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The burden of musculoskeletal pain and the role of topical Non-steroidal anti-inflammatory drugs (NSAIDs) in its treatment. Ten underpinning statements from a global pain faculty.

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Abstract
This document presents the conclusions of a detailed discussion on the role of topical NSAIDs during a round table Global Pain Faculty meeting held in Amsterdam in 2019 and subsequent discussions online. The aim of this evidence-based document is to describe the impact of musculoskeletal pain both in terms of the large numbers of sufferers and its economic impact. The document considers the place of topical therapies alongside other pharmacological and non-pharmacological treatments and presents the evidence for the benefits and harms of topical NSAIDS including indicators of efficacy for three main topical NSAIDs—diclofenac, ibuprofen and ketoprofen—based on almost 15,000 participants in randomised controlled trials for acute and chronic musculoskeletal pain. These topical NSAIDs have the largest body of evidence. For acute pain, numbers needed to treat to achieve at least 50% reduction in pain are as follows with 95% confidence intervals in brackets: Diclofenac emulgel 1.8(1.5-2.1) (5170 participants), Ibuprofen gel 2.7 (1.7-4.2) (436 participants), Ketoprofen gel 2.2 (1.7-2.8) (683 participants). For chronic pain, the NNTs are Diclofenac any formulation 9.5(7-14) (5995 participants). Ketoprofen 6.9(5.5-9.3) (2573 participants).

Randomised controlled trial evidence suggests that adverse events for active topical NSAIDs are similar to placebo. Finally the gaps in knowledge are considered with suggestions on how further research might help. The global pain faculty was brought together by GSK under an unrestricted educational grant.

Keywords: non-steroidal anti-inflammatory; topical treatments; musculoskeletal pain; consensus; efficacy; adverse effects

Background

We present the conclusions of a detailed discussion on the burden of musculoskeletal disease and the role of topical NSAIDs that took place during a round table Global Pain Faculty meeting held in Amsterdam in 2019 and subsequent discussions online. The Global Pain Faculty was organised by GSK under an unrestricted grant and the views expressed in this document are solely those of the authors.

1. **Musculoskeletal pain represents a substantial health problem, with an estimated 20–33% of people globally living with painful musculoskeletal conditions.**

The term musculoskeletal condition embraces a broad range of health conditions affecting bones, joints and muscles and rarer conditions of the immune system. This includes low back pain, osteoarthritis, neck pain, rheumatoid arthritis, gout and lupus. These disorders have multiple symptoms including pain, stiffness and a loss of mobility. They often interfere significantly with the normal daily activities of affected people. In the UK for instance, with a population of 70 million people, back pain alone is estimated to have an annual cost of £1.6 billion in direct and £10 billion in indirect costs while treating osteoarthritis and rheumatoid arthritis (the two most common forms of arthritis) in 2017 is estimated to have cost another £10.2 billion[1].

Painful musculoskeletal conditions are common and affect large numbers of people worldwide. The most common painful musculoskeletal conditions are low back pain and osteoarthritis, estimated to affect more than 10 million and 8.5 million UK citizens, respectively. Estimates are available of the numbers affected from surveys undertaken at a local through to global level. For instance, in the UK in 2017 about 18.8 million people lived with a musculoskeletal disorder[2]. This represented about 33% of females and 27% of males. The prevalence is age-related, with very few children suffering from these diseases, but more than 50% of those aged over 60 years.

A large survey[3] of more than 46,000 individuals in 16 European countries examined the prevalence and causes of persistent pain. It asked how many people suffered from pain lasting at least 6 months and occurring several times per week and rated numerically as scoring at least 5 out of 10. Of the 20% of the European population fulfilling these reasonably stringent criteria, 2/3 had musculoskeletal conditions, most commonly in the lower back. This survey was significant in that it also found that only a minority of people with persistent pain (34%) reported that medications offered adequate pain relief. Data from the 2009 National Health Interview Survey in America[4] found many individuals had suffered from musculoskeletal pain in a 3-month period: 28% pain in the lower back, 19% pain in the knee, 15% percent pain in the neck, and 8% pain in the hand.

