Retrospective Review

Ehlers-Danlos Syndrome: An Analysis of the Current Treatment Options

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Background: Ehlers-Danlos syndrome (EDS) is a multifaceted disease that can present with a variety of types of pain. Unfortunately, both the mechanisms and treatments for pain are poorly understood. The proposed treatments for the various musculoskeletal pain syndromes in EDS have had variable success, and it becomes much more imperative to better define and evaluate the current treatment modalities in treating this debilitating disease.

Objectives: The purpose of this study was to investigate the currently available treatment modalities for patients with EDS and their efficacies in pain and symptom relief.

Study Design: Retrospective cohort study.

Setting: Institutional physical medicine and rehabilitation primary care clinic.

Methods: All patients were seen between January 2015 and April 2019, in which 98 patients with EDS were identified through retrospective chart review. Institutional review board approval was obtained, and all patients provided written consent to be included in the study. We reviewed various treatment modalities, including complimentary/alternative treatments, opioids/opioid-like medications, nonsteroidal antiinflammatory drugs, physical therapy, occupational therapy, muscle relaxants, neuropathic modulators, steroids, surgery/procedures, and acetaminophen. Treatment methods were extracted from individual patient charts, and efficacy was grouped into 3 categories: improvement, no effect, or worsened symptoms.

Results: The most common treatments used were complimentary/alternative treatments (n = 88). Occupational therapy and bracing were the most effective options with 70% of patients reporting improvement. Neuropathic modulators were the least well tolerated with 47% of patients reporting adverse effects.

Limitations: Men were a small percentage of the study. Patients were not randomized, and pain score reporting was subjective. Patient data were extracted from a single practice setting. Timing and symptom onset were not measured.

Conclusions: There is a relative paucity of published literature regarding the various treatment methods for EDS. Although our study is able to identify positive and negative trends with certain modalities, it is vital to understand that EDS is not a uniform diagnosis among patients, and that a combination of several different treatments usually is needed for optimal symptom control. Further research and investigation are necessary to develop a comprehensive treatment database for this complex condition.

Key words: Ehlers-Danlos syndrome, pain, hypermobility, arthralgia, subluxation, genetic, physical therapy, interventional pain

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Ehlers-Danlos syndrome (EDS) is a multifaceted disease that can present with a variety of types of pain. Unfortunately, both the mechanisms and treatments for pain are poorly understood. At its nature, EDS is a disease of connective tissue causing joint hypermobility through laxity (1). There are several disparate types of EDS, including classic, hypermobile, vascular, kyphoscoliotic, arthrochalasic, dermatosparactic, tenascin X deficient, EDS with scoliosis, myopathy, hearing impairment, and musculocontractural (1). The most common, the hypermobile type (HT), has a higher incidence of pain, which it induces through soft tissue injury. This can lead to joint microtrauma and pain sensitization (2).

Chronic pain is widespread in the EDS population with an incidence of 90% (3). In fact, 75% of patients present with symptoms by age 15 years (4). There is some debate regarding the contributors to pain, but most experts agree that there are both nociceptive and neuropathic components. The nociceptive, joint-related pain is often the first presenting symptom in EDS (5). Joints most commonly affected by EDS, HT in particular, include the neck, shoulders, elbows, hips, knees, and ankles, which may reflect a musculoskeletal distribution of pain (3,4,6). Because EDS is at its origin a connective tissue defect, the extracellular membrane can also be damaged and can contribute to pain (3). At the same time, compression neuropathy can occur owing to deficiencies in collagen in the perineurium and endoneurium (3). Other factors include loss of proprioception that can cause joint instability, muscle weakness, and increased tendon laxity (7). It is especially important to be wary in children, as the unexplained bruising and joint dislocation in EDS can be misdiagnosed as behavioral disorders, Munchausen by proxy, or even child abuse (8).

