Review

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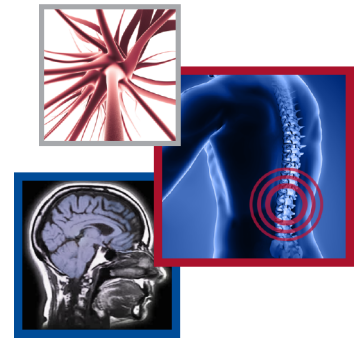
Pain Management



Consensus recommendations for managing osteoarthritic pain with topical NSAIDs in Asia-Pacific

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Osteoarthritis prevalence is expected to increase markedly in the Asia-Pacific region due to rapid population aging. Identifying effective and safe therapeutic options to manage osteoarthritic pain is viewed as a priority. The Asia-Pacific Experts on Topical Analgesics Advisory Board developed consensus statements for use of topical NSAIDs in musculoskeletal pain. Evidence supporting these statements in osteoarthritic pain was reviewed. Best available evidence indicates that topical NSAIDs have a moderate effect on relief of osteoarthritic pain, comparable to that of oral NSAIDs but with a better risk-to-benefit ratio. International clinical practice guidelines recommend topical NSAIDs on par with or ahead of oral NSAIDs for pain management in patients with knee and hand osteoarthritis, and as the first-line choice in persons aged ≥75 years.

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Osteoarthritis is one of the most common conditions on the musculoskeletal disorders spectrum and is a leading cause of pain and disability worldwide [1]. Although osteoarthritis can affect any joint, the most common sites are the hands, knee, hip and spine [2]. Advancing age and overweight/obesity are well-established risk factors for the development of osteoarthritis [2,3].

Primary symptoms of osteoarthritis include joint pain, stiffness and movement limitation with occasional effusion and variable degrees of local inflammation [4]. The briefer nature of morning stiffness (usually <30 min) is one of the main differentiating features between osteoarthritis and rheumatoid arthritis [5]. Patients with osteoarthritis typically experience 'flares' (i.e., episodes of recurrent or exacerbating pain) which respond to rest and analgesia; constant chronic pain tends to be a feature of more advanced disease [4]. Treatment goals in osteoarthritis are to manage pain, reduce inflammation and maintain joint function [6].

Some common nonpharmacological approaches to osteoarthritis management (especially of the knee) include muscle strengthening and aerobic exercise to improve joint function and alleviate pain [7]. Knee braces or personalized foot orthoses, where indicated to correct joint alignment (hip–knee–ankle angle), may also help maintain function and reduce symptoms in selected patients [8].

NSAIDs are central to the pharmacological management of osteoarthritis. However, frequent or prolonged use of oral NSAIDs in chronic conditions such as osteoarthritis raises tolerability and safety concerns, especially in more vulnerable populations such as the elderly and those with predisposing co-morbidities including high

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Box 1. Asia-Pacific expert group consensus statements on use of topical NSAIDs in musculoskeletal pain.

Statement 1: There are different topical analgesic preparations indicated for musculoskeletal pain – topical NSAIDs relieve pain by a distinct mode of action
Statement 2: Topical NSAIDs are effective and should be recommended as a first-line intervention for mild to moderate pain associated with musculoskeletal disorders
Statement 3: Topical NSAIDs have comparable efficacy with oral NSAIDs in terms of providing relief in musculoskeletal conditions and are preferred over systemic treatment of acute and acute-on-chronic, mild to moderate pain when local areas are affected
Statement 4: The use of therapeutic ultrasound enhances local penetration and absorption of topical NSAID gels, thus increasing drug effectiveness
Statement 5: Topical NSAID gel formulations have better absorption and acceptability compared with other formulations
Statement 6: Topical ketoprofen gel has the property of achieving higher local tissue concentration than plasma concentration
Statement 7: Topical NSAIDs are generally safe and have fewer of the systemic adverse effects associated with oral NSAIDs
Statement 8: While most topical NSAIDs are effective in the treatment of acute and acute-on-chronic musculoskeletal pain, there are limited head-to-head randomized controlled trials comparing the different topical NSAIDs

cardiovascular risk, type 2 diabetes and reduced renal function or a history of renal dysfunction [6]. Oral NSAIDs are well reported to be associated with age- and dose-related risks of gastrointestinal, cardiovascular, renal and hepatic adverse events [9,10]. To minimize risk, it is recommended that oral NSAIDs be used cautiously, at the lowest effective dose over the shortest period of time [9,10].

Topical NSAIDs have been developed as an alternative to oral NSAIDs. They offer potential to achieve analgesic efficacy comparable to that of oral NSAID formulations, while minimizing the risk of adverse events related to systemic exposure [5,11]. As topical NSAIDs must penetrate the skin to provide effective analgesic concentrations at the site of pain/inflammation, they are better suited for use on smaller superficial joints (e.g., knuckles) and joints with localized pain (e.g., knee) than on osteoarthritis of the hip or spine.

Although topical NSAIDs are licensed in Asia-Pacific for use in osteoarthritic pain, there are no clinical practice guidelines or recommendations in the region specific to their use in this indication. Previously the Asia-Pacific Experts (APEX) on Topical Analgesics Advisory Board (see Supplementary Material) – a group of clinicians with recognized expertise in the fields of Physical and Rehabilitation Medicine, Rheumatology, Orthopedics and Sports Medicine – developed a set of consensus statements on use of topical NSAIDs in the management of musculoskeletal pain (Box 1). To increase awareness and advance the role of topical NSAIDs as a therapeutic option in the management of osteoarthritic pain, the group identified the need to revisit the consensus statements as they relate to osteoarthritic pain and to publish the findings. This review examines evidence for the efficacy and safety of topical NSAIDs in the management of osteoarthritic pain.

