Adverse Effects of Topical Nonsteroidal Antiinflammatory Drugs in Older Adults with Osteoarthritis: A Systematic Literature Review

UNA E. MAKRIS, MINNA J. KOHLER, and LIANA FRAENKEL

ABSTRACT. ***Objective.*** To systematically review the literature on reported adverse effects (AE) associated with use of topical nonsteroidal antiinflammatory drugs (NSAID) 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 AE from topical NSAID in older adults with OA. Information was sought on study and participant characteristics, detailed recording of application site, and systemic AE as well as withdrawals due to AE.

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

Conclusion. Although topical NSAID are safer than oral NSAID (fewer severe gastrointestinal AE), a substantial proportion of older adults report systemic AE with topical agents. The withdrawal rate due to AE with topical agents is comparable to that of oral NSAID. Given the safety profile and withdrawal rates described in this study, further data are needed to determine the incremental benefits of topical NSAID compared to other treatment modalities in older adults with OA. (J Rheumatol First Release April 1 2010; doi:10.3899/jrheum.090935)

Key Indexing Terms:
ADVERSE EFFECTS TOPICAL ADMINISTRATION
NONSTEROIDAL ANTIINFLAMMATORY AGENTS AGED OSTEOARTHRITIS

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 antiinflammatory drugs (NSAID) 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 NSAID as an effective adjunct or alternative to oral NSAID for treatment of knee OA. Although the safety of topical NSAID in older adults with OA has not been extensively studied, these agents have been widely used outside the United States as a presumably safe alternative for 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 NSAID 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 NSAID. 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 NSAID, less is known regarding the safety of topical NSAID 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 literature regarding the safety of topical agents to help inform patients and healthcare providers on safe prescribing

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practices. Because of the heterogeneity of the data on this topic, we were unable to conduct a metaanalysis. Rather, this report is presented as a systematic review of the literature.

MATERIALS AND 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 (RCT), case reports, observational studies, letters, editorials, or dissertations reporting AE from topical NSAID in older adults with OA. Nonrandomized trials including case reports or case series were included since we wanted to identify all potential AE related to topical NSAID use. Relevant metaanalyses 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 (antiinflammatory agents, nonsteroidal, 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 NSAID; (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 NSAID; (6) more than 1 indication for NSAID. For promising titles and abstracts with insufficient information, the full text was retrieved to review the Methods section in 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 < 2 weeks ("several" was assumed to be more than 2); (3) no mention of AE 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 AE as well as withdrawals due to AE. 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 NSAID for the treatment of non-OA conditions. Figure 1 depicts the process of the search strategy.

