Study Report

Understanding the Long-Term Usage of Etodolac and Perception of S-Etodolac

Version No.: 1.1

The study was conducted according to the approved protocol and in compliance with the protocol, Good Clinical Practice (GCP), and other applicable local regulatory requirements.

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1 INTRODUCTION

Chronic pain is a significant symptom of rheumatic diseases and is also recognized as a standalone disease with extensive biopsychosocial effects [1]. In managing arthritis, the primary approach is often palliative, with nonsteroidal anti-inflammatory drugs (NSAIDs) serving as a cornerstone of treatment [2]. NSAIDs are widely utilized due to their ability to reduce inflammation, fever, and pain [3].

Etodolac, a member of the NSAID class, has shown efficacy in managing pain related to inflammatory arthritis, including rheumatoid arthritis (RA) and osteoarthritis (OA) [4]. Recently, attention has shifted towards S-Etodolac, a unichiral form of the drug, which is believed to offer improved pharmacokinetic and pharmacodynamic properties compared to racemic Etodolac [5].

Understanding healthcare professionals' perceptions and experiences regarding the long-term usage of Etodolac is crucial for optimizing pain management strategies. This study aims to investigate clinicians' perspectives, prescribing patterns, and perceptions concerning the utilization of Etodolac and S-Etodolac. By exploring factors such as patient caseloads, preferred treatment modalities, considerations in NSAID selection, and perceived advantages of unichiral NSAIDs, this study intends to contribute valuable insights into optimizing pain management approaches and enhancing patient outcomes.

2 RATIONALE OF THE STUDY

The rationale for conducting this study stems from the necessity to address gaps in the current understanding of the long-term usage of Etodolac, particularly the perception and utilization of its unichiral form, S-Etodolac, compared to conventional NSAIDs. Despite the widespread use of NSAIDs in pain management, there is limited comprehensive data on healthcare professionals' perspectives, clinical experiences, and preferences regarding the efficacy, safety, and long-term implications of these medications.

Etodolac, as a frequently prescribed NSAID, has established its role in managing inflammatory arthritis-related pain. However, the introduction of S-Etodolac, which is believed to have superior pharmacokinetic and pharmacodynamic properties, necessitates further exploration into its clinical benefits and acceptance among healthcare providers. Understanding these perceptions can provide valuable insights into optimizing pain management strategies and improving patient outcomes.

By investigating clinicians' perspectives, prescribing patterns, and perceptions concerning Etodolac and S-Etodolac, this study aims to fill the knowledge gap and contribute to evidence-based pain management practices. The findings will help in understanding the factors influencing NSAID selection and identifying potential advantages of unichiral NSAIDs, ultimately aiding in the development of more effective and safer pain management protocols.

3 STUDY OBJECTIVE

The study objectives are as follows:

1. To comprehend healthcare professionals' perspectives on the long-term usage of Etodolac.
2. To investigate prescribing practices and clinical experiences related to Etodolac.
3. To assess healthcare professionals' perceptions of S-Etodolac compared to conventional NSAIDs.

4 METHODS

This cross-sectional, questionnaire-based study included healthcare professionals specializing in pain management, rheumatology, and orthopedics. A structured questionnaire comprising 15 questions were utilized to gather information on clinical practice patterns and perceptions regarding the efficacy, safety, and long-term implications of Etodolac and S-Etodolac. Healthcare professionals were invited to participate in the study, ensuring a diverse representation. Participants were briefed about the study objectives and procedures before completing the electronic questionnaire. The study responses were collected anonymously and securely stored to protect participant confidentiality.

Descriptive statistics was used to summarize the demographic information and response frequencies. This study adhered to the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained, and participants had the right to withdraw from the study at any time without consequences.

5 RESULTS

A total of 117 HCPs participated in the survey. Below is the summary of the responses.

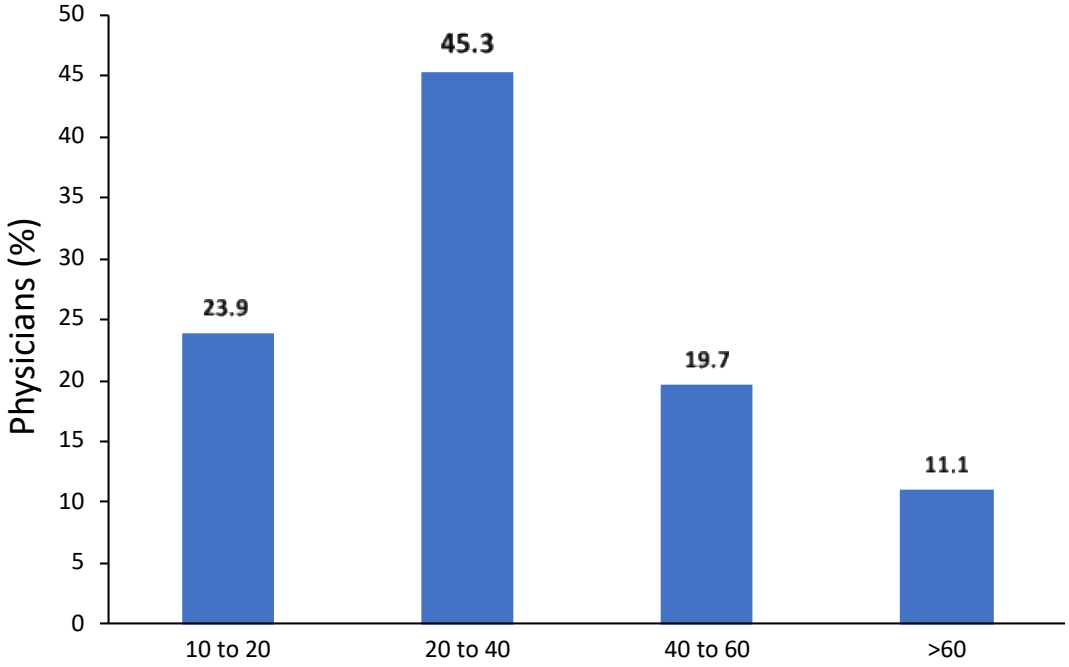
[1] In your clinical practice how many patients with pain do you see per week?

A. 10- 20

B. 20- 40

C. 40 - 60

D. > 60



- A total of 45.3% of physicians attend around 20-40 patients with pain, followed by 23.9% of them attend 10-20 patients with pain
- Around 20% of physicians attend 40-60 patients
- Only 11.1% of physicians attend >60 patients suffering from pain

[2] Which is the most common cause of pain presenting in your clinic?