The Asia-Pacific perspective

Despite the wide diversity in the Asia-Pacific region in terms of economic development and population characteristics [12], a feature common to most countries is the looming burden of osteoarthritis. Epidemiological data from China and Vietnam suggest a morbidity burden at least as great as that in Caucasian populations [13,14]. However, Asian populations are aging more rapidly than those in the Western world [15]; the proportion of persons aged ≥65 years is expected to escalate in coming decades from 7.9% in 2015, to 12.1% in 2030 and to 18.8% in 2050 [16]. In some areas, lifestyle changes due to rapid upward socioeconomic transition have led to rising obesity rates with associated implications [17]. In emerging economies, the strenuous physical occupational activity required of many rural dwellers is also a major risk factor for osteoarthritis [15].

Certain cultural aspects of populations within the Asia-Pacific region, as discussed at a 2016 meeting of the APEX on Topical Analgesics Advisory Board, suggest an important role for topical NSAIDs in the management of osteoarthritic pain. Across the region, clinical experience indicates that older patients tend to prefer topical over systemic analgesics because of their ease of use, perceived safety and simple storage requirements. In countries such as Malaysia with a significant (~60%) Muslim population, topical NSAIDs offer a useful alternative to oral therapies during Ramadan when fasting is observed from sunrise to sunset. The popularity of Traditional Chinese

Medicine in China is largely responsible for a general preference toward use of alternative methods (acupuncture, moxibustion, herbal medicines) for pain management. Although lack of awareness about topical NSAIDs and absence of government-subsidized accessibility to conventional medicines may be barriers to their use in China, topical therapies tend to align more closely than oral therapies with the Traditional Chinese Medicine approach to pain management.

The growing burden of osteoarthritis in the Asia-Pacific region suggested by epidemiological trends underscores the need for an evidence-based and practical management approach that is aligned with specific population characteristics.

Methods

A literature search was performed of the PubMed and Cochrane Library databases using the keywords 'topical NSAIDs' and 'osteoarthritis' to identify systematic reviews, meta-analyses, recent randomized controlled trials (RCTs) and general reviews. Reference lists of retrieved articles were searched. Other primary data sources included the *Asian Expert Group Consensus on the Use of Topical Non-steroidal Anti-inflammatory Drugs in Musculoskeletal Pain* publication and minutes of the 2016 meeting of the APEX on Topical Analgesics Advisory Board. To ensure that evidence informing the consensus statements was of the highest possible methodological quality, data sources reporting on the efficacy and safety of topical NSAIDs in osteoarthritic pain management were limited to systematic reviews and meta-analyses.

Evidence review

There are numerous NSAIDs formulated as topical preparations although the bulk of evidence exists for diclofenac and ketoprofen. Topical NSAIDS are presented commercially at various strengths and in a wide array of formulations (e.g., ointment, cream, lotion, gel, liquid, spray, patches, plasters). For purposes of this review, topical NSAIDS are regarded as a drug class except where discussing properties or attributes specific to an individual agent or formulation.

How do topical analgesics work?

The topical drug delivery system has been designed to pass through the stratum corneum of the skin. Transdermal and topical therapies have different therapeutic goals. Transdermal formulations (e.g., fentanyl or nitroglycerin patches) aim to achieve systemic absorption whereas topical formulations (e.g., topical NSAIDs) target local absorption.

Topical therapies indicated for management of musculoskeletal pain include topical rubefacients, topical capsaicin and topical NSAIDs. Each formulation provides analgesia via a unique mechanism of action.

Topical rubefacients

Topical rubefacients are typically mixtures of substances such as menthol, camphor, salicylates and benzyl nicotinate. Rubefacients act as a counter-irritant, dilating local blood vessels and causing erythema around the area of application. The feeling of warmth, along with increased tissue penetration brought about by rubbing, masks the perception of pain and produces an analgesic effect [18]. Topical rubefacients are also believed to stimulate Aβ fibers responsible for modulating pain signal transmission by C fibers to the dorsal horn of the spinal cord, preventing the pain signal from reaching the brain [19].

The efficacy of salicylate-containing rubefacients on acute and chronic musculoskeletal pain has been reported in an updated Cochrane review [18]. The authors examined the clinical success rate, which was defined as a $\geq$50% reduction on a visual analogue scale or numerical rating scale or an equivalent measure at 7 (range: 3–10) days and 14 (range: 7 to >14) days of treatment for acute and chronic pain, respectively. The number needed to treat (NNT) for benefit was 3.2 for acute pain (mainly sprains, strains and acute low back pain) and 6.2 for chronic pain (mainly osteoarthritis, bursitis and chronic back pain) but the evidence quality was very low. The authors concluded that the evidence for salicylate-containing rubefacients does not support their use for acute injuries or chronic conditions.

Topical capsaicin

Capsaicin is a naturally occurring compound found in chili peppers. Topical capsaicin is also categorized as a rubefacient in some literature. Capsaicin was initially thought to work by inducing local depletion of substance

P from nerve endings after prolonged use, thereby reducing pain transmission from the periphery to higher pain centers [20,21]. However, newer evidence suggests that capsaicin interacts with sensory afferents via vanilloid-1 receptors (TRPV1), which are cation channels from the transient-receptor potential family [22]. Repeated administration of capsaicin evokes pharmacological 'defuntionalization' of TRPV1 channels, inactivates voltage-gated sodium channels and reduces neuronal responsiveness and excitability to different types of painful stimuli [22,23].

A systematic review of topical capsaicin for treatment of neuropathic pain and musculoskeletal pain indicated moderate to poor efficacy [24]. Treatment for 4 weeks with 0.075% capsaicin for neuropathic pain produced a mean treatment response rate (percentage of patients with at least 50% pain relief) of 57 versus 42% with placebo (NNT 5.7). Treatment for 4 weeks with 0.025% capsaicin for musculoskeletal pain produced a mean treatment response rate of 38 versus 25% with placebo (NNT 8.1). Significantly more patients using topical capsaicin than placebo experienced local adverse events such as burning, stinging and erythema (54 vs 15%) or withdrew from treatment due to adverse events (13 vs 3%).

