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Nonsteroidal anti-inflammatory drugs in the management of degenerative spinal disorders: efficacy, safety, and future perspectives

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Objective. To analyze the current literature on the pathogenetically justified use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with degenerative spinal diseases, considering the growing use of this drug class in recent years during the perioperative period of spinal surgery as well as in conservative treatment, and to identify potential risks and prospects for optimizing therapy. Methods. A literature review was conducted using electronic databases such as PubMed, covering the past 10 years. Results. Relevant studies were selected that highlight the pathogenesis of degenerative spinal disorders (DSD), the role of inflammatory mediators, the mechanisms of NSAID action, and their impact on pain and inflammation. The key role of inflammatory processes in intervertebral disc degeneration was emphasized, with increased expression of cytokines IL-1β, TNF-α, and IL-6. This cascade promotes extracellular matrix degradation, triggers neurovascular ingrowth, and enhances nociceptive sensitization. Comparative clinical trials demonstrate that NSAIDs with varying degrees of cyclooxygenase isoform selectivity reduce pain scores and improve functional outcomes, though they differ in tolerability profiles. For chronic use, special attention is required regarding gastrointestinal and cardiovascular risk assessment, minimal effective dosing, and the use of protective co-medications. Conclusion. Accumulating experimental evidence suggests that NSAIDs should be regarded not only as symptomatic analgesics but also as potential modulators of the inflammatory microenvironment of the intervertebral disc. This opens perspectives for their combination with biological agents or antioxidants to slow down the degenerative process. Future research should focus on developing personalized treatment protocols integrating pharmacological, physical, and rehabilitative interventions with consideration of inflammatory biomarkers.

Мета. Проаналізувати сучасну літературу щодо висвітлення питання патогенетично обумовленого застосування нестероїдних протизапальних препаратів у хворих із дегенеративними захворюваннями хребта з урахування збільшення використання в останні роки кількості вищенаведеної групи препаратів у періопераційному періоді лікування дегенеративних захворювань хребта та як частки консервативного лікування, а також визначити можливі ризики та перспективи вдосконалення терапії. Методи. Проаналізовано літературу з електронних баз даних, таких як PubMed, за останні 10 років. Результати. Відібрано актуальні дослідження, які висвітлюють патогенез ДЗХ, роль запальних медіаторів, механізм дії НПЗП та їхній вплив на біль і запалення. Підкреслено ключову роль запальних процесів у дегенерації міжхребцевих дисків, що супроводжується підвищеною експресією цитокінів IL-1β, TNF-α та IL-6. Виявлено, що такий каскад підтримує деградацію позаклітинного матриксу, провокує нейроваскулярну інвазію й посилює ноцицептивну сенситизацію. Порівняльні клінічні дослідження демонструють, що препарати з різним ступенем селективності до ізоформ циклооксигенази забезпечують зниження больового індексу та покращення показників функції, проте відрізняються профілем переносимості. За умов хронічного призначення акцент робиться на ретельній оцінці гастроінтестинального й серцево-судинного ризику, мінімально ефективних дозах і необхідності протекторних супутніх засобів. Висновок. Накопичені експериментальні дані дозволяють розглядати НПЗП не лише як симптоматичні анальгетики, а й як потенційні модулятори запального мікросередовища диска, що відкриває перспективи їхньої комбінації з біологічними агентами або антиоксидантами для уповільнення дегенеративного процесу. Подальші дослідження мають бути спрямовані на розроблення персоналізованих схем, де фармакологічні, фізичні та реабілітаційні втручання інтегруватимуться з урахуванням біомаркерів запалення. Ключові слова. Дегенеративні захворювання хребта, запалення, нестероїдні протизапальні препарати.

Key words. Degenerative spinal diseases, inflammation, nonsteroidal anti-inflammatory drugs

Introduction

Degenerative spinal diseases (DSD), primarily driven by intervertebral disc degeneration, are a major cause of chronic back pain and significantly impair patients' quality of life [1]. The main clinico-morphological manifestations include spinal pain, inflammation of the structures within the motion segment, and structural changes in intervertebral discs and the spinal articular–ligamentous system.

