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Adverse Effects (AEs) of Topical NSAIDs in Older Adults with Osteoarthritis (OA): a Systematic Review of the Literature

UE. Makris, M.D. [Rheumatology Research Fellow][1], **MJ. Kohler, M.D. [Rheumatology Research Fellow]**[1], and **L. Fraenkel, M.D., M.P.H. [Associate Professor of Medicine (Rheumatology); Section Chief of Rheumatology at the West Haven Veterans Affairs Healthcare System]**[1,2]

[1]Yale University School of Medicine, Department of Medicine, Section of Rheumatology, New Haven, CT

[2]Department of Veterans Affairs, Section of Rheumatology, Connecticut Healthcare System, West Haven, CT

Abstract

Objective—To systematically review the literature on reported adverse effects (AEs) associated with topical NSAID use in older adults with osteoarthritis (OA).

Methods—A systematic search of Medline (1950 to November 2009), Scopus, Embase, Web of Science, Cochrane databases, Dissertation and American College of Rheumatology Meeting Abstracts was performed to identify original randomized controlled trials, case reports, observational studies, editorials or dissertations reporting AEs from topical NSAIDs in older adults with OA. Information was sought on study and participant characteristics, detailed recording of application site and systemic AEs as well as withdrawals due to AEs.

Results—The initial search yielded 953 articles of which 19 met eligibility criteria. Subjects receiving topical NSAIDs reported up to 39.3% application site AEs, and up to 17.5% systemic AEs. Five cases of warfarin potentiation with topical agents were reported; 1 resulting in gastrointestinal bleeding. In formal trials, the withdrawal rate from AEs ranged from 0-21% in the topical agents, 0-25% in the oral NSAIDs, and 0-16% in the placebo group.

Conclusion—In summary, although topical NSAIDs are safer than oral NSAIDs (fewer severe gastrointestinal AEs), a substantial proportion of older adults report systemic AEs with topical agents. Moreover, the withdrawal rate due to AEs with topical agents is comparable to that of oral NSAIDs. Given the safety profile and withdrawal rates described in this study, further data are needed to determine the incremental benefits of topical NSAIDs compared to other treatment modalities in older adults with OA.

Keywords

Adverse effects; Topical Administration; Anti-Inflammatory Agents; Non-Steroidal; Aged; Osteoarthritis

Address **correspondence** to Dr. Una Makris, Yale University School of Medicine, Section of Rheumatology, PO Box 208031, 300 Cedar Street, S-525 TAC. New Haven, CT 06520-8031. Telephone: 203-737-5430, Fax: 203-785-7053. una.makris@yale.edu.

INTRODUCTION

Osteoarthritis (OA) is common in older adults (1-3) and contributes to significant disability and loss of independence in this population. There is no cure for this disease and treatments focus on symptomatic relief, reducing disability, and improving quality of life (4). Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of OA in older adults despite the increased risk of toxicity in this population (5). The OA Research Society International (6) and the American Academy of Orthopaedic Surgeons (7) recent guidelines support topical NSAIDs as an effective adjunct or alternative to oral NSAIDs for treatment of knee OA. Although the safety of topical NSAIDs in older adults with OA has not been extensively studied, these agents have been widely used outside of the United States as a presumably safe alternative for the treatment of OA. The first agent, 1% diclofenac sodium, was approved in October 2007 for use in the United States.

Data suggest that some topical NSAIDs have comparable, or somewhat lower efficacy than their oral counterparts (8-13). Even if less effective, however, these agents are a reasonable treatment option if their safety profile is superior to that of oral NSAIDs. This is particularly true for older adults with OA, for whom data show that patients prefer safer medications, even if less effective (14).

Although considerable data have been published on the safety of oral NSAIDs, less is known regarding the safety of topical NSAIDs specifically in older adults with OA (15-23). Given the burden of OA in older adults and the potential toxicities with NSAID administration, we undertook a review of the existing literature regarding the safety of topical agents to help inform patients and providers on safe prescribing practices. Because of the heterogeneity of the data found on this topic, we were unable to conduct a meta-analysis. Rather, the following work is presented as a systematic review of the literature.

