Topical nonsteroidal anti-inflammatory drugs in the treatment of osteoarthritis

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Osteoarthritis is the most common degenerative joint disease and is particularly common in the elderly. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) may represent a rational treatment in this situation because of their favorable side-effect profile. The majority of topical NSAIDs decrease pain and relieve functional disability caused by osteoarthritis over the short term, however, there are insufficient data for their long-term efficacy.

Keywords: diclofenac, ibuprofen, ketoprofen, meta-analysis, osteoarthritis, piroxicam, randomized controlled trials, topical nonsteroidal anti-inflammatory drugs

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Osteoarthritis (OA) is the most common disease of synovial joints, associated with locomotor pain, chronic disability and morbidity [1]. It is estimated by the WHO to be the fourth most important cause of disability among women and the eighth amongst men [2]. Its prevalence and incidence are projected to rise as the elderly proportion of the population increases, which will have a significant impact on society [3]. The onset of the disease most commonly occurs between the age of 50 and 60 years and frequently affects the hands, spine, knees and hips [4]. Involvement of the wrists, elbows, ankles and shoulders is uncommon [5]. The majority of persons show radiographic evidence of OA by 65 years of age, although most are asymptomatic [6]. In the Framingham study, for example, 30% of patients aged over 60 years had radiological evidence of OA of the knee, which was not always symptomatic [4].

OA was previously thought to be a normal consequence of aging, thereby linked to the term degenerative joint disease. It is now recognized that OA results from a complex interplay of multiple factors, including joint integrity, genetics, metabolic, local inflammation, mechanical forces, previous injury of a joint, and cellular and biochemical processes [7,8].

To date, there are no means to prevent the occurrence of OA. Thus, treatment is directed towards pain relief, improving function and health-related quality of life [8]. A combination of nonpharmacologic (**Box 1**), pharmacologic (**Table 1**) and surgical (**Box 2**) treatment is usually needed and should be individualized according to patient needs, presence of comorbidities and drug–drug interactions.

Nonpharmacologic treatment

Current treatment guidelines recommend the combination of weight loss and exercise programs to reduce pain and improve function in patients with OA of the knees [9]. Other interventions include the use of assistive devices (cane or crutch), application of braces and patellar taping and/or orthotics, especially in patients with instability of the knee and varus malalignment [8,10,11]. Participation in patient self-management programs and personalized social support through telephone contact have also been shown to help in decreasing pain and improving function in patients with OA [10].

Acupuncture has been evaluated in randomized controlled trials and been shown to provide added benefit in patients with knee OA with a favorable safety profile [12,13].

Topical traditional Chinese medicine (TTCMs) and other alternative remedies are still widely used, especially in Chinese and other ethnic communities. When all the 'modern' preparations have been exhausted, some 'old remedies' have been explored by patients [14]. Litt has offered a list of 73 alternative topical measures that are often beneficial, mostly for dermatologic disorders [15]. TTCMs have many varieties. A common misconception is that TTCM is a complicated, exotic art. Difficulties in understanding these measures are due first to more than one ingredient in one formulation, second to the myriad of preparations available and third due to labeling, with brands such as Tiger Balm, 3-Snake Oil and Dragon Balm. First and foremost, it must be understood that brand names are just brand names. The names are symbolic [14]. Tiger Balm and 3-Snake Oil do not contain any material from either of these animals. Indeed, TTCMs are mixtures containing many herbs, ranging from three to 20 different types. Mixtures are based on the concept of traditional Chinese medicine. The formulations use different ingredients to balance the body and to balance the opposite properties of different herbals. However, all these myriads of preparations can be grouped into three classes, according to usage.

Box 1. Nonpharmacologic therapy for patients with osteoarthritis.

- Patient education
- Self-management programs
- Telephone contact
- Weight loss (if overweight)
- Physical therapy and aerobic exercise
- Patellar taping
- Corrective footwear, bracing, joint protection, lateral-wedged insoles (for genu varum)
- Assistive devices for activities of daily living
- Laser
- Pulsed electromagnetic field, ultrasound, transcutaneous electrical nerve stimulation
- Acupuncture
- Nutrients, herbal remedies, vitamins/minerals
- Spa

In each class, the ingredients revolve around a common theme, with only minor differences. The three classes are:

- Oils, ointments, pastes for aches and pains;
- Oils, ointments, pastes for orthopedic injuries;
- Lotions and ointments for skin diseases.

Here, only the first class will be briefly summarized [14,16].

The classic example of class 1 TTCMs used for rheumatic pain is Tiger Balm [17]. It is an oil-based balm containing camphor, menthol and one or more essential oils, such as cinnamon oil, oil of clove, cassia oil, citronella oil, oil of lavender or cajuput oil. These are compound together in a base oil or petrolatum. It can thus be appreciated that the formulation is meant to be soothing. They usually are not irritating to the skin unless the patients are allergic to these ingredients. Other paste preparations are mixtures of various herbals with a petrolatum base. *Zingiber officinale* rhizoma, *Polygonum multiflorum* radix, *Peonia lactiflora* radix, rhizoma et radix notopterygii, myrrha and other herbals are commonly used for rheumatic pain, a bi-syndrome in TTCM. None of these have been assessed in controlled trials available in english [14,17].