Other proposed theories explaining EDS pain include connective tissue spasm, nerve entrapment, joint instability secondary to arthritis, central sensitization, generalized hyperalgesia, and chronic regional pain syndrome (6). Central sensitization in the dorsal horn neurons, for one, can occur when persistent nociceptive input damages extracellular membranes (7,9). This can lead to diffuse pain, suggesting that the perceived pain is not necessarily related in proximity to nearby joints (5,7,9). Patients with EDS can also have lower pain thresholds even in pain-free locations, indicating that there may be a degree of central sensitization and that pain is compounded by multiple mechanisms (3). This pain causes severe debility even comparable to that of osteoarthritis, rheumatoid arthritis, and low back pain (10). Patients with EDS in general report higher pain scores, decreased quality of life due to sleep disturbance and increased fatigue, and lower satisfaction in the social setting (4,10,11).

There are 3 distinct phases of EDS. The first "hypermobility phase" presents in the first decade with joint instability and recurrent dislocations (12). During this period, patients can also exhibit coordination/fine motor instability, fatigue, incontinence, developmental dyspraxia, and hypotonia (6). The second "pain" phase presents in the second to third decade with reduced mobility (6,12). This phase is sometimes confused with fibromyalgia and can also present with pelvic pain, headaches, paresthesias, gastrointestinal (GI) disorders, and orthostatic imbalance (6). The final "stiffness" stage, which is seen in the fourth to fifth decade, results from deconditioning and can cause muscle loss, proprioception deficits, and joint damage (3,6).

The proposed treatments for the various musculoskeletal pain syndromes in EDS have had variable success. At the same time, diagnosis is particularly challenging as imaging and other tests, such as electromyelograms, are frequently negative when trying to identify structural causes of pain (6). In the past, EDS-HT has been treated ineffectively by providing symptomatic treatment to each joint individually (4). As a result of the lack of consensus in treatment plans and subsequent delay in treatment, affected patients often live with poorly controlled pain and disrupted quality of life (4). As more and more research is published on this topic, it becomes increasingly evident that a multidisciplinary approach incorporating treatments from different classes would be a more optimal strategy in controlling pain in this population.

Methods

This research was approved by the committee on research ethics at the institution in which the research was conducted in accordance with the Declaration of Helsinki. Institutional review board approval was obtained, and all patients provided written consent to be included in the study. A retrospective chart review was performed for all patients with EDS seen at the Physical Medicine and Rehabilitation Clinic between January 2015 and April 2019. Patients were deidentified. Individual charts were reviewed and information pertaining to different treatment modalities was extracted. Treatment efficacy was grouped into 3 categories:

improvement, no effect, or worsened symptoms. Individual modalities were grouped into several categories: conservative/alternative treatments, physical therapy (PT), occupational therapy (OT), nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen (Tylenol), opioids and opioid-like medications, neuropathic pain modulators, muscle relaxants, steroids, and surgery/procedures. Statistical analysis was performed using GraphPad Prism (GraphPad Software, San Diego, CA) using the Mann–Whitney U test.

Results

A total of 98 patient charts were reviewed. Ages ranged from 18 to 67 years, with a mean age of 37.5 years and standard deviation of 11.8. A total of 94 of the 98 (95.9%) patients were women. Basic demographic information is summarized in Table 1. A total of 76 of the patients carried a diagnosis of EDS-HT. The other 22 patients were classified as follows: classic (n = 1), cardiac valvular (n = 1), and uncharacterized (n = 20).

Pain control methods are summarized in Table 2. The most commonly reported treatment methods were complimentary/alternative treatments (n = 88), summarized in Fig. 1. Other popular treatments include opioids and opioid-like pain medications (n = 87), NSAIDs (n = 65), PT (n = 60), and OT (n = 54). Bracing/OT was most effective with 70% of patients reporting symptom improvement. Neuropathic modulators caused the most adverse effects (47%). Several treatments had high rates of low efficacy; these included acetaminophen (75%) and muscle relaxants (54%). Treatments ordered by most efficacious are summarized in Fig. 2, whereas treatments ordered by most adverse effects are summarized in Fig. 3.

Discussion

There are several considerations when treating EDS pain. In general, exercise programs should focus on improving joint stability and preventing spasms (6). They should also emphasize low resistance and gradually increasing repetitions to avoid injury (6). During exercise, however, patients with EDS should avoid high impact activities, stretch to prevent spasms, and optimize muscle tone and proprioception (6). Although patients are often fearful of overstretching due to joint instability, studies have shown only minimal risk with doing so (6). As with the general population, weight loss techniques, such as aquatic therapy and moderate intensity aerobic exercise, can help ease load off of all, especially weight-bearing, joints (6).