METHODS

A systematic search of Medline (1950 to November 2009), Scopus (including Embase), Web of Science, Cochrane databases, Dissertation Abstracts and American College of Rheumatology Meeting Abstracts was performed to identify original randomized controlled trials (RCTs), case reports, observational studies, letters, editorials or dissertations reporting AEs from topical NSAIDs in older adults with OA. Non-randomized trials including case reports or case series were included since we wanted to capture all potential AEs related to topical NSAID use. Relevant meta-analyses were reviewed, however, only original publications were included in this study. Bibliographies from all identified review articles and original articles were also reviewed for possible inclusion in the study.

Search strategy

The databases listed above were searched using variations of the following search strategy. The Medline search (via Ovid) included combinations of exploded Medical Subject Heading (MeSH) terms relevant to the drug class of interest [Anti-inflammatory agents, non-steroidal, cyclooxygenase inhibitors], the drug administration [Administration, topical, oral, pharmaceutical solutions, placebos, drug administration], the disease of interest [Osteoarthritis, arthralgia, arthritis], the population of interest [Aged, elderly] and searching MeSH subheadings and textwords [side effects, adverse effects, chemically induced, NSAIDs, topical, gels, solutions, solvents, placebo, aged, elderly, geriatrics, seniors]. The search strategy for Scopus and Web of Science was adjusted for the syntax appropriate for each database. (See Appendix).

Selection criteria

Exclusion criteria for title and abstracts (Tier 1)—Titles and abstracts identified from the initial review of the literature were excluded if the following criteria were met: 1) unrelated to topical NSAIDs, 2) unrelated to OA, 3) the title, abstract and full text of the article were not available in English, 4) no abstract available, 5) the treatment groups were taking both oral and topical NSAIDs, 6) more than 1 indication for NSAIDs. For promising titles and abstracts with insufficient information, the full text was retrieved to review the methods section in more detail.

Exclusion criteria for articles (Tier 2)—Full text articles for titles and abstracts not meeting the above exclusion criteria were reviewed and excluded from the analysis if they fulfilled the following criteria: 1) mean age <60 years old, 2) study duration of less than 2 weeks ("several" was assumed to be greater than 2), 3) no mention of AEs or inability to assign the AE to the study participant with OA.

Data abstraction

Two authors, MK and UM, used a standardized form to independently abstract data from each accepted article. Information was sought on study design, participant demographics, comorbidities, OA severity, number of target joints treated, frequency and amount of applied drug or placebo, detailed recording of application site and systemic AEs as well as withdrawals due to AEs. An informal method was used among the authors to achieve consensus when discrepancies arose.

RESULTS

The initial search yielded 1048 citations of which 95 were duplicates. Of the remaining 953 citations, 19 met our inclusion criteria and are described in this report (8-11,13,24-37). The majority of excluded articles in Tier 1 did not include a topical NSAID for the treatment of OA and many trials evaluated oral or topical NSAIDs for the treatment of non-OA conditions. Figure 1 depicts the flow diagram of the search strategy results.

Study characteristics

Of the 19 publications meeting eligibility criteria, 16 were RCTs: 2 two-arm trials compared a topical to oral NSAID (8,10); 2 three-arm trials compared a topical to oral NSAID and placebo (9,11); 1 five-arm trial compared topical to oral NSAID, vehicle (dimethylsulphoxide (DMSO)), and placebo (13); 2 RCTs compared different topical agents (34,35); and 9 compared a topical NSAID to either a vehicle or placebo (24-26,29-33,37). Of the remaining 3 publications, 1 was a case series (36), and 2 were case reports (27,28).

The duration of RCTs ranged from 2 to 12 weeks. Three (10,13,33) of the 16 RCTs were of 12 weeks duration. In the 16 RCTs, a total of 4,428 subjects were randomized; 2,043 subjects received a topical NSAID, 790 subjects received an oral NSAID, 735 received the vehicle and 860 subjects received a placebo topical/ oral agent or another topical agent (35). Table 1 shows each study design and duration, type and frequency of intervention and control groups used, as well as sample sizes.