A recent cross-sectional survey [5] of more than 52,000 subjects in 14 countries (in Europe, the Middle East, Latin and Central America, North America and in Asia-Pacifica) assessed the global burden of musculoskeletal pain. It found that half of the population surveyed felt they had pain that had some substantial, multifaceted impact on their lives.

These figures are representative of the burden on musculoskeletal pain in a wide range of countries.

The prevalence of musculoskeletal conditions appears to have remained approximately stable over the last 30 years, highlighting the continuing medical need in this area.

2. **Musculoskeletal conditions are a leading cause of disability, being responsible for more than 20% of all years lived with disability, and can profoundly impact quality-of-life as well as social and emotional well-being.**

One of the most respected methods for assessing the impact of particular medical disorders is the Global Burden of Disease Project[1]

The main metric at the heart of the Global Burden of Disease project is health loss resulting either from premature death or from disability. It is calculated for a wide range of health conditions and expressed as the so-called 'disability-adjusted life years' (DALY). Since many health conditions are not associated with loss of life (and this generally includes musculoskeletal conditions), a second measure that is also useful is the 'years lived with disability' (YLD).

The Global Burden of Disease survey in 2010 first identified that musculoskeletal pain conditions were amongst the leading causes of global disability and in 2016, low-back and neck pain were the third highest contributors to the total number of DALYs with only ischaemic heart disease and cerebrovascular disease contributing more on this measure.

Low-back pain was the most common cause of YLD for men in 2016 and had the highest age standardized YLD rates in 133 of the 195 countries assessed. In women, low-back pain similarly had the highest age-standardized YLD rates in 109 countries.

Over the decade from 2006 to 2016, the number of estimated YLD for low-back/neck pain and for osteoarthritis rose by 19.3% and 31.5%, respectively. Most of this increase appeared to be driven by population increase.[1] Musculoskeletal conditions accounted for 18% of all YLD globally in 2017.

3. Musculoskeletal pain is associated with a diverse range of societal consequences, and high economic costs reported to exceed those for heart disease, cancer and diabetes.

Musculoskeletal ill health results in significant costs for individuals, employers, the health service, and the wider economy. It also has a significant impact on the quality of life of the individuals affected as well as their family and friends.

The Pain in Europe survey found that pain sufferers (mostly with musculoskeletal conditions) had associated multiple adverse life experiences: 19% had lost a job because of their pain, 21% had been diagnosed with depression and over 40% reported feelings of helplessness or inability to think or function normally[3].

Musculoskeletal pain was recently reported to have significant negative effects on emotional wellbeing in 40%, and a significant adverse effect on quality of life in 59%, of a very large sample of individuals across 14 countries worldwide [5]

In monetary terms, musculoskeletal illness has direct costs of medical care associated with treating the conditions and the indirect costs due to lower economic productivity associated with lost wages, disability days, and fewer hours worked. In the UK for instance, with a population of 70 million people, back pain alone is estimated to have an annual cost of £1.6 billion in direct and £10 billion in indirect costs while treating osteoarthritis and rheumatoid arthritis (the two most common forms of arthritis) in 2017 is estimated to have cost another £10.2 billion[1].

4. Management of musculoskeletal pain requires an integrated approach, utilising non-pharmacological measures and pharmacological treatments which can include topical and/or systemic medications.

For self-limiting conditions such as strains and sprains, topical or oral NSAIDs are usually effective. [6,7] [8]

Systematic review evidence suggests that the initial steps in treating musculoskeletal pain related to osteoarthritis focus on non-pharmacological measures such as weight loss, exercise [9] and physiotherapy with escalation to pharmacological measures such as topical analgesics and then oral

NSAIDs. [10]. Paracetamol has been shown to be of limited benefit in osteoarthritis [11]. Opioids have in general been discredited as they are often ineffective in chronic musculoskeletal pain and can induce dependency [12], [13]). For more severe conditions, intra-articular injections or joint surgery may be necessary[10].