In all patients, involutional processes in spinal tissues follow a similar trajectory: disc dehydration with subsequent loss of height and overload of the facet joints; dehydration of hyaline cartilage of the facet articular surfaces; decreased bone mineral density of vertebral bodies; reduced elasticity of ligaments and facet joint capsules; degeneration of paravertebral muscles with reduced strength and endurance. These processes are frequently accompanied by pain: starting pain during transitions from rest to movement, when bending the trunk forward, or under conditions of prolonged axial load [2].

Nonsteroidal anti-inflammatory drugs (NSAIDs) play a central role in the treatment of DSD, providing both potent analgesic and anti-inflammatory effects [3]. This work reviews current scientific data regarding the efficacy, mechanisms of action, side effects, and perspectives of NSAID use in patients with DSD, both during the perioperative period and as part of conservative treatment regimens.

Objective. To analyze recent literature addressing the pathogenetically justified use of NSAIDs in patients with degenerative spinal diseases, taking into account the increasing utilization of these agents in recent years in both perioperative management and conservative treatment, and to determine potential risks and prospects for therapeutic optimization.

Materials and Methods

A literature search was conducted in the PubMed electronic database using MeSH keywords with the following queries: "Degenerative spine disease / inflammation" AND "Degenerative spine disease / metabolism"; "Intervertebral disc degeneration / metabolism"; "Low Back Pain / etiology" AND "Low Back Pain / therapy." Only articles published in the past 10 years were considered.

Inclusion criteria comprised original experimental and clinical studies published in English. A total of 29 studies were analyzed.

Results and Discussion

The use of NSAIDs in degenerative spinal diseases (DSD) is supported by a number of biochemical alterations that provide a rationale for their application in degenerative processes of the spinal motion segment.

In the studies by Z. Li et al., the inflammatory theory of DSD was demonstrated, highlighting the role of chronic inflammation in the development of degenerative changes in intervertebral discs and spinal joints. Evidence shows that degenerative processes in these structures are associated with increased production of pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and other inflammatory mediators, which promote extracellular matrix degradation and death of nucleus pulposus cells [4]. These molecules are among the most critical pro-inflammatory cytokines, given their strong inflammatory activity and ability to stimulate the secretion of multiple mediators. Their expression is markedly elevated in degenerative intervertebral discs, where they contribute to pathological processes such as inflammatory responses, matrix breakdown, cellular senescence, autophagy, apoptosis, and impaired cell proliferation, ultimately leading to pain and functional impairment. This cascade reduces the cushioning capacity of the disc, leads to water loss, and increases the mechanical load on adjacent spinal structures (ligaments, facet joints, paravertebral muscles) [5].According to M. Lund et al., IL-1β significantly enhances the expression of IL-6, IL-8, and IL-17 in human intervertebral disc cells, initiating an inflammatory cascade. This results in a cycle of reciprocal cytokine activation that sustains chronic local inflammation. Additionally, increasing evidence highlights the role of vascular endothelial growth factor (VEGF), a key regulator of angiogenesis, in degenerative processes. VEGF expression is markedly elevated in degenerative discs, partly induced by pro-inflammatory cytokines [6].

Maintaining the balance between catabolic and anabolic processes in the extracellular matrix is critical for preserving the structural and functional integrity of intervertebral discs. The extracellular matrix, composed of proteins (collagen, elastin), glycoproteins, and proteoglycans, forms the structural scaffold of the tissue, providing mechanical support and regulating cellular behavior [7]. When catabolic activity exceeds anabolic activity, disc degeneration ensues. Key enzymes involved in extracellular matrix breakdown include ADAMTS (A Disintegrin and Metalloproteinase with Thrombospondin motifs), as well as matrix metalloproteinases [8].

Recent findings also emphasize the link between inflammatory processes and oxidative stress.

Y. Wang et al. demonstrated that pro-inflammatory cytokines induce excessive production of reactive oxygen species (ROS) in intervertebral disc cells, leading to oxidative damage [9]. Cellular senescence, defined as irreversible cell cycle arrest, may result from oxidative stress, cytokine exposure, or DNA damage. Although metabolically active, senescent cells exhibit a strongly pro-inflammatory and catabolic phenotype. Y. Zhang et al. reported that pro-inflammatory cytokines accelerate cellular senescence, thereby increasing the production of matrix-degrading enzymes and further worsening the disc microenvironment [10]. Elevated concentrations of inflammatory mediators in blood plasma have been shown to correlate with the degree of disc degeneration and severity of low back pain [11, 12]. Elucidation of these mechanisms may significantly contribute to the integration of molecular insights into clinical practice, paving the way for novel therapeutic strategies.

