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Comparison of the efficacy and safety of non-steroidal anti-inflammatory drugs for patients with primary dysmenorrhea: A network meta-analysis

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Abstract

Objective: Non-steroidal anti-inflammatory drugs are used as first-line treatment of primary dysmenorrhea, but there has been no optimal clinical choice among non-steroidal anti-inflammatory drugs yet. The present study was to assess the relative benefits of different common non-steroidal anti-inflammatory drugs for primary dysmenorrhea patients with a network meta-analysis.

Methods: Randomized controlled trials were screened by our criteria and included in the network meta-analysis. Pain relief was considered as primary outcomes and adverse effect was supplied as a safety outcome, while additional rescue, assessment score, and pain intensity difference were secondary outcomes. All the indexes were evaluated with odds ratio or standardized mean difference. Surface under cumulative ranking curve result was used to calculate the ranking of each treatment.

Results: Totally, 72 randomized controlled trials of 5723 patients and 13 drugs were included in our study after screening. As for pain relief, all drugs except nimesulide, rofecoxib, and waldecoxib were superior to aspirin (odds ratio with 95% credible intervals, diclofenac: 0.28 (0.08, 0.86), flurbiprofen: 0.10 (0.03, 0.29), ibuprofen: 0.32 (0.14, 0.73), indomethacin: 0.21 (0.07, 0.58), ketoprofen: 0.25 (0.10, 0.64), mefenamic acid: 0.28 (0.09, 0.87), naproxen: 0.31 (0.15, 0.64), piroxicam: 0.15 (0.03, 0.59), and tiaprofenic acid: 0.17 (0.04, 0.63)). Aspirin also required additional rescue when compared with the majority of other drugs (flurbiprofen: 3.46 (1.15, 11.25), ibuprofen: 6.30 (2.08, 20.09), mefenamic acid: 7.32 (1.51, 37.71), naproxen: 2.66 (1.17, 6.55), and tiaprofenic acid: 9.58 (1.43, 94.63)). As for assessment of the whole treatment, ketoprofen, naproxen, rofecoxib, and ibuprofen got higher score significantly than placebo. In addition, ibuprofen performed better than placebo in pain intensity difference. Considering the safety, tiaprofenic acid and mefenamic acid were noticeable in low risk, and indomethacin revealed higher risk than any other drugs. According to the results of network analysis and surface under cumulative ranking curve, flurbiprofen was considered to be the best one among all the treatments in efficacy, and aspirin was worse than most of others. On the other hand, tiaprofenic acid and mefenamic acid were indicated as the safest drugs.

Conclusion: Considering the efficacy and safety, we recommended flurbiprofen and tiaprofenic acid as the optimal treatments for primary dysmenorrhea.

Keywords

Primary dysmenorrhea, non-steroidal anti-inflammatory drugs, efficacy, safety, network meta-analysis

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Introduction

Dysmenorrhea is commonly divided into two types: primary dysmenorrhea (PD) and secondary dysmenorrhea. PD is defined as the hypogastric pain originated from uterine without pathology during menstrual period which often occurs with the menarche or after the establishment of the ovulatory cycles of reproductive women and usually lasts two or three days during each period.[1] About 43%–91% adolescent females (under 20 years) are reported with PD and show a decreasing tendency as the age grows older.[2] Women experiencing severe PD will be debilitated to accomplish daily works, even absent from school or job. According to the previous studies, PD is often considered to be the result of abnormal prostaglandin release which leads to strong contracts of uterus and reduced oxygen supply to the uterus muscles.[3] Besides, unhealthy lifestyle (such as smoking, intemperance, and stressfulness) and family history may also have some negative influence on the symptoms of PD.[4]

There are several treatments for PD like non-steroidal anti-inflammatory drugs (NSAIDs), oral contraceptive drugs, physical therapy interventions, Chinese traditional herbology, and so on.[5] Among them, NSAIDs are the first-line treatment.[6] There are many types of NSAIDs which are widely used as analgesics and anti-inflammatory agent through inhibiting cyclooxygenase (COX) enzymes including COX-1 and COX-2. The pain relieve ability of NSAIDs is mainly attributed to COX-2 enzymes inhibition—an important pathway related to hormone release and the process of inflammation, while their adverse effects (such as indigestion, headaches, and lethargy, which are considered to be the most concerning adverse effects in PD patients) are thought to be involved with the COX-1 enzymes inhibition.[7,8] Recently, selective COX-2 inhibitors have been established to mitigate the adverse effects in gastrointestinal tract and extend the drug effects with lower dose.[9] However, this kind of drug has been discovered to be related to increase the risk of heart complications if taken regularly and thus should be used more prudently.[10] Therefore, the requirement to evaluate efficacy and safety of NSAIDs is imminent for patients with PD.

To date, a large number of randomized controlled trials (RCTs) assessing the efficacy and safety of NSAIDs have been conducted,[11,12] and several published meta-analysis studies also compared the mainly used NSAIDs in the PD treatment.[13] However, the traditional meta-analysis only evaluates the direct comparison of pair-wised drugs, and there also exists conflict between different studies. Therefore, the purpose of this network meta-analysis is to indicate the relative efficacy and safety among most of the NSAIDs through not only direct but also indirect comparisons. We expect to draw a conclusion about the optimal treatment of PD by analyzing all published RCTs data of 13 individual NSAIDs.

Materials and methods

Literature search and selection criteria

We searched through China National Knowledge Internet, MEDLINE, and Embase to obtain the relevant RCTs comparing the efficacy and safety of NSAIDs for patients with PD using the key words "primary dysmenorrhea," "randomized controlled trial," "non-steroidal anti-inflammatory agents," "aspirin," "diclofenac," "flurbiprofen," "ibuprofen," "indomethacin," "ketoprofen," "mefenamic acid," "nimesulide," "piroxicam," "rofecoxib," "tiaprofenic acid," and "valdecoxib" in searching process (Supplemental Material). As for ketorolac and celecoxib, they were not been included in this network meta-analysis due to their serious adverse effects and main function which are often in the treatment in arthritis.

One RCT would be included in this network meta-analysis if it fulfilled each of the following criteria: (1) trials evaluating the efficacy or safety of NSAIDs in patients with PD, (2) trials that were designed as single-/double-/triple-blind, (3) trials covering at least one of the outcomes of interest, and (4) trials that using the same or close evaluation index (the way to describe the pain intensity difference and other outcomes). Two investigators independently reviewed abstracts and studies to evaluate the trial eligibility, and all conflicts were solved through discussion. There was no language restriction.

Outcome measures and data extraction

The primary efficacy outcome was pain relief (the proportion of patients who received effective or at least moderate pain relief), and the incidence of total treatment-related adverse effects like insomnia and gastrointestinal disease was added as a complementally safety outcome. As for secondary outcomes, we also assessed the requirements for additional rescue and pain intensity difference from baseline to end point. Using rescue medication or other medical assistance beyond the trials during specified time periods would be regarded as additional rescue. Pain intensity difference was defined as change scores of pain intensity rated by patients from baseline to end point. Assessment of the whole treatment from patients in each trail was also included in the secondary outcome; a higher score represents a better global assessment of patients.[11] However, since all these outcomes contained more

than one score scale, we standardized each continuous data during analysis.