Utilising non-pharmacological and pharmacological measures in an integrated way is advisable

5. Topical administration of the NSAIDs diclofenac, ibuprofen and ketoprofen have been shown to provide effective relief of acute musculoskeletal pain.

Robust evidence from systematic reviews exists for the effectiveness of topical NSAIDs including diclofenac (5170 participants), ibuprofen (436 participants), and ketoprofen (683 participants) to provide pain relief for acute musculoskeletal pains such as sports injuries and other strains and sprains [6,8]. These topical NSAIDs have the largest body of evidence. We have defined effectiveness as a user reported reduction in pain intensity of at least 50% i.e. reducing pain by at least a half at 7 days after starting treatment. Numbers needed to treat (NNT) for the different NSAIDS when compared to a placebo using a similar base or vehicle were found to be as follows (presented with 95% confidence intervals):

- Diclofenac emulgel 1.8(1.5-2.1)
- Diclofenac (any formulation) 4.2 (3.6-5.1)
- Ibuprofen gel 2.7 (1.7-4.2)
- Ketoprofen gel 2.2 (1.7-2.8)

Taking diclofenac as an example the number needed to treat (NNT) means that for every 1.8 (say 2) people treated with this product at least one will achieve a reduction in pain of at least a half that would not have been achieved by the application of placebo[8,14].

6. The topical NSAIDs diclofenac and ketoprofen can provide effective relief of chronic pain for some patients with knee or hand osteoarthritis; there is no high quality evidence for or against effectiveness in other chronic musculoskeletal pain conditions.

Robust evidence from systematic reviews exists for the effectiveness of topical NSAIDs including diclofenac (5995 participants), and ketoprofen (2573 participants) to provide pain relief for chronic musculoskeletal pains such as knee or hand osteoarthritis [8,15]. We have defined effectiveness as a user reported reduction in pain intensity of at least 50% i.e. reducing pain by at least a half at 6-12 weeks after starting treatment. Numbers needed to treat for the different NSAIDS when compared to a placebo using a similar base or vehicles were found to be as follows (presented with 95% confidence intervals):

- Diclofenac (any formulation) 9.5 (7-14)
- Ketoprofen gel 6.9 (5.5-9.3)

Taking diclofenac as an example the NNT means that for every 9 people treated with this product at least one will achieve a reduction in pain of at least a half that would not have been achieved by the application of placebo. While the NNT may be considered as relatively large (poor), if a patient benefits from a topical NSAID then they may not need to consider the use of other interventions with a worse adverse effect profile.

Although studies in other osteoarthritis conditions were not identified in the systematic reviews, it would be reasonable to expect that topical NSAIDs would be similarly effective[15].

7. In acute and chronic musculoskeletal pain trials, topical NSAIDs are well tolerated with minimal risk of systemic adverse events; application site reactions occur at a similar rate as for placebo and are generally mild and transient.

Topical NSAIDs were developed to provide relief of musculoskeletal pain and eliminate or minimize the frequency of adverse events associated with oral or parenteral NSAIDs, which are sometimes severe and associated with mortality

Three systematic reviews have described adverse events[8,14,15]. Adverse events in these studies are not the primary endpoint and they are not always well collected by trialists. In acute pain, administration of NSAIDs is short-term, rarely lasting more than two weeks. Also, topical applications of NSAIDs are applied as creams, gels, plasters, sprays or foams which may deliver different amounts of NSAIDs, and therefore the carrier may be important in both efficacy and adverse events associated with the active compounds. In the same way, these carriers were applied as placebo arms and their effect may also be different, especially in terms of potential adverse events.

Reported local adverse events include irritation of the area of application described as reddens, erythema, itch, pruritus, and were usually mild and transient. The total number of participants included in the Cochrane meta-analysis for acute pain were 3619 with topical NSAIDs and 3121 with placebo [14]. The proportion of patients who reported a local adverse event was 4.3% with topical NSAIDs vs 4.6% with placebo (RR: 0.98 (95% CI 0.80 to 1.2). When NSAIDs were analysed individually, there were no differences with placebo, and the conclusion is that overall the frequency of local adverse events is very low with no difference between NSAIDs and placebo.