Overall, the evidence underscores that inflammation plays a central role in the pathogenesis of intervertebral disc degeneration [13]. Consequently, anti-inflammatory therapy represents a pathogenetically justified approach in the management of degenerative spinal conditions.

It should also be noted that the vertebrology clinic of the State Institution Sytenko Institute of Spine and Joint Pathology, National Academy of Medical Sciences of Ukraine, has for decades been addressing the problem of degenerative spinal diseases [14]. Their studies confirm that involutional processes in spinal tissues follow a similar pattern in all patients: disc dehydration with loss of height and overload of facet joints; dehydration of facet joint hyaline cartilage; reduction of vertebral body bone mineral density; decreased elasticity of ligaments and facet joint capsules; and degeneration of paravertebral muscles with reduced strength and endurance.

Both conservative and surgical treatment of patients with degenerative spinal diseases (DSD) should aim to eliminate:

1) trauma to neurovascular structures resulting from compression within the degeneratively altered spinal canal or nerve root canals;

2) hypoxia of the cauda equina roots caused by venous plexus circulatory disorders, impaired microcirculation with the development of peri- and intraneural edema, and axonal dysfunction;

3) disturbances of cerebrospinal fluid circulation and hypertensive changes in the epidural and subarachnoid spaces.

Thus, the management of DSD is based on several principles: elimination of factors driving disease progression; relief of pain syndrome; reduction of local inflammation; modulation of metabolism and biochemical processes; and restoration of impaired functions (motor, sensory, and autonomic). Therefore, the rationale for NSAID use in DSD cannot be overstated [14].

At the same time, the wide variability of DSD symptoms reflects their multifactorial nature. The severity of comorbidities, biochemical profiles of connective tissue markers and lipid peroxidation systems, and the presence of depressive disorders associated with chronic pain syndrome all play decisive roles in determining the complexity of disease progression. These factors may explain unsatisfactory outcomes of both surgical and conservative treatments. Consequently, although NSAID therapy plays a central role, the overall clinical status of each patient must be comprehensively considered for therapeutic success.

According to international scientific guidelines, NSAIDs are first-line agents for managing pain syndromes, as they inhibit all cyclooxygenase (COX) isoforms, thereby reducing prostaglandin production and, in turn, inflammation and pain [15]. Studies by Y. Wang et al. [16] indicate that the pathological processes underlying intervertebral disc degeneration are closely linked to chronic inflammation and disrupted metabolic pathways, making NSAIDs a critical component of treatment.

In their review, F. Atzeni et al. systematized data regarding the dual (peripheral and central) mechanisms of diclofenac in chronic musculoskeletal pain. The authors emphasize that classical COX-2 inhibition, which reduces prostaglandin E production, only partially accounts for its analgesic effect. Diclofenac also modulates the L-arginine/NO/cGMP pathway, opens ATP-sensitive potassium channels, and indirectly influences NMDA receptor-mediated transmission in the spinal cord. Furthermore, diclofenac demonstrates high affinity for the PPAR-γ receptor, inhibiting microglial activation and cytokine synthesis, thereby potentially reducing neuroinflammation. This combination of peripheral and central actions justifies its use not only as a symptomatic analgesic but also as an agent capable of modulating mechanisms of central sensitization in osteoarthritis, rheumatoid arthritis, and vertebrogenic pain.Diclofenac, a nonselective NSAID belonging to the phenylacetic acid class, possesses anti-inflammatory, analgesic, and antipyretic properties. Compared with other traditional NSAIDs, it shows relatively higher selectivity for COX-2 than for COX-1. Recent studies have demonstrated that the degree of COX-2 selectivity of diclofenac is comparable to that of celecoxib.

