



Emerging Clinical Concepts in Pain Management of Ehlers-Danlos Syndrome

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Abstract

Purpose of Review Ehlers–Danlos syndrome (EDS) is a congenital connective tissue disorder that is often marked by chronic pain and considerable functional impairment. Pain in EDS is typically multifaceted, involving musculoskeletal, neuropathic, autonomic, and centralized pain components. The present investigation, therefore, aims to examine common pain phenotypes and mechanisms in EDS and to discuss strategies for interdisciplinary pain management briefly.

Recent Findings Recent studies have identified multiple sources of pain etiologies in EDS, including joint instability, repetitive microtrauma, small fiber neuropathy, and dysfunctional central pain processing. There is also growing evidence that nociceptive pain mechanisms and psychological factors may play a role in pain experience. Furthermore, current literature promotes multidisciplinary care models that synthesize physical therapy targeting joint stabilization and neuromuscular control, symptom-specific pharmacologic therapy, and psychological interventions. In addition, recent studies have investigated complementary therapies, including trigger-point injections, that may provide benefit. Despite this, high-quality evidence supporting interventional and specific pharmacologic regimens remains sparse.

Summary EDS pain remains multifaceted and requires an individualized and mechanism-informed approach to treatment. Integrated care models that include rehabilitation, phenotype-guided pharmacotherapy, and behavioral interventions form the bedrock of management. Ongoing research is necessary to refine phenotype-driven treatment strategies further.

Keywords Ehlers-Danlos Syndrome · Neuropathic pain · Physical rehabilitation · Opioid management · Nerve blocks

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Introduction

Ehlers-Danlos syndrome (EDS) is an inherited connective tissue disorder caused by defective collagen biosynthesis, leading to a disorganized extracellular matrix. Current EDS guidelines divide presentations into 13 subtypes, including classical, vascular, and hypermobile subtypes [1]. Additionally, the Beighton score, a 9-point evaluation of generalized joint hypermobility, is often a core component of diagnostic evaluation [2].

The hypermobile subtype of EDS is the most common and is often associated with chronic musculoskeletal pain. Alternatively, the classical and vascular subtypes are characterized by hyperelasticity and vascular abnormalities, respectively. Although EDS is commonly described as a connective tissue disorder, it is now viewed as a multi-system condition including autonomic, neurological, and immunological problems [3].

One of the most common problems seen in patients with EDS is chronic pain. Patients with EDS typically express symptoms of headache, neuropathy, gastrointestinal dysmotility, and disorganized proprioception. These symptoms can cause a significant burden on patients and have a devastating impact on their daily lives. Despite the high incidence of pain seen in Ehlers-Danlos patients, there is still a frequent lack of care about the comfort of these symptoms. Common pain reliefs only target direct pain and fail to address the multisystem condition. An effective approach to the management of this pain consists of phenotype-directed pharmacologic therapy, psychological intervention, and rehabilitation. In this review, we will discuss the mechanisms of pain, clinical pain phenotypes, and pain management seen in patients with EDS.

Methods

To construct our review methodology, we followed established methodological guidelines for narrative reviews in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) framework. We included articles spanning 1992 to March 2026, encompassing both current investigations and pertinent historical data. Our search extended to abstracts, literature, complete manuscripts, consensus statements, clinical practice guidelines, and comparative studies about Ehlers-Danlos pain.

We used PubMed databases through March 2026. Search terms included varying combinations of the following: Ehlers-Danlos pain, neuropathic pain, Ehlers-Danlos pain management, rehabilitation, physical therapy, pain mechanisms, pain phenotypes. All authors independently performed the search and screened abstracts for relevance.

Full manuscripts were subsequently reviewed upon determination of inclusion. Additional references were obtained through snowballing from pertinent manuscripts. Only studies primarily presented in English were included, and final inclusion of studies in the review was based on unanimous agreement. Data abstracted encompassed the publication year, article purpose, study design, study objective, interventions, variables assessed, and principal findings. The literature included was synthesized into thematic categories rather than quantitatively.

Mechanisms of Pain

Connective Tissue Laxity and Mechanical Instability

The disruption of the extracellular matrix in patients with EDS is associated with joint hypermobility and tissue hyperelasticity, leading to altered load transmission in joints and tissues. Repeated injury due to increased ligament laxity and joint hypermobility can lead to ligament stretching and tearing, causing soft-tissue trauma and pain. As the disease progresses, increased muscular compensation is necessary to stabilize the hypermobile joints, which may contribute to fatigue and myofascial pain [4, 5].