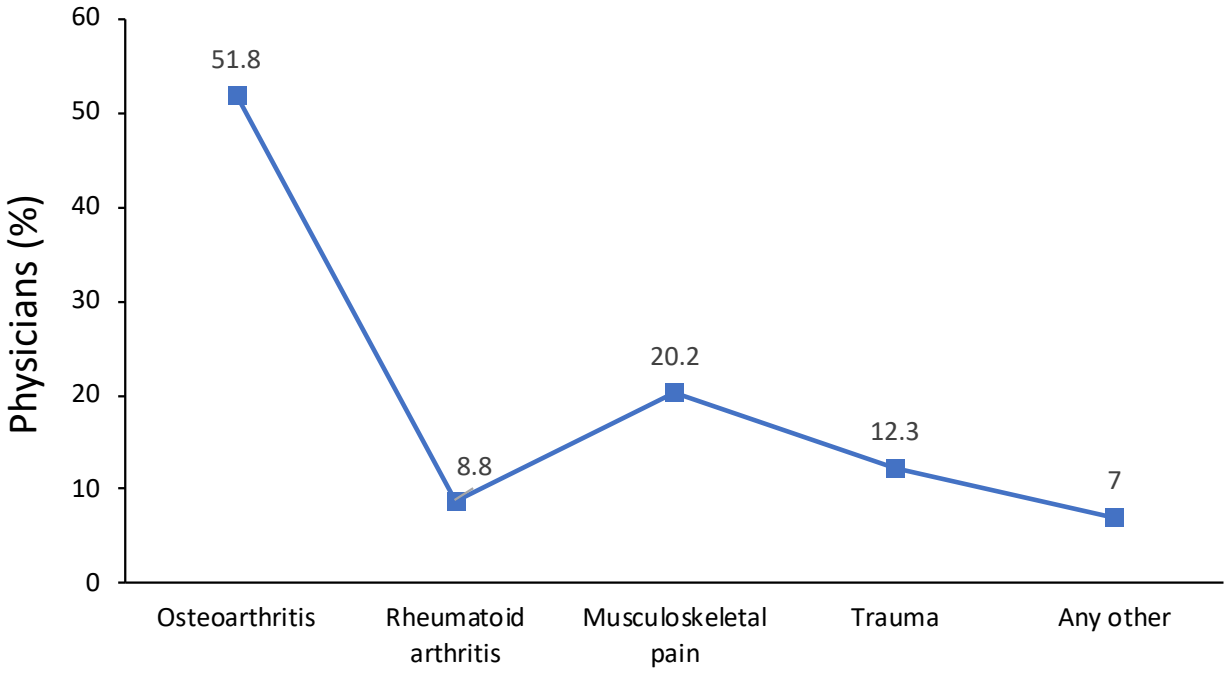
A. Osteoarthritis

B. Rheumatoid Arthritis

C. Musculoskeletal pain

D. Trauma

E. Any other



- Majority of physicians 51.8% reported that OA is the most common cause of pain
- However, some (20.2%) of them reported musculoskeletal pain, 12.3% trauma, 8.8% RA and 7% any other

[3] As per your clinical expertise, what should be the 1st line treatment for the management of pain?

A. Topical NSAID (Topical analgesic gel/Spray)

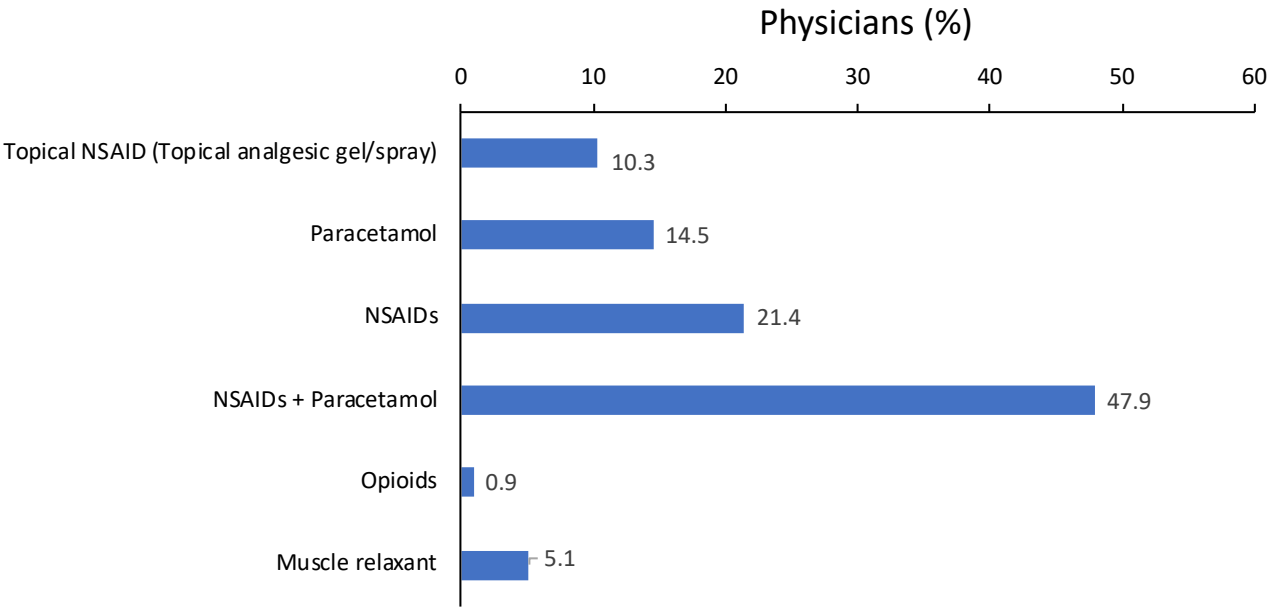
B. Paracetamol

C. NSAIDs

D. NSAID + Paracetamol

E. Opioids

F. Muscle relaxant



- A total of 47.9% of physicians reported NSAID + Paracetamol would be the first line of treatment for the management of pain
- Around 21% of physicians reported NSAIDs, 14.5% reported paracetamol, and 10.3% reported topical NSAID (topical analgesic gel/spray)
- Only 5.1% and 0.9% of physicians reported muscle relaxant and opioids as a first line of treatment for the management of pain, respectively

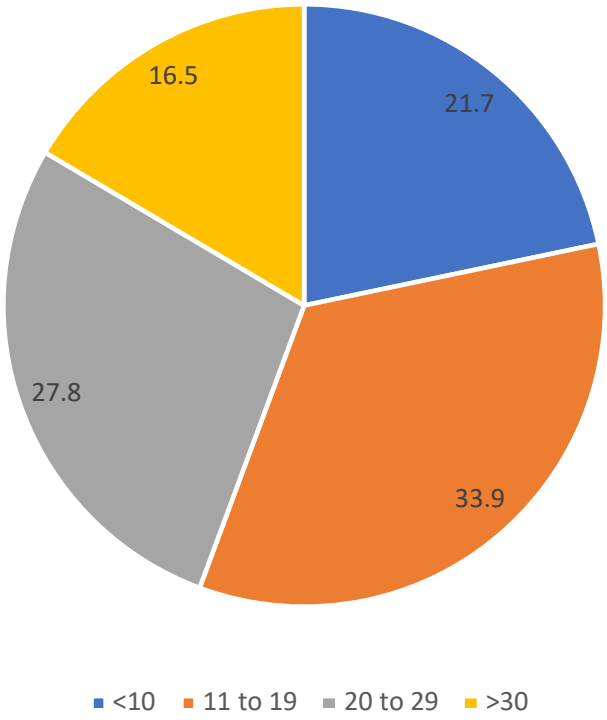
[4] In your clinical practice, how many patients of Osteoarthritis (OA) do you treat in a week?