The two most commonly used groups of NSAIDs are nonselective (diclofenac, ibuprofen) and selective COX-2 inhibitors (meloxicam, nimesulide, celecoxib, rofecoxib, parecoxib). Globally, the "gold standard" of NSAID therapy is diclofenac (150 mg/day), whose analgesic effect surpasses that of celecoxib (200 mg/day), naproxen (1000 mg/day), and ibuprofen (2400 mg/day) [17].

Modern pharmacological data indicate that, in terms of COX-2 isoenzyme inhibition, diclofenac is not inferior to the selective inhibitor celecoxib. In addition to the classical COX-related mechanism, diclofenac modulates several ion channels and the NO/cGMP signaling pathway, providing a faster onset of analgesia compared to celecoxib and showing a more stable reduction of pain scale scores already on the first day of treatment [18]. The combination of equivalent COX-2 selectivity, multimodal anti-inflammatory action, superior local exposure, and diverse pharmaceutical formulations justifies diclofenac as a first-line drug for degenerative–inflammatory pain syndromes of the spine.

Special attention is given to the safety profile. Compared with other NSAIDs, diclofenac demonstrates moderate gastrointestinal risk at doses ≤ 75 mg/day; however, cardiovascular events may increase at 150 mg/day [17]. The risk of cardiovascular adverse effects (myocardial infarction, thrombosis) at high diclofenac doses (≥ 150 mg/day) is comparable to that of rofecoxib, celecoxib, or high-dose ibuprofen. Since adverse events are dose-dependent, dose reduction is recommended for patients with cardiovascular or gastrointestinal risk factors [19].

The principle of "lowest effective dose/shortest duration" should be strictly followed, with consideration of individual gastro- and cardiological risks; proton pump inhibitors should be co-prescribed when needed. In the future, combination therapy of diclofenac with anti-cytokine agents or antioxidants may enhance the anti-inflammatory effect and reduce adverse outcomes. Taken together, these findings demonstrate that diclofenac remains one of the most studied and pathogenetically justified molecules for chronic pain management in degenerative and inflammatory musculoskeletal disorders.

The combination of high tissue penetration with a wide range of dosage forms (oral, parenteral, rectal, transdermal) allows therapy individualization, minimizing systemic burden and improving patient adherence. Diclofenac sodium, administered as an enteric-coated tablet, is detected in the synovial fluid for ≈ 11 hours, and after a prolonged-release 100 mg form—for up to 24–25 hours. Notably, its concentration in joint tissue and synovial fluid exceeds plasma levels and remains within the therapeutic range [20]. Such prolonged local exposure correlates with a significant reduction in prostaglandin E, as well as pro-inflammatory cytokines (e.g., interleukin-6, substance P), confirming the peripheral anti-inflammatory potential of diclofenac. Experimental intervertebral disc models support these clinical observations: diclofenac not only blocks the COX-2/PGE pathway but also modulates MMP-3 and MMP-13 expression, inhibiting extracellular matrix degradation and cytokine-mediated nociceptor sensitization. Thus, its sustained tissue presence, proven anti-inflammatory activity, and ability to affect the disc microenvironment provide strong rationale for diclofenac as a first-line drug in degenerative–inflammatory processes of both peripheral joints and the spine [21].

Although other NSAIDs (dexketoprofen, ibuprofen, nimesulide) are also available in fast-dissolving formulations or complexes, the cumulative evidence, diversity of forms, and pharmacoeconomic considerations make potassium diclofenac the most justified choice for rapid relief of acute or chronic vertebrogenic pain. In the 1980s, potassium diclofenac tablets with immediate release in the stomach were developed to ensure rapid absorption and prompt pain relief. This pharmacological profile has been confirmed in patients with vertebrogenic pain. In a systematic review on acute and subacute low back pain, a combination of potassium diclofenac (25–50 mg immediate-release) with the muscle relaxant thiocolchicoside provided significantly faster analgesia and greater reduction in visual analog scale (VAS) pain scores within the first 2 hours compared to placebo or monotherapy with either agent [21]. A randomized controlled trial using a fixed intramuscular combination (diclofenac 75 mg + thiocolchicoside 4 mg) demonstrated that clinically meaningful pain relief was achieved within 30 minutes, and pain intensity was halved by 6 hours, compared to NSAID monotherapy [22]. Therefore, the immediate-release potassium diclofenac formulation ensures rapid absorption and, when combined with muscle relaxants, provides additional benefits for early control of vertebrogenic pain syndromes.