Repetitive Microtrauma and Altered Proprioception

Not only are patients with EDS more likely to experience macroscopic injuries, but they also may be vulnerable to microtrauma. Proprioceptive impairment is a common finding in individuals with EDS. Individuals with EDS are less precise in identifying joint positioning than healthy controls [6]. The hyperelasticity observed in EDS also reduces structural support and impairs force transmission [7].

Furthermore, although direct research on repetitive microtrauma in patients with EDS is limited, the combination of altered gait mechanics, impaired proprioception, and abnormal tissue mechanical properties can repeatedly subject tissues to mechanical stress and negatively affect peripheral nociceptive input.

Peripheral and Central Sensitization

In 2022, a study by De Wandele et al. assessed the mechanical and thermal pain thresholds of 20 women with Ehlers-Danlos syndrome compared with 20 healthy control women. The patients with EDS had increased temporal summation of pain and reduced mechanical and thermal pain thresholds [8]. Increased temporal summation of pain is consistent with central sensitization and central pain processing in patients with Ehlers-Danlos.

An earlier study by Di Stefano et al. assessed patients with EDS who also showed increased wind-up ratios and decreased heat and cold pain thresholds [9]. However, these patients with EDS were found to have no somatosensory nervous system damage. These findings are consistent with abnormal central nervous system pain processing rather than large fiber peripheral neuropathy.

It has also been reported that endogenous pain inhibition is reduced in patients with EDS. Patients showed reduced ability to suppress pain during a conditioning stimulus, indicating impaired descending inhibitory control [8]. Together, these findings support altered pain modulation with abnormal central nervous system pain control in patients with Ehlers-Danlos.

Autonomic Dysfunction and Small Fiber Neuropathy

Another contributor to symptom burden in patients with EDS is autonomic dysfunction. In a 2017 study, patients with Ehlers-Danlos demonstrated an increased baroreflex sensitivity and an altered cardiovascular autonomic profile compared with healthy controls [10].

In a 2016 study, patients with EDS underwent structural and functional small-fiber assessments. They were found to have abnormal thermal pain thresholds and reduced intraepidermal nerve fiber density, indicating involvement of thin myelinated and unmyelinated fibers [11]. Dysfunction of these fibers may contribute to autonomic symptoms and impaired thermal sensation in patients with EDS.

The presence of both autonomic abnormalities and small fiber neuropathy suggests that altered autonomic and peripheral nerve signaling may contribute to the persistence of chronic pain in patients with EDS [10, 11].

Mast Cell Activation and Neuroimmune Contributions

A potential contributor to symptoms found in patients with EDS is mast cell activation. By releasing proinflammatory mediators, including histamine, prostaglandins, cytokines, and proteases, mast cells may influence inflammation, connective tissue remodeling, and multisystem effects [12]. While the mechanism remains uncertain, a 2026 study emphasizes that both EDS and mast cell activation syndrome share similar symptoms, including dysautonomia, allergies, and gastrointestinal problems [3].

Overall, the pain seen in EDS is multifactorial. The connective tissue hyperelasticity and joint hypermobility are common causes of dislocations and can also lead to repetitive microtrauma. Impaired proprioception can further

increase the patient's risk of more injuries due to altered gait mechanisms and increased mechanical stress. Defective central and peripheral pain sensitization can lead to decreases in pain inhibition. Autonomic and small fiber neuropathy can impair thermal sensation and contribute to persistent pain. Mast cell activation and neuroimmune mechanisms may contribute to a broad range of symptoms in patients with EDS, although the relationship remains incompletely understood. Collectively, these findings support the multifactorial nature of pain in EDS and the need for improved management strategies.

Clinical Pain Phenotypes

Since the pain in EDS can arise from multiple mechanisms, it is often categorized into several clinical pain phenotypes. These phenotypes help to explain the different ways pain can be present in individuals with EDS. It can also help explain why symptoms may vary among patients. Pain associated with EDS can appear as joint and musculoskeletal pain related to hypermobility, nerve-related pain, headaches, or visceral pain affecting internal organs [13]. The most commonly described phenotypes include musculoskeletal pain, headache, and craniofacial pain; neuropathic or widespread pain; and visceral or pelvic pain.