After excluding the studies that failed to fulfill the criteria, two independent reviewers screened each study and extracted relevant data concerning of the outcomes of this network meta-analysis. The main information was extracted including basic study background, enrollment numbers, detailed interventions, and outcome measures.

Statistical analysis

We used a Bayesian framework with STATA software (13.0) and R software (V3.3.1) for this network meta-analysis. One advantage of using the Bayesian framework was its ability to produce ranking probabilities which could be used to evaluate medications with respect to each end point. The forest plots showed the result of the meta-analysis included in this research. Furthermore, odds ratio (OR) and standardized mean difference were calculated for dichotomous outcomes and continuous outcomes, respectively, with 95% credible intervals (CrIs) between the two treatments on each outcome. Moreover, the surface under the cumulative ranking curve (SUCRA) was computed based on the outcomes above to estimate the performance of different interventions, and higher SUCRA represented better efficacy and safety. The inconsistency of each outcome between direct and indirect evidence was evaluated by node-splitting results and the heat plots.

Results

Study selection and characteristics of included trials

A total of 1476 potentially relevant publications were identified by literature research. Then, 316 publications were removed as duplicates and 1039 publications were excluded due to the weak relevance to the subject. As a result, we retrieved 121 publications with full length into systematic review and included 70 studies with 72 RCTs of 5723 patients into our network meta-analysis due to the selection criteria as shown earlier.[11,12,14–81] The flowchart of the whole process is shown in Figure 1. Among the 70 studies, 18 trials were three-arm studies, 48 trials were conducted between one intervention and placebo, and 6 trials were between two different interventions. All trials included 13 drugs as follows: aspirin, diclofenac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, mefenamic, nimesulide, piroxicam, rofecoxib, tiaprofenic acid, and valdecoxib. The network structure is shown in Figure 1 and Figure S1, the circle area represented the enrollment of each treatment,

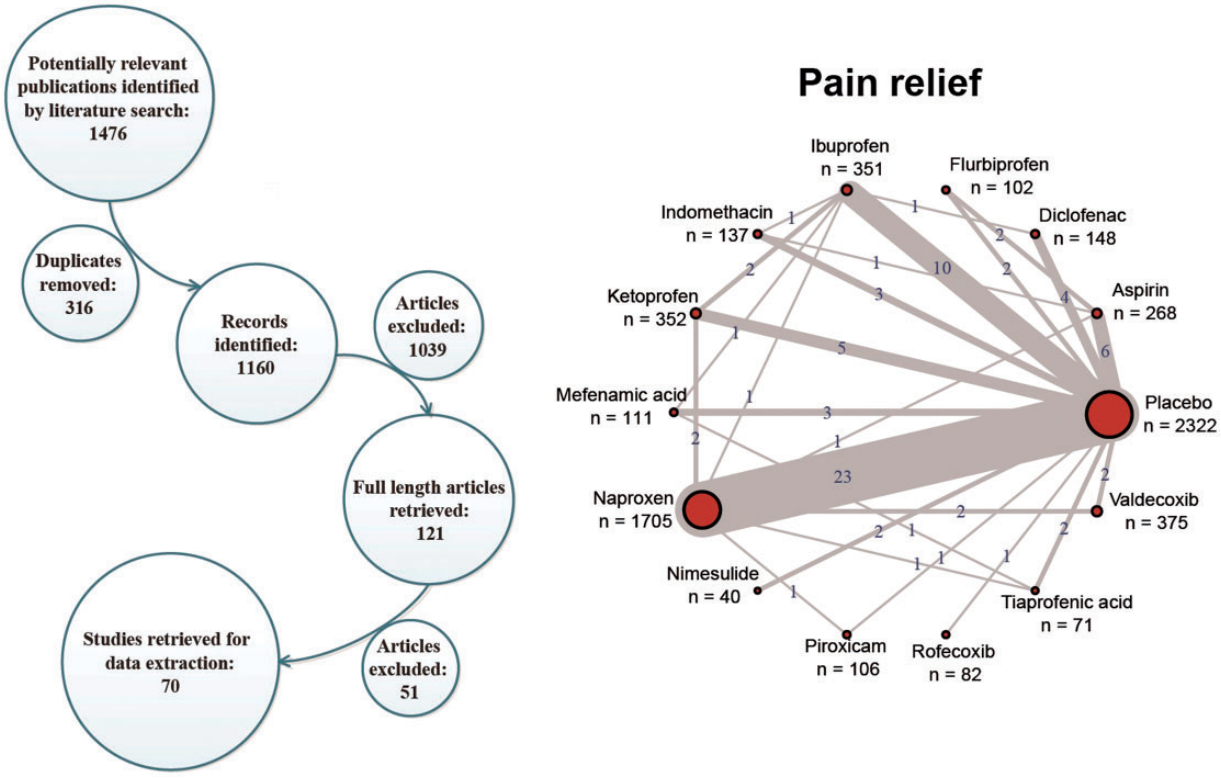

Figure 1. Flowchart and network structure for pain relief. The network plots show direct comparison of different drugs, with node size corresponding to the sample size. The number of included studies for specific direct comparison decides the thickness of solid lines.

Table 1. Main characteristics of included studies.