Table 1. Pharmacologic therapy of osteoarthritis.

Route	Pharmacologic agent
Oral therapy	Acetaminophen
	NSAIDs
	Cyclooxygenase-2
	Nonacetylated salicylate
	Tramadol
	Opioids
	Glucosamine sulfate
	Chondroitin sulfate
Intra-articular therapy	Glucocorticoids
	Hyaluronan
	Tidal irrigation
Topical therapy	NSAIDs
	Capsaicin

NSAID: Nonsteroidal anti-inflammatory drug.

Pharmacologic treatment

Paracetamol, up to 4 g/day, remains the most commonly prescribed drug in patients with mild-to-moderate pain. A meta-analysis published in 2004 confirmed the efficacy of acetaminophen in relieving pain due to OA, which should be the first-line treatment, reserving nonsteroidal anti-inflammatory drugs (NSAIDs) for patients who do not respond [18].

Both classical NSAIDs and cyclo-oxygenase (Cox)-2 inhibitors are used commonly and are more effective than placebo and acetaminophen in reducing pain and functional disabilities in patients with OA of knees and hips [19,20]. This superiority of NSAIDS over acetaminophen, however, is modest and because of the high inter-individual variability in patient response to both of these drug classes, it is impossible to predict the patient's response to them [8,21].

Opiate analgesic agents, including tramadol, can also be used and may be of benefit in patients with severe pain resistant to NSAIDs or in those who have contraindication to treatment with other drugs [11].

Glucosamine and chondroitin are natural substances derived from animal products that have acquired substantial popularity in the treatment of OA [22]. The most important merit is their safety, although their mechanisms of action are unclear [11]. In a 2003 meta-analysis that included 15 randomized, double-blind, placebo-controlled trials that assessed either glucosamine or chondroitin on structure modification of knee or hip OA, glucosamine was found to have a positive effect in reducing joint space narrowing [23]. In a recently published randomized controlled trial of glucosamine and chondroitin, the drugs were not helpful in effectively reducing pain in patients with OA of the knees. Exploratory analyses, however, suggest that the combination may be effective in the subgroup of patients with moderate-to-severe knee pain [24].

Box 2. Surgical treatment for patients with osteoarthritis.

- Arthroscopic management
  - Lavage
  - Debridement
  - Abrasion arthroplasty
  - Subchondral penetration procedures (drilling and microfracture)
  - Laser/thermal chondroplasty
- Osteotomy
- Arthodesis (stiffening of a joint by operative means)
- Total joint replacement/unicompartmental knee replacement
- Grafting and cell transplantation (autologous osteochondral transplantation)

Intra-articular treatment with hyaluran and hyalans has recently become a popular symptomatic therapy in OA of the knees and has been approved by the US FDA. However, data on their efficacy are controversial [5,8].

Intra-articular injection of long-acting corticosteroids are widely used in the management of patients with OA of the knees, and may be particularly beneficial in patients demonstrating signs of local inflammation with a joint effusion [25]. Evidence supports short-term (2–4 weeks) improvement in symptoms of OA of the knee after intra-articular corticosteroid injection and, compared with placebo, they significantly relieve pain but do not improve functional impairment [26,27]. Moreover, long-term (2 years) treatment of knee OA with repeated intra-articular steroid injections at a frequency not exceeding four times/year appears to be effective when compared with saline injections, with no evidence of a deleterious effect on the joint structure [28]. The adverse effects of more frequent injections or injections for a period exceeding 2 years is unknown.

Safety concerns

The typical patient with OA is an elderly person with multiple medical problems on several medications who will require treatment for weeks if not years, and thus is at high risk for toxicity. The elderly are especially vulnerable to drug toxicity for many reasons, including difficulties with treatment adherence, nutritional insufficiency, altered pharmacokinetics, end-organ responsiveness and the enhanced potential for drug–drug interactions arising from polypharmacy for various comorbidities [29]. The most common toxicity attributed to the treatment of OA is the increased morbidity and mortality from gastrointestinal (GI) events in patients taking NSAIDs [10,20]. In the UK, for example, the attributable risk of going to a hospital with GI problems for regular users of oral NSAIDs is 1.3–1.6% annually [30]. In the USA, GI tract bleeding secondary to NSAIDs accounts for 41,000 hospitalization and 3300 deaths each year [31]. Additionally, approximately 40% of hospital admissions with upper GI bleeding, and 40% of associated deaths in older people, are related to NSAID use [32]. Other significant side effects of NSAIDs include renal insufficiency, especially in patients with reduced renal perfusion, hypertension, leg edema and exacerbation of heart failure and an increased risk of cardiovascular events, especially with the use of the new Cox-2 inhibitors [3,5,22,29,33].