Musculoskeletal Pain

Of those phenotypes, musculoskeletal pain is the most prevalent and earliest symptom reported in individuals with EDS. Musculoskeletal pain is closely associated with joint hypermobility, which occurs when joints move beyond their normal range of motion due to abnormalities in connective tissue. As a result of this increased joint range of motion, joints may become less stable. Increased joint laxity can make some joints more vulnerable to subluxations, dislocations, and repeated minor injuries. The shoulders, knees, and ankles are among the joints most commonly reported as unstable or painful [14]. With repeated strain over time, both the joints and the surrounding muscles may develop chronic pain. In addition to joint pain, many affected individuals experience myofascial pain, characterized by tenderness in the muscles and surrounding connective tissue. Trigger points in these muscles can cause pain in a specific spot or spread to other parts of the body. Many people with EDS also experience axial pain in the spine, neck, and lower back, which may result from spinal instability and increased strain on the vertebral joints and surrounding soft tissues. While musculoskeletal pain is the most common phenotype in EDS, pain can also present in other forms, including headaches and craniofacial pain.

Headaches and Craniofacial Pain

Headaches and craniofacial pain are also commonly reported in patients with EDS. Migraines tend to occur more in individuals with hypermobile EDS. In fact, Henderson et al. note that people with EDS frequently experience multiple different types of headaches [15]. Cervicogenic headaches are another type of pain that can occur in individuals with EDS. Some people with EDS experience headaches that start in the neck and spread into the head. This may be related to craniocervical instability, where weakened ligaments in the upper neck make the area less stable and can irritate nearby nerves. Other issues, such as temporomandibular joint dysfunction (TMD), can also cause facial pain, including jaw pain, clicking, or difficulty chewing. Related conditions are also common in people with joint hypermobility. For example, JHS is linked to a wide range of coexisting medical conditions, including TMD, cervical disc disease, fibromyalgia, sleep disturbances, and anxiety [16]. Thus, headaches are not the only form of pain experienced by those affected, as some patients also develop neuropathic or widespread pain that involves the nervous system.

Neuropathic Pain

Pain does not always come from joints or muscles alone. It can also show up in forms of neuropathic or widespread pain involving the nervous system. Symptoms can include burning sensations, tingling, numbness, or sharp, shooting pain. Since this type of pain is not always linked to a specific joint or muscle problem, patients may find it difficult to pinpoint the source or clearly describe their sensations. In this regard, pain in EDS is more complex than expected and cannot be explained solely by musculoskeletal problems [17].

Nerve involvement is another source of pain for many patients. This type of pain is often described as peripheral neuropathic, meaning it affects nerves outside the brain and spinal cord. Some individuals with EDS have also been found to develop small fiber neuropathy, a condition that affects the small sensory nerve fibers responsible for detecting pain and temperature. There is also significant overlap between EDS and fibromyalgia. Fibromyalgia is associated with widespread pain, fatigue, and increased sensitivity to pain. This may further contribute to the chronic discomfort experienced by many people with connective tissue disorders.

Visceral and Pelvic Pain

Visceral and pelvic pain are also reported in those with EDS. Abdominal pain, bloating, nausea, and constipation are common gastrointestinal symptoms. Gastrointestinal

dysmotility, in which the digestive system does not move food through the body efficiently, has been linked to many of these symptoms. Research by Hakim and Grahame (2004) found that patients with hypermobile EDS seen in a hypermobility clinic reported gastrointestinal symptoms much more often than age and sex-matched individuals without the condition (37% compared to 11%) [18]. Some individuals with EDS also experience chronic pelvic pain, which is related to connective tissue laxity. These syndromes may be linked to pelvic floor dysfunction or irritation of the pelvic nerves. Since connective tissue is found throughout the body, it can cause problems beyond just the joints.

Pain in EDS can present in several ways.

Although musculoskeletal pain from joint instability is the most common, patients may also experience headaches, nerve pain, widespread body pain, and symptoms affecting the digestive and pelvic systems. Since all these symptoms can occur simultaneously, it is difficult to pinpoint the source of the patient's pain. This is why recognizing the different pain phenotypes associated with EDS is important for improving diagnosis. It also allows us to develop more effective treatments for individuals living with this condition.

