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ALTERNATIVE TREATMENTS FOR PAIN MEDICINE (M JONES, SECTION EDITOR)

A Comprehensive Review: Chronic Pain Sequelae in the Presence of Ehlers–Danlos Syndrome

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Abstract

Purpose of Review Patients diagnosed with Ehlers–Danlos syndromes (EDS), and especially those with the hypermobility subtype, often experience a diverse range of acute and chronic pain conditions throughout their lifetime. These can present in a variety of different phenotypes and comorbidities, making it difficult to develop structured treatment protocols. This review seeks to summarize the current literature to address old and novel treatments for EDS.

Recent Findings Historically, medications and surgery have been used to treat patients with EDS but with low efficacy. Newer therapies that have shown promising effects for both decreasing pain and increasing quality of life include physical/occupational therapy, transcutaneous electrical nerve stimulation units, trigger point injections, low-dose naltrexone, and laser therapy. In addition, addressing the psychosocial aspects of pain with EDS through methods like cognitive behavioral therapy and patient education has shown to be vital in minimizing pain. Most research also emphasizes that pain management should not only focus on pain reduction, but on helping reduce symptoms of hypermobility, central sensitization, and fatigue to make an impactful difference.

Summary Research on pain in EDS is still limited with good clinical practice guidelines often limited by poor sample size and lack of clinical studies. Treatment options should be structured based on the specific type of pain pathology and presenting symptoms of each patient and their comorbidities. Future research should attempt to prioritize larger sample sizes, clear definitions of EDS subtypes, randomized trials for treatment efficacy, and more studies dedicated to non-musculoskeletal forms of pain.

Keywords Ehlers–Danlos syndrome · Chronic pain · Hypermobility · Pain medicine · Anesthesiology · Treatments

Introduction

Ehlers–Danlos syndromes (EDS) are "a heterogeneous group of heritable connective tissue disorders (HCTDs) characterized by joint hypermobility, skin hyperextensibility, and tissue fragility" [1••]. Diagnosis can be made on clinical diagnosis and/or genetic testing, often through a primary care physician, geneticist, or pain medicine specialist. Clinical diagnosis includes physical examination checking for abnormal scarring or bruising, signs of skin hyperextensibility, questions regarding past injuries, and an assessment with the Brighton criteria for hypermobility [1••, 2, 3, 4]. The Brighton criteria consists of the Beighton score, which adds points for certain joint mobility maneuvers, in addition to symptoms like joint pain and frequent dislocations [3, 4]. Genetic testing can be used to verify an EDS diagnosis, but a diagnosis is not dependent on it. Most of these tests look at variants for genes encoding collagen, such as COL5A1 that can help distinguish EDS subtypes [1••].

As of 2017, there are 13 subtypes, with hypermobile EDS (hEDS) being the most common [1••, 5]. This subtype is the only one without a clear genetic association and includes criteria with higher general joint hypermobility scores (such as with the Brighton criteria) in addition to manifestations of systemic connective tissue disorder and other confounding disorders. It can be diagnosed more easily if present in a family member as it is mostly inherited as an autosomal dominant disorder [3]. Many patients show symptoms at a

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young age but are not diagnosed until much later in life due to disparate clinical presentations without clear pathological findings including fatigue, pain, and dysautonomia [1••, 6, 7••]. It has also been postulated that this delayed diagnosis is representative of a "prototypical description" for hEDS where the disease course goes through sequential stages of hypermobility, pain, and eventually stiffness, with the pain stage representing the first form of chronic instead of acute pain presentation [3].

The prevalence of chronic pain may be as high as 90% in this population, with higher pain severity being correlated to those with hEDS [6, 7••, 8]. This pain can be acute or chronic, with many experiencing their first episodes at a young age often associated with subluxations and dislocations [7••]. The chronic pain seen in EDS is both nociceptive and neuropathic, presenting as a variety of diagnoses including widespread pain, soft tissue pain, dislocations, joint pain, neuropathic pain, gastrointestinal pain, temporomandibular joint pain, and headaches [7••, 9–11].

The widespread pain experience often has a strong myofascial component that shares pathology with other many centrally mediated pain syndromes, such as fibromyalgia [3, 5, 7••]. Central sensitization, which describes the signal amplification and increased pain severity in widespread hyperalgesia, may play a key role [3, 12–15]. Potentially mediated by endogenous pain inhibitory control, this allows more thorough treatment options than those focused purely on neuropathic pain or as an understanding to the severe pain reports seen in these populations [14].

EDS has known biological markers, but the root cause of different pain phenotypes is still multi-determined. Some complications in understanding it include the loss of proprioception and development of kinesiophobia. Proprioception describes the sense of bodily position, and this loss is common particularly in hEDS [7••, 9]. Studies have shown a bidirectional root for this in predisposition for weaker proprioceptors, while hypermobility and overextension can also weaken or damage them. Kinesiophobia, or the fear of movement, is often developed with chronic widespread pain, fatigue, and hypermobility due to the acute incidents or increased centrally mediated pain that movement can cause [10, 16].

