

# PHARMACOLOGICAL MANAGEMENT OF MUSCULOSKELETAL PAIN: CLINICAL EVALUATION OF DRUG EFFICACY AND SAFETY

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## ABSTRACT:

Musculoskeletal pain has been a top cause of disability in the global population and it is also a significant clinical and socioeconomic burden. Pharmacological treatment continues to play a leading role in the management of symptoms, but rising data suggest that analgesic effects are weak most of the time and thus need to be weighed against significant safety concerns. It is a comprehensive review of existing evidence on the effectiveness and adverse-effect profile of key drug classes in the treatment of osteoarthritis, low back pain, and musculoskeletal issues associated with them. NSAIDs show a regular analgesic effect in the short term with a tendency to show an inflammatory phenotype, although they necessitate cautious cardiovascular, renal, and gastrointestinal risk evaluation. The limited benefit of acetaminophen is only adjunctive. The use of centrally acting agents like duloxetine can enhance the results in a selected patient with the characteristics of central sensitization. Routine opioid use cannot be supported in acute spinal pain, and long-term opioid treatment is also linked to major harm. Topical and intra-articular therapy provide local relief of symptoms with relatively desirable systemic safety issues. Overall, successful pharmacological treatment entails the need to undertake individual risk stratification, realistic treatment objectives, and combine with non-pharmacological measures to streamline the patient-centred outcome and reduce preventable adverse events.

**KEYWORDS:** Musculoskeletal Pain, Osteoarthritis, Low Back Pain, Non-Steroidal Anti-Inflammatory Drugs, Analgesic Safety

## 1. INTRODUCTION

Although musculoskeletal (MSK) pain is a highly prevalent and debilitating health-related issue on the global front, and the representatives of all age groups and healthcare environments are susceptible to it. Knee and hip osteoarthritis were the highest in causing pain, poor functioning and low life quality; and one of the most significant implications of health systems and society [1]. In addition to the articular degeneration, the MSK pain is currently acquiring a multifactorial and complex manifestation whereby the biomechanical stress, low grade of inflammation, neuromodulation and psychosocial factors are involved to define the level of symptoms and progression of the disease. Integrated interventional and rehabilitative therapy was also suggested in the knee OA, in which the peripheral or the central inputs of nociceptive information are involved, and the role of overall treatment models should also be mentioned [2].

The clinical practice guidelines have tried to homogenise non- surgical management of the various health systems, but the differences and variations between the various guidelines indicate that there is still confusion on priorities of the pharmacological use and risk assessment [3]. Similarly, the European guidelines for hand osteoarthritis are meant to treat the symptoms of the disease and preserve the functioning of the disease but the current pharmacologic agents do not have disease-modifying effects [4]. The more recent algorithm-derived solutions, including that suggested by the European professional working groups, are doomed to incorporate signs of efficacy, safety and patient-specific predisposition factors in the practical treatment options of knee osteoarthritis [5]. The processes are indicative of the larger problem of clinical decision-making to stay abreast with the continuously changing comparative effectiveness data.

Conventionally, the pharmacological management of MSK pain has been based on non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen and in certain cases on opioids. This is, however, presently evidenced that suggests that the trade-off between analgesic effect and possible harm is weaker than would otherwise have been deemed the case in chronic osteoarthritis. Significantly sized network meta-analysis evidence has shown that, by far, there is no evidence of an enhancement of pain intensity by various oral substances and at the same time, medical risks of gastrointestinal, cardiovascular, renal and addiction dangers against the clinical benefits of vulnerable populations have been reported [6]. Simultaneously, systematic

reviews of the topic of low back pain have indicated that the list of drugs that are commonly utilized does not add significantly to the benefit as compared to placebo and it is not evident why the pharmacologic escalation of non-specific presentation needs to be the norm [7].

The highest years with disability, especially on a global scale, is caused by low back pain, which can result in colossal socioeconomic consequences in terms of absenteeism at the workplace, and use and productivity of long-term healthcare services at the workplace [8]. The conservative interventions and community-based interventions (where it is specified that pharmacological treatment must be applied in a more restrained manner) developed by the World Health Organization have received special emphasis [8]. This new paradigm is sensitive to the fact that the analgesic use, in the absence of other factors that may be underlying persistent MSK pain, is unlikely to have the same complicated nature of the drivers of persistent pain and that such overuse may end up causing unnecessary harm.