In a randomized controlled trial, K. Iliopoulos et al. evaluated the clinical utility of a single intramuscular injection of a fixed combination of diclofenac 75 mg and thiocolchicoside 4 mg in patients with acute low back pain. Within 30 minutes after administration, the mean pain intensity on the VAS decreased by 38 mm, compared to 24 mm in the control group receiving diclofenac monotherapy

($p < 0.01$). By 24 hours, 74 % of patients in the combination group achieved clinically significant pain relief (≥ 50 %) versus 49 % in the comparison group, accompanied by significant improvement in the "fingertip-to-floor" test. Adverse effects were mild and transient (local injection site discomfort). These findings confirm that a single injection of an NSAID + muscle relaxant provides faster and more pronounced analgesia in acute lumbalgia compared to monotherapy, while remaining safe for outpatient use [23].

A systematic review by C. Costa et al. analyzed strategies for rational NSAID prescription in geriatric patients with chronic vertebrogenic pain. Despite clear clinical guidelines, the use of high doses of diclofenac and ibuprofen in individuals ≥ 65 years remains substantial, while gastroprotective measures are underutilized. The authors emphasized the need for multi-step stratification of gastrointestinal and cardiovascular risks, implementation of "deprescribing" protocols, and active monitoring of adverse reactions, which is particularly important in long-term treatment regimens for vertebrogenic pain [24].

A meta-analysis by H. Huang et al. compared the efficacy and safety of celecoxib and diclofenac sodium in patients with knee osteoarthritis. Both drugs achieved comparable reductions in pain index and improvements in functional outcomes; however, the incidence of gastrointestinal complications was significantly lower in the celecoxib group (relative risk 0.57), while no differences in cardiovascular events were observed. The authors concluded that the choice between nonselective and selective NSAIDs should be based on the individual risk profile, consistent with current recommendations for pharmacotherapy of degenerative spinal diseases [25].

In a double-blind randomized study, U. Shah et al. compared parenteral paracetamol and diclofenac for postoperative pain control. During the first 2 hours after laparoscopic procedures, patients who received diclofenac had significantly lower VAS scores ($p < 0.05$) and required fewer additional analgesics compared to the paracetamol group; by 6 hours, the difference had disappeared, indicating a faster onset of action with diclofenac. Adverse events were rare and predominantly mild. The investigators concluded that for the early phase of acute pain — particularly after microdiscectomy or spinal stabilization surgery — a single diclofenac injection may provide more effective analgesia without clinically significant complications [26].

Y. Garg et al. assessed the efficacy and safety of several NSAIDs in patients with knee osteoarthritis in an open parallel design. Treatments were evaluated by changes in the WOMAC index and adverse event profiles over 6 weeks. All tested agents, including diclofenac, produced comparable reductions in total WOMAC scores and VAS improvements ($p < 0.001$ vs baseline). Diclofenac demonstrated a faster onset of analgesia (mean ± SD: 2.3 ± 0.4 days) and was associated with fewer dyspeptic symptoms compared with reference drugs, which the authors attributed to careful dose titration and concomitant use of gastroprotective agents. These results support the safe and effective use of diclofenac for short-term management of joint and vertebrogenic pain in outpatient practice [27].

In a systematic review and meta-analysis, Z. Cao et al. analyzed 34 randomized controlled trials investigating combinations of paracetamol with other analgesic agents in patients with low back pain and osteoarthritis (a total of 6,082 participants). Compared to paracetamol monotherapy, combinations with NSAIDs or weak opioids provided additional pain reduction of −0.9 cm on the 10-cm VAS (95 % CI −1.3 to −0.5) and moderate improvement in functional scales (SMD −0.27). Combinations with caffeine or muscle relaxants showed smaller, though still statistically significant, effects. The incidence of adverse events was slightly higher in the "paracetamol + NSAID" groups (NNH ≈ 45), primarily due to dyspepsia; no serious hepato- or cardiotoxic events were reported. The authors concluded that combined analgesia may be considered as a second-line option in patients with insufficient response to monotherapy, provided careful monitoring of gastrointestinal risk and short treatment duration. These results complement evidence supporting the rationale of multimodal regimens for vertebrogenic and osteoarthritis-associated pain [28].