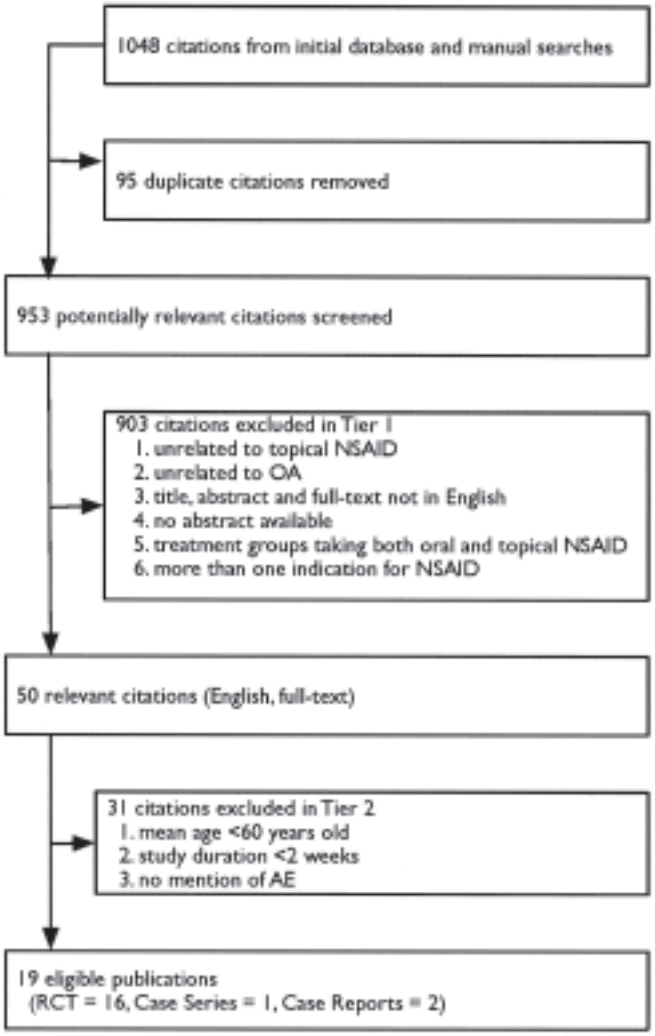

Figure 1. The process of the search strategy. NSAID: nonsteroidal antiinflammatory drug; OA: osteoarthritis; AE: adverse effect; RCT: randomized controlled trial.

Study characteristics. Of the 19 publications meeting eligibility criteria, 16 were RCT: 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]; one five-arm trial compared topical to oral NSAID, vehicle [dimethylsulfoxide (DMSO)], and placebo[13]; 2 RCT 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, one was a case series[36] and 2 were case reports[27,28].

The duration of RCT ranged from 2 to 12 weeks. Three of the 16 RCT were of 12 weeks' duration[10,13,33]. In the 16 RCT, a total of 4428 subjects were randomized; 2043 subjects received a topical NSAID, 790 received an oral NSAID, 735 received the vehicle, and 860 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.

Table 1. Characteristics of trials comparing efficacy and safety of topical NSAID vs oral NSAID vs placebo for OA.

Trial	Trial Duration, wks	Study Arms	No. Topical Applications/day	Total	Topical Agent	No. of Subjects NSAID or Other[a]	Vehicle	Placebo
RCT: Topical NSAID vs Vehicle and/or Placebo								
Altman[37]	8	2 g/hand diclofenac 1% gel Vehicle gel[b]	4	385	198	—[c]	187	—
Baer[24]	6	1.3 ml diclofenac 1.5% solution Vehicle (contains DMSO[d])	4	216	107	—	109	—
Bookman[25]	4	1.3 ml diclofenac 1.5% solution Vehicle (contains DMSO) Placebo solution[e]	4	248	84	—	80	84
Bruhlmann[26]	2	180 mg diclofenac epolamine Placebo patch	2	103	51	—	—	52
Dreiser[29]	15 days	180 mg diclofenac epolamine Placebo patch	2	155	78	—	—	77
Grace[30]	2	2.5 g diclofenac 2% gel Vehicle gel[f]	3	74	38	—	36	—
Niethard[31]	3	4 g diclofenac 1.16% gel Placebo gel	4	237	117	—	—	120
Ottillinger[32]	4	3 g eltenac gel: 0.1% (9mg), 0.3% (27 mg), 1% (90 mg)[g] Placebo gel[e]	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 NSAID vs Oral NSAID[h] +/– Vehicle +/– Placebo								
Dickson[8]	4	1 g 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 g 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 100 mg diclofenac SR PO daily Vehicle (contains DMSO) Placebo (PO and solution[i])	4	623	154	151	161	157
Tugwell[10]	12	1.55 ml diclofenac 1.5% solution 50 mg diclofenac PO tid[j]	3	622	311	311	—	—
RCT: Topical NSAID vs Topical Agent								
Waikakul[34]	4	1 g ketoprofen gel 1 g diclofenac emulgel	4	85	43	42	—	—
Widrig[35]	3	Ibuprofen 5% gel Arnica gel[k]	3	204	99	105	—	—
Yip[36]	> 2	Methylsalicylate ointment	Variable	4	4	—	—	—
Case Reports								
Chow[27]	2	Methylsalicylate ointment	"regularly"	1	1	—	—	—
Cooper[28]	2	Traxam gel[l]	—	1	1	—	—	—