Trial	Country	Type	Blinding	No.	Study period	Intervention 1			Intervention 2			Intervention 3	
						Drug	Size	Dosage	Drug	Size	Dosage	Drug	Size
Three-arm trials													
Daniels et al.[72]	USA	RCT, crossover	Double-blind	120	4 cycles	Valdecoxib	183	20 mg/40 mg	Naproxen	93	550 mg	Placebo	94
Daniels et al.[67]	USA	RCT, crossover	Double-blind	118	4 cycles	Valdecoxib	192	20 mg/40 mg	Naproxen	96	550 mg	Placebo	96
Morrison et al.[66]	USA	RCT, parallel	Double-blind	127	–	Rofecoxib	233	25 mg + 25 mg/ 50 mg + 25 mg	Naproxen	122	550 mg	Placebo	118
Marchini et al.[62]	Italy	RCT, crossover	Double-blind	60	3 cycles	Ibuprofen	56	400 mg	Diclofenac	56	50 mg	Placebo	57
Tilyard and Dovey[61]	New Zealand	RCT, crossover	Double-blind	50	8 cycles	Mefenamic acid	40	250 mg	Tiaprofenic acid	40	200 mg	Placebo	40
Mehlisch[60]	USA	RCT, crossover	Double-blind	70	3 cycles	Ketoprofen	180	25-mg LD/ 50 mg/75 mg	Naproxen	60	500-mg LD + 250 mg	Placebo	60
Pasquale et al.[56]	USA	RCT, parallel	Double-blind	74	1 cycle	Piroxicam	39	20 mg/40-mg 1d + 20 mg/40 mg	Ibuprofen	15	400 mg	Placebo	11
Palmisano and Lamb[55]	USA	RCT, crossover	Double-blind	36	3 cycles	Ketoprofen	36	150 mg	Ibuprofen	36	800 mg	Placebo	36
Mehlisch[54]	USA	RCT, crossover	Double-blind	43	3 cycles	Ketoprofen	26	150 mg	Ibuprofen	26	800 mg	Placebo	26
Shapiro[50]	USA	RCT, crossover	Double-blind	43	4 cycles	Flurbiprofen	43	50 mg	Aspirin	43	650 mg	Placebo	43
Kauppila et al.[49]	Finland	RCT, crossover	Double-blind	42	6 cycles	Tiaprofenic acid	31	200 mg	Naproxen	31	250 mg	Placebo	31
Roy[43]	USA	RCT, crossover	Double-blind	48	2 cycles	Mefenamic acid	48	–	Ibuprofen	48		Placebo	48
Gookin et al.[40]	USA	RCT, crossover	Double-blind	42	3 cycles	Ibuprofen	31	400 mg	Indomethacin	31	25 mg	Placebo	31
Delia et al.[37]	USA	RCT, crossover	Double-blind	59	3 cycles	Flurbiprofen	59	50 mg	Aspirin	59	650 mg	Placebo	59
Rosenwaks et al.[36]	USA	RCT, crossover	Double-blind	32	2 cycles	Naproxen	23	275 mg	Aspirin	23	325 mg	Placebo	16
Pogmore and Filshie[33]	UK	RCT, crossover	Double-blind	80	3 months	Flurbiprofen	39	50 mg	Aspirin	39	500 mg	Placebo	39
Pulkkinen and Csapo[29]	USA	RCT, crossover	Single-blind	15	2 cycles	Naproxen	15	1100 mg	Ibuprofen	15	800 mg	Placebo	30
Kajanoja[17]	Finland	RCT, crossover	Double-blind	47	6 cycles	Indomethacin	90	25 mg	Aspirin	89	500 mg	Placebo	90
Two-arm trials													
Salmalian et al.[81]	Iran	RCT, parallel	Triple-blind	56	2 cycles	Ibuprofen	24	200 mg	Placebo	28			
Iacovides et al.[12]	South Africa	RCT, crossover	Double-blind	24	2 cycles	Diclofenac	24	50 mg	Placebo	24			
Heidarifar et al.[80]	Iran	RCT, parallel	Double-blind	50	2 cycles	Mefenamic acid	24	250 mg	Placebo	23			
Nahid et al.[79]	Iran	RCT, parallel	Double-blind	120	3 cycles	Mefenamic acid	55	250 mg	Placebo	51			
Daniels et al.[77]	USA	RCT, crossover	Double-blind	149	3 cycles	Naproxen	123	550 mg	Placebo	122			
		RCT, crossover	Double-blind	154	3 cycles	Naproxen	120	550 mg	Placebo	121			
Iacovides et al.[78]	USA	RCT, crossover	Double-blind	10	–	Diclofenac	10	150 mg	Placebo	10			
Chantler et al.[76]	South Africa	RCT, crossover	Double-blind	12	3 cycles	Diclofenac	12	100 mg	Placebo	12			
Daniels et al.[11]	USA	RCT, crossover	Double-blind	135	3 cycles	Naproxen	124	500 mg	Placebo	125			
Doubova et al.[75]	Mexico	RCT, parallel	Double-blind	88	–	Ibuprofen	46	1200 mg	Placebo	42			
Dawood and Khan-Dawood[74]	USA	RCT, crossover	Double-blind	12	3 cycles	Ibuprofen	10	400 mg	Placebo	10			
Letzel et al.[73]	Germany	RCT, crossover	Double-blind	127	3 cycles	Naproxen	92	500 mg	Placebo	93			
De Mello et al.[71]	Brazil	RCT, parallel	Double-blind	337	3 cycles	Meloxicam	190	7.5 mg/15 mg	Mefenamic acid	97	500 mg		
Bitner et al.[70]	USA	RCT, crossover	Double-blind	109	3 cycles	Naproxen	89	500 mg	Placebo	88			
Malmstrom et al.[69]	USA	RCT, crossover	Double-blind	73	3 cycles	Naproxen	60	550 mg	Placebo	60			
Milsom et al.[68]	UK	RCT, crossover	Double-blind	1242	3 cycles	Naproxen	412	400 mg/200 mg	Placebo	206			
Di Girolamo et al.[65]	Argentina	RCT, crossover	Double-blind	24	3 cycles	Ibuprofen	24	400 mg	Placebo	24			
Ezcurdia et al.[64]	Spain	RCT, crossover	Double-blind	52	–	Ketoprofen	44	50 mg	Placebo	44			

(continued)

Table 1. Continued

Trial	Country	Type	Blinding	No.	Study period	Intervention 1			Intervention 2			Intervention 3	
						Drug	Size	Dosage	Drug	Size	Dosage	Drug	Size
Mehlisch and Fulmer[63]	USA	RCT, crossover	Double-blind	54	4 cycles	Naproxen	53	550 mg	Placebo	51			
Fedele et al.[59]	Italy	RCT, parallel	Double-blind	55	4 cycles	Naproxen	14	250 mg	Placebo	31			
Andersch and Milsom[58]	Sweden	RCT, crossover	Double-blind	60	4 cycles	Flurbiprofen	57	50 mg	Naproxen	57	250 mg		
Akerlund and Stromberg[57]	Sweden	RCT, crossover	Double-blind	42	2 cycles	Ketoprofen	39	100 mg	Naproxen	39	500 mg		
Pulkkinen[53]	Finland	RCT, crossover	Double-blind	14	4 cycles	Nimesulide	28	100 mg	Placebo	18			
Kapadia[52]	UK	RCT, parallel	Single-blind	56	3 cycles	Naproxen	28	550 mg	Ibuprofen	23	400 mg		
Fraser and McCarron[51]	Australia	RCT, crossover	Double-blind	38	6 cycles	Ibuprofen	38	400 mg	Placebo	38			
Wilhelmsson et al.[48]	Sweden	RCT, crossover	Double-blind	83	–	Piroxicam	83	40 mg + 20 mg	Naproxen	83	1000 mg		
Saltveit[47]	Norway	RCT, crossover	Double-blind	92	4 months	Piroxicam	92	20 mg	Placebo	92			
Osathanondh et al.[46]	USA	RCT, parallel	Double-blind	85	6 months	Aspirin	24	650 mg	Placebo	24			
Milsom and Andersch[45]	Sweden	RCT, crossover	Double-blind	60	4 cycles	Ibuprofen	57	6[a]200 mg	Naproxen	57	4[a]125 mg		
Rondel et al.[44]	Germany	RCT, crossover	Double-blind	12	4 cycles	Nimesulide	12	200 mg	Placebo	12			
Lalos and Nilsson[42]	Sweden	RCT, crossover	Double-blind	21	4 periods	Naproxen	20	250 mg	Placebo	20			
Jacobson et al.[41]	Sweden	RCT, crossover	Double-blind	39	4 cycles	Naproxen	39	500 mg + 250 mg	Placebo	39			
Gleeson and Sorbie[39]	Canada	RCT, crossover	Double-blind	27	6 cycles	Ketoprofen	27	–	Placebo	27			
Chan et al.[38]	USA	RCT, cross-over	Double-blind	12	3 cycles	Naproxen	12	275 mg	Placebo	12			
Riihiluoma et al.[35]	Finland	RCT, crossover	Double-blind	35	4 cycles	Diclofenac	58	25 mg	Placebo	57			
Chan et al.[34]	USA	RCT, crossover	Double-blind	14	–	Naproxen	20	550 mg + 275 mg	Placebo	20			
Morrison et al.[32]	USA	RCT, crossover	Triple-blind	55	3 cycles	Ibuprofen	51	400 mg	Placebo	51			
Hamann[30]	Denmark	RCT, crossover	Double-blind	30	4 cycles	Naproxen	26	250 mg	Placebo	26			
Henzl et al.[31]	–	RCT, parallel	Double-blind	431	–	Naproxen	212	–	Placebo	219			
Elder and Kapadia[24]	–	RCT, crossover	Double-blind	32	6 cycles	Indomethacin	32	25 mg	Placebo	32			
Pulkkinen 1979	USA	RCT, crossover	Single-blind	15	2 cycles	Ibuprofen	15	400 mg	Placebo	15			
Morrison and Jennings[27]	USA	RCT, crossover	Double-blind	32	4 cycles	Indomethacin	16	25 mg	Placebo	16			
Larkin et al.[26]	USA	RCT, crossover	Double-blind	22	–	Ibuprofen	22	400 mg	Placebo	22			
Jacobson et al.[25]	Sweden	RCT, parallel	Double-blind	34	2 cycles	Naproxen	16	250–500 mg	Placebo	18			
Dandenell et al.[23]	Sweden	RCT, parallel	Double-blind	97	2 cycles	Naproxen	48	250 mg	Placebo	49			
Budoff[22]	USA	RCT, crossover	Double-blind	46	6 cycles	Mefenamic acid	23	250 mg	Placebo	21			
Sande et al.[21]	Norway, USA	RCT, parallel	Double-blind	32	3 cycles	Naproxen	15	275 mg	Placebo	17			
Pulkkinen and Csapo[20]	Finland, USA	RCT, crossover	Single-blind	12	–	Ibuprofen	12	800 mg	Placebo	12			
Pauls[19]	Canada	RCT, parallel	Double-blind	17	3 cycles	Naproxen	9	275 mg	Placebo	8			
Lundstrom[18]	–	RCT, crossover	Double-blind	52	6 cycles	Naproxen	26	550 mg + 275 mg + 275 mg	Placebo	26			
Janbu et al.[16]	Norway	RCT, crossover	Double-blind	30	3 cycles	Aspirin	30	500 mg	Placebo	30			
Hanson et al.[15]	USA	RCT, parallel	Double-blind	64	3 cycles	Naproxen	29	275 mg	Placebo	35			
Henzl et al.[14]	USA	RCT, parallel	Double-blind	20	4 cycles	Naproxen	10	550 mg + 275 mg	Placebo	10			
		RCT, parallel	Double-blind	23	4 cycles	Naproxen	12	550 mg + 275 mg	Placebo	12			

