.* [19], 1987	26,1:1.06	8.5	pJIA	2.7/1.6	Piroxicam*	Naproxen 12.5 mg/kg/d	——	NA	NA	11.5	12
Kvien, *et al.* [20], 1984	80,1:1	10.2	pJIA, oJIA	1.0/1.3	Naproxen 10 mg/kg/d	Aspirin 75 mg/kg/d	——	0	0	0	24
Levinson, *et al.* [21], 1977	107,1:1.02	9.2	pJIA, oJIA sJIA	3.7/3.4	Tolmetin 15 mg/kg/d	Aspirin 50 mg/kg/d	——	NA	0	0	12

End points for all studies were efficacy and adverse events. NA: not applicable; pJIA: polyarticular juvenile idiopathic arthritis; oJIA: oligoarticular juvenile idiopathic arthritis; sJIA: systemic juvenile idiopathic arthritis; DMARDs: disease-modifying anti-rheumatic drugs; CS: corticosteroid; AEs: adverse events. *Piroxicam dose. 15-30 kg: 5 mg/kg/d; 31-45 kg: 10 mg/kg/d; 46-55 kg: 15 mg/kg/d.

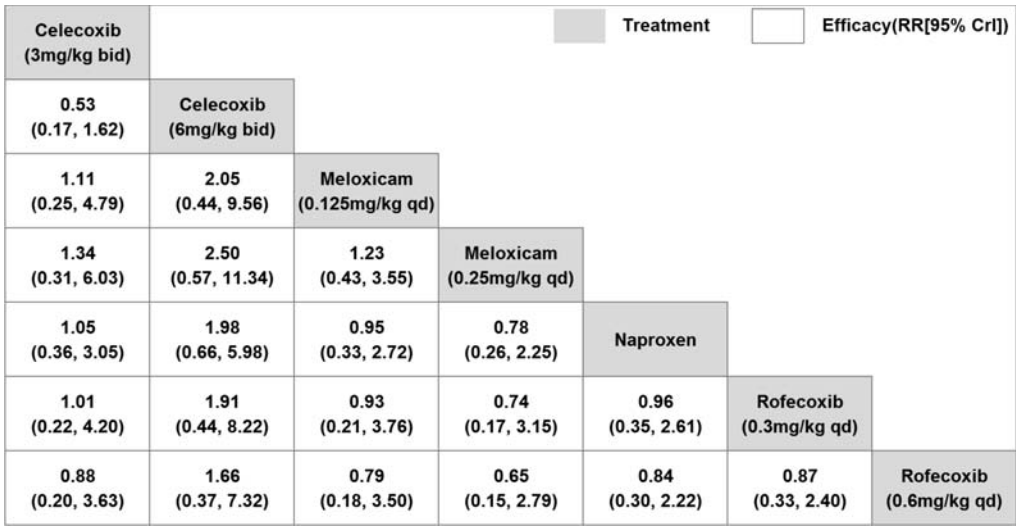

Fig. 3 Network meta-analysis of efficacy of non-steroidal anti-inflammatory drugs for juvenile idiopathic arthritis.