Topical NSAIDs

NSAIDs act by inhibiting cyclo-oxygenase, the enzyme that catalyzes the production of prostaglandins and thromboxane. Prostaglandins mediate various physiological functions such as maintenance of the gastric mucosal barrier, regulation of renal blood flow and endothelial tone, and play an important role in inflammatory and nociceptive processes [25]. Cyclo-oxygenase inhibition leads to a reduction in pain, fever, platelet aggregation and the inflammatory response [26]. Topical NSAIDs operate under the same mechanism of action as oral NSAIDs but with localized absorption and effect. Topical NSAIDs provide analgesic concentrations at the site of pain/inflammation, while avoiding systemic distribution of drug at physiologically active levels [27].

In the treatment of acute musculoskeletal pain (e.g., sprains, strains and overuse injuries) in adults, topical NSAIDs were found to provide significantly higher rates of clinical success (more patients with ≥50% pain reduction) than topical placebo during short-term use (~7 days), with an efficacy comparable to that of oral NSAIDs [25]. The best effects (NNT <4) were seen with diclofenac gel (NNT 1.8), ketoprofen gel (NNT 2.5), diclofenac plasters (NNT 3.2) and ibuprofen gel (NNT 3.9). Topical NSAIDs were well tolerated during short-term use. Local skin reactions were generally mild and transient and did not differ from those with topical placebo. Systemic adverse events or patient withdrawals due to adverse events were few.

Consensus Statement 1: There are different topical analgesic preparations indicated for musculoskeletal pain – topical NSAIDs relieve pain by a distinct mode of action.

What is the evidence for the efficacy of topical NSAIDs in the management of osteoarthritic pain?

This review examines evidence for use of topical NSAIDs in the management of osteoarthritic pain, a common condition on the spectrum of chronic musculoskeletal pain.

Topical NSAIDs versus placebo

The efficacy of topical NSAIDs relative to placebo in the treatment of osteoarthritic pain has been demonstrated in systematic reviews and meta-analyses that applied stringent criteria to include RCTs of the highest methodological quality [28–30] (Table 1). Included studies compared an NSAID in any topical formulation (cream, gel, patch, solution) with placebo (or vehicle) or an active comparator and involved mainly patients with hand or knee osteoarthritis. Apart from year of publication, and hence the number of studies analyzed, the main differentiating feature of these meta-analyses was the duration of treatment which ranged from 2 to 12 weeks.

The 2004 meta-analysis of Mason *et al.* involved 14 studies of topical NSAIDs in 1502 adults with chronic musculoskeletal disorders, 38% of whom had knee osteoarthritis [28]. The primary outcome was the clinical success rate, defined as the proportion of patients with ≥50% reduction in pain at 2 weeks or an equivalent measure. The analysis showed topical NSAIDs to be significantly superior to placebo. The clinical success rate of 48 versus 26% translated to a relative benefit of 1.9 (95% CI: 1.7, 2.2) and an NNT of 4.6 (95% CI: 3.8, 5.9) for one patient to experience improvement in pain at 2 weeks with topical NSAIDs compared with placebo.

The meta-analysis of Lin *et al.* included 13 RCTs comparing topical NSAIDs with placebo or oral NSAIDs in 1983 patients with osteoarthritis mainly of the knee or hand who were treated for up to 4 weeks [29]. Effect sizes were calculated for pain, function and stiffness. Topical NSAIDs were found to be significantly superior to placebo for pain reduction and functional improvement during the first 2 weeks of treatment. Pooled effect sizes for pain

Table 1. Summary of systematic reviews and meta-analyses of topical NSAIDs compared with placebo for chronic musculoskeletal pain (mainly osteoarthritis).

Number of studies	Number of patients	Study duration (weeks)	Primary end points	Results	Ref.
14	1502	1–2	Clinical success (≥50% reduction in pain at 2 weeks or equivalent measure)	NNT 4.6 (95% CI: 3.8–5.9)	[28]†
13	1983	Up to 4	Reduction in pain (global pain or pain at rest) from baseline	Effect size: 0.41 (95% CI: 0.16–0.66) at week 1 and 0.40 (95% CI: 0.15–0.65) at week 2 No benefit over placebo in weeks 3 and 4	[29]‡
39	10,631	2 to ≤6; 6–12	Clinical success (≥50% reduction in pain at 2–12 weeks or equivalent measure)	Topical diclofenac (six studies, n = 2343): NNT 9.8 (95% CI: 7.1–16) Topical ketoprofen (four studies, n = 2573): NNT 6.9 (95% CI: 5.4–9.3)	[30]

†Knee osteoarthritis (n = 567) or other musculoskeletal pain (n = 935).
‡Included four trials of topical salicylate.
NNT: Number needed to treat for clinical success.

relief at weeks 1 and 2 of treatment were 0.41 (95% CI: 0.16, 0.66) and 0.40 (95% CI: 0.15, 0.65), respectively. No benefit was observed with topical NSAIDs compared with placebo at weeks 3 and 4.