Note: RCT: randomized controlled trials.
[a]The article does not mention the type of dysmenorrhea. 1d: Day 1.

Table 2. Network meta-analysis results for pain relief (lower left) and adverse effects (upper right).

Placebo	0.99 (0.59, 1.65)	3.22 (0.97, 12.55)	1.82 (1.04, 3.29)	0.90 (0.56, 1.45)	3.60 (1.68, 7.46)	0.73 (0.36, 1.46)	0.66 (0.31, 1.39)	1.08 (0.87, 1.38)	–	1.14 (0.56, 2.20)	1.17 (0.64, 2.23)	0.45 (0.08, 1.68)	1.22 (0.75, 2.05)
0.57 (0.29, 1.11)	**Aspirin**	3.25 (0.84, 14.15)	1.86 (1.00, 3.46)	0.91 (0.42, 1.82)	3.60 (1.60, 8.08)	0.74 (0.32, 1.75)	0.65 (0.27, 1.68)	1.09 (0.64, 1.90)	–	1.14 (0.48, 2.69)	1.19 (0.54, 2.66)	0.46 (0.07, 1.93)	1.23 (0.61, 2.53)
0.16 (0.06, 0.39)	0.28 (0.08, 0.86)	**Diclofenac**	0.57 (0.13, 2.27)	0.28 (0.07, 0.91)	1.13 (0.22, 4.57)	0.23 (0.05, 0.93)	0.20 (0.05, 0.83)	0.34 (0.09, 1.15)	–	0.35 (0.08, 1.40)	0.36 (0.08, 1.48)	0.14 (0.02, 0.83)	0.38 (0.09, 1.42)
0.06 (0.02, 0.17)	0.10 (0.03, 0.29)	0.35 (0.09, 1.55)	**Flurbiprofen**	0.49 (0.21, 1.05)	1.93 (0.77, 4.85)	0.39 (0.17, 1.00)	0.35 (0.14, 0.91)	0.59 (0.33, 1.07)	–	0.61 (0.25, 1.48)	0.64 (0.28, 1.49)	0.25 (0.04, 1.05)	0.66 (0.32, 1.42)
0.18 (0.11, 0.30)	0.32 (0.14, 0.73)	1.14 (0.42, 3.22)	3.19 (0.95, 10.70)	**Ibuprofen**	4.06 (1.63, 9.30)	0.82 (0.35, 1.84)	0.73 (0.32, 1.67)	1.21 (0.76, 2.05)	–	1.28 (0.55, 2.83)	1.32 (0.61, 2.86)	0.51 (0.09, 1.95)	1.36 (0.70, 2.69)
0.12 (0.05, 0.29)	0.21 (0.07, 0.58)	0.73 (0.20, 2.75)	2.05 (0.50, 8.25)	0.64 (0.23, 1.77)	**Indomethacin**	0.20 (0.08, 0.57)	0.18 (0.07, 0.55)	0.30 (0.14, 0.67)	–	0.32 (0.11, 0.85)	0.33 (0.12, 0.90)	0.13 (0.02, 0.57)	0.34 (0.14, 0.85)
0.15 (0.07, 0.28)	0.25 (0.10, 0.64)	0.90 (0.30, 2.94)	2.56 (0.71, 9.03)	0.79 (0.37, 1.75)	1.23 (0.41, 3.86)	**Ketoprofen**	0.90 (0.32, 2.59)	1.48 (0.73, 3.06)	–	1.57 (0.57, 4.06)	1.60 (0.64, 4.10)	0.63 (0.10, 2.89)	1.67 (0.72, 3.94)
0.16 (0.06, 0.40)	0.28 (0.09, 0.87)	0.97 (0.27, 3.78)	2.77 (0.66, 11.59)	0.86 (0.31, 2.39)	1.34 (0.36, 5.10)	1.07 (0.35, 3.35)	**Mefenamic acid**	1.67 (0.76, 3.56)	–	1.73 (0.63, 4.53)	1.79 (0.70, 4.71)	0.70 (0.11, 2.89)	1.86 (0.77, 4.66)
0.18 (0.12, 0.25)	0.31 (0.15, 0.64)	1.09 (0.41, 3.03)	3.10 (0.98, 9.49)	0.97 (0.53, 1.77)	1.51 (0.56, 4.06)	1.21 (0.59, 2.41)	1.13 (0.41, 3.00)	**Naproxen**	–	1.05 (0.51, 2.01)	1.08 (0.58, 2.03)	0.41 (0.07, 1.57)	1.13 (0.68, 1.88)
0.21 (0.05, 0.92)	0.37 (0.07, 1.88)	1.30 (0.23, 7.77)	3.67 (0.56, 23.34)	1.15 (0.23, 5.64)	1.79 (0.30, 10.38)	1.43 (0.27, 7.39)	1.34 (0.22, 7.85)	1.19 (0.25, 5.47)	**Nimesulide**	–	–	–	–
0.08 (0.02, 0.28)	0.15 (0.03, 0.59)	0.53 (0.11, 2.51)	1.49 (0.28, 7.46)	0.46 (0.12, 1.73)	0.72 (0.15, 3.35)	0.58 (0.14, 2.29)	0.54 (0.11, 2.51)	0.48 (0.14, 1.60)	0.41 (0.06, 2.83)	**Piroxicam**	1.03 (0.43, 2.66)	0.40 (0.06, 1.84)	1.07 (0.48, 2.53)
0.21 (0.05, 0.99)	0.37 (0.07, 2.01)	1.31 (0.23, 8.41)	3.71 (0.57, 24.53)	1.16 (0.23, 5.99)	1.80 (0.30, 11.36)	1.46 (0.27, 7.85)	1.35 (0.22, 8.33)	1.20 (0.25, 5.99)	1.02 (0.12, 8.94)	2.48 (0.36, 19.11)	**Rofecoxib**	0.38 (0.07, 1.65)	1.04 (0.47, 2.27)
0.10 (0.03, 0.30)	0.17 (0.04, 0.63)	0.59 (0.13, 2.69)	1.67 (0.33, 8.17)	0.52 (0.14, 1.84)	0.81 (0.18, 3.67)	0.65 (0.17, 2.46)	0.61 (0.15, 2.39)	0.54 (0.16, 1.77)	0.45 (0.07, 3.06)	1.13 (0.21, 6.17)	0.45 (0.06, 3.06)	**Tiaprofenic acid**	2.72 (0.66, 14.59)
0.23 (0.09, 0.58)	0.41 (0.13, 1.26)	1.46 (0.41, 5.64)	4.10 (0.98, 16.78)	1.28 (0.45, 3.67)	1.99 (0.54, 7.46)	1.62 (0.53, 4.90)	1.49 (0.40, 5.53)	1.34 (0.54, 3.35)	1.13 (0.20, 6.62)	2.77 (0.63, 12.94)	1.11 (0.18, 6.62)	2.46 (0.57, 10.91)	**Valdecoxib**