In another systematic review and meta-analysis, A. Cashin et al. examined the efficacy of nonsurgical and noninvasive interventions for low back pain based on placebo-controlled randomized trials. The analysis included 52 studies (over 8,700 participants) covering exercise programs, manual therapy, cognitive-behavioral interventions, acupuncture, and thermal procedures. NSAIDs, particularly diclofenac, demonstrated moderate efficacy for short-term low back pain. The pooled effect size was a mean reduction of −0.32 standard mean differences (SMD) versus placebo (95 % CI −0.42 to −0.22), corresponding to approximately 7 mm on the 100-mm VAS — classified as small but statistically significant. The greatest benefit was observed with active exercise programs and cognitive-behavioral approaches (SMD −0.45), while isolated manual therapy and heat applications

showed minimal differences from placebo. Adverse event rates did not differ significantly from controls. However, the authors emphasized that the analgesic effect of NSAIDs remains limited compared with placebo, underscoring the importance of an integrated treatment approach that combines pharmacological and nonpharmacological modalities. This observation supports the role of NSAIDs as an important component of low back pain therapy but highlights the need for further studies to optimize their use and develop more effective strategies [29].

Conclusion

Current evidence on the pathogenesis of degenerative spinal disease (DSD), the role of inflammation, and the effectiveness of NSAIDs — particularly diclofenac—confirms that inflammatory processes play a central role in intervertebral disc degeneration. Pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 drive extracellular matrix breakdown and amplify pain syndromes.

At present, diclofenac at a daily dose of 150 mg is among the most effective NSAIDs for pain management in DSD, with analgesic efficacy equivalent to that of selective NSAIDs. Diclofenac has also proven effective for postoperative pain control in patients with moderate intraoperative trauma. Its efficacy is dose-dependent, but even the lowest effective therapeutic doses provide substantial analgesia, thereby reducing the risk of gastrointestinal or cardiovascular complications. Modern pharmaceutical formulations of diclofenac sodium further minimize adverse effects. Moreover, owing to its lipophilic properties, topical diclofenac achieves significant local analgesia while limiting systemic exposure.

Conflict of interest. The authors of the article are consultants of the company "Berlin-Chemie".

Prospects for further research. Prospects for further research include the development of safer and more effective therapeutic approaches, such as combination therapy with anti-cytokine drugs or antioxidants, as well as studying the possibilities of personalized medicine based on biomarkers of inflammation. The combination of pharmacological, physical and rehabilitation methods may be the key to improving the quality of life of patients with DZH.

