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Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials

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Abstract

Objective To assess the efficacy of topical non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of osteoarthritis.

Data sources Medline, Embase, Scientific Citation Index, CINAHL, Cochrane Library, and abstracts from conferences.

Review methods Inclusion criterion was randomised controlled trials comparing topical NSAIDs with placebo or oral NSAIDs in osteoarthritis. Effect size was calculated for pain, function, and stiffness. Rate ratio was calculated for dichotomous data such as clinical response rate and adverse event rate. Number needed to treat to obtain the clinical response was estimated. Quality of trial was assessed, and sensitivity analyses were undertaken.

Results Topical NSAIDs were superior to placebo in relieving pain due to osteoarthritis only in the first two weeks of treatment. Effect sizes for weeks 1 and 2 were 0.41 (95% confidence interval, 0.16 to 0.66) and 0.40 (0.15 to 0.65), respectively. No benefit was observed over placebo in weeks 3 and 4. A similar pattern was observed for function, stiffness, and clinical response rate ratio and number needed to treat. Topical NSAIDs were inferior to oral NSAIDs in the first week of treatment and associated with more local side effects such as rash, itch, or burning (rate ratio 5.29, 1.14 to 24.51).

Conclusion Randomised controlled trials of short duration only (less than four weeks) have assessed the efficacy of topical NSAIDs in osteoarthritis. After two weeks there was no evidence of efficacy superior to placebo. No trial data support the long term use of topical NSAIDs in osteoarthritis.

Introduction

Osteoarthritis is the most common form of arthritis and the major cause of disability in elderly people.[1 2] It represents a major disease burden for patients, health services, and society.[3] Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to relieve pain in musculoskeletal tissues, but their use comes at the cost of toxicity, with a 2-4% annual incidence of serious gastrointestinal ulcer and complications—four times higher than in non-users.[4–9] NSAIDs have been applied topically for decades. This route possibly reduces gastrointestinal adverse reactions by maximising local delivery and minimising systemic toxicity.[10] Some experimental evidence supports this, but at large joints such as the knee, bloodborne delivery may be the predominant mechanism for deep tissues.[11] Pain associated with osteoarthritis may be periarticular in origin rather than intracapsular, and topical application may act through effects on peripheral and central sensitisation.[12] Irrespective of the mechanism, topical NSAIDs are popular with health professionals and with patients as over the counter medicines. Several randomised controlled trials of short duration (less than four weeks) have been undertaken in both periarticular lesions and osteoarthritis.[13–26] A systematic review in 1998 confirmed that topical NSAIDs were superior to placebo over two weeks in the treatment of chronic pain, including pain due to osteoarthritis and tendinitis.[27] We did a meta-analysis to determine the benefit of NSAIDs in treating osteoarthritis beyond two weeks.

Methods

We identified reports of randomised controlled trials of topical NSAIDs compared with placebo or oral NSAIDs through a systematic search of the literature from 1966 to 31 October 2003. The MeSH search used in Medline, Embase, and CINAHL consisted of three steps, each containing any possible MeSH relevant to the target condition [osteoarthritis, osteoarthrosis or chronic pain associated with osteoarthritis or osteoarthrosis], study drug [topical NSAIDs], and study method [randomized controlled trial]. All MeSHs were exploded. The steps were then combined to produce relevant citations. We searched the Scientific Citation Index and Cochrane Library with the keywords osteoarthritis and topical NSAIDs. Titles and abstracts were reviewed for possible trials, and hard copies obtained for further scrutiny. The reference lists of original reports and review articles were searched, as were conference abstracts for 2002 and 2003 from international societies of rheumatology, such as the British Society for Rheumatology, the European League Against Rheumatism, the American College of Rheumatology, and the Osteoarthritis Research Society International.

Inclusion and exclusion criteria

We included randomised controlled trials comparing topical NSAIDs with placebo or oral NSAIDs. Studies were selected if patients had clinical or radiographical evidence of osteoarthritis. Two rheumatologists (JL and AJ) cross checked and agreed on the diagnostic criteria in each trial. We excluded studies in conditions such as non-osteoarthritic joint pain; rheumatoid arthritis; pain due to dental extraction, surgery, or injury; and studies with mixed patient groups such as those with osteoarthritis and rheumatoid arthritis, unless the subgroup data for osteoarthritis were available. No language restrictions applied.