The site of OA in 14 of 16 RCTs included the knee; 2 trials evaluated hand OA (35,37). In 7 of the RCTs, subjects were permitted to treat more than 1 affected joint (9-11,24,25,33,37). Among the RCTs, the measurement tools for documenting pain and physical function scores varied and included: WOMAC (visual analogue scale (VAS) or Likert), Lequesne index of severity (knee) and algofunctional index, Husskison's VAS, Goldberg's knee score, among others tools. The quality of RCTs also varied. The Jadad score (38) uses a 5-point scale (0-2 = low, 3-5 = high) to assess the quality of clinical trials based on randomization, blinding, and

accountability of all patients including withdrawals. Using the Jadad scale, 10 of the 16 RCTs scored a 'five', 2 scored a 'four', 2 scored a 'three', and 2 scored a 'two'.

Participant characteristics

The mean age range of participants varied between 60 and 67 years. The range of the proportion of females among the RCTs was 52% to 91%. Reporting of exclusion criteria varied among the 16 RCTs. Eight of the RCTs (10,11,13,24-26,33,34) document detailed exclusion criteria based on risk factors for oral NSAID-induced toxicity (32) including corticosteroid use, known sensitivity to NSAIDs or ASA (30), renal, hepatic and/or peptic ulcer disease (8), history of gastrointestinal bleeding within three years of the study (31), clinical or laboratory evidence of a hematopoeitic disorder (30,31), history of alcohol or drug abuse, and known skin disease at the application site (8,30,35). Comorbid conditions were only mentioned in the case series and case reports where 5 subjects were anticoagulated for cardiac valve replacements and 1 subject had known chronic venous leg ulcers.

Of the 16 RCTs, 1 study (13) described concomitant use of gastrointestinal protection; participants were allowed to continue stable treatment or start treatment with a proton-pump inhibitor if a gastrointestinal AE occurred during the trial. Nearly all of the RCTs (14 of 16) allowed the use of acetaminophen (≤ 2-4 grams) for breakthrough pain. Six of the 16 RCTs permitted ASA (≤ 325 mg/day) for cardiovascular prophylaxis (10,13,24,25,33,35).

Safety

Methods used to report AEs varied widely among RCTs and included: patient report (daily versus weekly), diary assessments, questionnaires, clinical observation, and/or blood testing. The range of the proportion of subjects in the RCTs reporting application site and systemic AEs is listed in Tables 2 and 3 respectively.

Of the application site AEs, dry skin, erythema, irritation, paresthesias, and pruritis were reported most commonly, especially among the topical NSAID, vehicle and placebo groups. Of the systemic AEs, gastrointestinal complaints and headache were reported most frequently, among both topical and oral NSAID groups. Anemia, LFT and renal abnormalities, and "severe" gastrointestinal AEs (defined as events that produced significant impairment of functioning or incapacitation and were a definite hazard to patient's health) (10) were higher among oral NSAID users.

The case series (36) and 1 of the case reports (27) report the potentiation of warfarin anticoagulation with methylsalicylate ointment (manifested as a rise in INR) in 5 subjects resulting in gastrointestinal bleeding in 1 subject. The other case report (28) described allergic contact dermatitis from the buffering agent, isopropanolamine, in Traxam gel (confirmed by patch testing) in 1 subject with known chronic venous stasis ulcers.

The proportion of withdrawals from AEs and perceived lack of efficacy are listed in Table 4.

DISCUSSION

To the best of our knowledge this is the first systematic review evaluating the safety of topical NSAIDs in older persons with OA. Evans and colleagues published a review on "Tolerability of Topical NSAIDs in the Elderly," (22) reiterating that previous studies have shown a preponderance of local skin sensitivity, contact dermatitis and photodermatitis with topical NSAID use. The authors summarized their record linkage case-control study from Scotland, with 1103 patients (78% were "aged over 50 years"), on the risk of upper gastrointestinal bleeding and perforation associated with topical NSAID use. They concluded that there was no significant independent associations between exposure to topical NSAIDs and upper

gastrointestinal toxicity (adjusted odds ratio (OR) for concomitant oral NSAID use and ulcer-healing drugs was 1.06, 95% confidence interval (CI) 0.6-1.88) (23). Further, in the review by Evans and colleagues (22), the authors report unpublished data from a similar analysis evaluating patients over the age of 65 suggesting that in older persons topical NSAIDs may convey a slightly higher risk of gastrointestinal AEs (adjusted OR 1.78, CI 0.91-3.46). These case-control studies had several limitations as they did not control for previous medical history of gastrointestinal events. Also, the authors were unable to adequately explore the temporal relationship between exposure to topical NSAID and gastrointestinal toxicity.