Topical NSAIDs

The use of topical NSAIDs is a highly controversial topic in the medical community. In Germany, for example, it accounts for two-thirds of the most frequently prescribed NSAIDs for both acute and chronic conditions, while in other parts of the world it is thought of as junk medicine and a marker of bad prescribing [34].

Topical NSAIDs, however, are attractive substitutes to oral therapy in reducing the symptoms of OA, with minimal adverse side effects, including peptic ulcer disease and GI hemorrhage [3,35]. They provide the advantage of local, enhanced drug delivery to affected tissues in combination with a reduced systemic absorption of NSAID, in addition to the lack of interactions and ease of use [3,35,36].

In the next section of this paper, we will answer common questions relating to these agents, including their efficacy in OA and other conditions and their safety profile.

Do topical NSAIDs penetrate into the joint?

The therapeutic effect of topically applied formulations is dependent on the ability of the active ingredients to penetrate into tissue layers beneath the application site, on the high interindividual difference of skin penetration and any other materials that are used to enhance skin diffusion [37].

The skin layers through which topical NSAIDs must be transported are the stratum corneum, epidermis, basement membrane and the dermis. Thus, for optimal penetration and absorption into deeper tissues and the systemic circulation, the topical NSAIDs require both hydrophilic and hydrophobic proportional qualities [38].

In general, plasma concentrations achieved via topical delivery are 1–10% of those achieved by systemic delivery [39]. Topical administration produces high concentrations in meniscus, tendon sheath and cartilage, higher than that in plasma or synovial fluid (**Figure 1**) [38,40].

For instance, the topical application of diclofenac solution in 248 patients with primary OA of the knee resulted in a peak serum level of 12 ng/ml, up to 125-times lower than peak plasma levels for an equivalent amount of oral diclofenac [41].

In another study comparing oral ketoprofen with topical ketoprofen in 100 patients with knee disorders requiring arthroscopy, levels of ketoprofen were higher in cartilage and meniscus after topical delivery as compared with the oral form. As expected, mean plasma level was significantly lower following the use of topical ketoprofen [42]. Similar findings were observed in a study comparing oral with topical ibuprofen [43].

Are some forms of delivery better than others?

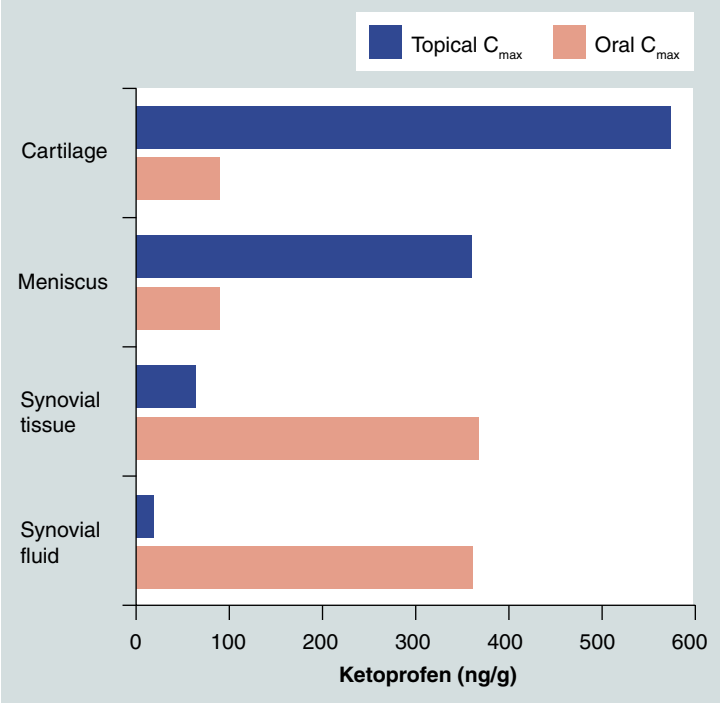
Several formulations of topical NSAIDs exist in the market, including gels, creams, foams, oil, aerosol, sprays and patches [35]. In general, creams are less effective in skin permeation than gels or sprays, but newer formulations such as microemulsions have better potential [44–47].

Some essential oils and their terpene constituents (e.g., eucalyptus and peppermint), as well as 10% ethanol and dimethyl sulfoxide are occasionally used as vehicles to enhance or accelerate absorption [3,48–50]. These enhancers may also provide a cooling effect, have a local analgesic effect and/or induce muscle relaxing action [48].

Phonophoresis and iontophoresis are two physical modalities used to improve penetration of topical medications transdermally. Although drug delivery may be enhanced with these two modalities, its usefulness in improving efficacy of the drug in patients with OA needs to be studied [51–53].