Table 1. *Demographics of 98 patients with EDS*

Number of patients	98
Age (range, mean, standard deviation)	18-67, 37.5, 11.8
Gender	94 female, 4 male
Type of EDS	76 HT, 20 uncharacterized, 1 classic, 1 cardiac valvular

Various studies have investigated the effective treatment modalities at different stages, finding that certain treatments tended to be more effective at the acute versus intermediate versus chronic stages (11). For acute pain, opioids, surgery, bracing, and heat proved most beneficial (11). If medications are preferred, oral analgesics, such as acetaminophen or NSAIDs, should be attempted first (6). Medications in general are more helpful for acute pain and less helpful for chronic pain as they do not solve the underlying problem (13). However, opioids, splints/bracing, surgery, and heat therapy were also helpful for chronic pain, whereas acetaminophen and homeopathy were less effective (11). For a combination of acute and chronic pain, opioids are most effective, followed by massage, splints/bracing, and heat therapy (11). It is also important to point out that because many over-the-counter medications and self-therapy options are not as effective nor appropriate for acute pain, patients are forced to see a health care professional for further options (11,14).

OT

OT was the most effective option in managing pain in our study, with 70% of patients reporting symptom improvement with splints and bracing. It was also commonly prescribed, with 54 patients reporting use. Its benefit can be attributed mostly to its role in improving proprioception and joint stability (13). It was relatively well tolerated, with only 11% of patients reporting negative effects. However, use can be inconsistent due to inconvenience, aesthetics, and discomfort. These options can also be helpful in combination with other therapies and treatments but should be used with caution as they can cause muscle weakness through disuse (13).

PT

In our study, PT was prescribed to the majority of patients (n = 60). Results were more variable, with 43% of patients reporting improvement and 38% with no relief. Similar to OT, PT was overall well tolerated with only 18% reporting adverse effects. These

Table 2. *Efficacy of treatments organized as improvement, no effect, or worsened symptoms.*

Complimentary/Alternative Treatments	Improvement #/%	No Effect #/%	Worsened Symptoms #/%	*P* value	Significant?
Chiropractor	4/29%	7/50%	3/21%	0.0001	Y
Acupuncture	4/36%	7/64%	0/0%	0.0005	Y
Dry needling	3/50%	3/50%	0/0%	0.0313	Y
Biofreeze	1/100%	0/0%	0/0%	n/a	N
Heat	7/58%	5/42%	0/0%	0.002	Y
Massage	9/60%	6/40%	0/0%	< 0.0001	Y
Glucosamine	0/0%	2/100%	0/0%	n/a	N
Blackseed oil	1/100%	0/0%	0/0%	n/a	N
Transcutaneous electrical nerve stimulation	3/50%	3/50%	0/0%	0.0313	Y
Yoga	2/100%	0/0%	0/0%	n/a	N
Testosterone	1/100%	0/0%	0/0%	n/a	N
Ice	2/40%	3/60%	0/0%	0.0625	N
Lidocaine	4/36%	6/55%	1/9%	0.001	Y
CBD oil	1/100%	0/0%	0/0%	n/a	N
Total: 88	42/48%	42/48%	4/5%	< 0.0001	Y
PT					
PT	26/43%	23/38%	11/18%	< 0.0001	Y
Total: 60	26/43%	24/38%	11/18%	< 0.0001	Y
OT					
Bracing/splints/orthotics	38/70%	10/19%	6/11%	< 0.0001	Y
Total: 54	38/70%	10/19%	6/11%	< 0.0001	Y
NSAIDs					
Meloxicam	2/29%	3/43%	2/29%	0.0156	Y
Diclofenac	6/24%	17/68%	2/8%	< 0.0001	Y
Naproxen	3/60%	2/40%	0/0%	0.0625	N
Celecoxib	2/33%	2/33%	2/33%	0.0313	Y
Ibuprofen	11/65%	5/29%	1/6%	< 0.0001	Y
Indomethacin	1/100%	0/0%	0/0%	n/a	N
Ketorolac	1/25%	1/25%	2/50%	0.125	N
Total: 65	26/40%	30/46%	9/14%	< 0.0001	Y
Surgery/procedures					
Surgery	5/29%	7/41%	5/29%	< 0.0001	Y
Nerve block	9/69%	3/23%	1/8%	0.0002	Y
Platelet rich plasma	2/67%	0/0%	1/33%	0.25	N
Hyaluronic acid	1/50%	1/50%	0/0%	n/a	N
Pain pump placement	0/0%	1/100%	0/0%	n/a	N
Prolotherapy	6/100%	0/0%	0/0%	0.0313	Y
Ablation	4/100%	0/0%	0/0%	0.125	N
Total:46	27/59%	12/26%	7/15%	< 0.0001	Y
Acetaminophen					
Acetaminophen	2/25%	6/75%	0/0%	0.0078	Y
Total: 8	2/25%	6/75%	0/0%	0.0078	Y