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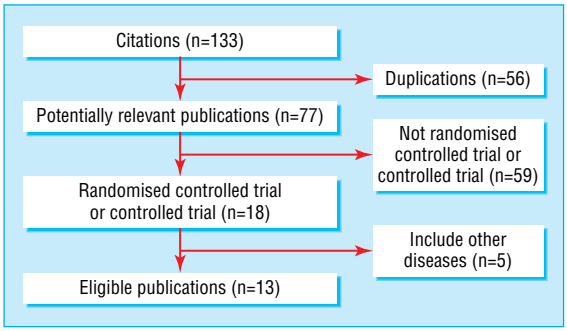


Fig 1 Selection of randomised controlled trials

Quality assessment

The quality of studies was assessed for randomisation, blinding, and withdrawal. We did not allocate additional scores for description of the method of randomisation as this is a feature of the reporting of the trials and allocation of such points may be arbitrary. Sensitivity analysis was used to assess the impact to the results of the quality components such as study design and withdrawal rate.[28]

Data extraction and outcome measures

Three of us (JL, WZ, AJ) undertook data extraction independently using a customised form. Disagreements were resolved by discussion.

The primary outcome measure was reduction in pain (global pain or pain at rest) from baseline. Other outcome measures included change in function and scores for stiffness. We assessed the clinical response rate, defined as the percentage of patients reporting at least moderate to excellent or greater than 50% pain relief or improvement in symptoms. Adverse events, expressed as the proportion of patients with any adverse events and the proportion of patients withdrawn due to adverse events, were analysed in total and by specific categories (for example, gastrointestinal events).

Statistical analysis

From individual studies we calculated the mean reduction and the standard deviation of the reduction from the means and standard deviations of the scores for pain, function, and stiffness at baseline and end point. The standard mean difference or effect size was then calculated using Hedges unbiased approach.[29] The rate ratio was estimated for dichotomous outcomes such as the clinical response rate and adverse event rate.[30] We estimated the numbers needed to treat and the 95% confidence intervals.[31]

We statistically pooled the data by the standard approach, weighted by the inverse of the sampling variance.[32] A random effects model was used for heterogeneous trials on the basis of the Q statistics for heterogeneity and if the reason for heterogeneity could not be identified. Possible publication bias was sought

Table 1 Characteristics of randomised controlled trials comparing topical non-steroidal anti-inflammatory drugs (NSAIDs) with placebo or oral NSAIDs in patients with osteoarthritis

Trial	Design	Site of osteoarthritis	Duration (weeks)	Mean (SD) age (years)	No male/No female	% baseline pain score*	Active treatment (No in group)	Control (No in group)	Effect size (SE)
Topical NSAIDs versus placebo:									
Algozziine 1982[34]	Double blind crossover	Knee	1, 1, and 1	62 (8)	24/2	NA	Salicylate four times daily (26)	Placebo (26)	NA
Bruhlmann 2003[35]	Double blind parallel	Knee	2	64 (11)	43/60	57	Diclofenac twice daily (51)	Placebo (52)	1.08 (0.21)
Dreiser 1993[18]	Double blind parallel	Knee	2	66 (11)	35/120	58	Diclofenac three times daily (78)	Placebo (77)	0.71 (0.17)
Grace 1999[20]	Double blind parallel	Knee	2	62 (12)	29/45	42	Diclofenac (38)	Placebo (36)	0.66 (0.24)
Ottillinger 2001[37]	Double blind parallel	Knee	4	67 (8)	54/183	55	Eltenac: 3 mg three times daily (59), 9 mg three times daily (59), 30 mg three times daily (57)	Placebo (59), placebo (59), placebo (59)	–0.04 (0.18), 0.20 (0.18), 0.14 (0.19)
Roth 1995[38]	Double blind parallel	Hip, knee, hand	2	67 (NA)	33/86	80	Diclofenac four times daily (59)	Placebo (60)	0.31 (0.18)
Rothacker 1994[39]	Double blind crossover	Hand	3 hours, 1 week, and 3 hours	66 (8)	8/41	NA	Salicylate (50)	Placebo (50)	NA
Rothacker 1998[22]	Double blind parallel	Hand	2 hours	61 (11)	21/60	85	Salicylate twice daily (41)	Placebo (40)	0.77 (0.23)
Rovensky 2001[23]	Double blind parallel	Knee	1	63 (8)	26/74	32	Ibuprofen three times daily (50)	Placebo (50)	0.64 (0.20)
Topical NSAIDs versus oral NSAIDs or placebo:									
Shackel 1997[40]	Double blind parallel	Hip, knee	4	61 (12)	52/64	33	Salicylate twice daily (58)	Placebo (58)	0.03 (0.19)
Sandelin 1997[24]	Double blind parallel	Knee	4	61 (8)	104/177	38	Eltenac three times daily (126)	Placebo (82)	–0.05 (0.14)
							Eltenac three times daily (126)	Diclofenac twice daily (82)	–0.10 (0.14)
Topical NSAIDs versus oral NSAIDs:									
Dickson 1991[36]	Double blind parallel	Knee	4	62 (12)	80/155	63	Piroxicam three times daily (117)	Ibuprofen three times daily (118)	NA
Zacher 2001[26]	Double blind parallel	Hand	3	62 (9)	38/283	50	Diclofenac (165)	Ibuprofen three times daily (156)	–0.05 (0.11)