The issues of adverse events of opioids have continued to impact the prescribing behavior of MSK disorders. The recent concerns on national guidelines released in the United States take into account the use of care when initiating, during dose titration, and in cases of recurrent re-evaluation of opioids, in case they are required due to either acute or chronic pain [9]. The awareness of the danger like dependence, overdose, and hyperalgesia, caused by opioids have made clinicians reconsider the use of the agents in circumstances in which it is not evident that the long-term functional improvement will be achieved [9]. Meanwhile, the therapeutic value of the other pharmacologic classes such as the muscle relaxants, has been called into question with respect to its short-term beneficial outcome and the likelihood of inducing sedation and other unwanted effects in the nonspecific low back pain [10].

These trends could all be signs of a fundamental paradox of the situation in which management of MSK pain occurs: the necessity to reduce suffering and more functioning and reduce the number of complications that the treatment predetermines. It requires the risk-stratified but not step-wise increment of the patient heterogeneity, comorbidity and pain procedures. The recent clinical practice is thus introduced by the integration of comparative efficacy data of the shared decision-making models and safety signalling and patient decisions.

It is on this note that the current review will aim at offering a holistic and clinically informed appraisal of the pharmacological interventions in musculoskeletal pain. The article will assist in the rational prescription, and also in the maximisation of patient-centred outcomes in the primary and specialist care, by incorporating the current evidence about the efficacy and safety of major drug classes, and placing the recommendations in the framework of the developing guidelines. The major aims of this review are:

To critically evaluate the efficacy and safety profiles of commonly used pharmacological agents in the management of musculoskeletal pain across major clinical conditions, including osteoarthritis and low back pain.

To synthesize current evidence and guideline recommendations to propose a risk-stratified, mechanism-informed framework for rational and patient-centred prescribing.

## **2. REVIEW METHODOLOGY**

It was grounded on a methodological and transparent approach to review and the determination of the most relevant evidence based on the literature review on the pharmacological management of musculoskeletal pains. The articles that have been published in January 2018 up to February 2025 were searched systematically with the help of electronic databases, including PubMed/MEDLINE and Scopus. The search strategy was composed of a Medical Subject Headings (MeSH) and free-text words combination that comprised the following: musculoskeletal pain, osteoarthritis, low back pain, antidepressants, gaba-, nsa-, opioid-, antidepressant-, and gabapentinoid-, and muscle relaxant.

The studies were included depending on randomized controlled trials, systematic reviews, network meta-analyses and high-quality clinical practice guidelines involving the non-cancer musculoskeletal pain use in adults. The observational studies were considered in the process of establishing the long-term safety results that were not adequately addressed in randomized studies. Research trials which included postoperative pain, malignant pain or trials which included pediatric population were excluded to maintain clinical homogeneity.

The precedence was given to methodologically rigorous evidence based on the meta-analyses and large randomized trials had more weight compared to smaller studies and non randomized studies. The synthesis of trial-reported adverse events with population-based risk estimates to combine safety data were used to have an equal assessment of the benefits risk profile of the drug classes.

## **3. PATHOPHYSIOLOGY OF MUSCULOSKELETAL PAIN AND PHARMACOLOGIC TARGETS**

The musculoskeletal pain is due to the overlaps between nociceptive, inflammatory and neuropathic factors that develop and change according to the clinical conditions. The inflammatory mediators such as the prostaglandins, bradykinin, and the cytokines normally activate the peripheral nociceptors, which results in the formation of an acute tissue injury. It also may enhance the activation of peripheral afferents through the manner of persistent stimulation, an action referred to as peripheral sensitization, which increases the response to mechanical or chemical stimulus. Persistent peripheral tissue stimulation in chronic disease conditions can initiate central sensitization, or elevation of neuron excitability of the spinal and supraspinal areas, and unreasonable appreciation of the pain in relation to the underlying structural pathology.

The neuropathy processes are of particular concern in the lumbar radicular syndromes; nerve root irritation is believed to be the cause of the shooting or burning pains along dermatomal paths. However, it is somewhat suggested that the application of the anticonvulsants commonly used in the management of assumed neuropathic low back pain does not have much clinical benefits since it is evident that neuronal hyperexcitability during mixed pain conditions is difficult to cure [11].

Inflammatory processes also provide some mechanistic reasons as to use non-steroidal anti-inflammatory drugs (NSAIDs) which prevent the synthesis of prostaglandins by the enzyme cyclooxygenase and relieve peripheral sensitization. Nonetheless, it is noted that the use of systemic NSAIDs is a risk factor of cardiovascular events particularly when some of them such as diclofenac are used, thus the applicability of drug selection and patient stratification [12], as is shown in Table 1. Topical NSAIDs are set to get into adequate concentrations of the local tissue and low levels in the systemic circulation, and safety research have indicated that the adverse-event profile of topical preparations is more favorable than oral preparations in osteoarthritis treatment [13].

