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Treating pain in patients with Ehlers–Danlos syndrome

Multidisciplinary management of a multisystemic disease

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Abstract

Background: The clinical picture of people with Ehlers–Danlos syndromes (EDS) is complex and involves a variety of potential causes of pain. This poses major challenges to patients and healthcare professionals alike in terms of diagnosis and management of the condition.
Objectives: The aim of the article was to provide an overview of the specific pain management needs of patients with EDS and address their background.
Material and methods: A selective literature search was performed to highlight the current state of research on pain management in EDS patients.
Results: Affected patients require multimodal pain management considering their individual needs, disease-specific features, and comorbidities.
Conclusion: Medical awareness and evidence need to be further improved to enhance the medical care situation of these patients with complex needs.

Keywords
Ehlers-Danlos · Hypermobility · Connective tissue · Analgesia · Pain management

In this article

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Ehlers–Danlos syndrome (EDS) comprises a group of genetic disorders of the connective tissue. While each of the 13 types has distinct features, aspects such as joint hypermobility, skin hyperextensibility, and tissue fragility are seen in variants in all of them (Figs. 1, 2, and 3).

The disorders are inherited in an autosomal recessive or dominant manner, but mutations may also occur de novo. Hypermobile EDS (hEDS) has not yet been associated with a specific gene and is diagnosed clinically. Yet hEDS in particular is comparatively common, with a prevalence of 1:3100–5000 [1].

Impact and course of pain

Ehlers–Danlos syndrome affects connective tissue everywhere in the body, which can directly and indirectly affect almost all organ systems and is often accompanied by pain. Approximately 90% of patients with EDS suffer from chronic pain. In this context, pain is correlated with moderate-to-severe impairment of everyday functions [2] and is a negative predictor for quality of life [3]. Late diagnosis and feelings of helplessness increase the likelihood of severe pain and poor quality of life [4].

The pain character of those affected is complex and shows a dynamic course over the years from initially circumscribed pain localizations with acute origin to a multi-

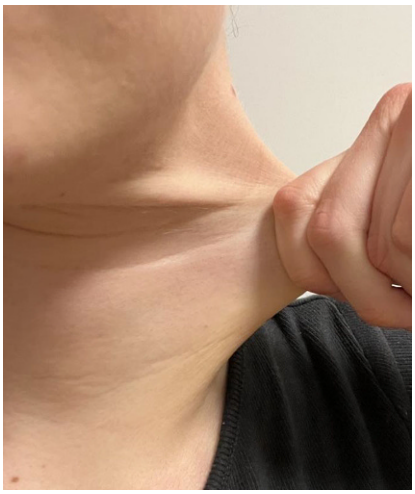

Fig. 1 ▲ Mild skin hyperextensibility in a patient with hypermobile Ehlers–Danlos syndrome

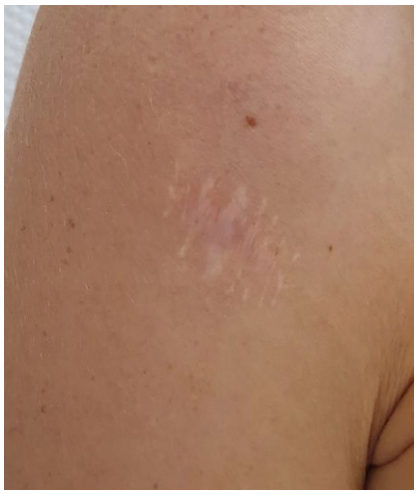

Fig. 2 ▲ Atrophic scarring in a patient with hypermobile Ehlers–Danlos syndrome

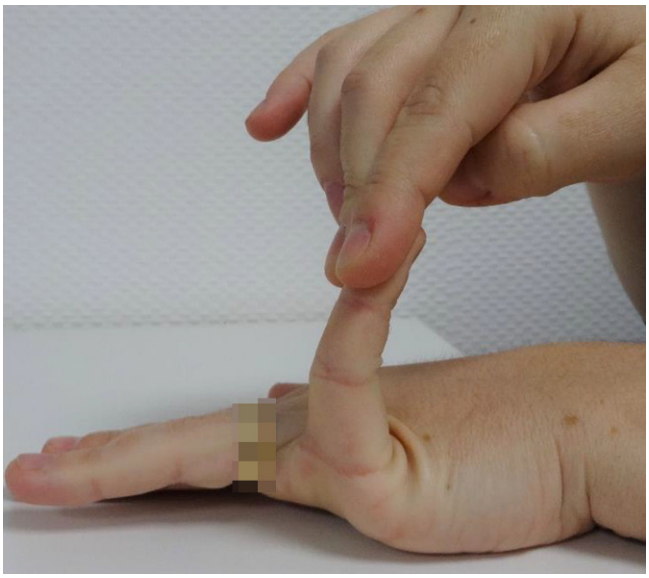

Fig. 3 ◀ Hyperextension of D5 beyond 90°

factorial, generalized, and chronic symptomatology [5].