NA=not available.
*Percentage of baseline pain score relative to maximum pain score: 0%=no pain, 50%=moderate pain, 100%=severe pain.

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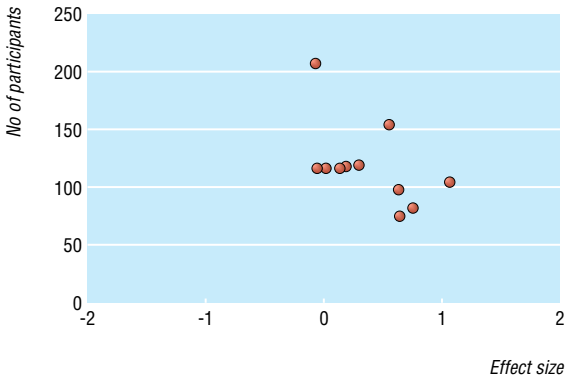


Fig 2 Funnel plot of randomised controlled trials comparing topical non-steroidal anti-inflammatory drugs with placebo (asymmetry P=0.04)

by a funnel plot and Egger test.[33] Analyses were performed with SPSS statistical software (version 11.0).

Results

We identified 133 citations, of which 77 remained after omission of duplicate articles. Overall, there were 18 potentially relevant randomised controlled trials (16 in English and two in German). Five were further excluded because either the participants did not exclusively have osteoarthritis or the comparison was between topical NSAIDs and oral NSAIDs compared with oral NSAIDs. Our inclusion criteria were met by 13 trials, representing 1983 patients (fig 1 and table 1). All trials, except for one with unknown sponsorship, were sponsored or partially sponsored with study drugs and placebo by pharmaceutical companies.[18] All were stated as randomised controlled trials, but there were no details on method of randomisation. The withdrawal rate was 1% to 23%. A funnel plot showed noticeable asymmetry in the 11 placebo controlled trials (fig 2).

Efficacy

Reduction in pain

Topical NSAIDs were superior to placebo in the first two weeks of treatment but not the following two weeks (fig 3 and table 2). Topical NSAIDs were less effective than oral NSAIDs numerically at any week and statistically in the first week (see table 2).

Improvements in function and stiffness

The effect size for improvement in function also showed superiority of topical NSAIDs over placebo in the first two weeks but not in weeks 3 and 4 (see table 2). A statistically significant effect size for improvement in stiffness was seen at one week but not at two weeks.

Clinical response rate

The clinical response rate ratio was statistically significant in the first but not fourth week (table 3). No difference was found between topical NSAIDs and oral NSAIDs.

Adverse events

Topical NSAIDs had no more side effects than placebo. Compared with oral NSAIDs, fewer patients taking topical NSAIDs had any adverse events, withdrawals due to side effects, and gastrointestinal side effects, but significantly more patients had local side effects such as rash, itch, and burning(table 4).