The most recent Cochrane review (2016) of topical NSAIDs in adults with chronic musculoskeletal pain included RCTs of minimum 2 weeks' and up to 12 weeks' duration [30]. In all, 39 RCTs met the inclusion criteria representing 10,631 patients with osteoarthritis mainly of the knee. The primary outcome measure was the clinical success rate (≥50% reduction in pain intensity). Topical NSAIDs investigated were diclofenac, eltenac, etoricoxib, felbinac, flufenamate, flurbiprofen, indomethacin, ibuprofen, ketoprofen, nimesulide, piketoprofen and piroxicam, which were formulated as solutions, gels or plasters (patches). Data sufficient to perform pooled analyses were available only for diclofenac and ketoprofen. In studies lasting 6–12 weeks, the NNT compared with carrier or other active treatment was 9.8 (95% CI: 7.1–16) with topical diclofenac (six studies; 2343 participants; moderate quality evidence), and 6.9 (95% CI: 5.4–9.3) with topical ketoprofen (four studies; 2573 participants; moderate quality evidence), leading the authors to conclude that topical diclofenac and topical ketoprofen "provide good levels of pain relief in knee osteoarthritis in people aged over 40 years".

Whether this recent Cochrane review provides a true account of the value of topical NSAIDs in the management of osteoarthritic pain is a matter of debate. To enhance the sensitivity of the analysis to detect a difference in efficacy, studies eligible for inclusion were to have enrolled patients with osteoarthritic pain of at least moderate intensity, suggesting a level of pain in some patients beyond the capacity of first-line treatments. The analysis focused mainly on studies of longer duration (i.e., 6–12 weeks) implying that the various agents were being investigated for their ability to manage chronic pain rather than episodes of recurrent pain (flares). Although the 6–12-week studies were, on the whole, of higher reporting quality than those of shorter duration, the placebo response rate of 50% at 12 weeks limited the potential of the analysis to show a difference between active treatments (diclofenac and ketoprofen) and placebo.

Worldwide recognition of the important role topical NSAIDs play in the management of osteoarthritic pain is evident from the increasing number of international societies and clinical practice guideline committees that recommend them as an early treatment option [31–40] (Table 2). The American College of Rheumatology 2012 guidelines identify topical NSAIDs as an initial therapeutic choice for osteoarthritis of the hand and knee, and strongly recommend use of topical NSAIDs over oral NSAIDs in patients aged ≥75 years [32]. The Chinese Orthopedic Association, European League Against Rheumatism and NICE advocate use of topical NSAIDs ahead of systemic treatments as a first-line pharmacological choice for hand and knee osteoarthritis due to their superior safety profile [34–36,38]. The NICE guidelines also recommend topical NSAIDs as an adjunct to paracetamol and exercise to cope with disease flares [38].

Consensus Statement 2: Topical NSAIDs are effective and should be recommended as a first-line intervention for mild to moderate pain associated with musculoskeletal disorders.

Table 2. Recommendations by international societies and guideline committees on use of topical NSAIDs to manage osteoarthritic pain of the hand and knee.

Group	Recommendations/remarks	Ref.
American Academy of Orthopedic Surgeons	Knee OA: We recommend NSAIDs (oral or topical) or tramadol	[31]
American College of Rheumatology	Hand OA: For initial pharmacological management of hand OA, we conditionally recommend one or more of the following: • Topical capsaicin • Topical NSAIDs, including trolamine salicylate • Oral NSAIDs, including COX-2 selective inhibitors • Tramadol Knee OA: For initial pharmacological management of knee OA, we conditionally recommend one of the following: • Acetaminophen • Topical NSAIDs • Oral NSAIDs • Tramadol • Intra-articular corticosteroid injections Persons aged ≥75 years with hand or knee OA should use topical NSAIDs rather than oral NSAIDs	[32]
Chinese Medicine Expert Consensus (2015)	Knee OA: Topical application includes fumigation, application, hot compressed, ironing and iontophoresis with Chinese herbs, etc. Chinese patent medicine for external use includes plaster, ointment, etc. Western medicine for external use includes mainly emulsion, ointment, plaster and embrocation containing NSAIDs	[33]
Chinese Orthopedic Association (2010)	Hand and knee OA: Topical treatment of pain is recommended prior to oral medications. For moderate to severe pain, topical and oral NSAIDs may be used in combination	[34]
European League Against Rheumatism	Hand OA: Local treatments are preferred over systemic treatments, especially for mild to moderate pain and when only a few joints are affected. Topical NSAIDs and capsaicin are effective and safe for hand OA	[35]
European League Against Rheumatism (2003)	Knee OA: Topical applications (NSAID, capsaicin) have clinical efficacy and are safe	[36]
European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis	Knee OA: Topical NSAIDs may provide additional symptomatic treatment with the same degree of efficacy as oral NSAIDs without the systemic safety concerns	[37]
National Institute for Health and Clinical Excellence (2014)	Hand and knee OA: Consider topical NSAIDs for pain relief in addition to core treatments (e.g. activity and exercise, weight loss). Consider topical NSAIDs and/or paracetamol ahead of oral NSAIDs, COX-2 inhibitors or opioids	[38]
Osteoarthritis Research Society International	Knee OA: Topical NSAIDs are appropriate for use in patients with or without co-morbidities. Benefit: 6/10	[39]
Philippine Rheumatology Association	Knee OA: Topical NSAIDs are recommended to control symptomatic or acute exacerbation of knee OA and improvement of function	
Royal Australian College of General Practitioners 2009	Knee OA: There is some evidence to support the use of topical NSAIDs in short-term treatment	[40]
Singapore Ministry of Health	Knee OA: Topical NSAIDs can be considered for short-term symptomatic relief of pain in OA	

OA: Osteoarthritis.

What is the evidence for the efficacy of topical versus oral NSAIDs in the management of osteoarthritic pain?

Systematic reviews and meta-analyses which compared topical NSAIDs with oral NSAIDs in patients with osteoarthritis have consistently reported a similar level of efficacy, thus supporting the positioning of topical NSAIDs in clinical practice guidelines on par with or ahead of oral NSAIDs as first-line treatments.