To date, there are no studies comparing the various delivery forms of topical NSAIDs with each other in OA. However, patches may be preferred by some patients because they offer a practical, easy-to-use treatment that allows delivery of a well-defined fixed amount of drug per application.

Figure 1. Comparison of median maximum concentrations of ketoprofen in joint tissue after topical and oral concentration.



C_{max}: Peak concentration.

Is there a difference between various topical NSAIDs?

A series of NSAIDs were studied *in vitro* to generate an index to predict topical efficiency. Indomethacin, ketorolac, ketoprofen and diclofenac exhibited acceptable efficiency for external use. However, for dermatological formulations of oxicams (piroxicam and tenoxicam), the use of penetration enhancers may be unavoidable [54]. In human subjects, alclofenac and ketoprofen, among several NSAIDs (bufexamac, indomethacin, flufenamic acid, ibuprofen, flurbiprofen, ketoprofen and naproxen), have the greatest absorption rates through the skin [55].

Few studies compared the clinical efficacy of topical NSAIDs head-to-head in OA. Only one study compared topical ketoprofen gel with diclofenac emulgel in patients with OA, and found no difference in clinical outcome and safety profile [56].

Head-to-head comparisons of topical NSAIDs are more extensively evaluated in acute pain, although the results may not necessarily be extrapolated to patients with OA. In a study of 1575 patients with acute soft-tissue injury, diclofenac was equivalent to ketoprofen with an added cooling effect observed with ketoprofen. Interestingly, in the same study piroxicam gel was less effective than both ketoprofen and diclofenac gel [57]. In another study of 384 patients with acute soft-tissue injuries, diclofenac showed higher efficacy than felbinac gel [40].

A recent meta-analysis of 26 randomized controlled trials of topical NSAIDs, which included 2853 patients with acute pain, demonstrated that topical NSAIDs were significantly better than placebo in 19 of 26 trials and that different NSAIDs have different efficacy, while indomethacin was barely distinguished from placebo. Ketoprofen was found to be significantly better than all other studied NSAIDs (ibuprofen, felbinac, piroxicam and indomethacin) [58]. Similar findings were found when topical indomethacin was compared head-to-head with topical piroxicam [58].

Are topical NSAIDs effective alternatives to oral treatments in OA?

The findings of randomized controlled trials and meta-analyses advocate the benefit of topical NSAIDs in the treatment of patients with symptomatic OA of the knees. In our search, we identified 18 randomized controlled trials evaluating the effect of topical NSAIDs in OA (**Table 2**); 12 compared topical NSAIDs with topical placebo, four compared topical with oral NSAIDs, one compared topical NSAIDs with oral NSAIDs and topical placebo, and only one compared different topical NSAIDs with each other.

In the 12 randomized controlled trials that compared the use of topical NSAIDs versus topical placebo or vehicle-controlled placebo (VCP) in patients with OA (15 OA knees, one OA of fingers and two different joints), there were three topical NSAID preparations: diclofenac (nine randomized controlled trials), ibuprofen (two randomized controlled trials) and eltenac (two randomized controlled trials). Eltenac is a topical NSAID that is similar in structure to diclofenac, with enhanced skin permeability that is not in use in humans anymore [49]. Of the 15 studies conducted over 4 weeks or less, only three extended beyond 6 weeks. Superiority of diclofenac and ibuprofen over placebo or VCP was demonstrated for the majority of defined efficacy variables, including pain, functional ratings, patient global assessment and physicians' global assessment [50,41,60–69].

In the five randomized controlled trials that compared the use of topical NSAIDs versus oral NSAIDs, only three topical NSAID preparations were studied: diclofenac (two randomized controlled trials), piroxocam (two randomized controlled trials) and eltenac (one randomized controlled trial). Duration of the studies varied from 4 to 12 weeks (two trials over 3 weeks, two trials over 4 weeks and one trial over 12 weeks) [3,35,49,70–72].

Topical diclofenac administered three- or four-times/day was compared with oral diclofenac (50 mg three-times/day) in one study and with oral ibuprofen (400 mg three-times/day) in another. In both studies, equivalent results were found between the topical and oral NSAIDs [3,70].

Piroxicam gel administrated three-times/day was compared with oral ibuprofen (400 mg three-times/day) and with routine NSAID use, and in both studies was equivalent to the oral form [71,72].

Only one randomized controlled trial compared topical NSAIDs with each other; ketoprofen gel (four-times/day) with diclofenac emulgel (four-times/day) in 85 patients with OA of the knee followed over a period of 4 weeks. Both groups had improvement in their knee functions, knee score and pain, with no significant difference between the groups at the end of the study [56].

In 1998, a systematic review assessed the effectiveness and safety of topical NSAIDs in acute and chronic pain conditions in 86 trials, involving 10,160 patients. In chronic conditions such as OA and tendonitis, topical NSAIDs were significantly better than placebo when given over 2 weeks [30].