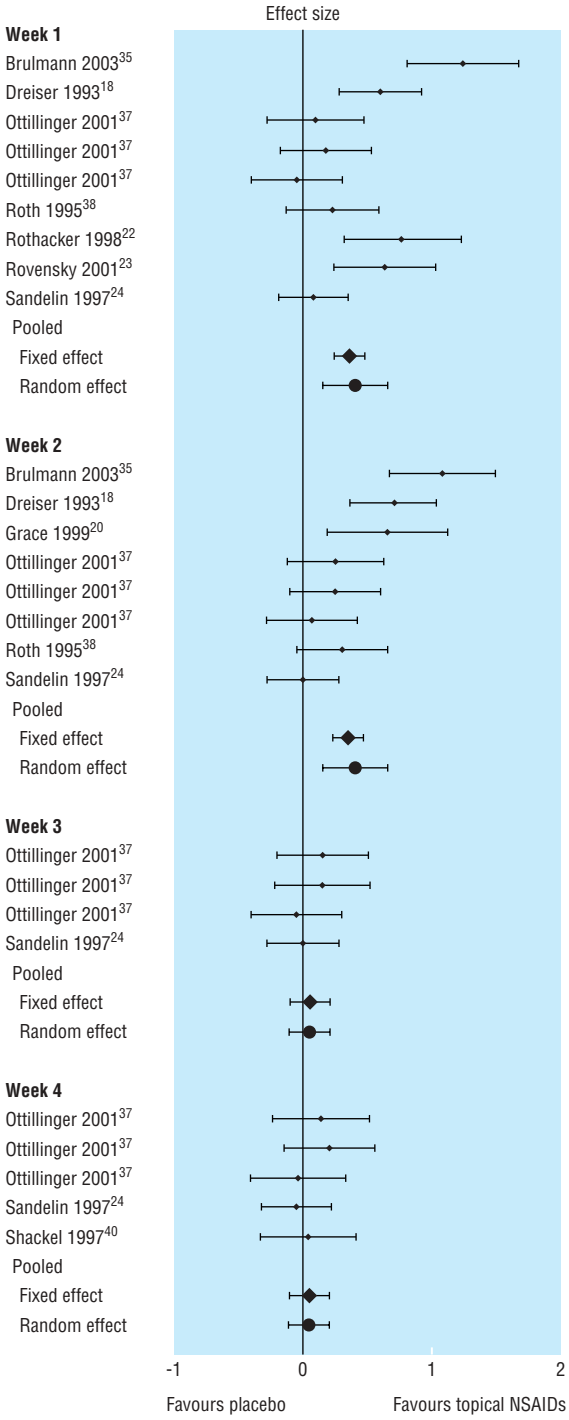


Fig 3 Effect sizes (95% confidence intervals) in pain relief between topical non-steroidal anti-inflammatory drugs and placebo

Sensitivity analysis

Sensitivity analyses showed that although baseline pain score influenced the statistical inference only, the type of topical NSAID produced significantly different effect sizes. Other factors did not affect the results (table 5).

Discussion

Most randomised controlled trials of treatment for osteoarthritis last only two weeks, and no trials go beyond four weeks. Meta-analysis of this limited data shows that treatment of osteoarthritis with topical NSAIDs is only beneficial in the first

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Table 2 Pooled effect sizes for pain relief and improvements in function and stiffness in randomised controlled trials comparing topical non-steroidal anti-inflammatory drugs (NSAIDs) with placebo or oral NSAIDs