[a] Widrig[35] used arnica gel in the second arm, not an NSAID. [b] 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. [c] Not mentioned in the text. [d] DMSO is a carrier (absorption enhancer), without active NSAID, composed of dimethylsulphoxide (45.5%), propylene glycol, glycerin, ethanol, and water. [e] Placebo topical agent used a token amount of DMSO, 4.55% wt/wt. [f] Vehicle gel composed of pluronic lecithin organogel base. [g] Ottillinger included 3 topical NSAID study arms; carrier composed of transparent polyacrylic acid gel with 2-propanol (no penetration enhancer). [h] Subjects receiving topical and oral NSAID received appropriate placebo drug. [i] Modified placebo solution composed of 2.3% DMSO. [j] Placebo solution used with oral diclofenac was modified carrier using 2.3% DMSO. [k] Arnica gel composed of 50 g tincture/100 g, DER 1:20 arnica. [l] Traxam gel composed of biphenylacetic acid 3% pet, carbomer 10% aqueous, isopropanolamine 1% aqueous.

The site of OA in 14 of 16 RCT included the knee; 2 trials evaluated hand OA[35,37]. In 7 of the RCT, subjects were permitted to treat more than one affected joint[9-11,24,25,33,37]. Among the RCT, the measurement tools for documenting pain and physical function scores varied and included the Western Ontario and McMaster Universities Osteoarthritis

Index [WOMAC; visual analog scale (VAS) or Likert scale], Lequesne index of severity (knee) and algofunctional index, Husskison's VAS, and Goldberg's knee score, among others tools. The quality of RCT 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 RCT scored a five, 2 scored a four, 2 scored a three, and 2 scored a two.

Participant characteristics. The mean age of participants varied between 60 and 67 years. The range of the proportion of females among the RCT was 52% to 91%. Reporting of exclusion criteria varied among the 16 RCT. Eight RCT[10,11,13,24-26,33,34] documented detailed exclusion criteria based on risk factors for oral NSAID-induced toxicity[32] including corticosteroid use, known sensitivity to NSAID or ASA[30], renal, hepatic and/or peptic ulcer disease[8], history of gastrointestinal (GI) bleeding within 3 years of the study[31], clinical or laboratory evidence of a hematopoietic disorder[30,31], history of alcohol or drug abuse, and known skin disease at the application site[8,30,35]. Comorbid conditions were mentioned only in the case series and case reports, where 5 subjects were anticoagulated for cardiac valve replacements and one subject had known chronic venous leg ulcers.

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

Safety. Methods used to report AE varied widely among RCT and included patient report (daily vs weekly), diary assessments, questionnaires, clinical observation, and/or blood testing. The ranges of subjects in the RCT reporting application site and systemic AE are listed in Tables 2 and 3, respectively.

Of the application site AE, dry skin, erythema, irritation, paresthesias, and pruritus were reported most commonly, especially among the topical NSAID, vehicle, and placebo groups. Of the systemic AE, GI complaints and headache were reported most frequently, among both topical and oral NSAID groups. Anemia, liver function test and renal abnormalities, and "severe" GI AE (defined as events that produced significant impairment of functioning or incapacitation and were a definite hazard to patient's health)[10] were more numerous among oral NSAID users.

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

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

DISCUSSION

To our knowledge this is the first systematic review evaluating the safety of topical NSAID in older adults with OA. Evans and colleagues published a review on tolerability of topical NSAID 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 GI bleeding and perforation associated with topical NSAID use. They concluded that there was no significant independent association between exposure to topical NSAID and upper GI toxicity [adjusted odds ratio for concomitant oral NSAID use and ulcer-healing drugs was 1.06 (95% CI 0.6–1.88)][23]. Further, in their review, Evans and colleagues[22] report unpublished data from a similar analysis evaluating patients

Table 2. Application site adverse effects among RCT.

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
Pruritus	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. NOS: not otherwise specified.