A. < 10

B. 11 to 19

C. 20 to 29

D. > 30



- Majority of physicians (33.9%) reported that they treat around 11 to 19 patients of OA in a week
- While another 27.8% of them treat 20 to 29 patients, 21.7% treat <10 patients and 16.5% of them treat >30 patients in a week

[5] What attributes do you keep in mind during selection of NSAIDs in patients with OA?

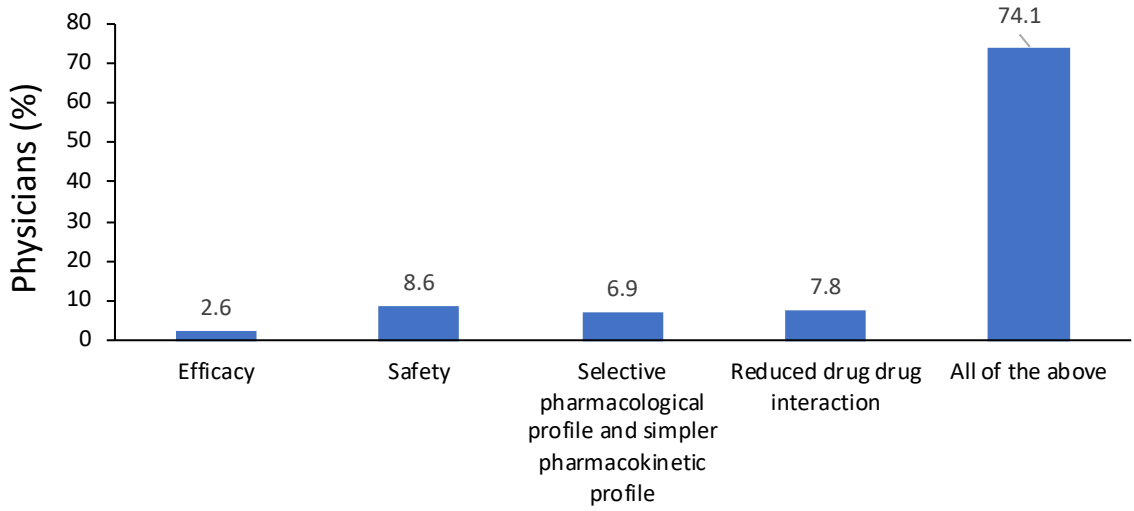
A. Efficacy

B. Safety

C. Selective pharmacological profile and simpler pharmacokinetic profile

D. Reduced drug–drug interactions

E. All of the above



- A total of 74% of physicians believe that it is important to keep in mind the efficacy, safety, selective pharmacological profile and simpler pharmacokinetic profile, and reduced drug-drug interactions during selection of NSAIDs in patients with OA
- While only 8.6% of physicians believe that safety is important that should be kept in mind
- However, 7.8% of physicians believe reduced drug-drug interaction and 6.9% of them believe selective pharmacological profile and simpler pharmacokinetic profile is important
- Only 2.6% of physician believe efficacy of NSAIDs is important to look at for considering patients with OA

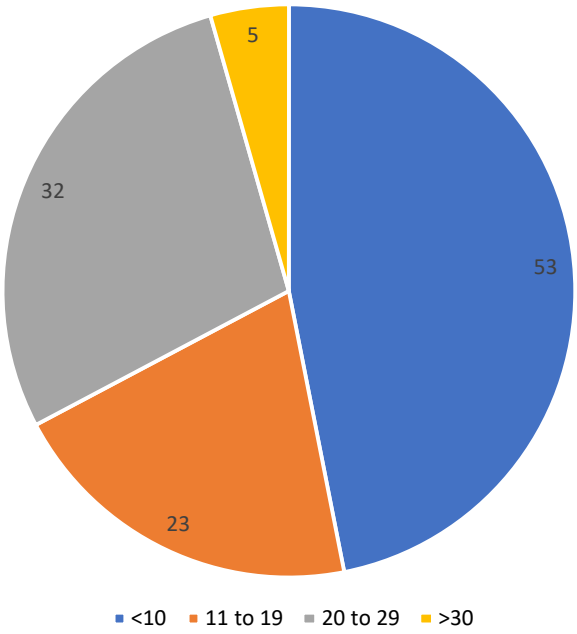
[6] In your clinical practice, how many patients of Rheumatoid Arthritis do you treat in a week?