Variable	No of trials	No of patients	Pooled effect size (95% CI)	χ^2 for heterogeneity
Topical NSAIDs versus placebo				
Pain:				
Week 1	7	1000	0.41 (0.16 to 0.66)*	35.49
Week 2	6	893	0.40 (0.15 to 0.65)*	27.48
Week 3	2	442	0.05 (–0.11 to 0.22)	1.02
Week 4	3	558	0.04 (–0.11 to 0.19)	1.68
Function:				
Week 1	4	566	0.37 (0.20 to 0.53)*	4.60
Week 2	4	540	0.35 (0.19 to 0.53)*	6.87
Week 3	1	208	0.10 (–0.18 to 0.38)	—
Week 4	1	208	0.26 (–0.02 to 0.54)	—
Stiffness:				
Week 1	1	74	0.64 (0.19 to 1.09)*	—
Week 2	1	81	0.33 (–0.13 to 0.79)	—
Week 3	NA	NA	NA	NA
Week 4	NA	NA	NA	NA
Topical NSAIDs versus oral NSAIDs†				
Pain:				
Week 1	1	208	–0.38 (–0.66 to –0.10)	—
Week 2	1	208	–0.19 (–0.47 to 0.09)	—
Week 3	2	529	–0.26 (–0.68 to 0.16)	5.83
Week 4	1	208	–0.10 (–0.37 to 0.18)	—
Function:				
Week 1	1	208	–0.32 (–0.60 to –0.04)	—
Week 2	1	208	–0.24 (–0.52 to 0.04)	—
Week 3	2	529	–0.11 (–0.28 to 0.06)	0.71
Week 4	1	208	–0.10 (–0.38 to 0.17)	—

NA=not available.
*P≤0.05.
†Data not available on stiffness.

two weeks and at one month is comparable to placebo. Our meta-analysis challenges current guidelines from Europe and America that topical NSAIDs are an effective treatment for osteoarthritis of the knee.[41–44]

This is only the second meta-analysis of topical NSAIDs. The first analysis, in 1998, reported that topical NSAIDs were effective for "chronic" painful conditions, including osteoarthritis, on the basis of data on pain relief at two weeks.[27] Unlike that study we focused solely on osteoarthritis, included studies published in the interim, examined outcomes of stiffness and function as well as pain, and examined data beyond two weeks of treatment. Our analysis had reasonable power since we identified 13 randomised controlled trials that specifically examined osteoarthritis. Although a positive effect superior to placebo was found at two weeks, trials lasting four weeks showed no benefit. The effect of topical NSAIDs may depend on time or more likely reflect the type of drug used (salicylic acid, eltenac, diclofenac, or ibuprofen), as detected by our sensitivity analyses. This seems to be more problematic in the first two weeks, as a statistically significant heterogeneity and different effects of topical NSAIDs were detected. We obtained a statistically significant asymmetrical funnel plot, indicating that negative studies are less likely to be published and that small studies are more likely to produce larger effect sizes. This publication bias may overestimate the benefit of topical NSAIDs.[33] We therefore draw two important conclusions from the data: firstly, that further well designed, long term studies (months rather than weeks) are required, and, secondly, that the benefit may be drug specific rather than class specific.

Only three trials compared topical NSAIDs with oral NSAIDs. Comparative efficacy data are limited by trial size and lack of comparison between the same drug given by different routes. The ongoing study of ibuprofen (topical versus oral) funded by the Health Technology Assessment in the United Kingdom should be helpful in this respect.

Table 3 Clinical response rate ratio and numbers needed to treat with 95% confidence intervals

Trial	Duration (weeks)	Crude rate		Rate ratio (95% CI)	Number needed to treat (95% CI)
		Active	Control		
Topical NSAIDs versus placebo:					
Rothecker 1994[39]	1	12/24	6/25	2.08 (0.93 to 4.66)	NS
Rovensky 2001[23]	1	43/50	27/50	1.59 (1.20 to 2.11)*	3.1 (2.1 to 6.6)*
Pooled				1.64 (1.26 to 2.13)*	3.3 (2.3 to 6.2)*
Dreiser 1993[18]	2	72/78	43/74	1.59 (1.30 to 1.95)*	2.9 (2.1 to 4.7)*
Shackle 1997[40]	4	32/58	32/56	0.97 (0.70 to 1.34)	NS
Topical NSAIDs versus oral NSAIDs:					
Dickson 1991[36]	4	68/107	71/118	1.06 (0.86 to 1.30)	NS

*P≤0.05.