A more recent second systematic meta-analysis by Mason and colleagues in 2004, which included 25 trials (14 of which examined general musculoskeletal disorders and 11 examined OA: nine knees, one finger joints and one mixed sites), produced similar results to the previous meta-analysis [59]. In this meta-analysis, 14 double-blind, placebo-controlled trials of 1502 patients showed that topical NSAIDs were significantly better than placebo in the treatment of chronic pain. Three trials with 764 patients comparing a topical with oral NSAID found no difference in efficacy. There were insufficient data, however, to allow comparisons of efficacy between different NSAIDs (**Figure 2**) [59].

In 2004, Lin and colleagues published a meta-analysis of the efficacy of topical NSAIDs in the treatment of OA. It included 13 randomized controlled trials, representing 1983 patients, and found that topical NSAIDs were superior to placebo in pain reduction and functional improvement, but only in the first 2 weeks of treatment. However, no benefit was observed from topical NSAIDs over placebo in weeks 3 and 4 and the efficacy was not sustained beyond 2 weeks [73]. Additionally, topical NSAIDs were inferior to oral NSAIDs in the first week of treatment and, as expected, caused more local side

Table 2. Topical nonsteroidal anti-inflammatory drugs trial .

Study	n	Active drug therapy	Formulation	Treatment regimen	Diagnosis	Length of study	Outcome			Ref.
							Same	Better	Worse	
Niethard (2005)	238	Topical diclofenac gel vs placebo gel	Diclofenac gel 1.16%	4 g of diclofenac gel q.i.d over the affected knee vs placebo gel q.i.d over the affected knee	OA knee	3 weeks		X		[60]
Baer (2005)	216	Topical diclofenac solution vs vehicle-control solution	Diclofenac solution 1.5%	1.3 ml of diclofenac solution q.i.d over the affected knee vs vehicle control solution q.i.d over the affected knee	OA knee	6 weeks		X		[61]
Roth (2004)	326	Topical diclofenac solution vs vehicle-control solution	Diclofenac solution 1.5%	1.3 ml of diclofenac solution q.i.d over the affected knee vs vehicle solution q.i.d over the affected knee	OA knee	12 weeks		X		[50]
Trnavsky (2004)	50	Topical Ibuprofen cream vs placebo cream	Ibuprofen cream 5%	200 mg of ibuprofen cream t.i.d over the affected knee vs placebo cream t.i.d over the affected knee	OA knee	1 week		X		[62]
Bookman (2004)	248	Topical diclofenac solution vs vehicle-control solution	Diclofenac solution 1.5%	1.3 ml of diclofenac solution q.i.d over the affected knee vs vehicle control solution q.i.d over the affected knee vs placebo solution q.i.d over the affected knee	OA knee	4 weeks		X		[41]
Tugwell (2004)	622	Topical diclofenac solution vs oral diclofenac	Diclofenac solution 1.5% vs 50 mg diclofenac capsules	1.55 ml of diclofenac solution t.i.d with oral placebo capsules t.i.d vs 50 mg diclofenac orally t.i.d and placebo solution t.i.d over the affected joint	OA knee	12 weeks	X			[3]
Giamber-ardino (2004)	20	Topical diclofenac epolamine bioadhesive plaster vs placebo	Flector tissugel 1% vs placebo	Flector tissugel 1% plasters in a 24- and 72-h trial over one affected knee vs placebo plasters over the other affected knee	OA knee	1 day and 3 days		X		[63]
Bruhlmann (2003)	103	Topical diclofenac plasters vs placebo plasters	DHEP containing 180 mg diclofenac	180 mg DHEP plasters bid on the affected joint vs placebo plasters b.i.d	OA knee	2 weeks		X		[64]
Ottillinger (2001)	237	Topical eltenac gel vs placebo gel	Eltenac gel 0.1%, eltenac gel 0.3%, eltenac gel 1%	90 mg of eltenac gel t.i.d over the affected knee vs 27 mg of eltenac gel t.i.d over the affected knee vs 9 mg of eltenac gel t.i.d over the affected knee vs placebo gel t.i.d over the affected knee	OA knee	4 weeks	X			[65]

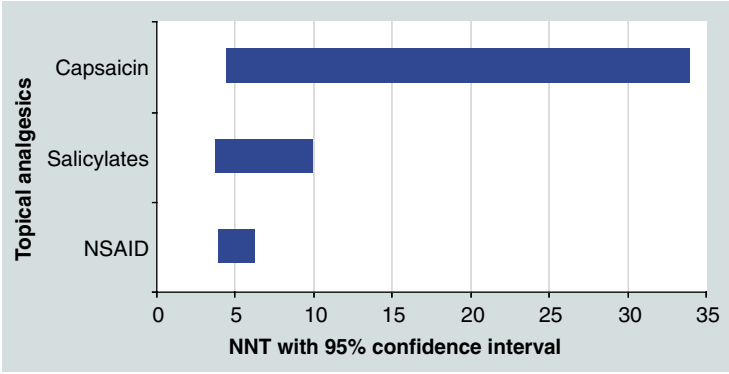
b.i.d: Twice daily; DHEP: Diclofenac hydroxyethylpyrrolidine plasters; NSAID: Nonsteroidal anti-inflammatory drug; OA: Osteoarthritis; q.i.d: Four-times daily; t.i.d: Three-times daily.