A. < 10

B. 11 to 19

C. 20 to 29

D. > 30

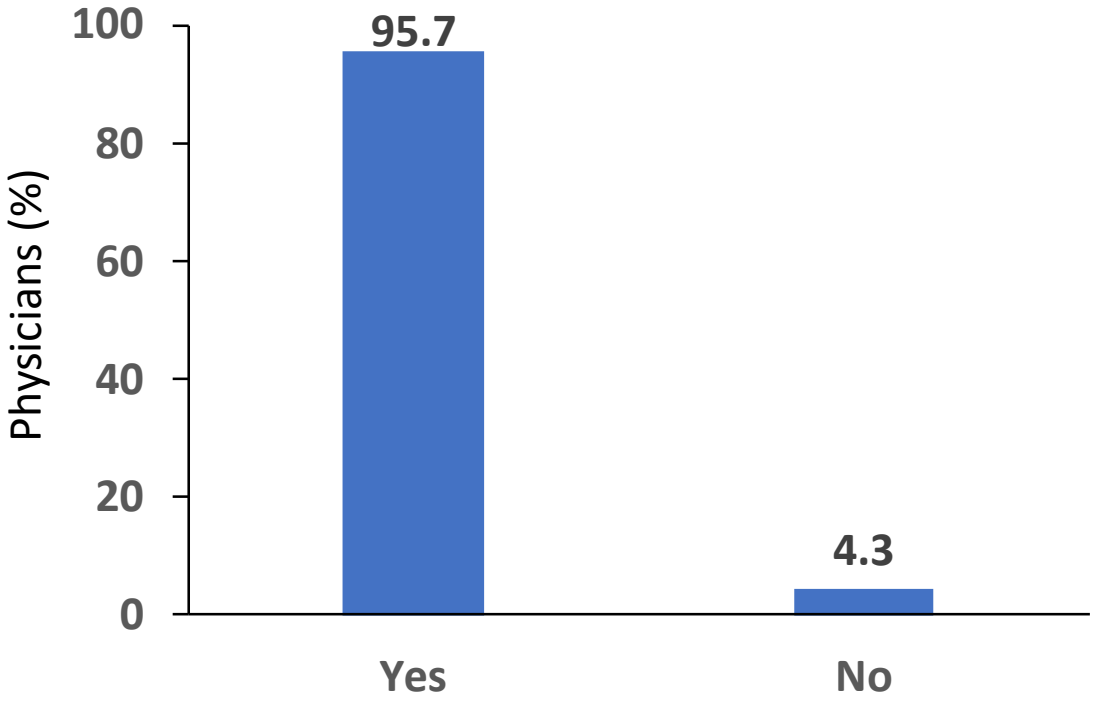


- Majority of physicians (46.9%) reported that they treat <10 patients of RA in a week
- While other 28.3% of them treat 20 to 29 patients
- Around 20% of them treat 11 to 19 patients and only 4.4% of them treat >30 patients in a week

[7] In your clinical practice do you see patients of OA with associated comorbidities?

A. Yes

B. No



- Almost 96% of physicians reported that patients of OA are associated with comorbidities
- However, only 4% of physicians found patients of OA with associated comorbidities

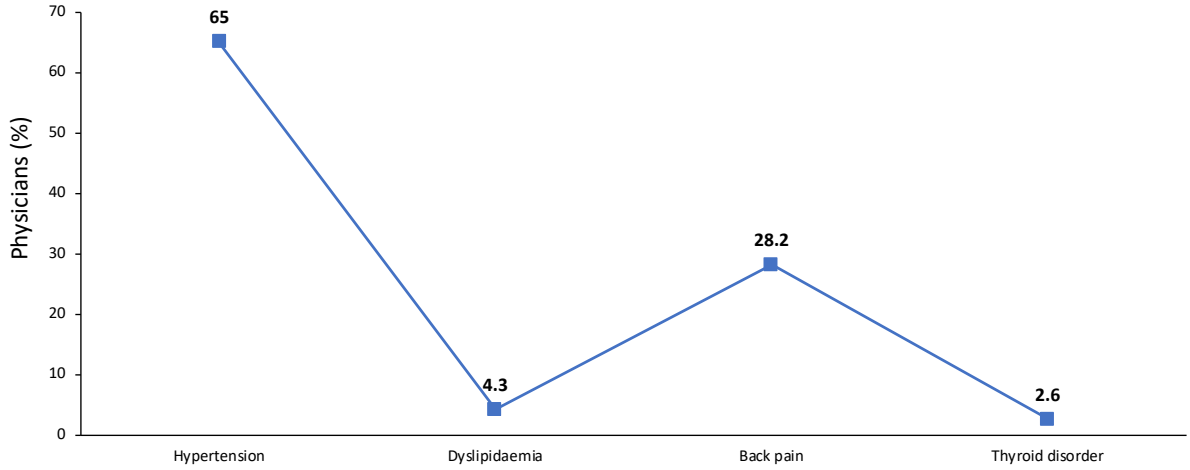
[8] Which co-morbidities are generally associated with osteoarthritis in your patients?

A. Hypertension

B. Dyslipidaemia

C. Back pain

D. Thyroid disorder

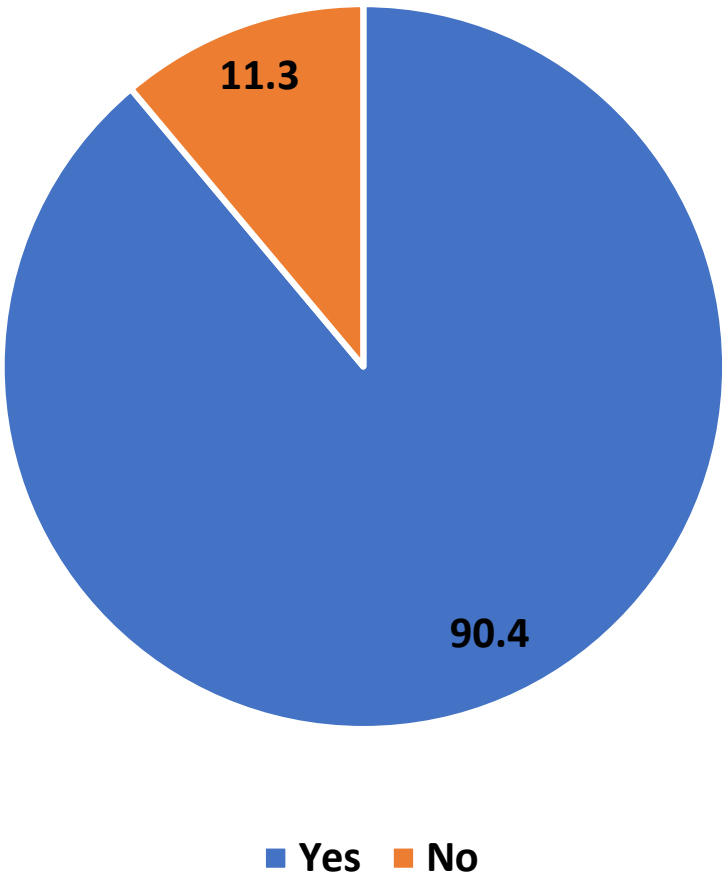


- According to physicians, the most commonly found co-morbidity associated with OA was hypertension (65%)
- However, 28% of physicians found back pain was associated with OA in their clinical practice
- Only 4.3% of them found dyslipidaemia and very few (2.6%) of them found thyroid disorder was associated with OA

[9] In your clinical practice do you prefer unichiral NSAIDS over NSAIDS for pain management?