Altman and colleagues recently presented (in abstract form) results from post hoc analyses of pooled data from 3 similar 12-week randomized, double-blind, parallel group, multi-center trials comparing safety and efficacy of topical diclofenac 1% gel with vehicle in subjects aged <65 years and ≥65 years with knee OA. The authors found that application site AEs occurred in 5.6% and 8.8% of topical diclofenac treated patients aged <65 years and ≥65 years respectively. The rates of gastrointestinal AEs were similar in both treatment and age groups (range between 4.0-5.1%). The authors conclude that topical diclofenac was generally well tolerated with similar AE rates in participants <65 years and ≥65 years (unpublished observations)

Previous meta-analyses evaluating topical NSAIDs focused on subjects with sports injuries, musculoskeletal pain (acute and chronic), or inflammatory arthritis (39-45) who, typically, were younger than 65 years old. These reviews concluded that topical NSAIDs are a safe alternative to oral NSAIDs. In the present review, several findings suggest that there may be additional safety concerns associated with the use of topical NSAIDs in older adults with OA.

In this systematic review, topical NSAID users reported fewer severe gastrointestinal events (as defined above) compared to oral NSAID users, however, we found that up to 39.3% of older adults report an application site AE and, despite the low (6%) systemic absorption of topical NSAIDs (46,47), up to 15% report a gastrointestinal-related systemic AE with these agents. Moreover, in the studies reviewed, the withdrawal rate due to AEs with topical agents is comparable to that of oral NSAIDs.

Topical NSAIDs differ by the active medication, vehicle components, formulations (gel, solution, cream, plaster, patch), and presence of a penetration enhancer (which improves transdermal drug delivery). Any of these components may contribute to application site toxicity. As suggested in the literature, and corroborated in our review, the vehicle or carrier may contribute to the toxicity associated with topical NSAIDs (25) as seen with the application site reactions due to DMSO. Other AEs, such as halitosis and body odor, may also result from application of DMSO from the metabolite dimethyl sulfide producing a garlic-like odor (25). The withdrawal rate of participants receiving the vehicle arm, containing DMSO, was reported up to 8% due to adverse effects and up to 26% for perceived lack of efficacy. In the case report by Cooper (28), patch testing revealed the buffering agent, isopropanolamine, to be the culprit for allergic contact dermatitis rather than the NSAID itself. The methods by which AEs are reported in these trials do not permit a detailed analysis of toxicity by dose; this is important especially for RCTs that allowed for more than 1 joint to be treated. Lastly, we found a comparable withdrawal rate due to AEs between the topical and oral NSAID group. Taken together, these data suggest that topical NSAIDs are not entirely safe in this patient population.

There are several limitations to this review. First, because of the wide range of study designs used in RCTs we were unable to perform quantitative analyses to better define the specific risks associated with topical NSAIDs. Second, this review is unable to comment on topical NSAID safety in specific subgroups of older adults. The RCTs included in this trial did not identify subsets of older populations (for example, age ranges 65-74, 75-84, 85+), nor did they

focus recruitment solely on older populations. We chose a mean age of 60 years as the cut-off definition for "elderly" as only 3 publications (28,31,32) fulfilled our criteria with the more stringent age criteria of 65 years. This finding corroborates previous research on deficiencies in reporting of age data in clinical trials of arthritis as well as under-representation of elderly in OA clinical trials (10,48,49).