Emerging Clinical Concepts in Pain Management

Pain in EDS can be chronic and often disabling. EDS pain often evolves, shifting from instability-driven musculoskeletal nociceptive pain in adolescence to a diffuse and centrally mediated neuropathic pain exacerbated by central nervous system sensitization in adulthood. This progression has been described in multiple literature reviews of the condition [4, 13]. Furthermore, this progression parallels the temporal model of central sensitization proposed by Halili, in which chronic peripheral nociceptive signals can lower pain amplification thresholds and alter responses to treatments [19]. Given this complexity, management strategies must be individualized and specific to the pain mechanism and stage of disease, targeting the multitude of causes, including musculoskeletal, neuropathic, autonomic, visceral, and central sensitization [4, 20, 21].

Non-Pharmacologic and Multidisciplinary Management

Nonpharmacologic Strategies consistently form the foundation of EDS pain management, as numerous reviews point to the efficacy of physical therapy in long-term pain management [20, 22, 23]. One review posits that multidisciplinary models combining physical strengthening with proprioceptive exercises, followed by gentle stretching, are especially effective [22]. In another review discussing the investigation of multidisciplinary approaches, rehabilitation

programs are consistently associated with improvements in pain and function [24]. Notably, however, this is primarily supported by low-level evidence. Lastly, another paper emphasizes gradual exercise progression, avoiding overly aggressive regimens that may exacerbate pain or cause joint dislocation [23]. However, in the context of the temporal model of central sensitization, patients demonstrating diffuse pain amplification may require symptom stabilization prior to progression to strengthening programs [19]. This subset of patients may benefit from interventions including psychologic therapies, activity pacing, and cautiously graded rehabilitation regimens [20, 22, 25]. Furthermore, inter-operator variability in administration limits consistent efficacy.

Myofascial pain presents as a potentially underrecognized component of symptomatic burden in EDS. One case study described the use of myofascial trigger point injections after little improvement from physical therapy for a patient with hEDS and reported a significant reduction in pain [26]. Notably, this report reveals the importance of identifying focal sources of pain within a broader multisystem presentation. Furthermore, another study emphasized that targeted myofascial interventions can provide significant benefit as part of a comprehensive pain management plan [21]. It should be noted, however, that rigorous randomized controlled trials on procedural interventions and EDS remain sparse and should comprise only a small part of a multimodal pain management plan.

Lastly, a few authors have explored the psychological aspect of pain and EDS. One narrative review describes high rates of hypervigilance, illness uncertainty, catastrophizing of pain, and medical invalidation amongst hEDS patients [25]. They further emphasize that cognitive and emotional processes exacerbate disability and the patient's ability to cope with illness. Strategies such as cognitive behavioral therapy and acceptance-based approaches may augment preexisting management strategies even without a reduction in pain intensity. Additionally, another study describing current pain control methods and their efficacy reported the prevalence and potential benefits of complementary behavioral therapies alongside current pain regimens for EDS patients [27].

Pharmacologic Management

Medication management of EDS pain exacerbations largely includes non-opioid analgesics such as acetaminophen, non-steroidal anti-inflammatory drugs, tricyclic antidepressants, and serotonin norepinephrine reuptake inhibitors. Multiple studies, however, have identified adverse effects such as gastrointestinal disturbance, dysautonomia-related symptoms, and mast cell-associated manifestations, which can

hinder widespread use [21, 23]. Importantly, neuropathic pain exacerbated by diffuse hyperalgesia can be addressed with centrally acting agents. Multiple reviews and expert recommendations corroborate the use of serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, and gabapentinoids for the treatment of impaired pain modulation in EDS [4, 20, 23]. However, the paucity of numerous large-scale randomized controlled trials and systematic reviews supporting their use should prompt careful consideration before their implementation into a pain management protocol. Importantly, patients experiencing significant centralized pain sensitization may also experience diminishing analgesic effects from increasing medication doses while remaining susceptible to secondary adverse effects [19]. These options should thus be explored as components of a stage-specific and phenotype-tailored strategy.

Controversially, opiates remain a viable option for EDS-related pain management. One review investigated the use of closely monitored and structured opioid regimens for patients with severe and refractory pain, finding potential benefit for these cases [20]. In contrast, another review discussed variability in patient-reported efficacy of opioid therapy for long-term EDS-related pain [27]. It should be noted, however, that these reviews caution against long-term opioid use due to known risks of tolerance, social implications, and opioid-induced hyperalgesia. Furthermore, it is imperative to assess risks and benefits for each patient before initiation of opiate regimens.