A. Yes

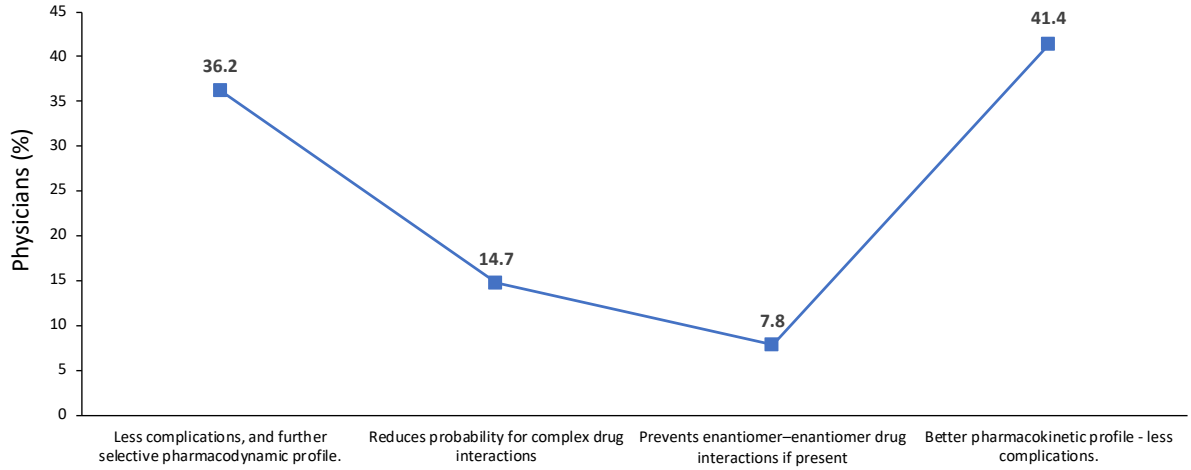
B. No



- Almost 90% of physicians prefer unichiral NSAIDS over NSAIDS for pain management
- However, 11% of them do not prefer unichiral NSAIDS over NSAIDS for pain management

[10] As per your clinical experience what are the advantages of unichiral NSAIDS?

1. Less complications, and further selective pharmacodynamic profile.
2. Reduces probability for complex drug interactions.
3. Prevents enantiomer–enantiomer drug interactions if present.
4. Better pharmacokinetic profile - less complications



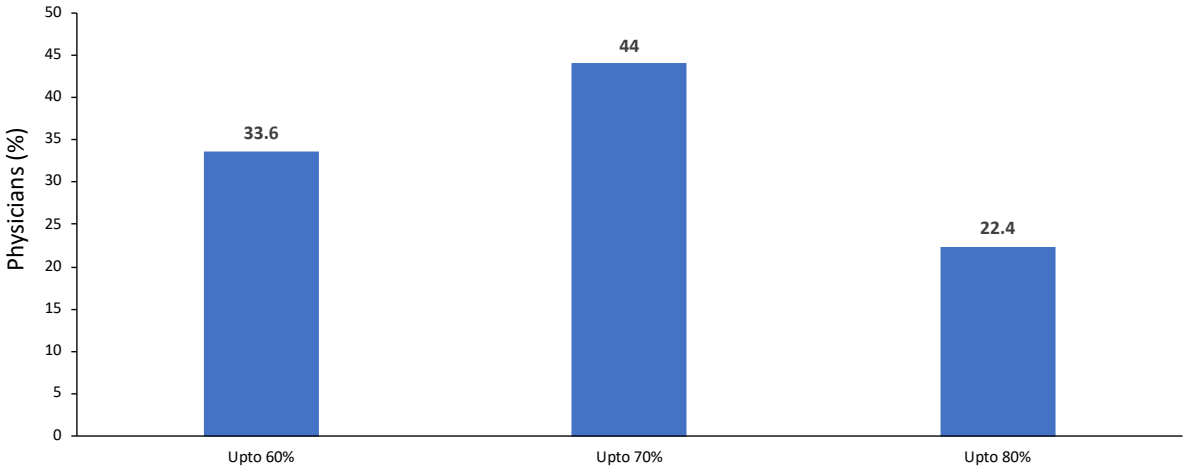
- According to 41% of physicians, the most important advantage of unichiral NSAIDS is better pharmacokinetic profile with less complications
- Around 36% of them reported less complications, and further selective pharmacodynamic profile
- However, 14.7% of them reported the advantage of unichiral NSAIDS is to reduce probability for complex drug interactions and 7.8% reported to prevent enantiomer–enantiomer drug interactions if present

[11] How much reduction in pain intensity do you see with S-Etodolac tablets in patients with OA?

A. Up to 60%

B. Up to 70%

C. Up to 80%



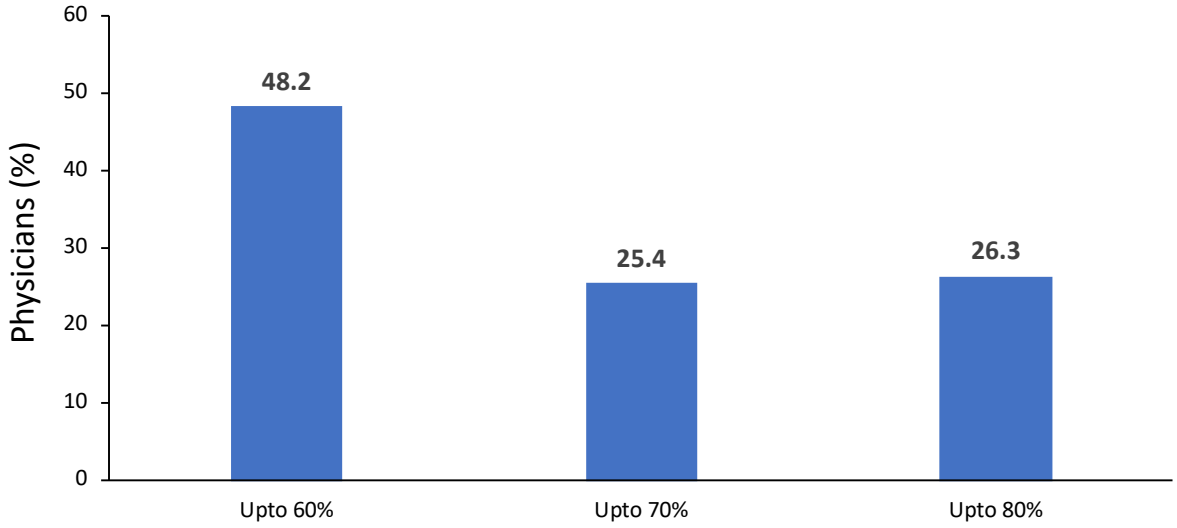
- Majority of physicians (44%) found reduction in pain intensity was upto 70% with S-Etodolac tablets in patients with OA
- Around 34% of them found reduction in pain intensity was upto 60%
- Only 22% of them found reduction in pain intensity was upto 80%

[12] How much reduction in pain intensity do you see with S-Etodolac tablets in patients with Rheumatoid arthritis?