**Table 1. Evidence-linked pharmacologic targets and safety priorities in musculoskeletal pain**

| Pain driver             | Typical clinical pattern | Main drug target | Preferred option         | Key safety flag    | Best-fit use        | Reference |
|-------------------------|--------------------------|------------------|--------------------------|--------------------|---------------------|-----------|
| Peripheral inflammation | OA flare, localized pain | COX → PGs        | Topical NSAID            | Skin/GI (low)      | Local joint pain    | [14]      |
| Central modulation      | Chronic OA/CLBP          | 5-HT/NE          | Duloxetine               | Nausea, sleep      | Widespread/chronic  | [15]      |
| Multifactorial chronic  | CLBP (mixed)             | Multi-domain     | Multimodal care          | Over-medication    | Add-on meds only    | [16]      |
| Chronic primary pain    | Diffuse, no clear lesion | CNS processing   | Avoid routine analgesics | Dependence harms   | Function-first plan | [17]      |
| Low efficacy analgesia  | Back pain/OA             | Mixed            | Paracetamol combos       | Hepatic risk       | Short-term trial    | [18]      |
| Local inflammation      | OA synovitis             | Cytokines/PGs    | IA corticosteroid        | Cartilage/systemic | Limited repeats     | [19]      |
| OA analgesia            | Knee/hip OA              | COX selectivity  | NSAID choice varies      | CV/GI/renal        | Risk-stratified     | [20]      |

All these procedures are aimed at the control of the pharmacologic interventions, which aim at the regulation of the inflammatory mediators, prevention of the neural sensitization and preservation of the balance between analgesic effect and the systemic danger.

#### 4. NON-OPIOID ANALGESICS

##### 4.1 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

The analgesic and anti-inflammatory effects of the nonsteroidal anti-inflammatory drugs are achieved primarily due to the blockage of the cyclooxygenase (COX)-1 and COX-2 enzymes, which block the synthesis of the prostaglandins and peripheral sensitization. There is widespread use of oral and topical preparations in osteoarthritis and low back pain, and these two methods have their selection depending on the intensity of pain, anatomical localisation in the affected area, and the risk profile of the patient. Oral NSAID is associated with gastrointestinal bleeding, cardiovascular collapse and renal failure, especially in geriatric and comorbidity patients. The prevention of risks is done through administration of the minimum effective dose at maximum duration and gastroprotective measures on the basis of need. Similar comparative studies, also relating to chronic non-cancer pain, show that substitution to the current treatment, such as medical cannabis, is not always demonstrate a better effect compared to the established pharmacologic ones, supporting the continuity of using NSAIDs as the initial therapy when closely supervised [21].

##### 4.2 Acetaminophen (Paracetamol)

Ten years on, acetaminophen is the most used analgesic for musculoskeletal pain as it has a better gastrointestinal and cardiovascular profile in comparison to the NSAIDs. Its action on the central nervous system has not been fully explained, but it is postulated to inhibit the synthesis of the prostaglandins centrally and modify the descending serotonergic pathways. The osteoarthritis and the low back pain clinical trials demonstrate that the small analgesic action exists and at the moment, the use of acetaminophen is being utilized not as an independent pain killer of chronic pain but rather as a complementary one. The most critical safety issue is hepatotoxicity, especially with increased cumulative dosages or in patients with underlying or existing

liver disease or who consume large amounts of alcohol. The patients on long-term opioid therapy also report the use of complete opioid agonists, which may include the use of partial agonists, and report the measures that should be taken to decrease the use of complete agonists in the effort of increasing the safety profiles and the opioid pain outcomes, in addition to which the primary aim of maximizing non-opioid therapy should be taken into consideration before the onset of the use of the more dangerous treatments [22], as shown in Table 2.