Interventional Approaches

In patients with specific structural or peripheral sources of pain, interventional approaches may be beneficial. Options for interventional procedures include trigger point injections, joint injections, peripheral nerve blocks, radiofrequency ablation, and neuromodulation for refractory cases of pain [20, 21, 26]. However, multiple factors may increase the risk of adverse effects, including tissue fragility, propensity for bruising, and impaired wound healing [23]. Evidence regarding interventional approaches in EDS patients remains extremely limited, however numerous cases of peripheral nerve blocks in patients of varying EDS subtypes have been reported. The distinction between subtypes should prompt additional consideration when evaluating patients for interventional procedures. Namely, patients with the vascular subtype may pose an increased risk for bleeding, arterial rupture, and hematoma formation [28–30]. Additionally, a theoretical risk for decreased block efficacy exists in hEDS patients, with proposed explanations positing that tissue scarring in hEDS patients may inhibit the spread of local anesthesia and that increased vessel permeability permits faster uptake of local anesthetics [30, 31]. A

Table 1 Management approaches for pain phenotypes in Ehlers-Danlos syndrome

Pain Phenotype	Clinical Features	Management Approach
Localized nociceptive musculo-skeletal pain	Joint pain exacerbated by activity, recurrent subluxations, focal tenderness	Targeted physical therapy emphasizing joint stabilization, proprioceptive retraining, and neuromuscular control [13, 20, 22, 23]. Short-term bracing during high-risk activities may be beneficial [13]. Intermittent acetaminophen or NSAIDs for acute flares [21, 23]. Selective image-guided joint injections in carefully selected patients [20, 21].
Myofascial pain	Palpable trigger points, regional muscle tightness, referred pain patterns	Myofascial release and graded strengthening within rehabilitation programs [22, 23]. Trigger point injections as adjunctive therapy in focal refractory cases [21, 26]. Integration within multidisciplinary framework recommended [24].
Axial spine pain	Cervical or lumbar back pain aggravated by posture or prolonged activity	Deep cervical and core stabilizer strengthening with postural retraining [13, 23]. Activity pacing and ergonomic modification [22]. Cautious consideration of facet or sacroiliac interventions in discrete structural pathology [20, 21].
Headache disorders	Migraine or tension headaches, posterior head/neck stiffness; photophobia,	Standard migraine pharmacotherapy according to established guidelines; cervical stabilization therapy in instability-related headache [4, 13]. Selective occipital nerve blocks or procedural interventions in refractory cases [20, 21].
Neuropathic pain	Burning pain, paresthesias, allodynia; small fiber involvement	Serotonin–norepinephrine reuptake inhibitors, tricyclic antidepressants, and gabapentinoids guided by phenotype [4, 20, 23]. Graded activity exposure within multidisciplinary care [22, 24].
Widespread/centralized pain	Diffuse pain, hyperalgesia, fatigue, sleep disturbance	Multidisciplinary rehabilitation emphasizing functional restoration [22, 24]. Centrally acting pharmacotherapy [20, 23]. Cognitive behavioral therapies addressing illness-related distress [25].
Visceral or pelvic pain	Abdominal pain, gastrointestinal-related dysmotility and discomfort, pelvic floor dysfunction	Multispecialty coordination with targeted pelvic floor therapy [21, 22]. Neuromodulatory medications [20]. Integrated management of multisystem pathologies.
Pain flares	Exacerbations related to subluxation, overuse, or stress	Activity modification and bracing [13]. Limited-duration pharmacologic support for flares [21, 23]. Pacing and self-management strategies [22, 27].

case series and additional case report investigated peripheral nerve blocks in EDS patients and no patients in either report developed complications from bleeding or hematoma formation [29, 31]. However, five out of the combined twenty three cases were deemed to have a block failure with all affected patients being of the hypermobile subtype [29, 31]. This preliminary evidence highlights the nuances of interventional approaches for pain relief in EDS patients.

Related to the lack of rigorous randomized controlled trials, definitive recommendations cannot be made at this time, and procedural interventions should be thoroughly discussed with patients in a shared decision-making model. Furthermore, these interventions should complement a comprehensive pain management regimen.

Complementary Therapies and Multidisciplinary Care

Sparse evidence exists for complementary therapies, though they may provide some benefit to patients as adjunctive modalities. Multiple reviews discuss current investigational therapies, including low-dose naltrexone and TENS units, which show some promise [20, 21, 32]. However, further research is necessary before implementation into pain protocols. On the other hand, current literature suggests that a multidisciplinary, longitudinal care model can achieve optimal pain outcomes for EDS patients, resulting in consistent improvements in functional capacity and quality of life [20, 22, 24]. This care must be well coordinated, as fragmented care contributes to poor patient outcomes.