A. Up to 60%

B. Up to 70%

C. Up to 80%



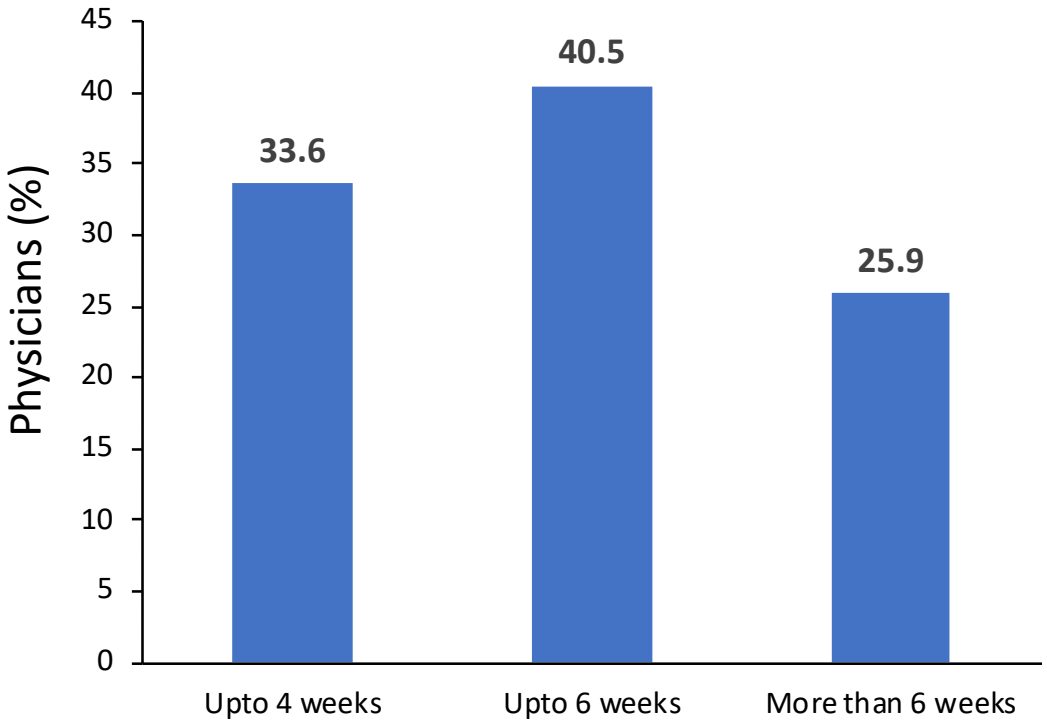
- Majority of physicians (48%) found reduction in pain intensity was upto 60% with S-Etodolac tablets in patients with RA
- Around 25% of physicians found pain reduction was upto 70% and 26% of physicians found pain reduction was upto 80%

[13] In your clinical practice, what is the usual duration required for OA/RA treatment with S-Etodolac?

A. Up to 4 weeks

B. Up to 6 weeks

C. More than 6 weeks



- As per 41% of physicians, the usual duration required for OA/RA treatment with S-Etodolac was upto 6 weeks
- Around 34% of physicians reported the duration to be upto 4 weeks
- And around 26% of physicians reported the duration required in patients with OA/RA with S-Etodolac was more than 6 weeks

[14] What are the benefits of unichiral S-Etodolac over racemic Etodolac as per your clinical practice?

