

The role of topical Non-Steroidal Anti-Inflammatory Drugs in the management of joint pain in the community.

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1 NICE guidelines recommend that topical NSAIDs and or paracetamol should be considered ahead of oral NSAIDs, opioids or COX-2 inhibitors

Joint pain is an extremely common cause of pain and disability¹ and accounts for a large number of presentations to pharmacists and their teams. Joint pain, including osteoarthritis, becomes more common with age, but other risk factors include obesity. With increasing life expectancy and an ever-growing incidence of obesity in the UK², coupled with government moves to encourage patients to purchase medications such as analgesics from their pharmacist rather than obtaining them on prescription³, the role of the pharmacist in the pharmacological management of joint pain looks set to continue to rise.

The most recent NICE guidance on the management of osteoarthritis recommends that paracetamol and/or topical non-steroidal anti-inflammatory drugs (NSAIDs) should be considered ahead of oral NSAIDs, opioids or cyclo-oxygenase 2 (COX-2) inhibitors⁴.

2 Topical NSAIDs are safer than and as efficacious as their oral equivalents in treating musculoskeletal problems including joint pain

In this paper we explore the rationale for this national recommendation to use topical NSAIDs as first line pharmacological treatment.

Oral NSAID safety

Common side effects of oral NSAIDs include dose and duration dependent dyspepsia and gastric inflammation⁵ and proton pump inhibitors are routinely recommended for gastroprotection⁶.

Over a decade ago, concern was raised about an increased risk of myocardial infarction (MI) linked to use of oral NSAIDs related to the COX-2 inhibitors^{7,8}, subsequent data suggest the risk is also increased with other oral NSAIDs⁹. A 2017 meta-analysis of 446 763 individuals showed a 48-58% increase of MI among patients taking oral ibuprofen, diclofenac, naproxen or rofecoxib at any dose for a week or more¹⁰. The size of the risk was dose but not duration dependent for periods of over 1 week.

A link between oral NSAIDs and heart failure has led to recommendations that they should

3 Topical diclofenac is comparable in efficacy to oral diclofenac, ibuprofen and naproxen and has a lower NNT than both ibuprofen and ketoprofen gel

be avoided or withdrawn in any patient with the condition¹¹. Finally, oral NSAIDs can cause both acute reversible and permanent renal toxicity (6,12) – of particular importance in older patients with osteoarthritis and joint pain, who are more likely than their younger counterparts to have chronic kidney disease.

Topical NSAID safety

In addition to lower GI side effects, studies directly comparing oral vs topical NSAIDs reveal a lower risk of CV events, including MI, unstable angina, heart failure and stroke among patients using the topical version¹³. Liver and kidney toxicity are also lower among patients using the topical formulation¹⁴. The only side effect seen more frequently with the topical formulation is dry skin. Efficacy of the topical formulation was similar to that of oral diclofenac.

Like oral NSAIDs, topical NSAIDs inhibit COX-1 and COX-2 enzymes, thus blocking synthesis of prostaglandins, prostacyclin and thromboxanes, which mediate inflammatory pain^{15,16}.

The lower incidence of side effects with topical NSAID use can be explained by their lower systemic level than oral formulations – in the case of diclofenac, 5-17 times lower¹⁷.

Importantly, side effect rates are not increased among older patients, or among those with hypertension, type 2 diabetes, or a history of stroke or MI¹⁸.

Topical NSAID efficacy

But, topical NSAIDs must be efficacious as well as safe if their use is to be widely recommended. A large number of studies, including a systematic review from the highly regarded Cochrane database, has considered precisely this issue.

Topical diclofenac has been shown to penetrate the skin and permeate to deeper tissues, with tissue levels after topical delivery sustained over time (at least several hours)¹⁹.

Topical diclofenac is comparable in efficacy to oral diclofenac, ibuprofen and naproxen, with improvements in functional capacity and mobility as well as pain and inflammation²⁰.

This equivalence in efficacy has been confirmed by a systematic review from the Cochrane database, which considered 61 studies, most placebo controlled RCTs, in patients suffering from acute pain as a result of strains, sprains or sports or overuse-type injuries. The review noted that since its previous review, information on diclofenac had been greatly expanded. It concluded that efficacy of topical NSAIDs among these patients was broadly equivalent to that seen with oral NSAIDs, and that 'Gel formulations of diclofenac (as Emugel®), ibuprofen, and ketoprofen, and some diclofenac patches, provided the best effects'²¹.

Comparative efficacy of topical NSAIDs

The Cochrane review evaluated relative efficacy using NNT – Numbers Needed to Treat. NNT is measured in terms of absolute, not relative benefit, and where NNT is concerned, lower is better. A drug which needs to be taken by 10 people in order for one to see a benefit they would not have had from placebo has an NNT of 10; a drug where only 3 patients need to take the drug for one to benefit has an NNT of 3.

The systematic review showed that Diclofenac Emugel had the lowest NNT of any of the topical gels tested:

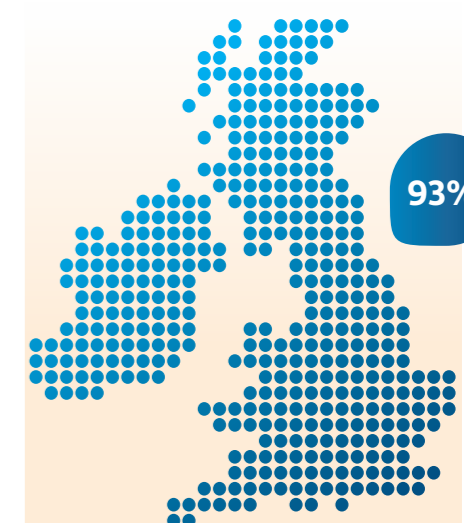
Topical NSAID	Numbers Needed to Treat (NNT)
Diclofenac Emugel®	1.8
Ketoprofen gel	2.5
Ibuprofen gel	3.9

While mode of administration was not specified in the trials, the efficacy of topical diclofenac gel may be further increased by rubbing it into the skin on application, so increasing local drug permeation²².

Conclusion

Topical NSAIDs are safer than and as efficacious as their oral equivalents in treating musculoskeletal problems, including joint pain.

- This positive risk-benefit ratio has resulted in their positioning by NICE as first line treatment for osteoarthritis, over oral NSAIDs.
- While Diclofenac Emugel®, Ketoprofen gel and ibuprofen gel are all efficacious, the lower NNT of the first shows that patients are more likely to achieve relief from Diclofenac Emugel® than from other topical NSAIDs or non-medicated topical applications.
- The pharmacist has an important role to play in guiding the patient on the relative safety and efficacy of different treatment options, as well as advising on mode of administration (rubbing rather than simply applying) and reinforcing adherence to the on-label dosing instructions.



93% of people living in the UK claim to have experienced 'everyday pain' within the last 12 months²³. 41% say they wish there was more variety when it came to pain medication²³.



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