The design of the RCTs, while appropriate to examine efficacy, may limit the ability to draw statistical conclusions about safety. In older adults where multiple comorbidities are frequent, reporting of risk factors and concomitant medication use is critical. Moreover, RCTs frequently exclude subjects with risk factors for NSAID-induced toxicity (as required by regulators and Ethics Review Boards), thus, likely underestimating the AE profile we may expect to see in the general older adult population. "Real world" trials comparing topical agents to placebo would be more likely to have generated data relevant for patients most in need of a safer alternative to oral NSAIDs.

Another study limitation is the lack of uniformity in recording and reporting of AEs. The reporting of specific AEs varied considerably between studies, resulting in ambiguity in interpreting some of the groups of AEs. For example, several studies used AE categories such as "GI NOS," "Upper GI NOS," "Rash" without specifying the specific signs or symptoms. We reported the AE results as ranges because of the heterogeneity encountered amongst the studies, however, the ranges do not take into account the quality of the studies, (as described in the Results section). We sought to capture any AE that was reported in the studies. In addition, although 7 RCTs allowed topical NSAIDs to be used for multiple joints, and the trials varied in the number of topical applications per day, the data are insufficient to permit evaluation of a possible dose effect.

Other specific limitations were encountered while initially creating selection criteria for inclusion into this review. Several publications were excluded because they did not differentiate between participants receiving topical NSAIDs from those receiving oral NSAIDs. The authors acknowledge that considerable literature exist on several other topical NSAIDs and their toxicity/safety (ie. ketoprofen and photoallergy (50)), however, these publications were not included in this study as they were often unrelated to OA or older adults. Kneer et al. (51) recently published a multiple-dose, open-label, long-term (18 months) study on the safety of topical ketoprofen (in transfersome) in subjects (median age of 63) with joint pain, musculoskeletal pain, stiffness or soft tissue inflammation; 69% of the subjects were treated for OA. Erythema and pruritis were the most common AEs and there were no reports of gastrointestinal bleeding or "major, treatment induced changes" in laboratory values or vital signs. While this is the first study to report AEs for an extended exposure, we were unable to assign AEs to the subjects with OA, thus excluding this study from our systematic review.

As the literature suggests (52), in order to obtain the information needed to guide decision making in older adults with OA, observational studies that include participants with various comorbidities (such as hypertension, diabetes, gastroesophageal reflux disease, renal insufficiency and conditions requiring anticoagulation) are needed. Future studies should also (13,24,25,33) consider the effect that the topical NSAID vehicle/carrier may have on both application site and systemic AEs. Examination of drug-related effects, including vehicles used and total dose (51) is also critical in order to assess tolerability.

In conclusion, despite the limitations and heterogeneity of existing data, this systematic review provides important insights into the safety of topical NSAIDs in older adults with OA. The literature supports that topical NSAIDs are almost as effective and carry a lower risk of severe AEs (gastrointestinal) compared to oral NSAIDs; though, topical NSAID users do report non-life threatening gastrointestinal events and many application site AEs. While topical NSAIDs

are safer than oral NSAIDs, given the AE profile and withdrawal rates described in this study, further data are needed to quantify the incremental benefits of these agents compared to other treatment modalities for older adults with OA.

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Appendix

Ovid MEDLINE Search Strategy

1	exp Anti-Inflammatory Agents, Non-Steroidal/
2	exp Cyclooxygenase Inhibitors/
3	exp Cyclooxygenase 2 Inhibitors/
4	NSAIDs.tw.
5	1 or 2 or 3 or 4
6	exp Administration, Topical/
7	exp Administration, Oral/
8	exp Pharmaceutical Solutions/
9	exp Placebos/
10	exp Drug Administration Schedule/
11	6 or 7 or 8 or 9 or 10
12	exp Osteoarthritis/
13	exp Arthralgia/
14	Arthritis/
15	osteoarthritis.tw.
16	12 or 13 or 14 or 15
17	(gel or gels or solution$ or solvent$).mp.
18	placebo$.tw.
19	(topical adj NSAIDs).tw.
20	exp Aged/
21	elderly.mp.
22	(aged or geriatric$ or seniors).tw.
23	11 or 17 or 18 or 19
24	20 or 21 or 22
25	5 and 23 and 16 and 24
26	randomized controlled trial.pt.
27	controlled clinical trial.pt.
28	randomized controlled trials.sh.
29	random allocation.sh.
30	double blind method.sh.
31	single blind method.sh.