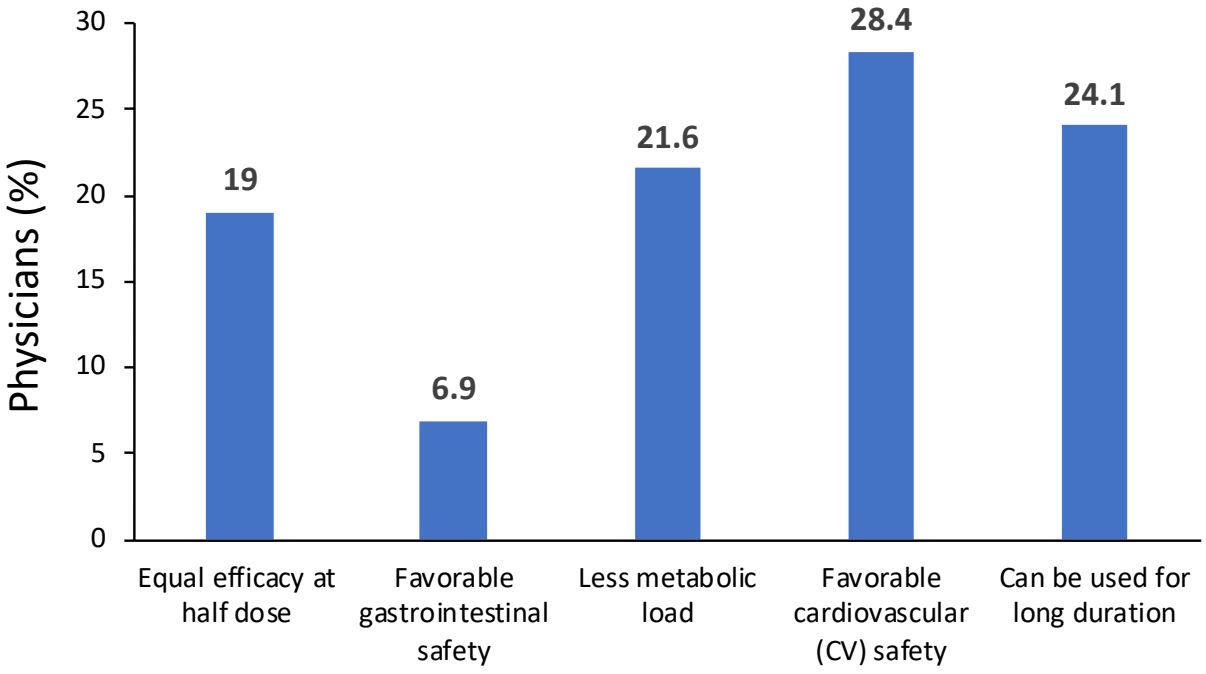
A. Equal efficacy at half dose

B. Favorable gastrointestinal safety.

C. Less metabolic load

D. Favorable cardiovascular (CV) safety

E. Can be used for long duration

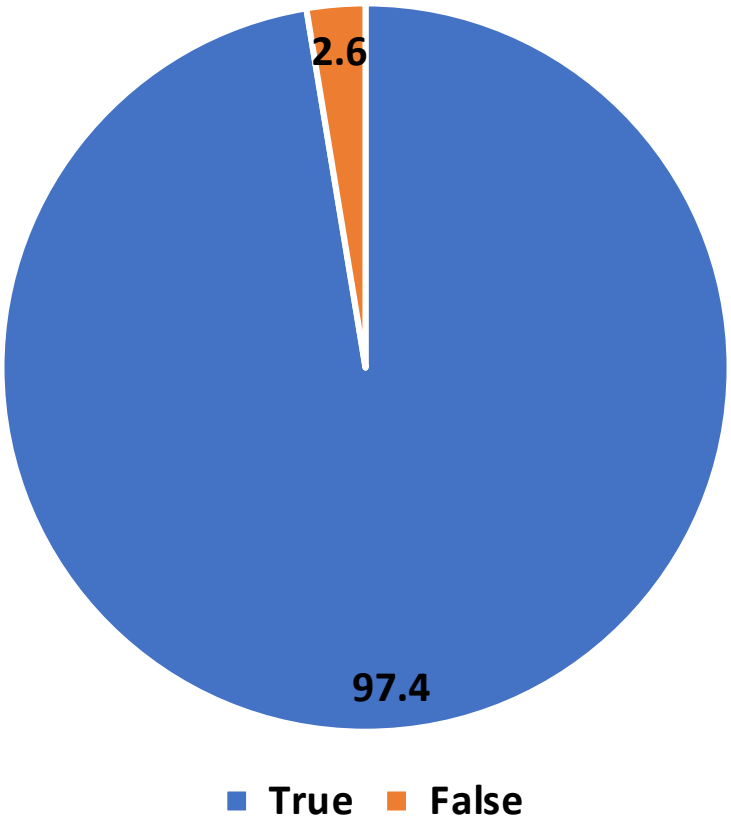


- According to 28% of physicians, the benefits of unichiral S-Etodolac over racemic Etodolac was favorable cardiovascular safety
- Around 24% of them reported unichiral S-Etodolac can be used for longer duration
- Additionally, 21.6% of them reported unichiral S-Etodolac has less metabolic load than racemic Etodolac
- Moreover, 19% of them reported unichiral S-Etodolac has equal efficacy at half dose as compared to that of racemic Etodolac

[15] S-etodolac has a better CV safety profile than conventional NSAIDS

A. True

B. False



- A total of 97.4% of physician reported S-etodolac has better CV safety profile than conventional NSAIDS
- However, only 2.6% of them reported that S-etodolac was not safe as compared to conventional NSAIDS in terms of CV outcomes

6 SUMMARY

The survey revealed that a significant number of physicians (45%) attend around 20-40 patients with pain and around only 11% attend more than 60 patients with pain per week. Additionally, it was revealed that OA was the most common cause of pain. The other cause were musculoskeletal pain, trauma, and RA. The first line of treatment for the management of pain was NSAID + Paracetamol. However, the less preferred treatment was muscle relaxant and opioids. Majority (34%) of physicians treat 11 to 19 patients of OA per week; however, only 17% of physicians treat more than 30 patients per week. Similarly, around 47% of physicians treat less than 10 patients of RA per week and only 4% of them treat more than 30 patients of RA. Patients with OA are significantly associated with comorbidities

Physicians emphasize efficacy, safety, selective pharmacological and pharmacokinetic profiles, and reduced drug interactions during selection of NSAIDs in patients with OA. The most common comorbidity associated with OA is hypertension. Others are back pain, dyslipidemia, and thyroid disorder. Unichiral NSAIDs preferred by 90% of physicians due to better pharmacokinetic profiles and reduced complications. In clinical practice, unichiral S-Etodolac had better cardiovascular safety and can be used for longer duration as compared to racemic Etodolac. The usual duration required for OA or RA is upto 6 week when treated with S-Etodolac. Around 97% perceive S-Etodolac as safer than conventional NSAIDs in terms of cardiovascular outcomes.

7 DISCUSSION

The present study reveals several key insights into the management of pain by physicians, particularly focusing on OA and RA. Our findings align with and expand upon existing literature. The current survey revealed that a significant proportion of physicians attend to 20-40 patients with pain per week, while only very few of physicians manage more than 60 patients weekly. This patient load reflects the chronic and widespread nature of pain conditions, particularly OA and RA, which are the most common causes of pain reported. This is consistent with the findings by Salaffi et al. (2018), which highlighted the chronic pain mechanisms in inflammatory arthritis, emphasizing the burden on healthcare providers.

The first line of treatment identified in our study is NSAID + Paracetamol, which is in line with current practice guidelines. Interestingly, muscle relaxants and opioids were the least preferred options, suggesting a cautious approach to pain management due to potential side effects and dependency issues. This conservative approach resonates with the findings of Sohail et al. (2023), who reviewed the gastrointestinal impacts of NSAIDs and the importance of gastroprotective strategies.

Osteoarthritis emerged as the predominant cause of pain, with a majority of physicians treating 11-19 OA patients weekly. Comorbidities such as hypertension, back pain, dyslipidemia, and thyroid disorders are significantly associated with OA, underscoring the complexity of managing these patients. The emphasis on the efficacy, safety, selective pharmacological, and pharmacokinetic profiles during NSAID selection is well-supported by Garg et al. (2017), who compared the clinical effectiveness and safety of newer NSAIDs. A noteworthy finding is the preference for unichiral NSAIDs by most of the physicians, attributed to their better pharmacokinetic profiles and reduced complications. Specifically, S-Etodolac was favoured for its cardiovascular safety and suitability for long-term use, as compared to racemic Etodolac. This preference is backed by the expert consensus presented by Prabhoo et al. (2023), which highlighted S-Etodolac's superior safety profile in the Indian context.

The typical duration of treatment for OA or RA with S-Etodolac is up to six weeks, with almost all of the physicians perceiving it as safer than conventional NSAIDs regarding cardiovascular outcomes. This perception aligns with Zvaifler (1989), who reviewed the antiarthritic efficacy and safety of Etodolac, reinforcing its favorable profile. Our study's findings are consistent with and corroborate existing literature on the management of OA and RA. The emphasis on the safety and efficacy of treatment options, particularly NSAIDs, and the careful consideration of patient comorbidities, reflect a comprehensive approach to chronic pain management.

8 CLINICAL RECOMMENDATIONS

The first-line treatment for managing pain in patients with OA and RA should be considered as NSAID + Paracetamol. This combination has been shown to be effective and is preferred by a significant number of physicians. Opioids and Muscle Relaxants should be used cautiously because of their potential for side effects and dependency, opioids and muscle relaxants should be reserved for cases where other treatments have failed or are contraindicated. Unichiral NSAIDs, such as S-Etodolac, should be preferred due to their superior pharmacokinetic profiles, reduced complications, and better cardiovascular safety compared to racemic formulations. When selecting NSAIDs, physicians should consider the patient's comorbidities. For instance, S-Etodolac is recommended for patients with cardiovascular concerns due to its safer profile. The typical duration for treating OA and RA with S-Etodolac is up to six weeks. Physicians should monitor patients regularly to assess the effectiveness and any potential side effects during this period. A comprehensive assessment and management plan addressing the comorbidities is crucial.

Continuous monitoring of comorbid conditions should be integrated into the treatment plan to avoid exacerbation of these conditions due to NSAID use. Physicians should emphasize the efficacy, safety, selective pharmacological, and pharmacokinetic profiles of NSAIDs when selecting treatments for OA and RA. Given that 97% of physicians perceive S-Etodolac as safer than conventional NSAIDs in terms of cardiovascular outcomes, it should be considered especially for patients with pre-existing cardiovascular conditions.