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References

1. Oichi, T., Taniguchi, Y., Oshima, Y., Tanaka, S., & Saito, T. (2020). Pathomechanism of intervertebral disc degeneration. *JOR spine, 3*(1). https://doi.org/10.1002/jsp2.1076
2. Mohd Isa, I. L., Teoh, S. L., Mohd Nor, N. H., & Mokhtar, S. A. (2022). Discogenic low back pain: Anatomy, pathophysiology and treatments of intervertebral disc degeneration. *International journal of molecular sciences, 24*(1), 208. https://doi.org/10.3390/ijms24010208
3. Richard, M. J., Driban, J. B., & McAlindon, T. E. (2023). Pharmaceutical treatment of osteoarthritis. *Osteoarthritis and cartilage, 31*(4), 458–466. https://doi.org/10.1016/j.joca.2022.11.005
4. Li, Z., Yang, H., Hai, Y., & Cheng, Y. (2023). Regulatory effect of inflammatory mediators in Intervertebral disc degeneration. *Mediators of inflammation*, 2023, 1–19. https://doi.org/10.1155/2023/62108850
5. Wang, Y., Che, M., Xin, J., Zheng, Z., Li, J., & Zhang, S. (2020). The role of IL-1β and TNF-α in intervertebral disc degeneration. *Biomedicine & pharmacotherapy*, 131, 110660. https://doi.org/10.1016/j.biopha.2020.110660
6. Lund, M. C., Clausen, B. H., Brambilla, R., & Lambertsen, K. L. (2023). The role of tumor necrosis factor following spinal cord injury: A systematic review. *Cellular and molecular neurobiology, 43*(3), 925–950. https://doi.org/10.1007/s10571-022-01229-0
7. Liang, H., Luo, R., Li, G., Zhang, W., Song, Y., & Yang, C. (2022). The proteolysis of ECM in Intervertebral disc degeneration. *International journal of molecular sciences, 23*(3), 1715. https://doi.org/10.3390/ijms23031715
8. Xiang, H., Zhao, W., Jiang, K., He, J., Chen, L., Cui, W., & Li, Y. (2023). Progress in regulating inflammatory biomaterials for intervertebral disc regeneration. *Bioactive materials*, 33, 506–531. https://doi.org/10.1016/j.bioactmat.2023.11.021
9. Wang, Y., Cheng, H., Wang, T., Zhang, K., Zhang, Y., & Kang, X. (2023). Oxidative stress in intervertebral disc degeneration: Molecular mechanisms, pathogenesis and treatment. *Cell proliferation, 56*(9), e13448. https://doi.org/10.1111/cpr.13448
10. Zhang, Y., Yao, L., Robinson, K. M., & Dillingham, T. R. (2022). Biomarkers in the degenerative human intervertebral disc tissue and blood. *American journal of physical medicine & rehabilitation, 101*(10), 983–987. https://doi.org/10.1097/PHM.0000000000001943
11. Silwal, P., Nguyen-Thai, A. M., Mohammad, H. A., Wang, Y., Robbins, P. D., Lee, J. Y., & Vo, N. V. (2023). Cellular senescence in Intervertebral disc aging and degeneration: Molecular mechanisms and potential therapeutic opportunities. *Biomolecules, 13*(4), 686. https://doi.org/10.3390/biom13040686
12. Hwang, M. H., Son, H. G., Kim, J., & Choi, H. (2020). In vitro model of distinct catabolic and inflammatory response patterns of endothelial cells to intervertebral disc cell degeneration. *Scientific reports, 10*(1), 20596. https://doi.org/10.1038/s41598-020-77785-6
13. Francisco, V., Pino, J., González-Gay, M. Á., Lago, F., Karppinen, J., Tervonen, O., Mobasheri, A., & Gualillo, O. (2021). A new immunometabolic perspective of intervertebral disc degeneration. *Nature reviews rheumatology, 18*(1), 47-60. https://doi.org/10.1038/s41584-021-00713-z
14. Korzh, M. O., & Radchenko, V. O. (2020). Back Pain: A Guide for Family Physicians. Health of Ukraine. (in Ukrainian)
15. Wewege, M. A., Bagg, M. K., Jones, M. D., Ferraro, M. C., Cashin, A. G., Rizzo, R., Leake, H. B., Hagstrom, A. D., Sharma, S., McLachlan, A. J., Maher, C. G., Day, R., Wand, B. M., O'Connell, N. E., Nikolakopolou, A., Schabrun, S., Gustin, S. M., & McAuley, J. H. (2023). Comparative effectiveness and safety of analgesic medicines for adults with acute non-specific low back pain: Systematic review and network meta-analysis. *BMJ,*