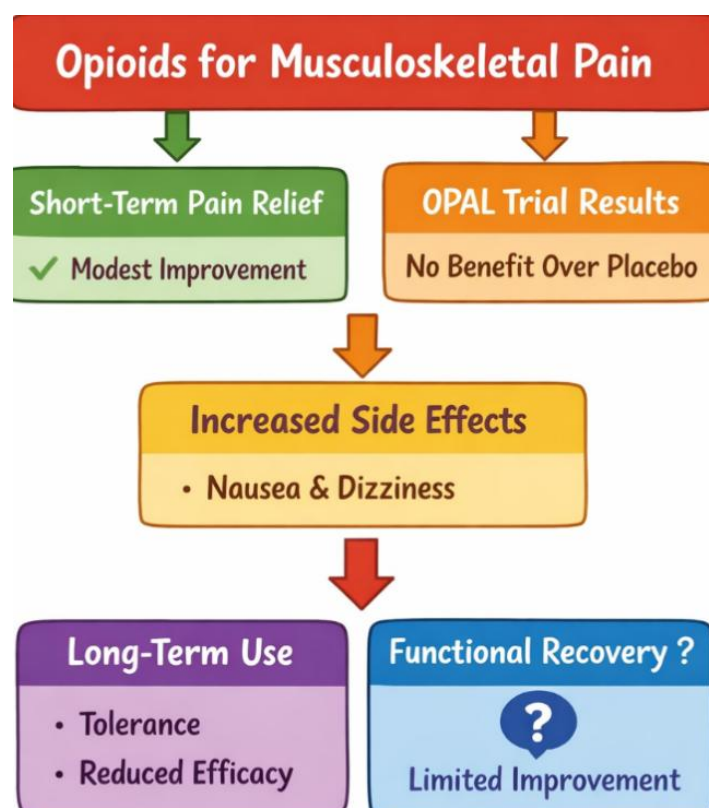
**Table 2. Pharmacologic options for osteoarthritis pain: benefit focus and key safety signals**

| Therapy class      | Typical role         | Benefit signal    | Key caution         | Reference |
|--------------------|----------------------|-------------------|---------------------|-----------|
| Standard OA drugs  | Core pharmacotherapy | Modest pain ↓     | Comorbidity risk    | [23]      |
| Topical capsaicin  | Local adjunct        | Local pain ↓      | Burning/irritation  | [24]      |
| Tramadol           | Rescue/last-line     | Short-term ↓      | Mortality/harms     | [25]      |
| Perioperative meds | Surgical context     | Continuity/safety | Interaction/bleed   | [26]      |
| Guideline pathway  | Stepwise care        | Evidence-based    | Avoid overtreatment | [27]      |

## 5. OPIOID AND OPIOID-RELATED ANALGESICS

### 5.1 Weak and Strong Opioids

The role of opioids has also been to treat moderate to severe musculoskeletal pain in cases when first-line treatment does not adequately manage the symptoms. Cross-over randomized trials have shown some statistically significant improvements in the intensity of pain in the short term; nevertheless, current high-quality studies question their use in acute spinal pain. The trial of OPAL revealed that opioid analgesia failed to deliver clinical significance over placebo in acute low back or neck pain, whereas it raised the frequency of adverse events, including nausea and dizziness [28]. These results indicate that the better the pain scores, the better the functional recovery as in Figure 1. Furthermore, there is a growing body of evidence that suggests that sustained opioid treatment correlates with decreasing analgesic efficacy, which underscores the issue of tolerance and lack of sustained efficacy [29].



**Figure 1. Clinical Benefit–Risk Profile of Opioids in Musculoskeletal Pain**

### 5.2 Tramadol and Dual-Mechanism Agents

The  $\mu$ -opioid receptor weak agonism and the serotonin and norepinephrine reuptake inhibition of the dual-mechanism agents such as tramadol that technically enhances descending inhibitory mechanisms. The pharmacologic profile of tramadol above has positioned it at the mid between the non-opioid analgesics and the stronger opioids. Nevertheless, it contains an opioid component that poses the risk of addiction like other

representatives of this group, including central nervous system depression, and serotonergic drug interaction. The availability of relative data on the trials of acute spinal pain has demonstrated that opioid-based treatment does not consistently surpass the non-opioid one in improving the line of recovery, and raises the question of the value-added effect of tramadol in clinical practice [30]. The careful choice and establishment of the treatment objectives of patients, therefore, is crucial in the case of dual-mechanism agents (Table 3).

**Table 3. Comparative non-opioid options in knee osteoarthritis and spinal pain: efficacy–safety signals**

| Option                     | Main use     | Efficacy signal | Safety signal    | Reference |
|----------------------------|--------------|-----------------|------------------|-----------|
| Acetaminophen vs NSAIDs    | Knee OA      | NSAIDs > APAP   | Systemic risk    | [31]      |
| Antidepressants            | Back/OA pain | Small benefit   | AEs common       | [32]      |
| Diclofenac (formulations)  | Knee OA      | Similar benefit | Skin AEs         | [33]      |
| Diclofenac solution        | Knee OA      | Pain ↓          | Mild local AEs   | [34]      |
| Topical NSAID vs capsaicin | OA pain      | Both effective  | Local irritation | [35]      |