Systemic adverse events were also infrequent with no differences between the topical NSAID and placebo (3.1% vs 3.5 with placebo (RR: 0.96; 95% CI 0.7-1.3). It was a similar story for withdrawals due to adverse events.

In conclusion, the available literature confirms that topical NSAIDs do not show a higher incidence of local adverse events than the placebo carrier, and that it shows a lower incidence of systemic events compared to oral NSAIDs, although the incidence of serious adverse events is almost negligible in short-term treatments of acute musculoskeletal pain.

Two reviews on chronic musculoskeletal pain[8,15] also reported adverse events with topical NSAIDs used up to 12 weeks. As in the acute pain review, most local adverse events included redness, erythema, and pruritic or dry skin. The higher number of days of application was associated with a higher frequency of local adverse events compared to acute pain studies

Local adverse events with diclofenac were reported in 14% of patients vs.7.8% in patients treated with placebo carrier (RR: 1.8; 95% CI 1.5 to 2.2, NNH (number needed to harm) was 16; 95% CI: 12-23) in the combined analysis of 15 studies available. Ketoprofen was tested in four clinical trials, with local adverse rates of 15% vs 13% with placebo carrier (RR: 1.0; 95% CI: 0.85-1.3) [15].

When topical application of NSAIDs was compared to oral NSAIDs, local adverse events were more frequent in patients with topical application of the NSAID (22% vs 5.8%), but the systemic events were more frequent in patients taking oral NSAIDs (17% vs 26%; RR for GI adverse events was 0.66 (95% CI 0.56 to 0.77). More patients taking oral NSAIDs withdrew from the studies compared to topical NSAIDs due to adverse events. In another systematic review oral NSAIDs in knee osteoarthritis were associated with higher systemic adverse events compared to topical ketoprofen [5].

In conclusion, based on the evidence provided and compared to placebo, topical application of NSAIDs for longer periods of time in chronic pain was associated with similar or somewhat higher local adverse events. Topical NSAIDs were also associated with less systemic adverse events than oral NSAIDs and absence of serious adverse events.

8. Topical products other than NSAIDs are available; however, evidence for the efficacy of these products is negative for some and weak for others and their possible role in the management of musculoskeletal pain is undetermined.

Topical products other than NSAIDs include products containing capsaicin, salicylates and menthol as well as Ayurvedic medicines and herbal medicines. However, there have been few well conducted studies to determine their effectiveness for musculoskeletal pain.

A meta-analysis of studies of topical capsaicin in osteoarthritis included five randomised controlled trials and one case control cross over study using topical capsaicin formulations ranging in strength from 0.025 – 0.075% for period of 4-12 weeks[16] . Compared with placebo, capsaicin was associated with a modest reduction in a 10-point VAS score of 0.44 95% CI 0.25, 0.62); however, 35-100% of patients reported mild application site burning associated with capsaicin (RR vs. placebo 4.42 (95% CI 3.25, 5.48). Although generally mild, this burning sensation can be intolerable for some patients leading to treatment withdrawal in some patients in clinical studies [17,18] .

Topical salicylate preparations, including methyl-salicylate, have shown some effects in acute and chronic musculoskeletal pain and osteoarthritis; however, larger, more recent studies have failed to demonstrate a benefit of topical salicylates over placebo for musculoskeletal pain[19]. Based on limited evidence, the use of topical salicylates appears to be well tolerated. However, potentiation of the anti-coagulant effect of warfarin by topical methyl-salicylate has been reported [20].