Children with generalized hypermobility report musculoskeletal pain. Joint pain in general was reported by 67% of children with hypermobility [6]. Patients also remember so-called growing pains or joint injuries as their first pain events [7]. Others suffer from the symptoms of pronounced kyphosis and/or scoliosis [8].

In children, there is a risk that recurrent joint dislocations, tendency to hematoma, and abdominal pain in particular will lead to misdiagnosis of Munchausen by proxy syndrome, child abuse, or behavioral and somatoform disorders [9, 10].

In general, pain in adolescent and adult EDS patients increases over the years and is negatively correlated with the Beighton score, which reflects the extent of generalized hypermobility ([2, 5]; ◘ **Fig. 4**; ◘ **Tables 1 and 2**). At the beginning pain has a primarily nociceptive character, while in the subsequent course central sensitization also plays a role [2, 5, 11]. The causes and localizations of pain are multifold [5].

Causes and types of pain

The severity of musculoskeletal pain in EDS patients is also closely related to the aspect of proprioception. Proprioception is reduced in affected individuals [12] and is correlated with the extent of pain [13].

Different types of headaches are also frequently present in EDS patients. Whereas the diagnosis of migraine is common, there is also a high rate of cervicogenic headaches, as joint instability affects the cervical spine too and can lead to spondylolisthesis or atlantoaxial or craniocervical instability and muscular tension [5, 14, 15]. Temporomandibular joint dysfunction is common in this group of patients and may also be accompanied by headache [16].

» Temporomandibular joint dysfunction is common in EDS patients

Headache in EDS patients may also be caused by Chiari malformations or pathologic cerebrospinal fluid (CSF) pressure [5, 17]. Trigeminal neuralgia, particularly bilateral trigeminal neuralgia, is also strongly associated with the presence of connective tissue disease [18]. Especially in patients with vascular EDS, arterial rupture has to be ruled out when a sudden, new-onset headache occurs [19].

Neuropathic pain is also a common problem in EDS patients [5, 20] and includes nerve compression syndromes, such as intercostal neuralgia, carpal tunnel syndrome, or ulnar nerve syndrome [5, 20, 21]. As a differential diagnosis of thoracic pain, especially in the vascular type, the possibility of spontaneous pneumothorax or intrathoracic aortic dissection should be considered [19].

Small-fiber neuropathy (SFN) is common, as an expression of damage to the terminal Aδ and C fibers [22, 23]. In the case of consistent symptoms with tingling paresthesia, hypesthesia, and burning pain as well as signs of an autonomic dysregulation, an extension of the neurological diagnostic procedure is therefore recommended ([23]; see article on SFN by Maier et al. in this issue of *Der Schmerz*).

Pain in the sacral region as well as in dermatomes S1–5 that increases in the sitting and standing position is a possible sign of symptomatic Tarlov cysts, and often associated with bladder and bowel dysfunction. Symptomatic Tarlov cysts have also been described in association with EDS but in the case of such symptoms, the differential diagnosis should also consider herniated

Fig. 4 ▲ Beighton score to evaluate joint hypermobility [59]. (With permission Ehlers–Danlos Society)

discs, spondylolisthesis, and tethered cord syndrome [24].

Approximately 70% of hEDS patients complain of gastrointestinal pain [25, 26]. This kind of pain is usually aggravated by food intake. Possible causes that occur cumulatively in connection with EDS, in particular in hEDS, are reflux esophagitis, chronic gastritis, gastrointestinal motility disorders, small intestinal bacterial overgrowth, as well as painful flatulence and diarrhea as a result of food intolerance and systemic mast cell activation syndrome (MCAS). However, structural problems may also cause increased abdominal discomfort in affected individuals. These include intra-abdominal vascular compression syndromes (such as Dunbar syndrome, superior mesenteric artery syndrome, nutcracker syndrome, May–Thurner syndrome, and pelvic congestion), visceroptosis, hernias, diverticular disease, rectoceles, and rectal/anal prolapse [10, 27, 28]. Especially in patients with vascular EDS, however, acute abdominal symptoms should always prompt exclusion of intra-abdominal hemorrhage or intestinal rupture [19].