There are also psychosocial factors involved with EDS. It is very common for these patients, and those with chronic pain, to have some psychiatric comorbidities, such as anxiety, depression, attention disorders, autism spectrum disorders, and addiction [6, 17•, 18, 19, 20, 21]. These may be primary or secondary symptoms to the quality of life and physical dysfunction caused by EDS. Ishiguro et al. [17•] review article goes into detail for the genetic and psychosocial correlations between these comorbidities and patients with EDS [17•]. Those with the hEDS subtype, and those with general hypermobility, have an even higher prevalence of psychiatric disorders and neurodivergence [17•, 21–23]. The relationship between the psychosocial factors EDS, pain, and psychiatric illness often leads to lower quality of life (QOL) [10, 20, 24].

The treatment of chronic pain in EDS, and particularly hEDS, is still developing. Complications in establishing good clinical practice guidelines in adults and pediatric populations stem from complicated physiological comorbidities, psychological comorbidities, small sample size (since EDS is classified as a rare disease), lack of sample diversity (female-heavy), poorly understood etiology, and varied individual symptoms [10, 25]. This review seeks to summarize the current literature to address old and novel treatments along with future directions needed in this area.

Traditional Therapies

Many medication options have been used with EDS patients to address the different types of pain phenotypes, but many are ineffective in this patient population or should be used in combination with other management options. Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are prescribed for inflammation reduction with mixed results on their effectiveness [7••, 26•, 27]. Opioids are a common pain management option but shown to have minimal benefit with significant adverse side effects for EDS patients [7••, 26•]. They have not been proven to be helpful in cases of centrally mediated pain and often negatively impact cognitive functioning and memory [7••, 12, 26•, 28]. Medications aimed at neuropathic pain, like tricyclic antidepressants, anticonvulsants, and SNRIs, may help but often worsen dysautonomia or other comorbidities [13, 26•, 27]. Acetaminophen works well in combination therapy to minimize adverse effects of less desirable treatment options, both when prescribed by a physician or advised to take as needed [26•]. Nefopam, originally used under the name fenazoxine as a muscle relaxant, is now commonly given intravenously for the management of post-operative pain [29–32]. Nefopam's pain relief is considered similar to that of NSAIDs and can be used in combination with NSAIDs as well, with one of its most notable factors being its use in the reduction of opioid use [30, 32, 33].

When choosing which medication, it is also important to note the common comorbidities seen with EDS and the interactions these may have. Gastrointestinal issues, mast cell activation syndrome (MCAS), and dysautonomia have symptoms that are worsened by taking NSAIDS, opioids, and steroids [7••, 10, 11, 27, 34]. Many of the psychiatric ones, like anxiety and depression, can also be worsened by certain medications [17•].

Other than medication, most previous treatment has been through surgery, both prior to diagnosis and after. Surgical

options are rarely suggested though due to the systemic nature of EDS and patients' poor healing prognosis. It is sometimes used to correct severe cases of joint instability or for nerve decompression, but that does not address the full spectrum of EDS pain phenotypes [26•, 35]. Alternative treatments often used, such as lidocaine (topical and injected), present conflicting information for efficacy that makes utilizing this with treatment difficult [26•, 27, 34].

Novel Therapies

The use of cognitive behavioral therapy (CBT) for EDS patients can be helpful in managing psychological comorbidities impacting pain and impacted by pain [17•]. It is widely known that poor mental health impacts quality of life and is often associated with pain syndromes. This multidirectional relationship can be from lower QOL due to pain limiting patients' ability to engage in normal activities or it can stem from the hypothesized pain-causing pathology associated with many mental health disorders [6, 17•, 20, 36]. CBT and other similar therapies can help address these psychiatric comorbidities to improve QOL, pain severity, and pain interference connected to EDS or chronic pain [17•, 37].

CBT can be useful in modulating pain catastrophizing and improving a patient's ability to manage pain experiences [12, 13, 19, 28, 38]. In a recent study that divided hEDS patients by high and low anxiety, those in the high anxiety group reported more severe fatigue, increased rates of depressive symptoms, increased pain catastrophizing, increased somatosensory amplification, and a lower overall functioning [18]. This connects to the ways pain can negatively impact cognitive functions [28, 39]. Addressing the neurocognitive impacts of pain, including perception, can help reduce pain scores and pain interference [40]. This was especially helpful in combination with physical therapy [40].

Physical therapy (PT) and occupational therapy (OT) have been shown to be an effective way to decrease pain and increase quality of life for patients with EDS, in addition to minimizing kinesiophobia [9, 10, 24, 26•, 27, 36, 40–42]. Due to joint instability and pain severity, many patients with EDS are wary to begin any intense training program, and even for those that do begin, there is a high dropout rate [3, 42, 43]. Thus, all PT/OT programs should be very carefully titrated and aimed at addressing not only decreasing pain and improving function, but also regulating expectations and increasing autonomy. Fatigue should additionally be considered in training regimens, as common comorbidities, like POTS and dysautonomia, can amplify fatigue and pain [11, 36, 44].