A comparative effectiveness review of analgesics for the management of osteoarthritis (knee or fingers) identified eight studies in which topical NSAIDs had been compared directly with oral NSAIDs in patients with localized osteoarthritis [41]. In seven studies of 2–12 weeks' duration employing various outcome measures but mainly the Western Ontario and McMaster Universities Arthritis Index Pain, Physical Function and Stiffness indices, head-to-head comparisons showed no statistically significant differences in efficacy between topical NSAIDs (diclofenac, eltenac, ibuprofen, ketoprofen, piroxicam) and oral NSAIDs (celecoxib, diclofenac, ibuprofen). The review also included a randomized trial involving older subjects (≥50 years) with chronic knee pain who had been treated in general practices in the UK [42]. After 12 months' observation, clinical outcomes were equivalent between patients given initial advice to use topical ibuprofen and those given advice to use oral ibuprofen for pain relief, as measured by changes in global Western Ontario and McMaster Universities Arthritis Index scores.

Klinge and Sawyer reviewed evidence comparing topical NSAIDs with oral NSAIDs in the treatment of acute and chronic musculoskeletal injury [43]. Their analysis included six studies involving 600 patients with various acute injuries and nine studies involving 2403 patients with chronic injury, almost exclusively osteoarthritis of the knee. The majority of studies were well-designed, double-dummy and placebo-controlled. For both acute and chronic injury, results with topical and oral NSAIDs were statistically superior to those with placebo. In all head-to-head comparisons, topical NSAIDs and oral NSAIDs showed comparable efficacy for treatment of acute and chronic injuries.

The 2016 Cochrane systematic review of topical NSAIDs for chronic musculoskeletal pain included five studies (duration 3–12 weeks) comparing topical NSAIDs with oral NSAIDs in adults with mainly knee osteoarthritis [30]. A total of 877 patients were treated with a topical NSAID (diclofenac, ketoprofen, piroxicam) and 858 patients were treated with an oral NSAID (celecoxib, diclofenac, ibuprofen). Based on moderate quality evidence, the proportion of patients experiencing successful treatment (≥50% reduction in pain intensity) was 55% with a topical NSAID and 54% with an oral NSAID.

Consensus Statement 3: Topical NSAIDs have comparable efficacy with oral NSAIDs in terms of providing relief in musculoskeletal conditions and are preferred over systemic treatment of acute and acute-on-chronic, mild-to-moderate pain when local areas are affected.

Does phonophoresis affect skin permeation of topical NSAIDs?

In the management of musculoskeletal conditions, supplementary forms of treatment such as heat, cold, pressure, light and electricity may be used to accelerate healing. Therapeutic ultrasound (phonophoresis) is a treatment modality commonly used in physical medicine. Phonophoresis uses ultrasonic energy to provide deep heating (an additional 4–5°C at a depth of 8 cm) to muscles, tendons, joints and ligaments and has a long-standing history of use in musculoskeletal conditions such as tendinitis, tenosynovitis, epicondylitis, bursitis and osteoarthritis [44].

The medium used to apply phonophoresis is important as it must transmit ultrasound energy effectively. A study compared the relative transmission of commonly used phonophoresis media (e.g., ointments, creams, gels) with that of degassed water, the ideal standard [45]. Transmission greater than 80% that of water was defined as good, and transmission less than 40% that of water was defined as poor. Sound waves were transmitted best with gels, which had a transmission relative to water of 88–97% whereas the transmission of creams and ointments, even when mixed with a gel, ranged from 0 to 36%.

The log p-value (octanol–water partition coefficient) measures the ability of a substance to partition between lipid and water and is the most reliable predictor of transdermal absorption. Drugs with a log p-value less than 2 are considered to be ideal for transdermal delivery. The log p-values described in the literature of 0.97 for ketoprofen and 1.8, 3.2, 3.6 and 3.8 for piroxicam, naproxen, ibuprofen and indomethacin, respectively, were shown to correlate with area under the plasma–time curve values for these selected NSAIDs after topical gel administration [46]. The value of 0.97 described for ketoprofen is regarded as close to the optimal value indicated for topical NSAIDs [46].

Phonophoresis enhances the penetration of topical NSAIDs [47], potentially hastening recovery time for patients, while minimizing systemic exposure. In a study that assessed local absorption and distribution of ketoprofen gel after phonophoresis in relation to plasma concentration, both pulsed and continuous ultrasound produced significantly higher levels of ketoprofen in the synovial tissue compared with fat while plasma levels remained negligible [48].

The importance of factoring in drug properties when selecting an adjunct to phonophoresis was shown in a study that evaluated skin permeation of diclofenac gel and ketoprofen gel in the Franz diffusion cell model adapted to an ultrasound transducer under conditions of no ultrasound, one application of ultrasound and two applications of ultrasound [49]. Permeation of ketoprofen increased with two ultrasound applications, whereas that of diclofenac decreased in the presence of ultrasound.

Consensus Statement 4: The use of therapeutic ultrasound enhances local penetration and absorption of topical NSAID gels, thus increasing drug effectiveness.

Are there differences in absorption & acceptability among topical NSAIDs?

To reach the site of action, a topically administered drug must traverse through several skin layers: the stratum corneum, epidermis, basal membrane and dermis. Drugs with a balance between lipophilic and hydrophilic properties are suitable candidates for transdermal delivery. Lipophilic properties enable diffusion through the 'waterproof' epidermis, whereas hydrophilic properties facilitate diffusion through the 'water permeable' dermis. As discussed above, the log value (partition coefficient) of the NSAID determines the ability of the substance to

Table 3. Cosmetic acceptability of various topical NSAIDs.