Overall, 71% of biologically female EDS patients also report pelvic pain, which manifests as dysmenorrhea and dyspareunia, among other symptoms [29].

The symptom burden of those affected is further aggravated by frequently occurring concomitant symptoms, some of which are a direct consequence of the underlying disease, while others are of a secondary nature. These phenomena include fatigue, MCAS, sleep disturbances, and autonomic dysfunction with orthostatic intolerance such as postural orthostatic tachycardia syndrome (POTS), impaired gastrointestinal motility, or SFN, leading to anxiety disorders and depression [5, 26, 30].

» The average time to diagnosis is more than 10 years

The complex and often diffuse picture presented to sufferers and medical staff often leads to misdiagnosis and a long medical odyssey for EDS patients [31]. While pain is usually one of the first symptoms, the average time to diagnosis of the underlying disease is more than 10 years [32].

Once the diagnosis is made, patients need support from an interdisciplinary team, including effective and high-quality multidisciplinary pain management [5, 33].

Nonpharmacological treatment of pain

Among the non-drug-based therapies, physiotherapy is indisputably an essential component. Especially for patients with hEDS, several studies have shown a significant effect on pain intensity, proprioception, and quality of life for exercises that aim to improve proprioception [5, 33, 34]. In general, but especially with regard to upper cervical spine instability (UCI), further randomized long-term studies are needed to identify uniform criteria for specific functional limitations and to establish therapeutic standards [33, 35].

» Among the non-drug-based therapies, physiotherapy is an essential component

Experience shows that extreme caution must be used when considering exercise. Exercises or physical therapy performed aggressively lead to micro-trauma and damage to the weak connective tissue. Damaged connective tissue in EDS takes longer to heal. Exercises should be limited to muscle movement with joint loading and well below the individual limit of tol-

Table 1 The Five-Part Questionnaire (*5PQ*) for defining generalized joint hypermobility [8]
One point may be added to the Beighton score if two or more of the following apply:
Can you now (or could you ever) place the hands flat on the floor without bending the knees?
Can you now (or could you ever) bend the thumb to touch the forearm?
As a child did you amuse your friends by contorting your body into strange shapes OR could you do the splits?
As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?
Do you consider yourself double-jointed?

Table 2 Age-adjusted interpretation of the Beighton score [1]	
Age	**Score interpreted as hypermobility**
Prepubertal children and adolescents	6 or higher
Pubertal men and women to age 50	5 or higher
Men and women over the age of 50	4 or higher

erance. Supine exercises or aqua therapy are the recommended modalities.

Somatosensory orthoses also contribute to joint stabilization, pain reduction, and improved proprioception. Central to this is the use of class I compression garments, preferably custom-made. The combination of physiotherapy with compression garments has an even stronger effect than physiotherapy alone [36].

Supportive measures such as transcutaneous electrical nerve stimulation (TENS) units, hypnotherapy and—to address the psychosocial consequences of the disease—cognitive behavioral therapy can be recommended as supportive features. More specific concomitant symptoms and sequelae such as MCAS, intra-abdominal vascular compression syndromes, hernias, endometriosis, and fatigue require additionally an individually adapted therapeutic approach [5, 37].

Obstacles in pharmacological pain treatment

It must be taken into account that aspects such as idiopathic mast cell activation, intra-abdominal compression syndromes, or disturbed peristalsis of the gastrointestinal tract have a significant influence on oral drug therapy: Patients with MCAS tend to have intolerance reactions to drugs, especially to their co-formulants. The use of so-called pure substance preparations (e.g., based on rice starch) should therefore be considered [38, 39]. On the other hand, an impaired absorption capacity of the gastrointestinal tract due to compromised peristalsis reduces the oral bioavailability of drugs [40]. Lastly, the possibility of a pharmacogenetically determined, altered metabolism of analgesics should also be considered in EDS [41, 42]. In practice, it has proven useful to start with low doses and, if possible, to initially avoid combining several substances in order to be able to directly assign unexpected reactions to a specific preparation.

Large-scale randomized case-control studies are still lacking for the use of drug therapy interventions specifically for EDS; therefore, conventional therapy approaches are generally adapted to individual needs [5].