32	26 or 27 or 28 or 29 or 30 or 31
33	(animals not humans).sh.
34	32 not 33
35	clinical trial.pt.
36	exp Clinical Trial/
37	(clin$ adj25 trial$).ti,ab.
38	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
39	placebos.sh.
40	placebo$.ti,ab.
41	random$.ti,ab.
42	research design.sh.
43	35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44	43 not 33
45	44 not 34
46	comparative study.sh.
47	exp evaluation studies/
48	follow up studies.sh.
49	prospective studies.sh.
50	(control$ or prospectiv$ or volunteer$).ti,ab.
51	46 or 47 or 48 or 49 or 50
52	51 not 33
53	52 not (34 or 45)

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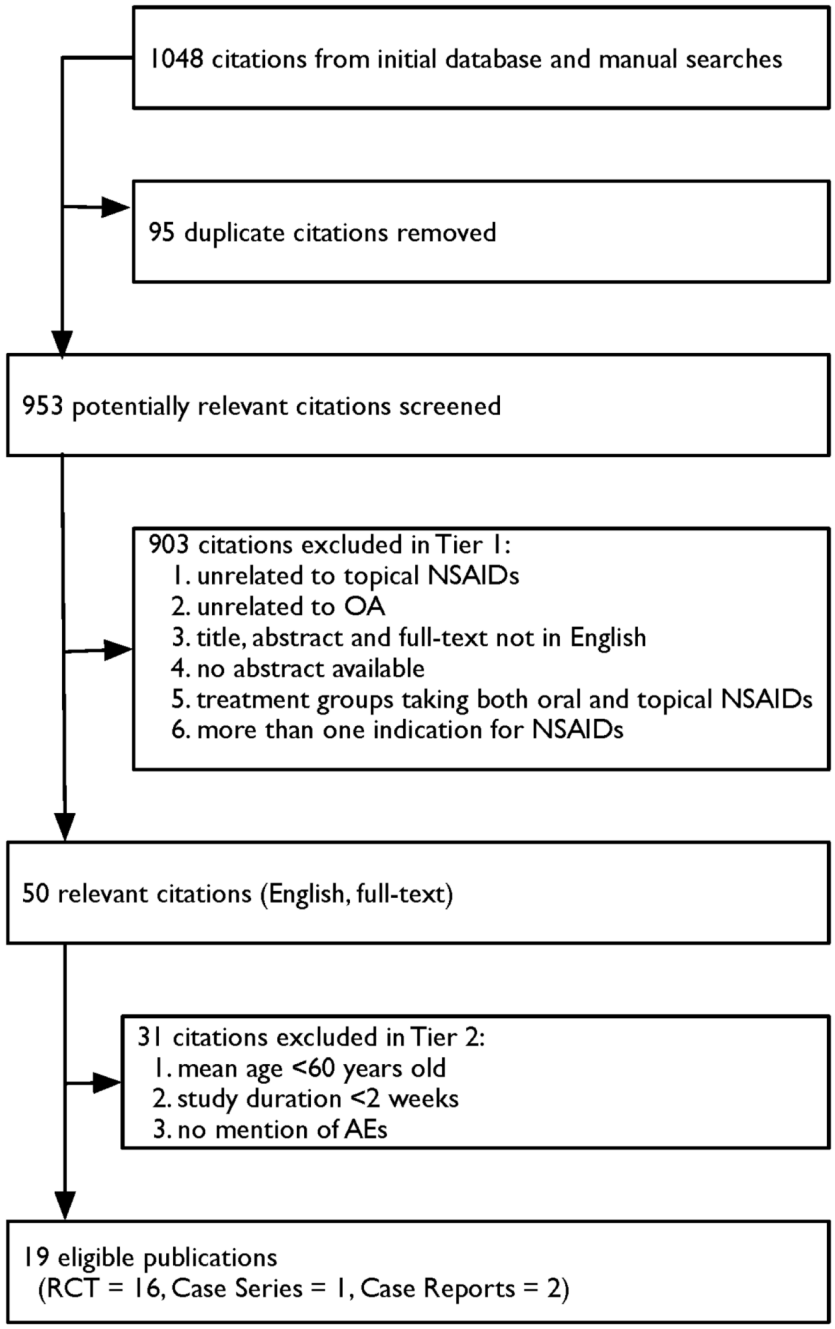