### 5.3 Safety and Public Health Considerations

The increased awareness of the harm associated with opioids has altered the society approach to managing musculoskeletal pain in the international arena. Dependence, misuse, tolerance, hyperalgesia by opioids, disruption of endocrine functions, and increased vulnerability to fracture with exposure to opioids in the long term are the side effects. International guidelines, in instances of contraindication of NSAIDs, recommend the cautious use of such agents in individuals who have cardiovascular, renal, or gastrointestinal comorbidities yet opioids, despite their safety, should not be replaced by the safer agents in the absence of a clear benefit [36]. The concept that the opioid use on the acute basis of spinal pain cannot be supported with any evidence and can pose patients with an unwarranted risk is also reinforced by the authors of the OPAL study [30]. The recent practice has thus accorded more consideration to deprescribing interventions, collaborative decision making and close observation during opioid start.

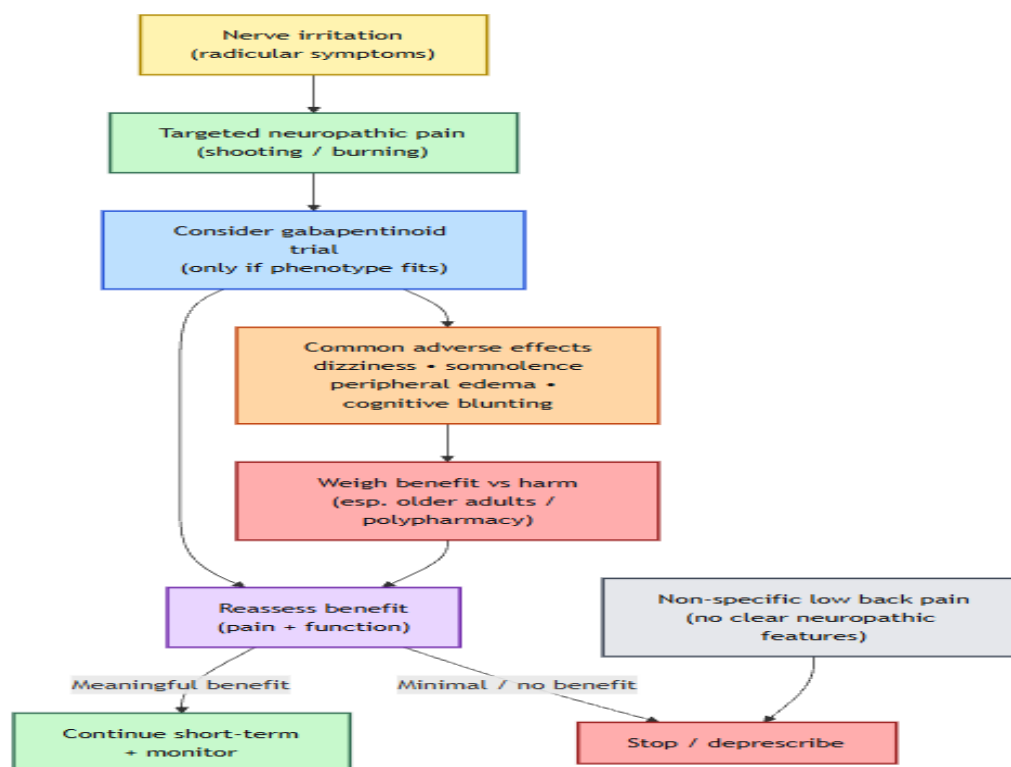
## 6. ADJUVANT ANALGESICS

### 6.1 Antidepressants (e.g., Duloxetine)

Antidepressants, particularly serotonin-norepinephrine reuptake inhibitors such as duloxetine, are increasingly being used in chronic musculoskeletal pain with a suspected central sensitization. Their analgesic action is also linked to a rise in the descending inhibitory systems in the central nervous system, which might be particularly effective in persistent low back pain and osteoarthritis with excessive levels of pain. Suggestions have been made to the effect that the multimodal approaches that use centrally acting agents through physical and psychological interventions are better in managing pain phenotypes and patient expectations in moderate to severe knee osteoarthritis [36]. Although antidepressants may provide small advantages in the spheres of pain and functionality, their tolerability profile also comprises such effects as nausea, sleep disruption and cessation of therapy and must be evaluated. Such agents are used with paracetamol, though it is stated that the analgesic effect of such agents by itself is limited, which is why the combination of all of them should be individualized rather than increased by default [36].