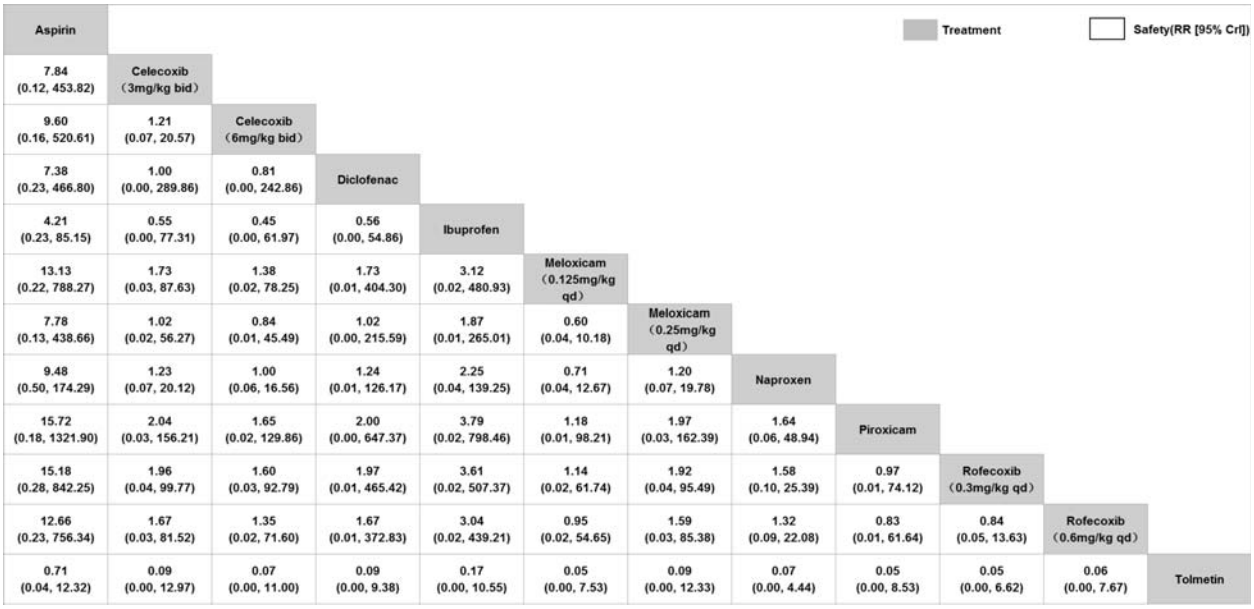

Fig. 4 Network meta-analysis of safety of non-steroidal anti-inflammatory drugs for juvenile idiopathic arthritis.

disorders were mild, while serious gastropathy such as gastrointestinal perforation and massive gastrointestinal hemorrhage was lower than adults. The combination of glucocorticoid, leflunomide, and methotrexate can aggravate gastrointestinal adverse reactions. While children have a very low risk of cardiovascular thromboembolic and serious gastro-intestinal events, prolonged use of NSAIDS into adulthood could make them vulnerable to such risks, especially when associated with other risk factors such as obesity or smoking [36].

We used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach to assess the quality of the evidence related to our outcomes. The eight included studies themselves were of moderate quality; however, there may be circumstances where the overall rating for a particular outcome would need to be adjusted per GRADE guidelines [37]. The sample size for some comparisons was assessed as a high bias of risk, which largely restricts the quality of meta-analysis. Among the included studies, there were no two studies

that investigated the same type of NSAID compared with another type of NSAID, which might overestimate the efficacy and safety of treatments. Additionally, the inconsistent criteria of efficacy make it impossible to make a comprehensive comparison of some NSAIDs. Also, there was no data on the stratification of subtypes and concomitant therapy, thus it is unlikely to eliminate the impact of these factors on efficacy and safety. The follow-up time points were limited from only 2 to 24 weeks. The quality of the evidence (GRADE rating) for the efficacy and safety of NSAIDs is very low, meaning there is no evidence to support or refute the findings.

In conclusion, this Bayesian network meta-analysis involving eight RCTs with low quality of evidence showed that, in terms of efficacy, celecoxib (6 mg/kg bid) ranked best among the four NSAIDs (celecoxib, rofecoxib, meloxicam, and naproxen). In terms of safety, rofecoxib, piroxicam, and meloxicam may be better than others. However, the limitations of the study and suboptimal quality of evidence bar us from making strong conclusions about the comparative efficacy or safety of NSAIDs used to treat JIA. Further well-designed RCTs are needed to figure out the best NSAID for JIA.