Figure 1.
Flow Diagram of Search

Table 1

Characteristics of trials comparing efficacy and safety of topical NSAIDs vs oral NSAIDs vs placebo for OA

				Number of subjects				
Trial	**Trial duration (wks)**	**Study Arms**	**Number of topical applications per day**	**Total**	**Topical agent**	**NSAID or other***	**Vehicle**	**Placebo**
RCT: Topical NSAIDs vs Vehicle and/or Placebo								
Altman (37)	8	2 grams/hand diclofenac 1% gel Vehicle gel†	4	385	198	-‡	187	-
Baer (24)	6	1.3 mL diclofenac 1.5% solution Vehicle (contains DMSO§)	4	216	107	-	109	-
Bookman (25)	4	1.3 mL diclofenac 1.5% solution Vehicle (contains DMSO) Placebo solution**	4	248	84	-	80	84
Bruhlmann (26)	2	180 mg diclofenac epolamine Placebo patch	2	103	51	-	-	52
Dreiser (29)	15d	180 mg diclofenac epolamine Placebo patch	2	155	78	-	-	77
Grace (30)	2	2.5 grams diclofenac 2% gel Vehicle gel††	3	74	38	-	36	-
Niethard (31)	3	4 grams diclofenac 1.16% gel Placebo gel	4	237	117	-	-	120
Ottillinger (32)	4	3 grams eltenac gel: 0.1% (9mg), 0.3% (27 mg), 1% (90mg)‡‡ Placebo gel **	3	237	59, 60, 59	-	-	59
Roth (33)	12	1.3 mL diclofenac 1.5% solution Vehicle (contains DMSO)	4	326	164	-	162	-
RCT: Topical NSAIDs vs Oral NSAIDs§§ +/− Vehicle +/− Placebo								
Dickson (8)	4	1 gram piroxicam 0.5% gel 400 mg ibuprofen PO tid	3	235	117	118	-	-
Rother (9)	6	110 mg ketoprofen gel 100 mg celecoxib PO bid Placebo (PO and gel)	2	397	138	132	-	127
Sandelin(11)	4	3 grams eltenac 1% gel 50 mg diclofenac PO bid Placebo (PO bid and gel tid)	3	281	124	78	-	79
Simon (13)	12	1.2 mL diclofenac 1.5% solution	4	623	154	151	161	157

				Number of subjects				
Trial	**Trial duration (wks)**	**Study Arms**	**Number of topical applications per day**	**Total**	**Topical agent**	**NSAID or other***	**Vehicle**	**Placebo**
		100 mg diclofenac SR PO daily Vehicle (contains DMSO) Placebo (PO and solution***)						
Tugwell (10)	12	1.55 mL diclofenac 1.5% solution 50 mg diclofenac PO tid†††	3	622	311	311	-	-
RCT: Topical NSAIDs vs Topical agent								
Waikakul (34)	4	1 gram ketoprofen gel 1 gram diclofenac emulgel	4	85	43	42	-	-
Widrig (35)	3	ibuprofen 5% gel arnica gel‡‡‡	3	204	99	105	-	-
Case Series								
Yip (36)	>2	Methylsalicylate ointment	Variable	4	4	-	-	-
Case Reports								
Chow (27)	2	Methylsalicylate ointment	“regularly”	1	1	-	-	-
Cooper (28)	2	Traxam gel§§§	-	1	1	-	-	-

*Widrig used arnica gel in the second-arm, not an NSAID

†Vehicle gel composed of isopropyl alcohol, propylene glycol, cocoyl caprylocaprate, mineral oil, ammonia solution, perfume cream 45/3, carbomer 980, polyoxyl 20 cetostearyl ether and purified water

‡Not mentioned in the text

§DMSO is a carrier (absorption enhancer), without active NSAID, composed of dimethylsulphoxide (45.5%), propylene glycol, glycerin, ethanol, and water