Educate patients about the potential side effects of NSAIDs, the importance of adhering to prescribed treatments, and the need for regular follow-ups to monitor efficacy and side effects. Encourage patients to adopt lifestyle modifications that can help manage OA and RA symptoms, such as weight management, physical activity, and dietary changes. Encourage participation in and support for ongoing research into safer and more effective therapeutic options for OA and RA, particularly focusing on the long-term outcomes of unichiral NSAIDs.

9 CONSULTANT OPINION

Conduct long-term studies to evaluate the efficacy and safety of unichiral NSAIDs like S-Etodolac. These studies should focus on chronic use beyond the typical six-week duration to determine their impact on cardiovascular health and overall patient outcomes. Perform comparative studies between unichiral and racemic NSAIDs to further delineate their pharmacokinetic profiles, therapeutic efficacy, and safety, especially in patients with comorbid conditions. Investigate integrated treatment approaches that address both OA/RA and their associated comorbidities, such as hypertension, dyslipidemia, and thyroid disorders. Developing comprehensive care models can improve patient outcomes and quality of life. Explore the impact of various comorbidities on the progression and treatment response of OA and RA to tailor more personalized treatment plans.

Conduct research that focuses on patient preferences, treatment satisfaction, and quality of life. Understanding patient perspectives can help in developing treatment protocols that are not only effective but also aligned with patient expectations. Study factors affecting patient adherence to prescribed treatments, including NSAIDs, and develop strategies to improve compliance through patient education and support. Investigate the role of complementary and alternative therapies, such as physical therapy, acupuncture, and dietary supplements, in managing OA and RA. These studies can provide insights into holistic treatment approaches that can be used alongside pharmacological treatments. Explore the role of genetic factors in the response to NSAIDs and other treatments for OA and RA. Pharmacogenomic studies can lead to personalized medicine approaches that optimize treatment efficacy and minimize adverse effects based on individual genetic profiles.

Identify biomarkers that can predict treatment response and disease progression in OA and RA. These biomarkers can help in tailoring treatments to individual patients, improving outcomes and reducing trial-and-error approaches. Encourage research into new therapeutic targets and the development of novel drugs for OA and RA. The focus should be on agents that can modify the disease process and offer better safety profiles.

Given the emerging interest in the JAK-STAT pathway as highlighted by Salaffi et al. (2018), further research into inhibitors of this pathway could provide new avenues for treatment. Investigate barriers to accessing effective treatments for OA and RA, particularly in underserved populations. Policies should be developed to ensure equitable access to the latest and most effective treatments. Conduct cost-effectiveness studies of various treatment options to inform healthcare policy and ensure that patients receive cost-effective, high-quality care.

10 MARKET OPPORTUNITIES

There is a significant opportunity to develop and market new unichiral NSAIDs, given their superior pharmacokinetic profiles and reduced complications. Companies can invest in research and development to create NSAIDs that offer better safety and efficacy. Highlighting the cardiovascular safety of unichiral NSAIDs like S-Etodolac can differentiate these products in the market, especially for patients with comorbid cardiovascular conditions. Diagnostic tests that identify genetic profiles to predict NSAID response can be developed and marketed to healthcare providers. Invest in the discovery and commercialization of biomarkers that can predict treatment response and disease progression, enabling more personalized and effective treatment regimens.

Develop and market comprehensive care models that address both the primary condition (OA/RA) and associated comorbidities. These packages can include medication, lifestyle modification plans, physical therapy, and regular monitoring services. Create patient support programs that offer education, adherence support, and lifestyle coaching to improve treatment outcomes and patient satisfaction. Given the concerns about the gastrointestinal side effects of traditional NSAIDs, there is an opportunity to develop and market NSAIDs that are formulated with gastroprotective agents. These products can appeal to patients and physicians seeking safer long-term pain management options.

There is a growing interest in non-pharmacological treatments such as physical therapy, acupuncture, and dietary supplements. Developing and marketing these

therapies as part of a holistic treatment plan for OA and RA can meet the demand for alternative pain management options. Invest in digital health solutions, such as mobile apps and telemedicine platforms, that provide patients with access to physical therapy exercises, diet plans, and real-time consultation with healthcare professionals.

There is a market opportunity for the development of disease-modifying drugs that can alter the progression of OA and RA. Companies can focus on innovative therapies that target specific pathways, such as the JAK-STAT pathway. The market for biologic treatments for RA is expanding. Developing new biologics or biosimilars that offer improved efficacy, safety, or cost advantages can capture a significant market share. Explore opportunities to expand into emerging markets where there is a growing prevalence of OA and RA and an increasing demand for effective pain management solutions. Develop cost-effective treatment options that provide high-quality care at a lower cost, making them accessible to a broader patient population, particularly in low-income regions.

11 MARKET POSITIONING

Position the company as a leader in developing advanced NSAIDs, emphasizing the superior pharmacokinetic profiles and reduced complications of unichiral NSAIDs like S-Etodolac. Highlight the cardiovascular safety and long-term efficacy of these products. Promote the use of diagnostic tests to predict treatment response. Market the company as a provider of comprehensive care models that address both the primary condition and associated comorbidities. Emphasize the integration of medication, lifestyle modification, physical therapy, and monitoring services. Position the company as a patient-centric organization that offers robust support programs, including education, adherence support, and lifestyle coaching to improve patient outcomes and satisfaction.

Promote the company's offerings of complementary and alternative therapies as part of a holistic treatment approach. Position the company at the forefront of digital health innovation by offering mobile apps and telemedicine platforms that provide

patients with comprehensive care solutions and real-time consultation options. Market the company's NSAIDs formulated with gastroprotective agents as safer alternatives for long-term pain management. Emphasize the reduced gastrointestinal side effects and improved patient safety. Position all products with a strong emphasis on safety and efficacy, appealing to healthcare providers who prioritize these factors in treatment selection. Position the company as an educational leader by offering extensive professional education programs that keep healthcare providers informed about the latest advancements in pain management. Highlight efforts in patient education, providing resources that increase awareness about OA and RA, the benefits of various treatment options, and the importance of adherence to prescribed therapies.

Position the company as a key player in expanding access to effective pain management solutions in emerging markets. Highlight efforts to provide high-quality, cost-effective treatments. Promote the longevity and sustained efficacy of the company's pain management solutions, particularly unichiral NSAIDs like S-Etodolac, for long-term use in chronic conditions. Position the company as dedicated to enhancing the quality of life for patients with OA and RA through comprehensive, effective, and safe treatment options.

12 REFERENCES

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