Table 2 (cont.). *Efficacy of treatments organized as improvement, no effect, or worsened symptoms.*

Complimentary/Alternative Treatments	Improvement #/%	No Effect #/%	Worsened Symptoms #/%	*P* value	Significant?
Opioids and opioid-like medications					
Morphine	2/33%	2/33%	2/33%	0.0313	Y
Hydrocodone/paracetamol	0/0%	2/67%	1/33%	0.25	N
Oxycodone	1/25%	2/50%	1/25%	0.125	N
Methadone	1/50%	0/0%	1/50%	n/a	N
Hydrocodone/acetaminophen	12/60%	6/30%	2/10%	< 0.0001	Y
Oxymorphone	0/0%	0/0%	1/100%	n/a	N
Tramadol	7/29%	13/54%	4/17%	< 0.0001	Y
Tylenol/codeine	4/29%	5/36%	5/36%	0.0001	Y
Hydrocodone	2/50%	1/25%	1/25%	0.125	N
Oxycodone/acetaminophen	2/100%	0/0%	0/0%	n/a	N
Tapentadol	1/100%	0/0%	0/0%	n/a	N
Naltrexone	1/100%	0/0%	0/0%	n/a	N
Hydromorphone	1/33%	1/33%	1/33%	0.25	N
Buprenorphine	0/0%	1/100%	0/0%	n/a	N
Fentanyl	1/100%	0/0%	0/0%	n/a	N
Total: 87	35/40%	33/38%	19/22%	< 0.0001	Y
Neuropathic modulators					
Pregabalin	2/18%	3/27%	6/55%	0.001	Y
Gabapentin	3/21%	4/29%	7/50%	0.0001	Y
Amitriptyline	2/29%	2/29%	3/43%	0.0156	Y
Duloxetine	0/0%	8/53%	7/47%	< 0.0001	Y
Milnacipran	0/0%	1/100%	0/0%	n/a	N
Topiramate	0/0%	1/100%	0/0%	n/a	N
Total: 49	7/14%	19/39%	23/47%	< 0.0001	Y
Steroids					
Steroid injections	12/52%	9/39%	2/9%	< 0.0001	Y
Oral steroids	10/56%	5/28%	3/17%	< 0.0001	Y
Trigger point injections	3/43%	4/57%	0/0%	0.0156	Y
Total: 48	25/52%	18/38%	5/10%	< 0.0001	Y
Muscle relaxants					
Tizanidine	2/25%	5/63%	1/13%	0.0078	Y
Cyclobenzaprine	4/29%	10/71%	0/0%	0.0001	Y
Clonazepam	2/100%	0/0%	0/0%	n/a	N
Baclofen	5/56%	4/44%	0/0%	0.0039	Y
Valium	4/100%	0/0%	0/0%	0.125	N
Botulinum	4/67%	2/33%	0/0%	0.0313	Y
Lorazepam	0/0%	1/100%	0/0%	n/a	N
Methocarbamol	1/17%	4/67%	1/17%	0.0313	Y
Temazepam	0/0%	1/100%	0/0%	n/a	N
Metaxalone	0/0%	1/100%	0/0%	n/a	N
Total: 52	22/42%	28/54%	2/4%	< 0.0001	Y

Abbreviations: CBD, cannabidiol; N, no; n/a, not available; Y, yes.