Most PT/OT protocols in the current literature are 4–8 weeks and involve the use of integrated techniques, such as motor imagery and correcting poor proprioception, with high efficacy in EDS, hEDS, and general pain populations [40, 42, 45]. An example of this integration includes what Celletti et al. described as "touch sense," which could include applying pressure with one's hands for contact with specific areas that were described as painful [40]. This was complemented by other adjunct techniques like biofeedback, heat/ice, and chiropractic manipulations [7••, 26•].

Transcutaneous electrical nerve stimulation (TENS) is also helpful in alleviating pain severity with PT [26•]. TENS works to dampen neuropathic pain via both central and peripheral pathways. The research involving TENS overall though is still limited, with the most significant results of its efficacy obtained from patient-reported opinions of treatment options [46, 47]. Recent Cochrane Review articles further highlight the scarcity of research with quantifiable and comparable data for the efficacy of TENS in chronic pain [48, 49]. TENS continues to be an option for EDS patients due to its low side effect profile.

Along with exercise and adjuvants, orthoses (brace, taping, etc.) and energy conservation strategies can be used to help manage pain and joint displacement [9, 26•, 36, 50, 51]. Although there has been clear benefit shown from these techniques and the use of any PT/OT, there are still overall limited randomized studies with varying methods for how to evaluate their effectiveness in this population [42].

There are many new procedure options that have shown promise, although the long-term effects are still unknown and many studies are conducted in more general chronic pain populations. Trigger point injections can address musculoskeletal pain. Steroid injections in peripheral joints can help relieve the arthritic pain caused by joint degeneration, and the local administration of corticosteroids helps reduce the systemic side effects of steroids when compared to oral administration [26•]. Peripheral nerve blocks have also shown positive results in the EDS patient population, both with children and adults, although with potentially higher failure rates and some debated risk for hEDS [7••, 34, 52, 53]. In a 2020 retrospective cohort study, patients received the most benefit from this intervention [26•].

Low-dose naltrexone is a growingly popular mu opioid antagonist being prescribed at doses below its original 50 mg dose for patients unresponsive to opioids or with centrally mediated pain diagnoses [7••, 54, 55]. With more streamlined titration and lower adverse effects, it is a good option for physicians. It can also help in those with mixed nociceptive and neuropathic pain and may even help with mood disorders [7••, 56]. The research involving low-dose naltrexone within a specifically EDS population is severely lacking though, so this data is based on overlapping pain syndromes. Dosing remains variable, and long-term benefits are not understood.

Laser therapy is a non-invasive and painless treatment modality that can be beneficial for patients with EDS to

treat soft tissue pain. Diffuse soft tissue pain is prevalent in the EDS population due to the constant activation of muscles to counter joint laxity and repeated injury in strained tendons and ligaments. Laser therapy utilizes non-ionizing light source in the visible (400–700 nm) and near-infrared (700–1100 nm) electromagnetic spectrum [57]. It helps to increase cellular metabolism, new protein synthesis, reduce inflammation, and improve microcirculation to injured tissue and accelerate the healing process [57, 58]. While there have been no studies looking at the efficacy of laser therapy on EDS patients specifically, it has been shown to be effective in various musculoskeletal disorders that EDS patients often suffer from. In a meta-analysis done by Song et al., the effectiveness of high-intensity laser therapy was evaluated across various musculoskeletal disorders, including cervical and lumbar spondylosis, myofascial pain syndrome, adhesive capsulitis, subacromial impingement syndrome, and lateral epicondylitis. Laser therapy was shown to significantly reduce pain scores and disability scores not only for musculoskeletal disorders overall, but also for different treatment areas [59]. It is a non-invasive treatment with no known significant side effects and can be a good non-pharmacological alternative for pain relief.

In addition to treatment, education for patients about symptom pathology and improvement expectations are vital, particularly since many patients struggle for years to find an accurate diagnosis or have experienced poor healthcare interactions due to a lack of awareness in EDS [6, 19, 20, 24, 60]. Setting realistic goals and timelines improves compliance, which leads to more beneficial symptom relief overall [36, 43]. This includes the psychological symptoms many patients with EDS also face, which can help normalize both the experience of chronic pain and help patients better accept the etiology [17•, 19, 24]. Providing more detailed education to patients like this also helps with their perceived control of their illness and often leads to better patient–physician interactions and improved treatment compliance [37].

Future

Future studies should first focus on EDS subtypes when finding patient populations, with the most common for their pain presentation being hEDS. In addition, research should separate the acute pain from the chronic pain phenotypes, both in developing treatment guidelines and better understanding the pain etiologies. Longitudinal studies may help in these cases to also see if earlier intervention in EDS minimizes the progression of acute to chronic pain later in life. In addition, increases in awareness and education about EDS, its pain expectations, and treatment options are vital for both physicians and patients.

Conclusions

Pain management for patients with Ehlers–Danlos syndromes should not only focus on pain reduction, but on helping reduce symptoms of hypermobility, central sensitization, and fatigue in order to make an impactful difference. Treatment options should be structured based on the specific type of pain pathology and presenting symptoms of each patient and their comorbidities. Future research should attempt to prioritize larger sample sizes, clear definitions of EDS subtypes, randomized trials for treatment efficacy, and more studies dedicated to non-musculoskeletal forms of pain.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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