### 6.2 Gabapentinoids

The voltage-gated calcium channels are affected by gabapentinoids, and they are major agents in the management of the neuropathic pain syndrome. Their contribution is usually taken into consideration in musculoskeletal disorders on musculoskeletal syndromes of the radicular syndromes of nerve root irritation as another factor in shooting or burning symptoms. It does however contain some little evidence as to its routine use in non-specific low back pain and the benefits cannot be seen to be consistent across trials. Pharmacologic agents that target neuropathic mechanisms should be regarded as components of a more general multimodal management model and not a reflection of diffuse nociceptive pain [37]. Its side effects are dizziness, somnolence, peripheral edema, and cognitive blunting which is likely to affect day-to-day functioning, especially in the older adults. With such marginal analgesic effects of the application of various non-opioid drugs such as paracetamol, clinicians must consider the incremental benefit and possible harm of the interventions applied in the use of the addition of gabapentinoids to multifaceted therapy (Figure 2).



**Figure 2. Clinical Decision Pathway for Gabapentinoid Use in Musculoskeletal Pain**

### 6.3 Skeletal Muscle Relaxants

Skeletal muscle relaxants are also commonly used to treat acute low back pain in which it is presumed that muscle spasm is a cause of the intensity of the symptoms. These agents are centrally acting agents whose mechanism in pain relief is not fully understood. There is some evidence to show short-term positive changes in pain intensity but functional gains tend to be small and might not be maintained between the acute phase and beyond. The most frequent side effects include sedation, dizziness, and poor coordination, which put people at risk of falls and accidents, especially in comorbid or old age populations. The choice of the drug in case of patients who have cardiovascular risk factors and need analgesic therapy should be based on a general safety profile, including possible interactions and systemic effects of specific anti-inflammatory drugs [38]. Therefore, muscle relaxants should be used on a limited time with strict monitoring as part of a larger treatment plan unique to rehabilitation.

**Table 4. Guideline-aligned medication choices in MSK pain: efficacy focus and safety constraints**

| Context                     | Preferred meds       | Avoid/limit         | Key safety focus   | Reference |
|-----------------------------|----------------------|---------------------|--------------------|-----------|
| Arthritis + CV/renal risk   | COX-2/NSAID select   | High-risk NSAIDs    | Cardiorenal events | [39]      |
| Knee OA (non-surgical)      | Topical/oral NSAIDs  | Long-term opioids   | Risk-stratify      | [40]      |
| Low back pain (global CPGs) | NSAIDs (short)       | Routine opioids     | Benefit small      | [41]      |
| LBP meds overview           | NSAIDs first         | Antibiotics/opioids | AEs outweigh       | [42]      |
| LBP guideline audit         | Variable prescribing | Non-guideline meds  | Overuse risk       | [43]      |

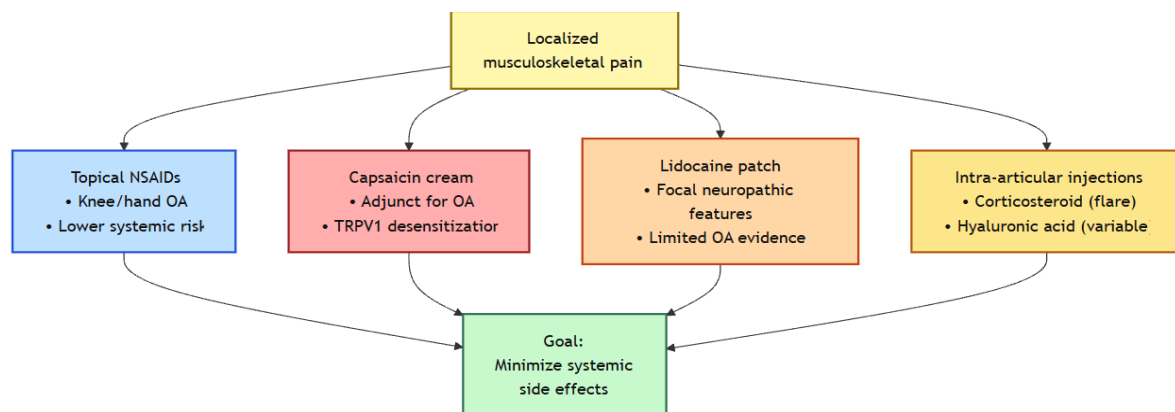
## 7. TOPICAL AND LOCAL PHARMACOLOGIC THERAPIES

Topical and local pharmacologic therapy is also significant in musculoskeletal pain management whereby it is important to focus on the peripheral causes of pain and the effect of such therapy has few systemic implications. Non-steroidal anti-inflammatory drugs (NSAIDs), especially topical applications, have been interestingly suggested in the treatment of osteoarthritis, especially in the knee and hand, as they cause clinically significant

pain alleviation and reduce instances of gastrointestinal and cardiovascular side effects in comparison with orally administered contraceptives. The capsaicin preparations work by desensitisation of the transient receptor potential vanilloid 1 (TRPV1) channel, causing the activity of nociceptor to decrease with the repetitive application and are generally assumed to have adjunctive action in localised osteoarthritis pain. The lidocaine patching can potentially have a beneficial effect on some patient with focal neuropathic characteristics, and practice on the purely nociceptive osteoarthritis is a limited one.