Note: The column treatments are compared against row treatments.

Table 3. Network meta-analysis results for additional rescue (lower left) and assessment (upper right).

Placebo	−0.12 (−0.93, 0.68)	–	−0.69 (−1.29, −0.10)	−0.65 (−1.42, 0.12)	−0.91 (−1.73, −0.10)	–	−0.71 (−1.11, −0.30)	−1.05 (−2.33, 0.23)	–	−0.86 (−1.62, −0.11)	–	−0.60 (−1.60, 0.40)
1.19 (0.52, 2.64)	**Aspirin**	–	−0.57 (−1.55, 0.40)	−0.53 (−1.47, 0.41)	−0.79 (−1.93, 0.35)	–	−0.58 (−1.48, 0.31)	−0.93 (−2.44, 0.58)	–	−0.74 (−1.84, 0.36)	–	−0.48 (−1.76, 0.81)
4.10 (1.49, 11.59)	3.46 (1.15, 11.25)	**Flurbiprofen**	–	–	–	–	–	–	–	–	–	–
7.46 (3.42, 17.12)	6.30 (2.08, 20.09)	1.80 (0.50, 6.69)	**Ibuprofen**	0.04 (−0.83, 0.92)	−0.22 (−1.12, 0.69)	–	−0.01 (−0.73, 0.71)	−0.36 (−1.77, 1.05)	–	−0.17 (−1.13, 0.79)	–	0.09 (−1.07, 1.26)
–	–	–	–	**Indomethacin**	−0.26 (−1.36, 0.84)	–	−0.05 (−0.92, 0.81)	−0.40 (−1.89, 1.09)	–	−0.21 (−1.29, 0.87)	–	0.05 (−1.21, 1.31)
2.27 (0.55, 9.78)	1.92 (0.38, 10.38)	0.55 (0.10, 3.22)	0.31 (0.06, 1.58)	–	**Ketoprofen**	–	0.21 (−0.70, 1.11)	−0.14 (−1.66, 1.38)	–	0.05 (−1.06, 1.16)	–	0.31 (−0.98, 1.60)
8.67 (2.2, 34.81)	7.32 (1.51, 37.71)	2.10 (0.38, 11.70)	1.16 (0.23, 5.75)	–	3.82 (0.5, 27.66)	**Mefenamic acid**	–	–	–	–	–	–
3.16 (2.29, 4.66)	2.66 (1.17, 6.55)	0.77 (0.28, 2.20)	0.42 (0.19, 0.98)	–	1.39 (0.35, 5.58)	0.36 (0.09, 1.55)	**Naproxen**	−0.35 (−1.69, 1.00)	–	−0.16 (−0.96, 0.64)	–	0.11 (−0.9, 1.11)
–	–	–	–	–	–	–	–	**Nimesulide**	–	0.19 (−1.30, 1.67)	–	0.45 (−1.17, 2.08)
3.67 (1.19, 11.70)	3.10 (0.79, 12.81)	0.90 (0.19, 4.14)	0.49 (0.13, 1.79)	–	1.62 (0.25, 10.18)	0.43 (0.07, 2.53)	1.16 (0.35, 3.82)	–	**Piroxicam**	–	–	–
1.22 (0.45, 3.46)	1.03 (0.29, 3.90)	0.30 (0.07, 1.25)	0.17 (0.05, 0.59)	–	0.54 (0.09, 3.00)	0.14 (0.03, 0.79)	0.39 (0.14, 1.05)	–	0.33 (0.07, 1.54)	**Rofecoxib**	–	0.26 (−0.97, 1.50)
11.25 (2.01, 95.58)	9.58 (1.43, 94.63)	2.75 (0.37, 28.79)	1.52 (0.23, 14.44)	–	5.00 (0.52, 62.18)	1.32 (0.14, 15.96)	3.56 (0.62, 29.96)	–	3.10 (0.39, 33.78)	9.30 (1.25, 95.58)	**Tiaprofenic acid**	–
2.69 (1.30, 5.87)	2.27 (0.79, 7.10)	0.65 (0.19, 2.32)	0.36 (0.12, 1.06)	–	1.19 (0.24, 5.81)	0.31 (0.07, 1.52)	0.85 (0.39, 1.79)	–	0.73 (0.19, 2.89)	2.20 (0.63, 7.61)	0.24 (0.03, 1.58)	**Valdecoxib**

Note: The column treatments are compared against row treatments.

and lines width showed the number of compared trials. Main characteristics of the included publications and trials are presented in Table 1.

Overall outcomes

All the data of this network meta-analysis results for five outcomes are presented in Tables 2 to 4 and the forest plots in Figure 2 and Figures S2 to S5. For the primary outcomes shown in Table 2, the comparison between each pair of drugs was evaluated. As for pain relief, all drugs except aspirin were superior to placebo. When aspirin was compared with other drugs, the results showed that it was worse than most of the drugs such as diclofenac (OR = 0.28, 95% CrI = 0.08–0.86), indomethacin (OR = 0.21, 95% CrIs = 0.07–0.58), and flurbiprofen (OR = 0.10, 95% CrI = 0.03–0.29), and so on. On the other hand, considering the safety, tiaprofenic acid and mefenamic acid were noticeable in low incidence of adverse effects, and indomethacin revealed higher adverse effects than any other drugs.