Table 2. Topical nonsteroidal anti-inflammatory drugs trial (Cont.).

Study	n	Active drug therapy	Formulation	Treatment regimen	Diagnosis	Length of study	Outcome			Ref.
							Same	Better	Worse	
Rovensky (2001)	100	Topical Ibuprofen cream vs placebo cream	Ibuprofen cream 5%	200 mg of ibuprofen cream t.i.d over the affected knee vs placebo cream t.i.d over the affected knee	OA knee	1 week		X		[66]
Zacher (2001)	321	Topical diclofenac emulgel vs oral ibuprofen	Diclofenac emulgel (concentration not specified) vs 400 mg ibuprofen tablets	Diclofenac emulgel q.i.d over the affected joint and placebo tablet orally t.i.d vs placebo emulgel t.i.d and 400 mg ibuprofen tablets orally t.i.d	OA fingers	3 weeks	X			[70]
Grace (1999)	74	Topical diclofenac gel vs placebo gel	Diclofenac lecithin organogel 2%	2.5 gm of diclofenac gel t.i.d over the affected joint vs placebo gel t.i.d	OA knee	2 weeks	X			[67]
Sandelin (1997)	290	Topical eltenac gel vs oral diclofenac and placebo gel	Eltenac gel 1% vs 50 mg diclofenac tablets	3 gm of eltenac gel t.i.d plus one placebo tablet orally b.i.d vs 50 mg diclofenac tablet orally b.i.d with placebo gel t.i.d vs placebo gel t.i.d with one placebo tablet orally b.i.d	OA knee	4 weeks	X			[49]
Waikakul (1997)	85	Topical ketoprofen gel vs diclofenac emulgel	Ketoprofen hydroalcoholic gel vs diclofenac emulgel (concentration not specified)	1 gm of ketoprofen hydroalcoholic gel q.i.d on the affected knee vs 1 g of diclofenac emulgel q.i.d	OA knee	4 weeks	X			[56]
Roth (1995)	119	Topical diclofenac gel vs vehicle-control gel	Diclofenac gel 3%/2.5% sodium hyaluronate gel	2 gm of diclofenac gel q.i.d vs placebo gel q.i.d	OA of different joints	2 weeks		X		[68]
Browning (1994)	191	Topical piroxicam gel vs oral NSAID	Piroxicam gel vs oral NSAID	1 g of piroxicam gel t.i.d or q.i.d for 14 days plus half the dose of prestudy NSAID followed by piroxicam alone for 14 days over affected peripheral joints vs oral NSAID for 28 days	OA of superficial joints	3 weeks and 1 day	X			[71]
Dreiser (1993)	155	Topical diclofenac plasters vs placebo plasters	DHEP plasters containing 180 mg diclofenac	180mg DHEP plasters bid on the affected joint vs placebo plasters b.i.d	OA knee	2 weeks and 1 day		X		[69]
Dickson (1991)	235	Topical piroxicam vs oral ibuprofen	Piroxicam gel 0.5% vs 400 mg ibuprofen	1 g of piroxicam gel (over affected knee) tid and one placebo tablet orally t.i.d vs 400 mg ibuprofen orally t.i.d plus placebo gel t.i.d	OA knee	4 weeks	X			[72]

b.i.d: Twice daily; DHEP: Diclofenac hydroxyethylpyrrolidine plasters; NSAID: Nonsteroidal anti-inflammatory drug; OA: Osteoarthritis; q.i.d: Four-times daily; t.i.d: Three-times daily.

Figure 2. Comparison of NNT of topical analgesics in chronic musculoskeletal pain.



NNT: Number needed to treat; NSAID: Nonsteroidal anti-inflammatory drug. Extracted from [59].

effects. The conclusions regarding long-term efficacy, however, were based on the studies of eltenac gel only versus placebo gel [73].

More recently, topical diclofenac solution (Pennsaid®) in patients with OA of the knee demonstrated effectiveness in a systematic review and meta-analysis of four randomized controlled trials (1385 patients), with a mean trial duration of 8.5 weeks [20].

Biswal and colleagues approached the question of intermediate-term (4–12 weeks) efficacy of topical NSAIDs for pain control in primary knee OA in another meta-analysis [74]. Four trials were included and the duration of studies varied from 4 to 12 weeks. Four of them compared topical NSAID with placebo or VCP. Pooled effect of topical NSAID (diclofenac or eltenac) measured at 4 weeks or beyond was superior to placebo/vehicle in pain relief in knee OA; however, this may not hold true for all the preparations [74].