Intra-articular treatments are designed to provide good levels of concentrations of drugs in the joint. The clinical consequences of corticosteroid injections are on the inflammatory exacerbation in the short term, and hyaluronic acid on the lubrication of the joints and the control of the synovial inflammation has been suggested, although the clinical outcomes have been inconsistent.

Although duloxetine has systemic administration, its clinical trial in knee osteoarthritis reveals the spirit of centrally acting agents in the instances of peripheral failures. Duloxetine has been demonstrated to have a low degree of analgesic activity in the chosen patients with knee osteoarthritis, especially when central sensitisation is present [44]. Nonetheless, preoperative analgesia before a joint arthroplasty has not consistently been linked to long-term benefits of chronic postoperative pain and most likely local structural drivers may prevail at the latter disease stages as shown in Figure 3. Regularly, topical and intra-articular techniques are used for local pain and more complicated or general manifestations are treated with systemic therapy.



**Figure 3. Localized Pharmacologic Strategies in Musculoskeletal Pain: Topical and Intra-Articular Approaches**

## 8. COMPARATIVE EFFECTIVENESS AND TREATMENT ALGORITHMS

The comparative evidence of the applicable classes of pharmacologic demonstrates that the decision which should be made in the treatment of musculoskeletal pain in the patient should be informed by the chronicity, inflammatory process, and patient-specific risks rather than the amount of pain. Statistically significant, rather small decreases in pain and functional impairment have been demonstrated in chronic muscle skeletal disorders with duloxetine, also in cases where there are features that suggest the presence of central sensitization in patients [46]. These outcomes predispose its application as an addition to the initial peripheral analgesics in the cases when pain treatment is not effective enough. Effect sizes on the other hand are moderate and this promotes the need to make realistic goals and decisions jointly.

The new reevaluations of the analgesic interventions in rheumatic and musculoskeletal diseases are founded on the growth of advantage over the accumulation of damage with the specified emphasis on the elderly with multimorbidity [47]. The use of short courses of NSAID (in general topical in cases of localized osteoarthritis) is of priority in cases of acute nociceptive pain where there is no significant inflammatory activity (Table 5). The most recent multidisciplinary recommendations help the rational use of topical NSAIDs as firstline mediators in localized joint pain due to their favorable safety estimates when compared to systemic agents [48].

**Table 5. Adjunct and intra-articular options in knee osteoarthritis: efficacy–safety summary**

| Therapy                 | Role            | Efficacy signal  | Duration        | Ref  |
|-------------------------|-----------------|------------------|-----------------|------|
| Diacerein               | SYSADOA         | Pain ↓ (modest)  | Residual effect | [49] |
| Glucosamine/Chondroitin | Supplement      | Small/variable ↓ | Long-term use   | [50] |
| Hyaluronan (IA)         | Viscosupplement | Pain ↓           | Mid-term        | [51] |
| IA Corticosteroid       | Flare control   | Short-term ↓     | Weeks           | [52] |

|                     |                  |                  |               |      |
|---------------------|------------------|------------------|---------------|------|
| Mixed interventions | Network evidence | Variable benefit | Context-based | [53] |
|---------------------|------------------|------------------|---------------|------|

Rather, a step-by-step algorithm includes risk assessment and non-pharmacological foundations comprised of exercise and education, then topical agents or short-course oral NSAIDs where appropriate. In a phenotype of persistent or extensive pain, centrally acting agents, including duloxetine, may be considered. The cases that are being carefully selected with a reassessment should not be used with opioids. To achieve the maximum outcomes and minimize the unwanted adverse events, it is the combination of the pharmacologic and non-pharmacologic treatments imposed in the individual care paths.