Table 3. Systemic adverse events among RCT.

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. ** GI bleed includes melena and rectal hemorrhage. † Percentage of patients changing from normal to abnormal creatinine clearance (ml/min). †† Respiratory disorder includes asthma, cough, and dyspnea. GI: gastrointestinal; NOS: not otherwise specified; CNS: central nervous system.

over age 65 years, suggesting that in older adults topical NSAID may convey a slightly higher risk of GI AE (adjusted OR 1.78, 95% CI 0.91–3.46). These case-control studies had several limitations, as they did not control for medical history of GI events. Also, the authors were unable to adequately determine the temporal relationship between exposure to topical NSAID and GI toxicity.

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

Table 4. Range of proportion of withdrawals from randomized controlled trials due to adverse effects and perceived lack of efficacy.

	Adverse Effects, %	Perceived Lack of Efficacy, %
Topical NSAID	0–21	0–17
Oral NSAID	0–25	2–3
Placebo	0–16	0–12

NSAID: nonsteroidal antiinflammatory drugs.

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

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

Topical NSAID 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 NSAID[25], as seen with the application site reactions due to DMSO. Other AE, 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 by up to 8% due to AE and up to 26% for perceived lack of efficacy. In the case report by Cooper and Shaw[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 AE are reported in these trials do not permit a detailed analysis of toxicity by dose; this is important especially for RCT that allowed for more than one joint to be treated. Lastly, we found a comparable withdrawal rate due to AE between the topical and oral NSAID groups. Together, these data suggest that topical NSAID are not entirely safe in this patient population.

There are several limitations to our review. First, because of the wide range of study designs used in RCT we were unable to perform quantitative analyses to better define the specific risks associated with topical NSAID. Second, this review is unable to comment on topical NSAID safety in specific subgroups of older adults. The RCT included in this analysis 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 cutoff definition for "elderly," as only 3 publications[28,31,32] fulfilled our criteria with the more stringent age criterion of 65 years. This finding corroborates previous research on deficiencies in reporting of age data in clinical trials of arthritis as well as underrepresentation of elderly in OA clinical trials[10,48,49].

The design of the RCT, 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, RCT 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 NSAID.

Another study limitation is the lack of uniformity in recording and reporting of AE. The reporting of specific AE varied considerably between studies, resulting in ambiguity in interpreting some of the groups of AE. For example, several studies used AE categories such as "GI NOS," "Upper GI NOS," "Rash" without including the specific signs or symptoms. We reported the AE results as ranges because of the heterogeneity among the studies; however, the ranges do not take into account the quality of the studies (as described in the Results section). We sought to identify any AE that was reported in the studies. In addition, although 7 RCT allowed topical NSAID 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 NSAID and those receiving oral NSAID. The authors acknowledge that considerable literature exists on several other topical NSAID and their toxicity/safety (i.e., 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, longterm (18 months) study on the safety of topical ketoprofen (in Transfersome) in subjects (median age 63 years) with joint pain, musculoskeletal pain, stiffness, or soft tissue inflammation; 69% of the subjects were treated for OA. Erythema and pruritus were the most common AE and there were no reports of GI bleeding or "major, treatment induced changes" in laboratory values or vital signs. While this was the first study to report AE for an extended exposure, we were unable to assign AE to the subjects with OA, thus this study was excluded 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 consider the effect[13,24,25,33] that the topical NSAID vehicle/carrier may have on both application site and systemic AE. Examination of drug-related effects, including vehicles used and total dose[51], is also critical in order to assess tolerability.

Despite the limitations and heterogeneity of existing data, our systematic review provides important insights into the safety of topical NSAID in older adults with OA. The literature supports that topical NSAID are almost as effective and carry a lower risk of severe AE (gastrointestinal) compared to oral NSAID, although topical NSAID users do report non-life-threatening gastrointestinal events and many application site AE. While topical NSAID are safer than oral NSAID, given the AE profile and withdrawal rates we describe, 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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