**Placebo topical agent used a token amount of DMSO, 4.55% wt/wt

††Vehicle gel composed of pluronic lecithin organogel base

‡‡Ottilinger included 3 topical NSAID study arms; carrier composed of transparent polyacrylic acid gel with 2-propanol (no penetration enhancer)

§§Subjects receiving topical and oral NSAIDS received appropriate placebo drug

***Modified placebo solution composed of 2.3% DMSO

†††Placebo solution used with oral diclofenac was modified carrier using 2.3% DMSO

‡‡‡Arnica gel composed of 50g tincture/ 100g, DER 1:20 arnica

§§§Traxam gel composed of biphenylacetic acid 3% pet, carbomer 10% aqueous, isopropanolamine 1% aqueous

Table 2
Application Site Adverse Events among RCTs

Adverse Effects	Treatment Group/ Drug Administration (range %)			
	Topical	PO	Vehicle*	Placebo
Dry skin	0.79-39.3	1-2.6	11.2-25.3	1-3.2
Rash NOS	0.8-13	0-2	1.2-13.9	0
Rash†	1.4-21	0-13.6	-	0-16.5
Dermatitis‡	0-4.8	0.7-1	3.1	0-0.6
Paresthesia	0-14	0.6	1.1-22	0.6-6
Pruritis	0-11	0-3.8	0-8	0-4
Urticaria	0.3-1.4	0.3-0.8	-	0.8
Vesiculobullous rash	0.6-5	0	0	-

*Vehicle contains DMSO or pluronic lecithin organogel base, or isopropyl alcohol, propylene glycol, cocoyl caprylocaprate, mineral oil, ammonia solution, perfume cream 45/3, carbomer 980, polyoxyl 20 cetostearyl ether, and purified water

†Rash grouped as erythema, irritation, “local effects,” exanthema

‡Dermatitis includes allergic dermatitis, contact dermatitis and contact eczema

Table 3
Systemic Adverse Events among RCTs

Adverse Effects	Treatment Group/ Drug Administration (range %)			
	Topical	PO	Vehicle*	Placebo
Upper GI NOS(8)	10.3	8.5	-	-
GI NOS(8, 11)	2.6-4.8	0.8-13.4	-	7.3
Abdominal pain	1.4-12	3-22	0.9-3.1	0.6-2.4
Dyspepsia	0.7-15	3-26	0.9-5	0.8-6
Gastritis	0.9-2.2	0	0	0-2.4
Nausea	0-8	2-13	0.6-5.6	0
Diarrhea	0-9	1.5-17	0-2	0-4
Constipation	0.9-8	0-10	0.6-1	1
GI Bleed†	0-1	0-2	0-1.2	0
Halitosis	0-5	0.3	0-1.2	0
Liver function abnormality	0-6.9	7.9-19.6	1.3-5.3	0.6-4.2
Renal abnormality‡	0-7.6	7.2-10	6	0-5.7
Change in hemoglobin	0-2.1	5.8-10	3.3	4.9
Respiratory disorder§	0-3.2	2-5.3	0.5-2.5	3.8
CNS NOS(8, 11)	6-9.5	6.8-7.3	-	4.9
Dizziness	0.6-1.2	4	0	-
Vertigo	0-1	-	-	-
Headache	5-17.5	6-17.2	4.3-13	11.5

*Vehicle contains DMSO, pluronic lecithin organogel base, or isopropyl alcohol, propylene glycol, cocoyl caprylocaprate, mineral oil, ammonia solution, perfume cream 45/3, carbomer 980, polyoxyl 20 cetostearyl ether, and purified water

†Gastrointestinal bleed includes melena and rectal hemorrhage

‡% of patients changing from normal to abnormal creatinine clearance (ml/min)

§Respiratory disorder includes asthma, cough, and dyspnea

Table 4

Range of Proportion of Withdrawals from RCTs due to Adverse Effects and Perceived Lack of Efficacy

	Adverse Effects (%)	Perceived Lack of Efficacy (%)
Topical NSAIDs	0-21	0-17
Oral NSAIDs	0-25	2-3
Placebo	0-16	0-12