Pharmacological pain treatment

Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used for EDS patients and should be considered primarily for short-term use when pain is inflammatory in nature. In addition to their usual spectrum of side effects, worsening of systemic mast cell activation symptoms is possible [5]. Alternatively, paracetamol (acetaminophen) can be used for mild-to-moderate pain [5, 43].

» The establishment of appropriate inpatient rehabilitation centers would be desirable

Due to its internationally inhomogeneous distribution, no studies are yet available for the use of metamizole in EDS. In the authors' experience, however, a therapeutic attempt with the drug is justified. In addition to the required regular blood count tests, caution is advised in those patients who already suffer from severe orthostatic complaints. In countries with a corresponding drug approval, an attempt with nefopam, a non-opioid centrally acting analgesic, is another option [5].

The tendency for gastrointestinal motility disorders, fatigue, impaired concentration, and circulatory problems (such as POTS) in EDS patients is a relevant factor that could be aggravated by the use of opioids [1, 5]. In the authors' view, it is advisable to critically examine the individual constellation before and during opioid therapy. Furthermore, it is known that the long-term use of opioids can significantly contribute to central sensitization [5, 44], which is a relevant factor in EDS patients anyway [11]. Indeed, approaches with opioid-free anesthesia in patients in general [45], but also in hypermobile patients, resulted in reduced postoperative pain levels [46]. Of note, a study published in *The Lancet* in June 2023 found that opioids showed no significant effect compared with placebos in patients with acute lumbar spine and neck pain in a triple-blind, placebo-controlled trial [47]. On the other hand, there are some case reports of benefit to EDS patients from the temporary use of tramadol [5].

To date, no relevant disease-specific studies are available for the treatment of neuropathic pain in EDS patients. However, since SFN is a common aspect of neuropathic pain in EDS patients [22] it is advisable to follow the recommendations for the treatment of SFN. Therefore, tricyclic antidepressants, anticonvulsants, and norepinephrine reuptake inhibitors are a valid therapeutic option. Special attention should be paid to a possible worsening of phenomena such as orthostatic problems, gastrointestinal complaints, and fatigue in EDS patients during therapy [5].

The successful use of cannabinoids in EDS has already been reported sporadically in the literature [48, 49]. For dystonia, a phenomenon common in EDS [24], there are also indicators of significant symptom improvement with cannabinoid therapy. Interesting in this context are also findings that suggest a positive effect of cannabinoids on symptoms of gastroparesis. At

the same time, potential side effects such as diarrhea, headache, and fatigue should be kept in mind [50].

Two agents that have already shown promising results in the context of chronic regional pain syndrome (CRPS) and other conditions with central sensitization are low-dose naltrexone (LDN; [51, 52]) and ketamine [53, 54].

In addition to its pain-reducing effect, LDN is known to have an immunomodulatory component affecting the lymphocytic immune response, cytokine production, and most likely mast cell activity. As LDN increases endorphin levels and toll-like receptors it may also have an impact on pain and fatigue [55].

In patients with fibromyalgia, the effect of intravenous ketamine administration on chronic pain depends on the frequency and duration of infusions. Repeated, low-dose administrations over a longer period tend to achieve a lasting effect [56]. Low-dose application also aims to prevent side effects such as hallucinations and nightmares. Ketamine is an important aspect of opioid-free anesthesia, for which a significant decrease in postoperative pain after craniocervical fixation compared to opioid-containing anesthesia has already been shown in a small group of hypermobile patients [46]. The antidepressant effect of ketamine may be of additional interest in chronic pain and has most recently led to the approval of esketamine, the S(+) enantiomer of ketamine, as a nasal spray for treatment-resistant moderate or severe depression.

Levodopa/carbidopa or levodopa 50 mg/benserazide 12.5 mg may improve dystonia, pain, and fatigue [5].

Topical use of lidocaine may be considered for localized pain or painful oral mucosa, as well as trigger point infiltration for musculocutaneous pain [5] However, a large proportion of patients with hEDS show insufficient pain inhibition after injection of local anesthetics [57].

Due to its frequent occurrence in EDS and its negative impact on quality of life [29], the presence of gynecological pain should be openly discussed with the patients. If endometriosis or other treatable causes of pain have been excluded or addressed, dysmenorrhea can also be treated by the temporary use of NSAIDs. In the case of persistent symptoms and/or a cycle-dependent worsening of the overall symptoms, the use of a progestogen can be considered [5]. For the treatment of dyspareunia, mast cell therapy, pelvic floor physiotherapy, lubricants, or topical estrogens in combination with hyaluronic acid and benzydamine may be helpful. In extreme cases, gel containing lidocaine may be used before intercourse [5].