In conclusion, a balanced care plan that includes rehabilitation, phenotype-directed pharmacologic therapy, and psychological interventions is required for optimal patient outcomes, with procedural interventions helping only a minority of patients. Furthermore, physicians must match treatment modalities to the pain phenotypes observed in EDS patients, as summarized in Table 1. Despite growing discussion on the topic, high-quality interventional and pharmacologic trials remain limited and are necessary to bolster recommendations for treatment strategies to optimize longitudinal outcomes.

Recent Updates

In recent years, studies on EDS have evolved as scientists and clinicians have gained a better understanding of connective tissue disorders and the wide variation in symptoms between patients. Many have focused on identifying genetic markers for the hypermobile subtype. The genetic cause of hEDS has not yet been clearly identified, unlike other EDS subtypes that

are linked to specific genetic mutations. Large genetic meta-analyses have been conducted to understand better this condition—one of these projects aimed to identify potential genetic factors in the genomes of 1,815 individuals with hEDS [33]. The authors identified multiple genes with genome-wide significance, including those implicated in neuroimmune and pain signaling pathways, connective tissue zinc transportation, and central nervous system development.

Another notable advancement is a recent pilot randomized trial of the Hypermobile Online Pain Management (HOPE) program. This study examined how an online, self-paced behavioral pain intervention performed on feasibility, acceptability, and appropriateness measures in addition to eight clinical effectiveness outcomes for 70 hEDS patients [34]. The authors report that the program was associated with modest improvements in condition and pain intensity. On the other hand, another retrospective cohort study of 290 EDS patients assessing the efficacy of 17 treatment modalities found that fewer than 30% of hEDS patients showed significant improvement with any of the treatment modalities used [35]. Among the most helpful interventions were physical therapy and targeted exercise, findings that echo those of prior studies on this topic. These studies highlight the persistent challenge of implementing effective pain treatments for EDS and emphasize the importance of individualized care planning for patients.

Other recent studies are beginning to shape future EDS pain care. Small fiber neuropathy and autonomic dysregulation have been implicated in both pain generation and sensory processing mechanisms, in addition to the comorbid presentation of functional neurologic phenomena in many hEDS patients [36, 37]. Evidence for the former stems from a robust retrospective case-control study of 270 hEDS patients examining a litany of outcome measures including validated surveys, autonomic function, cerebrovascular, respiratory, neuropathic, and inflammatory markers [36]. However, the study examining functional neurologic phenomena only examined 24 hEDS patients and assessed for seven functional neurologic signs [37]. Furthermore, a recent scoping review of orthopedic surgery outcomes highlights the dearth of high-quality evidence guiding operative decision-making, underscoring the need for caution when evaluating surgical options for pain relief [38]. Lastly, a newly published review on anesthetic resistance cited increasing rates of anesthetic failure in EDS patients [39]. One revisited potential mechanism was increased vascular permeability precipitating increased systemic absorption, as previously mentioned. However, evidence supporting this theory remains mixed. The review also discusses persistent inflammatory states in tissues that serve to lower extracellular pH, therefore increasing the ionized fraction of anesthetic molecules and decreasing neuronal penetration.

Continued research will provide additional opportunities to better understand EDS mechanisms, contributing to improved diagnoses and more accurate approaches to managing symptoms.

Conclusion

EDS can often cause complex and multifaceted chronic pain in many patients, which can often go unrecognized by physicians. Further understanding of this topic is paramount, as successful pain management requires approaches tailored to patients' pain etiologies beyond traditional musculoskeletal practices. As discussed, EDS pain can arise from a litany of mechanisms, including joint instability, repetitive micro trauma, neuropathic pathologies, and centrally mediated pain sensitization. These mechanisms can present themselves as chronic craniofacial, musculoskeletal, gastrointestinal, neuropathic, and pelvic pain.

Therefore, effective pain management in EDS requires a multidisciplinary approach integrating physical rehabilitation, individualized pharmacologic therapy, and behavioral interventions, with complementary therapies in select cases. Recognizing the diversity of pain phenotypes is paramount, as tailored treatment protocols can improve patient outcomes and reduce long-term disability. Furthermore, future research on the development of stage-specific treatment regimens may provide significant benefit to patients experiencing central pain sensitization. The current literature supports a comprehensive, patient-centered approach to management, but further research is needed to understand pain mechanisms better and refine evidence-based treatment strategies.

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Declarations

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Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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