Recently, Bjordal and colleagues, in a meta-analysis comparing seven pharmacotherapeutic interventions (including topical NSAIDs) in knee OA, argued that none of the trials of topical NSAIDs have demonstrated clinically relevant mean effects above the minimally perceptible threshold of 9.7 mm after 2 weeks or more of therapy [75]. However, because of the favorable safety profile, they remain an alternative choice, especially in the elderly population [75].

Owing to the plethora of positive literature on topical NSAIDs, the 2003 European League Against Rheumatism guidelines for the medical management of OA of the hip and knee have given greater consideration to the role of topical NSAID in OA compared with the 2000 American College of Rheumatology guidelines, where topical NSAIDs have been considered as adjunctive or as monotherapy [10,25].

What are the side effects of topical compared with oral NSAIDs?

Skin reactions (erythema, rash and itching) are the most frequent of all adverse events (**Table 3**). Adverse event rates, however, are not significantly different from those of placebo ingredients, as has been demonstrated in several trials [35].

Mason and colleagues, in their meta-analysis involving 18 placebo trials, described no statistically significant difference between topical NSAIDs and topical placebo in the number of patients experiencing local adverse events (6%), systemic adverse events (3%) or the number withdrawing due to an adverse event (1%) [59].

Similar findings were found in a meta-analysis of topical NSAIDs for acute musculoskeletal pain [58].

The incidence of GI adverse events, including nausea, vomiting, diarrhea and dyspepsia, is low and occurs at a similar rate in patients receiving placebo and topical NSAIDs. No GI adverse events were considered severe, and no patient developed perforation, ulcer or bleeding in any of the studies. The rate of GI events in these 18 randomized, controlled trials was lower than the percentage reported with oral NSAIDs and similar or higher to placebo/vehicle control.

Conclusion

The current evidence supports the use of topical NSAIDs in the treatment of OA of the knees. These agents provide an attractive method of treatment in the elderly because of their favorable side-effect profile. Long-term trials, however, are needed to confirm their long-term benefit and safety.

Future perspective

Today, OA is regarded as a disease that affects the whole joint, including subchondral bone, periarticular muscles, ligaments, capsule, sensory nerve endings and synovium. Diagnostic tools, chemical and radiographic, that will permit earlier detection of the disease will enable better understanding of this condition and possibly less disability.

Future therapeutic modalities should go beyond the cartilage and address the treatment of the periarticular structures as well as the correction of the mechanical abnormalities. Safety of therapy should remain a priority as the majority of those affected are in their golden years.

Table 3. Side effects of topical nonsteroidal anti-inflammatory drugs .

Study	Overall adverse events (no. patients/% patients)		Adverse reactions requiring dropout		Local skin reactions* (no. patients/% patients)		Gastorintestinal‡ (no. patients /%patients)		Ref.
			Active drug	Control					
Niethard (2005)	Placebo (n = 11/9)	NSAID (n = 4/3.4)	Not reported	Not reported	Placebo (n = 3/2.5)	NSAID (n = 4/3.4)	Placebo (n = 2/1.7)	NSAID (n = 0 /0)	[60]
Baer (2005)	Placebo (n = 49/45)	NSAID (n = 70/65)	8.40%	8.30%	Placebo (n = 31/28.4)	NSAID (n = 46/43)	Placebo (n = 6/5.5)	NSAID (n = 12/11.2)	[61]
Roth (2004)	Placebo (n = 88/54.3)	NSAID (n = 126/77)	Topical diclofenac 3%	No dropout	Placebo (n = 53/33)	NSAID (n = 81/49.4)	Placebo (n = 18/11.1)	NSAID (n = 24/14.6)	[50]
Trnavsky (2004)	No side effects		No side effects	No side effects	no side effects		No side effects		[62]
Bookman (2004)	Placebo (n = 24/29)	NSAID (n = 78/93) Vehicle-control (n = 58/72.5)	Topical diclofenac 6%	Topical vehicle 4% Topical placebo 0%	Placebo (n = 12/14.2)	NSAID (n = 62/73.8) Vehicle-control (n = 41/51.3)	Placebo (n = 11/13.1)	NSAID (n = 8/9.6) Vehicle-control (n = 12/15)	[41]
Tugwell (2004)	Topical diclofenac	Oral diclofenac	Not reported	Not reported	Topical diclofenac (n = 157/51)	Oral diclofenac (n = 14/4.5)	Topical diclofenac (n = 108/35)	Oral diclofenac (n = 150/48)	[3]
Bruhlmann (2003)	Placebo (n = 3/5.8)	NSAID (n = 4/7.8)	Topical diclofenac 2%	Topical placebo 4%	Placebo (n = 2/3.8)	NSAID (n = 3/5.9)	Placebo (n = 0/0)	NSAID (n = 1/2)	[64]
Giamberardino (2004)	Not reported		Not reported	Not reported	Not reported		Not reported		[63]
Ottillinger (2001)	Placebo + NSAI (n = 16/6.8)		Not reported	Not reported	Not reported		Not reported		[65]
Rovensky (2001)	No side effects		No side effects	No side effects	No side effects		No side effects		[66]

**Application site reaction: erythema/redness, irritation, dry skin, dermatitis, burning, numbness, pruritis, paresthesia and Quincke's edema.*

‡Nausea, dry mouth, epigastric pain, vomiting, diarrhea, constipation, melena and dyspepsia.