Attribute	Ketoprofen gel	Diclofenac gel	Piroxicam gel	Niflumic gel
Easy application	3.14	2.72	2.66	0.86
Fresh sensation	2.48	2.16	2.34	1.58
Rapid penetration	2.92	2.54	2.38	0.76
Nongreasy feel	3.14	2.70	2.18	1.02
Scent	2.72	1.26	2.12	1.84

Parameters were scored from 0 to 4 where 0 = very poor, 1 = poor, 2 = average, 3 = good, 4 = excellent.
Data taken from [53].

partition between lipid and water. Ketoprofen has the lowest log p-value (0.97) among several commonly used topical NSAIDs, making it ideal for effective transdermal drug delivery [46]. Ketoprofen gel was shown to have the highest percentage of active substance penetrating the tissue, at 21.9 versus 11.2, 4.4 and 0.5% for diclofenac gel, niflumic acid gel and piroxicam gel, respectively [50].

A study compared the skin permeability and anti-inflammatory effects of several topical NSAID formulations (ketoprofen, diclofenac, flurbiprofen and piroxicam patches; and ketoprofen, diclofenac, piroxicam, niflumic acid and ibuprofen gels) [51]. In an *in vitro* skin permeation experiment using mouse skin, ketoprofen patch and ketoprofen gel showed higher skin permeability compared with all other topical NSAID preparations. In rat models of acute and chronic inflammation, the most potent analgesic and anti-inflammatory activity was observed with ketoprofen patch and gel, reflecting the good skin permeability of ketoprofen. The study reproduced results from previous *in vitro* percutaneous absorption experiments using human skin which showed that diffusion of ketoprofen from the gel formulation was significantly faster and more intensive than that of other topical NSAIDs gels (diclofenac as gel or emulgel, piroxicam gel and niflumic acid gel) [52].

Topical NSAIDs are available in a variety of formulations. The type of vehicle influences the migration of active drug across the skin layers. Ointments, which have a fatty base, have relatively poorer absorption and form a layer on the skin that tends to make their application messy. Compared with ointments and creams, well-formulated gels have superior skin permeation due to their high aqueous component that allows the drug to dissolve and migrate easily. Many topical gel formulations contain penetration enhancers (e.g., alcohol) that facilitate faster drug release [11]. Gels also have better cosmetic acceptability since they spread and vanish more readily and are devoid of fatty components that leave a greasy residue [53]. When assessed for ease of application, rate of penetration, after-feel and scent, ketoprofen gel scored higher than diclofenac, piroxicam and niflumic acid gels [53] (Table 3).

Consensus Statement 5: Topical NSAID gel formulations have better absorption and acceptability compared with other formulations.

Local tissue concentrations of ketoprofen

Topical NSAIDs were developed to achieve anti-inflammatory and analgesic activity in the musculoskeletal apparatus where local action is preferred. Topical application allows direct transport of the active substance to the affected area while minimizing the risk of systemic adverse effects. The transdermal penetration of ketoprofen gel has been described in several investigations.

In a study investigating the diffusion and release kinetics of topical NSAID preparations by the percutaneous route, ketoprofen gel had an *in vitro* penetration capacity of 21.9%, whereas diclofenac emulsion, niflumic acid gel and piroxicam gel liberated their active substance at much lower rates: 11.2, 4.4 and 0.5%, respectively [50].

Generally, topical ketoprofen achieves high-drug concentrations in joint tissue whereas plasma levels remain significantly low. A single topical application of ketoprofen gel to rabbit knee joint showed higher concentrations in synovial fluid than in plasma at 2, 4, 6 and 12 h after application [54]. Ketoprofen concentrations decreased rapidly in plasma and synovial fat tissue, but were more sustained in joint capsule and synovial fluid. The increased residence time of ketoprofen in synovial fluid may underlie its efficacy in managing joint pain and inflammation.

Studies in humans reported results similar to those in the animal model. Ketoprofen gel was topically administered to the knee joint once daily for 3 days in six patients about to undergo a surgical intervention [55]. Blood samples drawn at 2, 6 and 12 h after the last application showed that ketoprofen levels were detectable from the second hour, peaked at the sixth hour, and remained constant until the 12th hour. Local concentrations from tissues recovered during surgery were: 4.70 ± 3.87 μg/g in the intra-articular adipose tissue; 2.35 ± 2.41 μg/g in the capsular tissue

Table 4. Topical NSAIDs for chronic musculoskeletal pain (osteoarthritis of the hand and knee) in adults: safety analysis.

Outcome	Treatment	No. of participants	RR (95% CI)	Evidence quality
Topical NSAIDs versus placebo				
Local adverse events	Topical diclofenac Topical ketoprofen	3658 2621	1.8 (1.5–2.2) 1.0 (0.85–1.3)	Moderate
Systemic adverse events	Topical diclofenac All other topical NSAIDs combined	1266 971	0.89 (0.59–1.3) 1.2 (0.77–1.8)	Very low
Withdrawals due to adverse events	Topical diclofenac Topical ketoprofen	3552 2621	1.6 (1.1–2.1) 1.28 (0.92–1.8)	Moderate
Topical NSAIDs versus oral NSAIDs				
Local adverse events	Topical NSAIDs	1651	3.7 (2.8–5.1)	Very low
Systemic (gastrointestinal) adverse events	Topical NSAIDs	1961	0.66 (0.56–0.77)	Very low
Withdrawals due to adverse events	Topical NSAIDs	1961	0.85 (0.68–1.1)	Very low

RR: Risk ratio.
Data taken from [30].

and 1.31 ± 0.89 μg/g in the synovial fluid. These concentrations were about 100-times higher than those found in plasma samples drawn at the same time, indicating that direct transcutaneous diffusion, not plasma diffusion, is the mechanism of uptake of ketoprofen into the joint.

Continuous and pulsed phonophoresis of ketoprofen gel in patients with knee disorders requiring arthroscopy resulted in significantly higher concentrations of ketoprofen in synovial tissue than in fat tissue, whereas plasma concentrations of ketoprofen were below the level of detection (0.002 μg/ml) in the sham ultrasound and continuous ultrasound groups, and were low (0.004 μg/ml) in the pulsed ultrasound group [48].