In-patient pain management

In addition to outpatient management of EDS patients with the challenging aspects of an adequate multimodal pain therapy, the establishment of appropriate inpatient rehabilitation centers would be desirable. These are already available in France and are able to significantly improve quality of life, fatigue, and functional training capacity [58]. An adaptation of these successful concepts in selected facilities in most countries would be desirable in order to provide access to rehabilitation measures for the individual needs of EDS.

Practical conclusion

- **Patients with Ehlers–Danlos syndrome (EDS) are affected by their disease in many ways, sometimes with severe limitations in terms of quality of life.**
- **Moreover, the clinical picture has long been neglected and patients are still regularly subjected to a medical odyssey for years.**
- **At the same time, some subtypes, such as hypermobile EDS, are quite common for a rare disease, and pain is often an initial symptom.**
- **The authors therefore recommend that all patients with non-specific, chronic, non-localized pain should be screened for the presence of hypermobility using the easy-to-learn and quick-to-implement Beighton score.**
- **If an age-adjusted elevated score is found, appropriate diagnostics should be initiated in order to prevent further loss of quality of life by providing adequate management.**

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Declarations

Conflict of interest. N. Börsch: Member of the Medical–Scientific Board of *Ehlers–Danlos Selbsthilfe* e. V. and has received a lecture honorarium from the Ehlers-Danlos Initiative once in the last 5 years. Prof. Dr. Martin Mücke has received lecture and project fees from Kyowa Kirin, TAKEDA, Chiesi, Sanofi and Boehringer Ingelheim Pharma, which are also active in the field of rare diseases, over the past 5 years. A. Maier: Medical–Scientific Board of the *Deutsche EDS Initiative and POTS und andere Dysautonomien*; research grants: Takeda Pharmaceuticals, Standing Up to POTS Research Fund, Centogene GmbH. Despite these relationships, the authors declare that the data and conclusions presented in this article are objective and independent of these financial relationships. R. Conrad, J.T. Pantel, J. Sellin, K. Mani and P. Chopra declare that they have no competing interests.

For this article no studies with human participants or animals were performed by any of the authors. All studies mentioned were in accordance with the ethical standards indicated in each case.

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Schmerzbehandlung bei Patienten mit Ehlers-Danlos-Syndrom. Multidisziplinäre Versorgung einer multisystemischen Erkrankung

Hintergrund: Das Beschwerdebild von Betroffenen, die an Ehler-Danlos-Syndrom (EDS) leiden, ist komplex und bringt eine Vielzahl potenzieller Ursachen für Schmerzen mit sich. Das stellt Patient:innen und medizinisches Personal vor große Herausforderungen in Hinblick auf Diagnostik und Management der Erkrankung.
Ziel der Arbeit: Über die spezifischen schmerztherapeutischen Bedürfnisse von Patient:innen mit EDS wird ein Überblick gegeben, deren Hintergründe werden thematisiert.
Material/Methoden: Dazu erfolgte eine selektive Literaturrecherche, um den aktuellen Stand der Forschung zum Thema Schmerztherapie bei EDS-Patient:innen zu ermitteln.
Ergebnisse: Betroffene benötigen eine multimodale Schmerztherapie unter Berücksichtigung der individuellen Bedürfnisse, krankheitsspezifischen Besonderheiten und Komorbiditäten.
Schlussfolgerung: Medizinisches Bewusstsein und Studienlage müssen weiter vertieft werden, um die medizinische Versorgungslage dieser Patient:innen mit komplexen Bedürfnissen zu verbessern.

Schlüsselwörter
Ehlers-Danlos · Hypermobilität · Bindegewebe · Analgesie · Schmerztherapie

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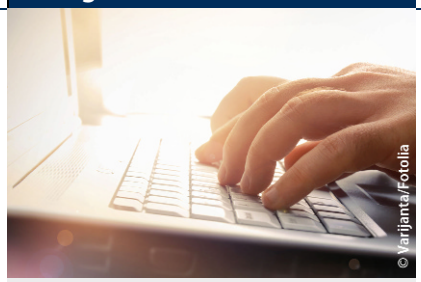

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