NSAID: Nonsteroidal anti-inflammatory drug.

Table 3. Side effects of topical nonsteroidal anti-inflammatory drugs (Cont.).

Study	Overall adverse events (no. patients/% patients)		Adverse reactions requiring dropout		Local skin reactions* (no. patients/% patients)		Gastorintestinal‡ (no. patients /%patients)		Ref.
			Active drug	Control					
Zacher (2001)	Topical diclofenac (n = 4/2.4)	Oral ibuprofen (n = 9/6)	Topical diclofenac 3%	Oral ibuprofen 10%			Topical diclofenac (n = 1/0.6)	Oral ibuprofen (n = 8/5)	[70]
Grace (1999)	Placebo (n = 9/25.7)	NSAID (n = 6/17.1)	Topical diclofenac 2.90%	Topical placebo 0%	Placebo (n = 7/20)	NSAID (n = 4/11.4)	Placebo (n = 2/5.7)	NSAID (n = 1/2.9)	[67]
Sandelin (1997)	Placebo (n = 13/15.90)	Diclofenac (n = 20/24.4) Eltenac (n = 34/27.0)	Topical eltenac 3.20%	Oral diclofenac 0%	Placebo (n = 5/6.1)	Diclofenac (n = 1/1.2) Eltenac (n = 16/12.7)	Placebo (n = 6/7.3)	Diclofenac (n = 11/13.4) Eltenac (n = 6/4.8)	[49]
Waikakul (1997)	No side effects		No dropout	No dropout	No side effects		No side effects		[56]
Roth (1995)	Placebo (n = 26/43.3)	NSAID (n = 12/20.3)	Topical diclofenac 5%	Topical placebo 6.70%	Placebo (n = 26/43.3)	NSAID (n = 12/20.3)	No side effects		[68]
Browning (1994)	Topical feldene (n = 3/2.8)	Oral NSAID (n = 1/1.2)	Topical feldene 0.90%	Oral NSAID (no dropout)	Topical feldene (n = 1/0.9)	Oral NSAID (n = 0/0)	Topical feldene (n = 2/1.9)	Oral NSAID (n = 0/0)	[71]
Dreiser (1993)	Placebo (n = 4/5.2)	Topical diclofenac (n = 1/1.3)	No dropout	Topical placebo1.30%	Placebo (n = 3/3.9)	Topical diclofenac (n = 1/1.3)	Placebo (n = 1/1.3)	Topical diclofenac (n = 0/0)	[69]
Dickson (1991)	Topical piroxicam (n = 31/26.5)	Oral ibuprofen (n = 27/22.9)	Topical piroxicam 7.70%	Oral ibuprofen 5.90%	Topical piroxicam (n = 3/2.5)	Oral ibuprofen (n = 4/3.3)	Topical piroxicam (n = 15/12.9)	Oral ibuprofen (n = 11/9.3)	[72]

**Application site reaction: erythema/redness, irritation, dry skin, dermatitis, burning, numbness, pruritis, paresthesia and Quincke's edema.*

‡Nausea, dry mouth, epigastric pain, vomiting, diarrhea, constipation, melena and dyspepsia.

NSAID: Nonsteroidal anti-inflammatory drug.

Executive summary

Osteoarthritis

- Osteoarthritis is the most common disease of synovial joints in the elderly.
- Nonpharmacologic, pharmacologic and surgical treatment modalities are available that help to reduce pain and improve functional ability.
- Current pharmacologic treatment, especially nonsteroidal anti-inflammatory drugs (NSAIDs), is associated with increased risk of morbidity and mortality in the most affected population, the elderly.

Penetration of topical NSAIDs into the joint

- Currently available topical NSAIDs have adequate penetration through the skin into the joint.
- Levels of topical NSAIDs in plasma are significantly lower than levels achieved by oral route.
- Levels of topical NSAIDs in cartilage and meniscus are higher with topical route than oral route.

Efficacy of topical NSAIDs in osteoarthritis

- Eighteen randomized controlled trials and several meta-analyses compared topical NSAIDs with either placebo, oral NSAIDs or with each other.
- The majority of topical NSAIDs decrease pain due to osteoarthritis and improve functional ability over the short term.
- There are insufficient data for long-term efficacy of these drugs.

Safety

- The most common side effects of topical NSAIDs are local skin reactions.
- Gastrointestinal side effects are minimal, comparable with placebo and better than oral NSAIDs.

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