Consensus Statement 6: Topical ketoprofen gel has the property of achieving higher local tissue concentration than plasma concentration.

What is the evidence for the safety of topical NSAIDs in the management of osteoarthritic pain?

Topical NSAIDs versus placebo or oral NSAIDs

The 2016 Cochrane systematic review and meta-analysis provides the most current and comprehensive safety data on topical NSAIDs for management of chronic musculoskeletal (osteoarthritic) pain in adults [30]. The results point to a relatively benign adverse event profile overall for topical NSAIDs in this therapeutic setting.

The analysis included 39 studies representing 10,631 patients who had been treated with a topical NSAID, topical placebo or oral NSAID for a minimum of 2 weeks up to a maximum of 12 weeks. As the studies varied considerably in their adverse event reporting, the evidence quality was regarded as 'moderate' at best and often as 'very low'. Similar to the efficacy analysis, data sufficient to perform pooled analyses were available only for diclofenac and ketoprofen. The main results are summarized in Table 4. Local adverse events reported in studies related primarily to irritation at the application site and included mainly dry skin, redness and itch. Compared with carrier (placebo), the proportion of patients experiencing local adverse events was significantly higher with topical diclofenac (14 vs 7.8%; risk ratio [RR]: 1.8) but not topical ketoprofen (15 vs 13%; RR: 1.0). Systemic adverse events tended to be poorly reported and the events were wide ranging, consisting mainly of headache, diarrhea, drowsiness and dyspepsia. Most systemic events were described as mild. Compared with carrier (placebo), the proportion of patients experiencing systemic adverse events did not differ significantly for topical diclofenac (RR: 1.1) or for all other topical NSAIDs combined (RR: 1.2). Serious adverse events were infrequent and not different between topical NSAIDs and carrier. Compared with carrier (placebo), there were significantly more treatment withdrawals due to adverse events with topical diclofenac (RR: 1.6) but not with topical ketoprofen (RR: 1.3).

In studies comparing topical NSAIDs and oral NSAIDs (five studies; 1651 participants), the incidence of local adverse events was higher with topical NSAIDs (22 vs 5.8% of patients; RR: 3.7; 95% CI: 2.8–5.1). Among six studies (1961 participants) which specifically reported gastrointestinal adverse events, the incidence was lower with topical NSAIDs versus oral NSAIDs (17 vs 26%; RR: 0.66; 95% CI: 0.56–0.77). There were too few serious adverse events reported to draw conclusions. Slightly fewer patients treated with topical NSAIDs than oral NSAIDs withdrew due to an adverse event (12 vs 15%; RR: 0.85; 95% CI: 0.68–1.1).

Consensus Statement 7: Topical NSAIDs are generally safe and have fewer of the systemic adverse effects associated with oral NSAIDs.

What is the evidence for the relative efficacy & safety of topical NSAIDs?

Topical NSAID versus topical NSAID

To qualify for inclusion in the 2016 Cochrane systematic review and meta-analysis of topical NSAIDs for chronic musculoskeletal pain, studies had to meet stringent quality criteria with at least ten participants in each treatment arm and application of treatment at least once daily [30]. In terms of head-to-head comparisons of topical NSAIDs, only one RCT which compared flurbiprofen patch with piketoprofen cream in 129 patients with soft tissue rheumatism met the criteria [56]. As such, no conclusions can be drawn about the relative efficacy and safety of one topical NSAID to another. Standardization of study design, methods and assessment is a challenge when investigating topical NSAIDs due to the wide variety of commercially available products, formulations and absorption characteristics. Head-to-head comparisons of topical NSAIDs may also be hampered by the large sample sizes that would be required to show statistically significant differences between products.

Consensus Statement 8: While most topical NSAIDs are effective in the treatment of acute and acute-on-chronic musculoskeletal pain, there are limited head-to-head RCTs comparing the different topical NSAIDs.

Discussion

Demographic transitions in the Asia-Pacific region, driven by population aging in particular, are expected to markedly increase the prevalence of osteoarthritis in the years ahead [12,15]. To prepare for this looming burden, pain management experts from key countries in the Asia-Pacific region identified the need to develop strategic guidance on the management of osteoarthritic pain. This consensus document is the outcome of the APEX on Topical Analgesics Advisory Board's activity.

In Asia-Pacific, topical NSAIDs are indicated for local relief of pain and inflammation associated with rheumatic and muscular disorders and for soft tissue injuries such as acute strains and sprains. Application is generally two- or three-times daily to the affected area depending on the formulation. Maximum duration of use is generally not to exceed 10 days to minimize the risk of local reactions. This prescribing advice suggests that the primary role of topical NSAIDs in the management of osteoarthritis is for short-term symptomatic relief of acute/recurrent pain (i.e., flares). As such, it was interesting to note that many of the more recent and larger RCTs of topical NSAIDs in osteoarthritic pain management were of longer duration (i.e., 6–12 weeks) [30], which exceeds the recommended duration of their use in Asia-Pacific.

Based on best available evidence from the 2016 Cochrane systematic review and meta-analysis, topical NSAIDs appeared, at best, to have a relatively modest effect on osteoarthritic pain [30]. The NNTs of 9.8 for diclofenac (gel or solution) and 6.9 for ketoprofen gel, which were calculated from respective pooled analyses of 6–12-week studies, suggested that only about 10% more patients would benefit from treatment with a topical NSAID versus a topical carrier (placebo). Although lower (better) NNTs were derived from shorter duration studies, the authors considered these values to reflect larger biases. At closer inspection, however, the placebo response rate of 50% in the 6–12-week studies severely limited the potential of the analysis to show a separation in efficacy between topical NSAID (diclofenac or ketoprofen) and placebo. It could be argued that the true efficacy of topical NSAIDs in osteoarthritic pain is higher than that reported in the meta-analysis. In 6–12-week studies of topical versus oral NSAIDs, topical NSAIDs were shown to have a similar level of efficacy and a more benign adverse event profile than oral NSAIDs [30].