The secondary outcomes of this network meta-analysis are listed in Tables 3 and 4. According to the outcomes, most of the drugs needed less additional rescue after assigned interventions compared with placebo. Nevertheless, aspirin still required additional rescue when compared with the majority of other drugs. As for assessment of the whole treatment, ketoprofen, naproxen, rofecoxib, and ibuprofen got higher score significantly than placebo. In addition, ibuprofen performed better than placebo in pain intensity difference.

Ranking conclusion

The results of SUCRA under five outcomes are shown in Table 5. According to the standing list of the primary outcomes, flurbiprofen (SUCRA: 0.904) ranked first in pain relief, successively followed by piroxicam (SUCRA: 0.787), tiaprofenic acid (SUCRA: 0.751), and indomethacin (SUCRA: 0.678). Besides, aspirin was indicated to be the worst among all of the NSAIDs in pain relief. In terms of adverse effects, the lower SUCRA suggested the higher incidence of adverse effects. Tiaprofenic acid (SUCRA: 0.872) performed best with mefenamic acid (SUCRA: 0.824) and ketoprofen (SUCRA: 0.781) followed. Combining these two primary outcomes, flurbiprofen was the most efficacious treatment in our result, and tiaprofenic acid was also a good treatment when took efficacy and safety into consideration. The ranking in secondary outcomes also revealed the excellent performance of these drugs. In addition, aspirin was considered to be the worst intervention because it ranked last among all the interventions except for placebo in most outcomes.

Table 4. Network meta-analysis results for secondary pain intensity difference.

Placebo										
−0.02	**Aspirin**									
(−1.94, 1.91)										
−1.86	−1.84	**Diclofenac**								
(−3.89, 0.17)	(−4.64, 0.95)									
−1.99	−1.97	−0.13	**Flurbiprofen**							
(−5.00, 1.03)	(−5.55, 1.60)	(−3.76, 3.51)								
−1.56	−1.54	0.30	0.43	**Ibuprofen**						
(−2.92, −0.20)	(−3.90, 0.81)	(−2.14, 2.75)	(−2.64, 3.50)							
–	–	–	–	–	**Indomethacin**					
−1.62	−1.61	0.24	0.37	−0.06	–	**Ketoprofen**				
(−4.33, 1.09)	(−4.93, 1.72)	(−3.15, 3.62)	(−3.69, 4.42)	(−3.10, 2.97)						
−0.95	−0.94	0.91	1.04	0.60	–	0.67	**Mefenamic acid**			
(−2.52, 0.62)	(−3.42, 1.55)	(−1.66, 3.47)	(−2.36, 4.43)	(−1.47, 2.68)		(−2.46, 3.80)				
−1.00	−0.98	0.86	0.99	0.56	–	0.62	−0.05	**Naproxen**		
(−2.36, 0.35)	(−3.34, 1.37)	(−1.58, 3.30)	(−1.71, 3.68)	(−0.91, 2.03)		(−2.41, 3.65)	(−2.12, 2.02)			
−0.88	−0.86	0.98	1.11	0.68	–	0.75	0.08	0.12	**Tiaprofenic acid**	
(−3.34, 1.59)	(−3.99, 2.27)	(−2.21, 4.18)	(−2.78, 5.01)	(−2.14, 3.50)		(−2.92, 4.41)	(−2.39, 2.54)	(−2.69, 2.94)		

Note: The column treatments are compared against row treatments.

Inconsistency test

Node-splitting analysis of five outcomes for all the drugs is shown in Tables 6 and 7. A value of P less than 0.05 indicated that there was a significant inconsistency. As the results of the analysis show that there was no significant difference in the outcome of pain relief, additional rescue, pain intensity difference, and assessment. As for the outcome of adverse effects, inconsistency between flurbiprofen and aspirin ($P = 0.012$), as well as naproxen and flurbiprofen ($P = 0.036$), was found. The net heat plot results of consistency test are also shown in Figure 3 and Figures S6 to S9, which revealed the same result.

Discussion

PD is a high-frequency female disease which will disturb the quality of normal lives of women.[82] NSAIDs are considered to be the first-line treatment for patients with PD; they are certain to be effective in relieving pain, but there is still no conclusion about the optimal choice in clinic.[13] Therefore, the objective of this network meta-analysis is to draw a conclusion about the optimal treatment within several types of NSAIDs through direct and indirect statistical analysis. Although only a small amount of studies in our database performed in the recent years, the results of our research were still meaningful since NSAIDs system has been developed a long time ago and maintained its crucial role in relieving PD in the last 30 years.

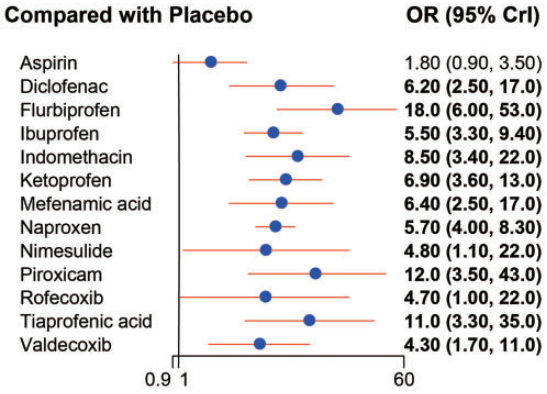

Figure 2. Forest plots for pain relief using ORs and 95% CrIs. OR: odds ratios; CrIs: credible intervals.

The results of our network meta-analysis suggested that all the drugs except aspirin were significantly more efficacious than placebo. However, there is no significant difference between each pair of NSAIDs concerning pain relief through direct evidence, which is consistent with the research by Marjoribanks et al.[3] In their research, they pointed out that NSAIDs were effective in relieving dysmenorrhea, whereas the sample size was too small to conduct a suitable meta-analysis for the comparison between two NSAIDs. Complementary to their results, the SUCRA ranking in our research provided the information of more efficacious treatments: flurbiprofen, piroxicam, and tiaprofenic acid. Naproxen was an analgesic that has been applied widely in many disease and showed significant relief of pain in PD in early time.[38] However, with the development of NSAIDs drugs, several other drugs have been illustrated as similar efficacy to naproxen.[11,73] In our result, naproxen was not significant efficacious compared to other NSAIDs drugs and showed an average efficacy in ranking.

As for the safety outcome, tiaprofenic acid and mefenamic acid were indicated as the safest NSAIDs drugs, while indomethacin was the worst one which was more likely to cause mild gastrointestinal discomfort. Naproxen, different from the research by Marjoribanks et al., was not reported with higher

Table 5. Surface under the cumulative ranking curve (SUCRA) results of six outcomes.