## 9. SAFETY, RISK STRATIFICATION AND SPECIAL POPULATIONS

Safe pharmacological methods of musculoskeletal pain management include systematic risk evaluation in the elderly and in individuals with multiple morbidities. Medical treatment such as intra-articular corticosteroids, hyaluronic acid and biologic preparations is commonly mentioned in the case of the cumulative risk of systemic exposure being too large, but the indications, frequency and selection of patients must be carefully individualized to avoid the occurrence of cumulative joint or systemic problems [54]. Combination techniques of platelet-rich plasma with hyaluronic acid have been researched intra-articularly to enhance symptom control but with mixed results in terms of safety information and the effectiveness comparatively in the long-term [55]. Hyaluronic acid injection systematic reviews show weak but positive results in a chosen population, and it is necessary to align the expectations of the patients with evidence and not to repeat unnecessary procedures [56].

The topical agents are particularly suit the weak populations, which are susceptible to cardiovascular, renal, or gastrointestinal complications. Topical diclofenac was found safer than oral NSAIDs in chronic and acute musculoskeletal pain, hence indicating that it should be used in preference over local osteoarthritis [57]. Nevertheless, the systemic NSAIDs remain widely administered and are associated with gastrointestinal mucosal injury that could be expanded to the small intestine and this is the reason why caution is taken in relation to NSAID enteropathy in predisposed patients [58]. Capsaicin topical treatments, which contain topical Capsaicin, can offer additional local treatment and minimal absorption into the system, but are associated with temporary local irritation [59]. New approaches to the use of diclofenac are aimed at increasing tissue perfusion and reducing peripheral exposure that can increase the benefit-harm ratio in the patient at risk [60].

Across special populations, clinicians must evaluate renal function, cardiovascular status, hepatic reserve, and concomitant medications before initiating or continuing analgesics. Regular monitoring, dose adjustment, and deprescribing when risk outweighs benefit remain central to patient-centred musculoskeletal pain management.

## 10. FUTURE DIRECTIONS AND CONCLUSIONS

The existing paradigm of a wide and symptomatic pharmacological care of musculoskeletal pain is sure to be substituted with a more objective-based and patient-centric one in the future. The new approaches are directed at peripheral-acting anti-inflammatory drugs that are more tissue-localizing, new topical delivery techniques that are more tissue-selective and less systemic-exposing, and centrally acting agents that are tissue-selective without excessive sedation and dependency. The accuracy of analgesia can be achieved by developments in the phenotyping of clinical features, functional measurements, and perhaps biomarkers to classify patients as most likely to respond to an anti-inflammatory, neuromodulatory or mixed-mechanism regimen.

Despite the fact that it has been extensively discussed, there remain a lot of gaps. The vast majority of the trials are short, poorly powered to reach safety, and target the degree of pain, rather than long-term functionality, engagement, and quality of life. The data of comparative effectiveness available on a drug-class basis lack in the necessary subgroups of older adults with multimorbidity, among chronic kidney disease patients, and when they are taking more than two interacting agents. Long-term studies should be done, both gastrointestinal and cardiovascular, but also cognition, falls, frailty curves, and harms with opioids.

In conclusion, the musculoskeletal pain pharmacological management requires setting realistic goals, properly risk stratifying, and non-pharmacological therapies. The answer is a gradual, individualized attitude, where the preferable alternative and unceasing assessment are placed first in order to make the results superior and the amount of adverse events that are preventable is diminished.

## 11. CONCLUSION

Musculoskeletal pain is one of the biggest causes of disability in the world yet the pharmacological treatment of musculoskeletal pain has been characterized by low effectiveness and high safety concerns. As it is constantly demonstrated in the contemporary evidence, there is no single type of drug that could have a universal or lasting effect of relief in all musculoskeletal diseases. The central role of NSAIDs in inflammatory and localized nociceptive pain persists when taken at a minimum dose and duration. Intra-articular treatment and topical formulations are a helpful alternative when the patient is at high risk of the system. The centrally acting drugs such as duloxetine may be effective in few individuals with certain features of central sensitization but the regular use of opioids, especially in acute spinal pain should be evaluated with care due to lack of functional utility and side effects which are depicted by side effects.

Since the musculoskeletal disorders are heterogeneous and as a result, risk-stratified prescribing is necessary instead of stepwise incremental increase. There is a trade-off between expected analgesic benefit and risks to a

patient, including cardiovascular, renal, hepatic, and neurocognitive risks. However, integration of pharmacologic therapy into a broader biopsychosocial model that includes more stress on exercise, education and functional restoration is also significant.

Lastly, the most appropriate care will be administered not through augmenting the intensity of medication but through making sure that the therapy is congruent with the mechanisms, preferences of the patient and safety. The key tenets of responsible and effective pharmacological management of musculoskeletal pain are continual review, deprescribing when appropriate and shared decision making. Top of Form

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