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Contributers: TX: conceived and designed the study, critically revised the manuscript; SC: acquired data, interpreted data, and drafted and critically revised the manuscript. ZY, ZZ, ZJ: critically revised the manuscript; SC, TX: screened and selected articles; SC, ZY, TX: assessed the quality of included trials. All the authors read and approved the final manuscript.
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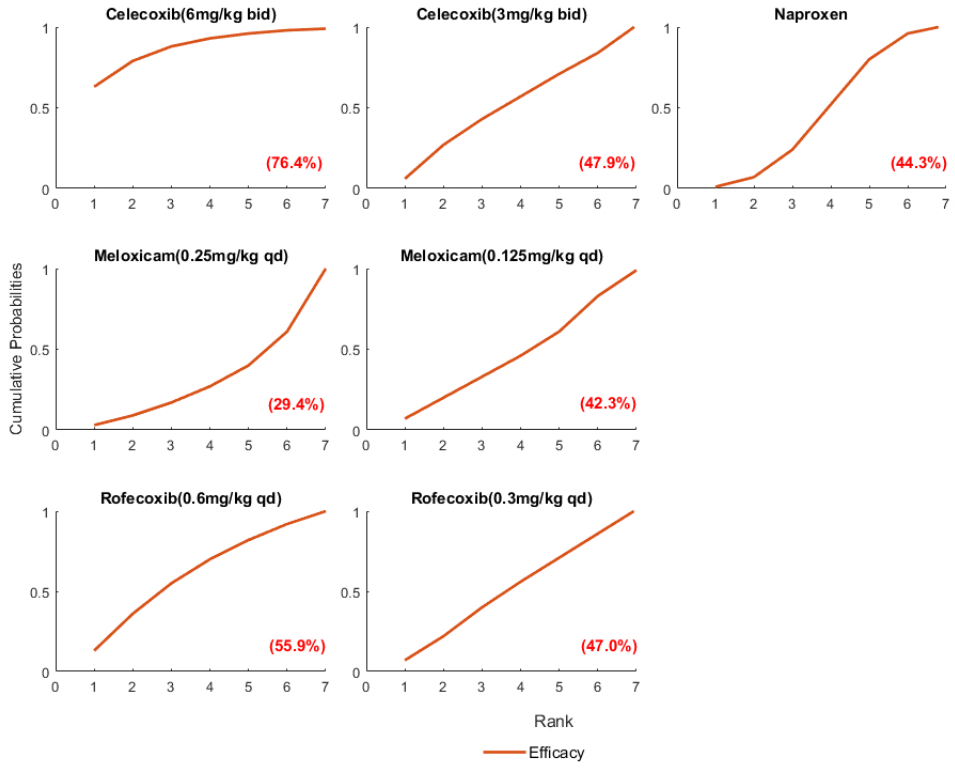
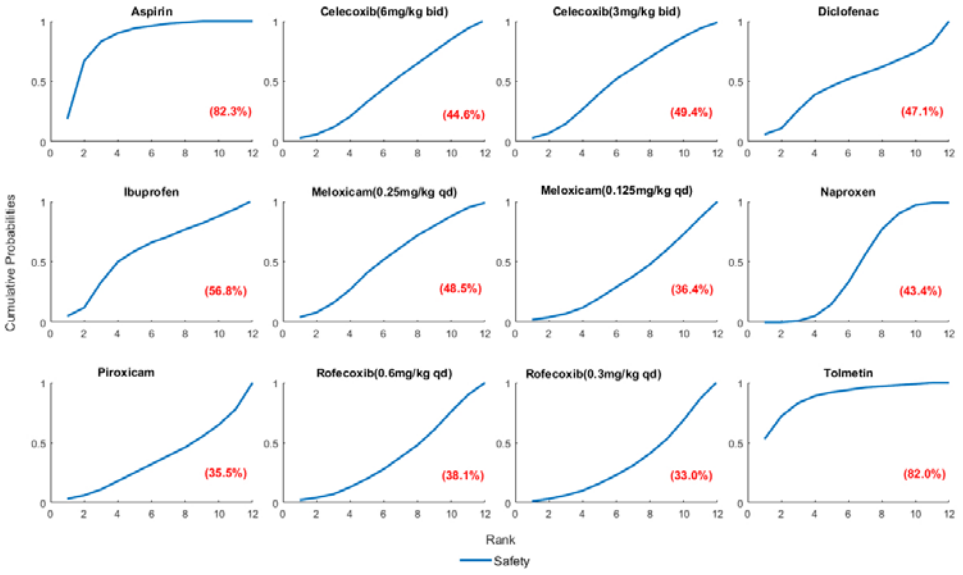
Web Table I Eligibility Criteria for The Selection of Studies

Inclusion criteria	*Rationale*
Population Gender: any Race: any	The population was restricted to patients of both genders with a diagnosis of JIA.
Disease: JIA	
Intervention	
Any NSAIDs	NSAIDs used to treat JIA. Different formulations or routes of administration were included.
Comparison (if applicable)	
Any NSAID Placebo	Comparative studies were selected if a NSAID was compared to any NSAID or placebo
Outcomes	
The efficacy and (or) safety	We select studies to assess their effect on efficacy and (or) adverse events.
Language	
No language restrictions were applied to the search strategy	The systematic review was meant to be as comprehensive as possible
Publication timeframe	
No timeframe restrictions were applied to the search strategy	The systematic review was meant to be as comprehensive as possible
Study design	
RCTs	RCTs are the standard of clinical evidence due to their design
Exclusion Criteria	
Population	
Not JIA	Due to the primary objective of this review, studies with multiple disease states were excluded.
Study design	
Unpublished data (conference abstracts, oral and poster presentations), reviews, meta analyses and editorials	Only original research, published in a peer-reviewed journal, was included in this review

JIA: Juvenile idiopathic arthritis; NSAID: Nonsteroidal anti-inflammatory drug; RCT: Randomized clinical trial.



Web Fig. 1 Cumulative efficacy rankings of different non-steroidal anti-inflammatory drugs for juvenile idiopathic arthritis in children.



Web Fig. 2 Cumulative safety rankings of different non-steroidal anti-inflammatory drugs for juvenile idiopathic arthritis.