	Pain relief	Adverse effects	Additional rescue	Pain intensity difference	Assessment
Placebo	0.007	0.593	0.081	0.188	0.130
Aspirin	0.099	0.585	0.151	0.265	0.251
Diclofenac	0.529	0.098	–	0.678	–
Flurbiprofen	0.906	0.194	0.623	0.680	–
Ibuprofen	0.450	0.667	0.831	0.653	0.552
Indomethacin	0.677	0.047	–	–	0.526
Ketoprofen	0.585	0.781	0.396	0.606	0.658
Mefenamic acid	0.538	0.824	0.836	0.478	–
Naproxen	0.468	0.494	0.520	0.497	0.567
Nimesulide	0.430	–	–	–	0.673
Piroxicam	0.787	0.483	0.573	–	–
Rofecoxib	0.424	0.451	0.169	–	0.642
Tiaprofenic acid	0.751	0.873	0.870	0.461	–
Valdecoxib	0.348	0.409	0.448	–	0.497

Note: The warm color represents a high SUCRA value, which also suggests a relatively high ranking.

Table 6. Node-splitting results of the network meta-analysis for three dichotomous outcomes.

Outcomes	Comparison	OR (95% CrI)			*P* (Direct vs. indirect)
		Direct	Indirect	Network	
Pain relief	Ibuprofen vs. placebo	5.30 (3.00, 9.80)	2.80 (0.41, 19.00)	5.50 (3.30, 9.20)	0.5200
	Ketoprofen vs. placebo	6.60 (2.90, 15.00)	4.30 (0.75, 26.00)	6.90 (3.70, 13.00)	0.6550
	Naproxen vs. placebo	5.10 (3.50, 7.70)	14.00 (4.10, 51.00)	5.70 (4.10, 8.50)	0.1150
	Piroxicam vs. placebo	29.00 (3.80, 260.00)	7.20 (1.50, 34.00)	11.00 (3.70, 42.00)	0.2663
	Indomethacin vs. aspirin	3.80 (0.65, 17.00)	5.90 (1.30, 28.00)	4.80 (1.70, 14.00)	0.6425
	Naproxen vs. aspirin	5.80 (0.89, 35.00)	3.00 (1.30, 6.70)	3.20 (1.50, 7.00)	0.5188
	Ibuprofen vs. diclofenac	0.76 (0.16, 3.30)	0.65 (0.14, 2.50)	0.87 (0.31, 2.30)	0.9000
	Indomethacin vs. ibuprofen	0.87 (0.14, 4.70)	2.70 (0.69, 9.40)	1.60 (0.60, 4.60)	0.2913
	Ketoprofen vs. ibuprofen	2.00 (0.58, 7.50)	0.94 (0.33, 2.70)	1.30 (0.58, 2.70)	0.3688
	Mefenamic acid vs. ibuprofen	1.10 (0.22, 5.00)	1.80 (0.41, 7.00)	1.20 (0.43, 3.20)	0.6338
	Naproxen vs. ibuprofen	2.00 (0.28, 12.00)	0.95 (0.51, 1.80)	1.00 (0.59, 1.90)	0.4413
	Naproxen vs. ketoprofen	1.10 (0.35, 3.40)	0.60 (0.25, 1.60)	0.82 (0.41, 1.70)	0.4513
	Tiaprofenic acid vs. mefenamic acid	1.80 (0.22, 17.00)	1.30 (0.18, 10.00)	1.60 (0.47, 6.00)	0.8063
	Piroxicam vs. naproxen	1.30 (0.29, 5.80)	5.40 (0.62, 53.00)	2.00 (0.65, 7.30)	0.2850
	Tiaprofenic acid vs. naproxen	1.70 (0.28, 10.00)	3.20 (0.49, 28.00)	1.80 (0.59, 5.80)	0.6088
Adverse effects	Flurbiprofen vs. placebo	2.20 (1.00, 4.50)	0.75 (0.26, 2.00)	1.80 (1.00, 3.20)	0.0888
	Ibuprofen vs. placebo	0.99 (0.53, 1.90)	0.67 (0.30, 1.50)	0.91 (0.57, 1.50)	0.4925
	Ketoprofen vs. placebo	0.67 (0.30, 1.50)	1.80 (0.24, 14.00)	0.74 (0.36, 1.40)	0.3750
	Naproxen vs. placebo	1.10 (0.83, 1.40)	1.50 (0.75, 3.00)	1.10 (0.87, 1.30)	0.3500
	Piroxicam vs. placebo	0.90 (0.38, 2.10)	1.60 (0.53, 5.10)	1.10 (0.55, 2.20)	0.4275
	Flurbiprofen vs. aspirin	3.10 (1.40, 6.70)	0.53 (0.15, 1.80)	1.90 (0.99, 3.50)	**0.0125**
	Indomethacin vs. aspirin	2.50 (0.91, 6.80)	5.20 (1.20, 25.00)	3.70 (1.60, 8.30)	0.3913
	Naproxen vs. aspirin	0.61 (0.06, 4.40)	1.20 (0.66, 2.10)	1.10 (0.63, 2.00)	0.5225
	Naproxen vs. flurbiprofen	1.40 (0.49, 4.00)	0.39 (0.20, 0.80)	0.60 (0.34, 1.10)	**0.0363**
	Indomethacin vs. ibuprofen	6.30 (0.70, 180.00)	3.70 (1.40, 8.80)	4.00 (1.70, 9.40)	0.6863
	Ketoprofen vs. ibuprofen	0.52 (0.09, 2.70)	0.95 (0.37, 2.50)	0.81 (0.35, 1.70)	0.5288
	Mefenamic acid vs. ibuprofen	0.38 (0.10, 1.20)	1.20 (0.36, 4.00)	0.72 (0.31, 1.80)	0.1713
	Naproxen vs. ibuprofen	1.60 (0.75, 3.40)	0.97 (0.52, 1.90)	1.20 (0.74, 1.90)	0.3150
	Naproxen vs. ketoprofen	0.64 (0.06, 4.30)	1.70 (0.85, 3.80)	1.50 (0.72, 3.10)	0.3413
	Tiaprofenic acid vs. mefenamic acid	0.63 (0.06, 4.30)	0.48 (0.02, 5.00)	0.69 (0.13, 3.00)	0.8838
	Piroxicam vs. naproxen	1.50 (0.52, 4.20)	0.81 (0.31, 1.90)	1.00 (0.49, 2.10)	0.4000
	Rofecoxib vs. naproxen	0.96 (0.41, 2.50)	0.83 (0.31, 2.20)	1.10 (0.57, 2.10)	0.8150
	Tiaprofenic acid vs. naproxen	0.18 (0.01, 2.40)	0.55 (0.07, 3.30)	0.42 (0.08, 1.70)	0.5313
Additional rescue	Flurbiprofen vs. placebo	0.12 (0.03, 0.49)	0.57 (0.10, 3.10)	0.25 (0.09, 0.71)	0.1638
	Ibuprofen vs. placebo	0.10 (0.04, 0.26)	0.23 (0.05, 0.90)	0.14 (0.06, 0.29)	0.3200
	Naproxen vs. placebo	0.35 (0.23, 0.48)	0.11 (0.03, 0.44)	0.32 (0.21, 0.43)	0.1088
	Flurbiprofen vs. aspirin	0.20 (0.05, 0.89)	0.62 (0.09, 4.40)	0.30 (0.09, 0.93)	0.3650
	Naproxen vs. aspirin	0.13 (0.01, 0.88)	0.45 (0.15, 1.20)	0.38 (0.14, 0.82)	0.2663
	Naproxen vs. flurbiprofen	0.59 (0.12, 2.80)	2.40 (0.60, 9.60)	1.30 (0.42, 3.50)	0.1738
	Naproxen vs. ibuprofen	1.30 (0.31, 5.70)	3.10 (1.10, 8.80)	2.30 (0.99, 5.40)	0.2875
	Piroxicam vs. ibuprofen	1.70 (0.26, 18.00)	2.70 (0.39, 19.00)	2.00 (0.53, 7.30)	0.7175