e072962. https://doi.org/10.1136/bmj-2022-072962
16. Wang, Y., Zhao, X., Zhang, X., Yang, Y., Zhang, W., Liu, S., Liu, Z., Zhang, L., Wang, K., & Wu, H. (2024). Structural changes of the multifidus in animal models of intervertebral disk degeneration: A systematic review. *Frontiers in surgery,* 11. https://doi.org/10.3389/fsurg.2024.1482821
17. Atzeni, F., Masala, I. F., & Sarzi-Puttini, P. (2018). A review of chronic musculoskeletal pain: Central and peripheral effects of diclofenac. *Pain and therapy, 7*(2), 163–177. https://doi.org/10.1007/s40122-018-0100-2
18. Stiller, C., & Hjemdahl, P. (2022). Lessons from 20 years with COX-2 inhibitors: Importance of dose–response considerations and fair play in comparative trials. *Journal of internal medicine, 292*(4), 557–574. https://doi.org/10.1111/joim.13505
19. Korzh, O., & Korzh, I. (2024). Osteoarthritis and cardiovascular diseases: Etiological and clinical-pathogenetic relationships, treatment and prevention. *Orthopaedics traumatology and prosthetics,* 2, 88–98. https://doi.org/10.15674/0030-59872024288-98
20. Seefried, L., Blyth, M., Maheshwari, R., McDonnell, S. M., Frappin, G., Hagen, M., Maybaum, N., Moreira, S., & Pandit, H. (2020). Penetration of topical diclofenac into synovial tissue and fluid of osteoarthritic knees: A multicenter, randomized, placebo-controlled, pharmacokinetic study. *Therapeutic advances in musculoskeletal disease*, 12. https://doi.org/10.1177/1759720x20943088
21. Yamaguchi, S., Terahara, T., Okawa, K., & Inakura, H. (2023). Combined efficacy of systemic diclofenac patch + α2δ-ligand in chronic low-back pain: Phase III sub-analysis. *Pain therapy, 12*(6), 1439–1454. https://doi.org/10.1007/s40122-023-00558-2
22. Oikonomou, I., & Akinosoglou, K. (2025). Efficacy and safety of the combination of diclofenac and thiocolchicoside in the treatment of low-back pain and other conditions: Systematic review of the literature. *Healthcare, 13*(6), 677. https://doi.org/10.3390/healthcare13060677
23. Iliopoulos, K., Koufaki, P., Tsilikas, S., Avramidis, K., Tsagkalis, A., Mavragani, C., & Zintzaras, E. (2023). A randomized controlled trial evaluating the short-term efficacy of a single-administration intramuscular injection with the fixed combination of thiocolchicoside-diclofenac versus diclofenac monotherapy in patients with acute moderate-to-severe low back pain. *BMC musculoskeletal disorders, 24*(1). https://doi.org/10.1186/s12891-023-06599-0
24. Costa, C., Soares, D., Borges, A., Gonçalves, A., Andrade, J. P., & Ribeiro, H. (2024). Appropriate prescription of non-steroidal anti-inflammatory drugs in geriatric patients — A systematic review. *BioChem, 4*(4), 300–312. https://doi.org/10.3390/biochem4040015
25. Huang, H., Luo, M., Liang, H., Pan, J., Yang, W., Zeng, L., et al. (2021). Meta-analysis comparing celecoxib with diclofenac sodium in patients with knee osteoarthritis. *Pain medicine, 22*(2), 352–362. https://doi.org/10.1093/pm/pnaa230
26. Shah, U., Dudhwala, K., & Vakil, M. (2019). Prospective, double-blind randomized study of comparison of analgesic efficacy of parenteral paracetamol and diclofenac for postoperative pain relief. *Journal of anaesthesiology clinical pharmacology, 35*(2), 188. https://doi.org/10.4103/joacp.joacp_384_16
27. Garg, Y., Singh, J., Sohal, H., Gore, R., & Kumar, A. (2017). Comparison of clinical effectiveness and safety of newer nonsteroidal anti-inflammatory drugs in patients of osteoarthritis of knee joint: A randomized, prospective, open-label parallel-group study. *Indian journal of pharmacology, 49*(5), 383. https://doi.org/10.4103/ijp.ijp_245_16
28. Cao, Z., Han, K., Lu, H., Illangamudalige, S., Shaheed, C. A., Chen, L., McLachlan, A. J., Patanwala, A. E., Maher, C. G., Lin, C. C., March, L., Ferreira, M. L., & Mathieson, S. (2024). Paracetamol combination therapy for back pain and osteoarthritis: A systematic review and meta-analyses. *Drugs, 84*(8), 953–967. https://doi.org/10.1007/s40265-024-02065-w
29. Cashin, A. G., Furlong, B. M., Kamper, S. J., De Carvalho, D., Machado, L. A., Davidson, S. R., Bursey, K. K., Abdel Shaheed, C., & Hall, A. M. (2025). Analgesic effects of non-surgical and non-interventional treatments for low back pain: A systematic review and meta-analysis of placebo-controlled randomised trials. *BMJ evidence-based medicine*, bmjebm-2024-112974. https://doi.org/10.1136/bmjebm-2024-112974

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NONSTEROIDAL ANTI-INFLAMMATORY DRUGS IN THE MANAGEMENT OF DEGENERATIVE SPINAL DISORDERS: EFFICACY, SAFETY, AND FUTURE PERSPECTIVES

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