9. Topical NSAIDs have a role in the management of mild-to-moderate musculoskeletal pain.

NSAIDs are more effective than other pharmacological approaches in the management of pain associated with different musculoskeletal conditions. However, when used as oral treatment they may be associated with systemic (especially gastrointestinal, and less frequently cardiovascular) adverse events, As a result, they are usually placed as the second or third step in the hierarchy or algorithms of management of pain associated with these conditions [21].

Since the occurrence of adverse events with oral or parenteral NSAIDs is dose-dependent, another approach has been the use of topical NSAIDs. The aim of this approach is to deliver a high concentration of drug locally, while reducing systemic exposure to the drug and therefore decreasing the risk and frequency of adverse events. The most recent systematic reviews and meta-analysis reported in the previous statements have shown that topical administration of NSAIDs are more effective than placebo in the treatment of both acute and chronic musculoskeletal pain, have similar local adverse events to placebo and are safer than oral NSAIDS with no systemic adverse events [8,14,15].

Based on these advantages, [22,23], most guidelines recommend now the use of topical NSAIDs (alone or combined with other measures) in the algorithms of pain treatment associated with musculoskeletal conditions, especially osteoarthritis.

The recent 2018 update of the EULAR (The European League Against Rheumatism) recommendations for the management of hand OA indicate that topical treatments are preferred over systemic treatments because of safety reasons and put topical NSAIDs as the treatment of choice within this category [21] Also, the 2018 Asia-Pacific expert consensus on the use of topical NSAIDs in musculoskeletal pain points out that they should be recommended as a first-line intervention for mild to moderate pain and that they have comparable efficacy to oral NSAIDs [24] .

The American College of Rheumatology recommended the use of topical NSAIDs in the management of hand and knee OA at the same level than oral NSAIDs or other pharmacological treatments, but no recommendations were made for topical NSAIDs for patients with hip OA due to the lack of data from RCTs [25] The more recent guidelines published by the Osteoarthritis Research Society International (OARSI) strongly recommends the use of topical NSAIDs in the treatments of knee OA, whereas the use of oral NSAIDs is conditional based on the presence of either GI or CV comorbidities [26].

Similar recommendations are given by other societies such as the European Society for Clinical and Economic aspects of osteoporosis and osteoarthritis (ESCEO), where topical NSAIDS are placed on the top of the algorithm in the management of knee OA after the use of symptomatic slow acting drugs for osteoarthritis and short-term paracetamol rescue analgesia [23].

In summary, topical application of NSAIDs is considered as treatment of choice among the pharmacological approaches in patients with musculoskeletal pain. Guidelines of different scientific societies strongly recommend the use of topical NSAIDs on the top and first step of any pharmacological treatment in the management of knee and hand osteoarthritis.

10. Studies are needed to establish the best use of topical NSAIDs in the management of acute and chronic musculoskeletal pain, including: Agent, formulation and dose of topical NSAIDS.

As reviewed above, there is clear and robust evidence for analgesic efficacy of topical NSAIDs in some acute and chronic musculoskeletal conditions. However, there are many questions about the use of topical NSAIDs that are currently not well answered. Some of these are: What is the best type of NSAID?; best dose?; best formulation? What conditions are ideally treated by topical NSAIDs?

The relative lack of head to head comparison studies partly underlies this uncertainty. But another reason is that there are limited published mechanistic studies of the effects of topical NSIADs. Of course, there is a good understanding of how NSAIDs in general produce analgesia but the spatial and pharmacodynamic distribution of different NSAIDs in different formulations and at different concentrations is not widely available. These data would be of considerable value in understanding and comparing different formulations of agents. It would also provide a rationale for topical NSAIDs use in different conditions. It might also facilitate a wider exploration of the potential benefits of topical NSAIDs. One example is low back pain. This is an extremely common form of musculoskeletal pain (see above) but is not generally considered as a target for topical NSAID treatment at the current time.

The systematic reviews failed to identify any clinical trials comparing one topical NSAID with another. There does seem to be a difference in the effectiveness of different formulations and needs to be investigated further. Finally the role of topical NSAIDs in chronic pain needs wider exploration as almost all studies have been conducted in osteoarthritis.

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