Importantly, the level of efficacy reported for topical NSAIDs in the published literature has been sufficient for many international and national clinical guideline groups to position these agents as a first-line option or adjunct to oral medications (paracetamol/acetaminophen, selective and nonselective NSAIDs, opioids) for the management of osteoarthritic pain of the knee and hand [31–40]. On the basis of their superior risk-to-benefit profile, topical NSAIDs are recommended as the first-line option in patients aged ≥75 years [32]. The APEX on Topical Analgesics Advisory Board strongly supports these recommendations and advocates use of topical NSAIDs as the first-line choice for persons in the Asia-Pacific region with osteoarthritic pain of the hand and knee.

The large number and diversity of commercially available preparations of topical NSAIDs, together with the methodological heterogeneity of clinical trials performed in patients with osteoarthritic pain, complicate the conduct of comparative analyses. Due to the lack of head-to-head comparisons of topical NSAIDs, no definitive conclusions can be drawn about the relative efficacy and safety of any particular agent or formulation over another. Nevertheless,

the pharmacokinetic properties of the NSAID itself and the type of formulation influence the absorption and distribution characteristics of a topically applied NSAID. Of the various formulations (e.g., ointment, cream, lotion, gel, liquid, spray, patches, plasters), the balance of lipophilic and hydrophilic components in gel-based formulations allows for faster diffusion across the skin, greater absorption in local tissues and better transmission of ultrasound energy. Gel-based preparations also have better cosmetic acceptability than other formulations. The log p-value of ketoprofen (0.97) is considered close to the optimal value indicated for topical NSAIDs [46]. Ketoprofen achieves local tissue concentrations 100-times higher than plasma concentrations [55], greatly minimizing the risk of any adverse events associated with systemic exposure.

Conclusion

Best available evidence indicates that topical NSAIDs have a moderate effect on osteoarthritic pain, comparable to that of oral NSAIDs but with a superior risk-to-benefit ratio. Topical NSAIDs have an increasingly important role in the first-line management of osteoarthritic pain. The APEX on Topical Analgesics Advisory Board supports topical NSAIDs as the treatment of choice for short-term symptomatic relief of acute/recurrent osteoarthritic pain of the hand and knee, especially in the elderly. As percutaneous absorption from topical NSAID formulations can vary considerably depending on the agent, underlying condition and application site, using sound clinical judgement when prescribing a topical NSAID is paramount to optimizing their use. When selecting a topical NSAID product for use in an adult patient with osteoarthritic pain, the patient, the drug and the drug delivery mechanism must all be taken into consideration [57].

Future perspective

In line with the rapid aging of the world's population, more so in Asia-Pacific than in other world regions, osteoarthritis of the hands, knees and lower back is expected to be one of the major challenges to maintaining physical function and quality of life in the elderly. The ideal pharmacological solution to osteoarthritic pain management would be a drug that is effective and with no or minimal side effects, adverse reactions or potential to interact with other medications. In this regard, topical NSAIDS are expected to be at the forefront of providing relief

Executive summary

- The burden of osteoarthritis is expected to increase markedly in the Asia-Pacific region in upcoming years, mainly because of rapid population aging.
- While NSAIDs are central to the pharmacological management of osteoarthritis, oral NSAIDs must be used with caution.
- Topical NSAIDs are an alternative to oral NSAIDs.
- To provide strategic guidance in the Asia-Pacific region, the Asia-Pacific Experts on Topical Analgesics Advisory Board developed consensus recommendations for use of topical NSAIDs in the management of musculoskeletal pain.
- Supporting evidence for the consensus statements in osteoarthritic pain (a main subset of musculoskeletal pain) was examined in this review.
- Cochrane systematic reviews of randomized controlled trials showed significant superiority of topical NSAIDs over placebo for symptomatic management of hand and knee osteoarthritic pain, especially during short-term (2 weeks) use. The ability to show superiority during longer-term (6–12 weeks) use was limited by a high placebo response rate (50%).
- International guidelines recommend topical NSAIDs as an early treatment option for management of osteoarthritic pain of the hand and knee, positioning them on par with or ahead of oral NSAIDs due to their superior safety profile.
- Topical NSAIDs are strongly recommended for use in patients $\geq$75 years of age.
- Systematic reviews have shown comparable efficacy between topical NSAIDs and oral NSAIDs.
- Gel formulations of topical NSAIDs are highly acceptable to patients and provide the optimal medium for phonophoresis (ultrasound).
- Ketoprofen's physical properties are ideal for effective transdermal drug delivery, and local concentrations greatly exceed plasma concentrations.
- Topical NSAIDs are generally safe to use and have fewer of the systemic adverse effects associated with oral NSAIDs.
- The Asia-Pacific Experts on Topical Analgesics Advisory Board supports the short-term use of topical NSAIDs for relief of localized osteoarthritic pain of the hand and knee in persons in the Asia-Pacific region.

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from osteoarthritic pain. Topical NSAIDs provide effective short-term relief of osteoarthritic pain while avoiding systemic exposure – an important consideration in a patient population with frequent co-morbidities and age-related decline in renal and hepatic function – and thus are a valuable alternative to oral first-line analgesics. Significant relief of osteoarthritic pain allows elderly patients to gain the benefits of maintaining or pursuing vocational and avocational pursuits, thus enhancing their psychosocial and general health and lessening the economic burden of this condition. Use of topical NSAIDs, together with regular exercise, should be an integral part of clinical practice guideline recommendations for managing osteoarthritic pain and, indeed, international guidelines are increasingly positioning topical NSAIDs further up the management algorithm, especially in the elderly. This trend is expected to continue.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.future-science/doi/suppl/10.4155/pmt-2017-0047

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