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Table 4 Pooled rate ratio (95% confidence intervals) of side effects

Characteristics	Crude rate		Rate ratio (95% CI)
	Active	Control	
Topical NSAIDs versus placebo:			
No of patients with adverse events	108/577	85/531	1.02 (0.62 to 1.68)
No of patients withdrawn due to adverse events	16/577	6/531	1.51 (0.63 to 3.66)
Gastrointestinal events*	14/577	15/531	0.81 (0.43 to 1.56)
Central nervous system events†	14/577	14/531	0.90 (0.43 to 1.89)
Local events‡	119/577	71/531	1.14 (0.51 to 2.55)
Others	22/577	19/531	0.96 (0.57 to 1.63)
Topical NSAIDs versus oral NSAIDs:			
No of patients with adverse events	101/408	89/356	0.99 (0.77 to 1.27)
No of patients withdrawn owing to adverse events	18/408	24/356	0.72 (0.37 to 1.38)
Gastrointestinal events*	36/408	44/356	0.74 (0.48 to 1.13)
Central nervous system events†	19/243	14/200	1.08 (0.55 to 2.13)
Local events‡	18/243	2/200	5.29 (1.14 to 24.51)§

*Includes nausea, vomiting, abdominal pain, and diarrhoea.
†Includes dizziness and drowsiness.
‡Skin reactions such as rash, itch, and burning.
§P≤0.05.

Several caveats need to be mentioned. Firstly, language bias cannot be completely avoided because many studies in non-English are not indexed in the databases.[45] Secondly, results may have been confounded by different numbers of trials being pooled at different time points. Finally, we pooled trials that examined different topical NSAIDs that may have different efficacy. To minimise this bias, we used a sensitivity analysis.

In conclusion, research evidence to support the long term use (more than one month) of topical NSAIDs in osteoarthritis is absent. Current recommendations that support their use in osteoarthritis need to be revised.[41–44]

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Contributors: JL was involved in reading the papers, quality assessment, data extraction, analysis, and writing. WZ was involved in planning, searching, reading the papers, quality assessment, data extraction, analysis, and writing. AJ was involved in reading the papers, quality assessment, data extraction, and editing. MD was involved in planning and editing; he will act as guarantor for the paper.

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Competing interests: None declared.

Ethical approval: Not required.

Table 5 Sensitivity analysis of effect size (95% confidence interval) for reduction in pain between topical non-steroidal anti-inflammatory drugs (NSAIDs) and placebo, according to quality of studies, site of osteoarthritis, and pain scores at baseline

Variable	Weeks 1 and 2	Weeks 3 and 4
Study design:		
Double blind parallel	0.39 (0.19 to 0.59)*	0.08 (–0.04 to 0.19)
Double blind crossover	0.77 (0.32 to 1.22)*	NA
Withdrawal rate:		
<10%	0.54 (0.27 to 0.82)*	–0.02 (–0.22 to 0.17)
≥10%	0.20 (0.06 to 0.34)*	0.12 (–0.01 to 0.26)
Site of osteoarthritis:		
Hand	0.77 (0.32 to 1.22)*	NA
Knee	0.41 (0.18 to 0.63)*	0.08 (–0.04 to 0.20)
Hand, hip, and knee	0.27 (0.02 to 0.53)*	0.03 (–0.34 to 0.39)
Baseline pain score:		
<50%	0.32 (–0.06 to 0.70)	–0.01 (–0.18 to 0.16)
≥50%	0.44 (0.21 to 0.67)*	0.14 (–0.01 to 0.92)
Topical NSAIDs:		
Salicylate	0.77 (0.32 to 1.22)*	0.03 (–0.34 to 0.39)
Diclofenac	0.68 (0.38 to 0.99)*	NA
Eltenac	0.10 (–0.01 to 0.22)	0.08 (–0.04 to 0.19)
Ibuprofen	0.64 (0.23 to 1.04)*	NA

NA=not available.
*P≤0.05.

What is already known on this topic

Topical non-steroidal anti-inflammatory drugs (NSAIDs) have been used to relieve the pain of osteoarthritis

Current guidelines recommend topical NSAIDs as an effective treatment for osteoarthritis

What this study adds

No evidence supports the long term use of topical NSAIDs in osteoarthritis

Current recommendations for their use in osteoarthritis need to be revised

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