Note: Three dichotomous end points include pain relief, adverse effects, and additional rescue. Direct, indirect, or network odds ratios (ORs) and 95% credible intervals (CrIs) indicate the relative efficacy or safety. Bold values means *P*-value is smaller than 0.05, which indicated that there was significant inconsistency.

incidence of gastrointestinal side effects according to our network meta-analysis. Importantly, it is generally believed that selective COX-2 inhibitors, for example, rofecoxib and valdecoxib, are related with higher risk of serious cardiovascular disease with long-term usage.[9] Accordingly, our research demonstrated that the inferior performance of both rofecoxib and valdecoxib which were already announced withdrawal from the U.S. market in 2004 and 2005, respectively. Furthermore, it should be noted that flurbiprofen and tiaprofenic acid revealed good efficacy and were recommended to be the suitable choices for the patients with severe adverse effects. The safety ranking of flurbiprofen was not ideal in our results; however, the inconsistency of direct and indirect evidence was significant between flurbiprofen and naproxen as well as flurbiprofen and

Table 7. Node-splitting results of the network meta-analysis for two continuous outcomes.

		Mean difference						
		Direct		Indirect		Difference		
Outcomes	Comparison	Coef.	Standard error	Coef.	Standard error	Coef.	Standard error	*P*
Pain intensity difference	Ibuprofen vs. placebo	−1.2558	1.0796	−2.4998	1.6782	1.2440	1.9946	0.533
	Naproxen vs. Placebo	−1.4379	1.0737	−0.1431	1.6798	−1.2948	1.9926	0.516
	Tiaprofenic acid vs. placebo	−0.3432	1.8128	−3.5687	4.0633	3.2254	4.4491	0.468
	Naproxen vs. flurbiprofen	0.9860	1.7619	−16.6152	63.4955	17.6012	63.5210	0.782
	Naproxen vs. ibuprofen	1.0838	1.2938	−0.1717	1.5209	1.2556	1.9967	0.529
	Tiaprofenic acid vs. mefenamic acid	−0.4577	1.8129	2.7677	4.0631	−3.2254	4.4491	0.468
Assessment	Aspirin vs. placebo	0.2518	0.6091	−1.5296	2.1541	1.7814	2.2388	0.426
	Ibuprofen vs. placebo	0.6275	0.4445	1.5780	1.6097	−0.9505	1.6704	0.569
	Indomethacin vs. placebo	0.6747	0.6239	0.4538	1.4531	0.2210	1.5815	0.889
	Ketoprofen vs. placebo	0.9528	0.6320	0.5631	1.8575	0.3897	1.9633	0.843
	Naproxen vs. placebo	0.6854	0.3055	1.8207	2.2829	−1.1353	2.3033	0.622
	Rofecoxib vs. placebo	0.8675	0.6165	0.8525	1.6429	0.0150	1.7561	0.993
	Valdecoxib vs. placebo	0.6082	0.8688	0.5697	1.6436	0.0384	1.8622	0.984
	Indomethacin vs. aspirin	0.8192	0.8590	−0.0481	1.1864	0.8673	1.4648	0.554
	Indomethacin vs. ibuprofen	−0.4408	0.8810	0.3675	0.9207	−0.8083	1.2745	0.526
	Ketoprofen vs. ibuprofen	0.1405	0.9008	0.3077	0.9797	−0.1672	1.3307	0.900
	Rofecoxib vs. naproxen	−0.0010	0.8642	0.3188	0.8571	−0.3198	1.2178	0.793
	Valdecoxib vs. naproxen	−0.1140	0.8685	−0.0756	1.6440	−0.0384	1.8622	0.984

Note: Three continuous outcomes include pain intensity difference and assessment. Direct, indirect, or network results of standardized mean difference and standard error indicate the relative efficacy or safety.

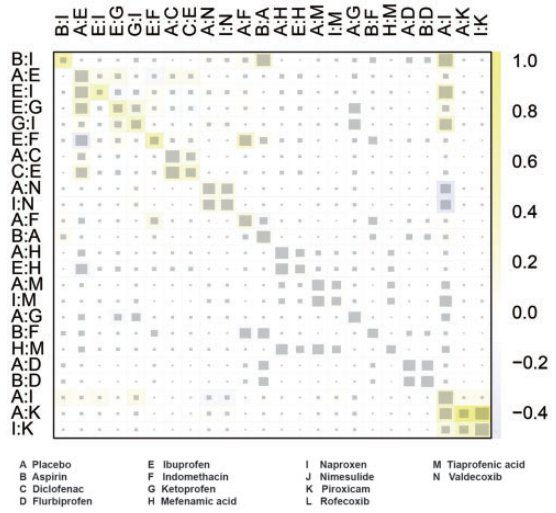

Figure 3. Heat plots for pain relief. The size of the gray squares indicates the contribution of the direct evidence (shown in the column) to the network evidence (shown in the row). The colors are associated with the change in inconsistency between direct and indirect evidence. Blue colors indicate an increase in inconsistency, and warm colors indicate a decrease in inconsistency.

aspirin. Besides, there was only one trial having direct comparison of each pair. Thus, the relevant safety of flurbiprofen lacked enough credibility, and more researches are needed in the future.

Although the result of our network meta-analysis was relatively comprehensive, there were still several limitations which may affect the strength of each result. Firstly, even though the trials included in the research were various, the population employed was small scale (many trials included less than 100 people), and the reliability of the data was lightly weakened, especially in recommended NSAIDs like tiaprofenic acid (assessed in only 71 patients). Moreover, the availability and cost of these drugs have not been taken into consideration when they are regarded as recommended therapies. Secondly, we only evaluated the difference of efficacy and safety among NSAIDs but overlooked the dosage and frequency factor related to one drug. Also, we did not provide the optimal intake way of one single drug. Furthermore, previous studies have mentioned that the symptoms of PD were similar to the adverse effects of drug treatments which may also reduce the credibility of the results.[63] Thirdly, some included studies are pharmaceutically funded and may have risks of bias, though it can be adjusted with network meta-analysis method in some degree.

In conclusion, according to our network meta-analysis, we advocate flurbiprofen and tiaprofenic acid as the recommended NSAIDs therapies for patients with PD. Naproxen, as a well-established drug, did not show superior in efficacy or safety in our result. More efforts

need to be made to further explore the characteristic of NSAIDs for PD patients.

Author Contributions

XF contributed to research conception and design, data analysis, interpretation, and drafting of the manuscript. XW contributed to data analysis, interpretation, and statistical analysis. XW and XF are involved in critical revision of the manuscript, approval of final manuscript, and taking public responsibility for appropriate portions of the content.

Supplemental Material

Supplementary material is available for this article online.

Declaration of Conflicting Interests

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