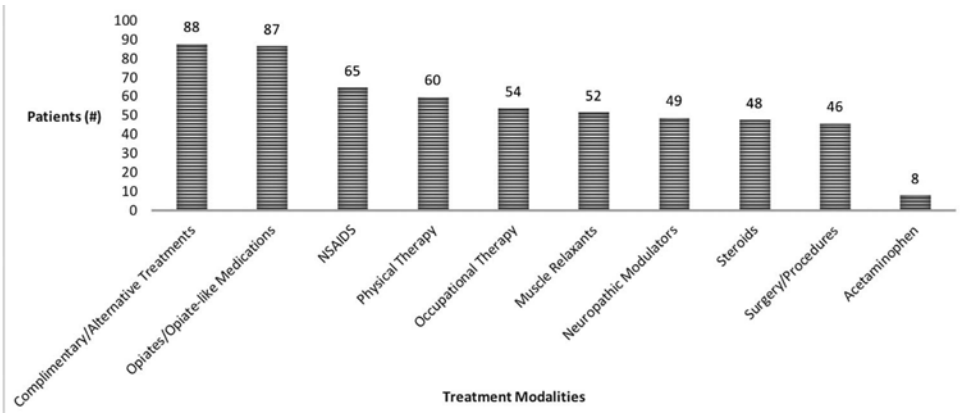

Fig. 1. *Most commonly prescribed treatment modalities in EDS. Treatments were graphed with reference to number of patients using each modality and ordered from most to least prescribed.*

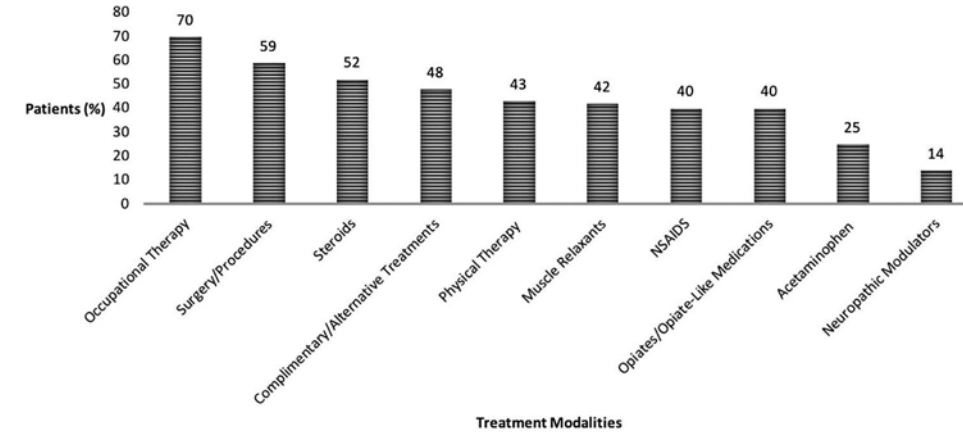

Fig. 2. *Efficacy of treatment modalities in EDS. Treatments were graphed with reference to percentage of patients citing "improvement" from each modality and ordered from most to least efficacious.*

statistics are slightly lower than that of other studies, which reported an efficacy of 63.4% (3). One particular advantage of PT is its multifactorial approach and flexibility to address pain from a psychological and physical perspective (6). However, it does have intrinsic weaknesses in therapist variability, long-term efficacy, and patient fear of kinesiophobia (fear of pain because of movement) (2). Thus, it is recommended that patients be educated thoroughly on their disease and cautioned against overstretching or hyperextension (2). It is just as imperative that patients be referred to a therapist who is experienced in treating patients with EDS. PT is most effective in conjunction with medications and other treatments, such as hot fomentation or massage (2). Specifically, PT should be combined with OT to optimize muscle strengthening, coordination, and proprioception. PT can also be a conduit for weight loss when coupled with exercise to reduce joint strain (11).

Surgery and Procedures

We found that 59% of patients who underwent surgery or interventional procedures experienced pain relief. Of these, nerve blocks demonstrated the most individual benefit in 69% of patients. Surgery yielded poor results with only 29% of patients reporting relief

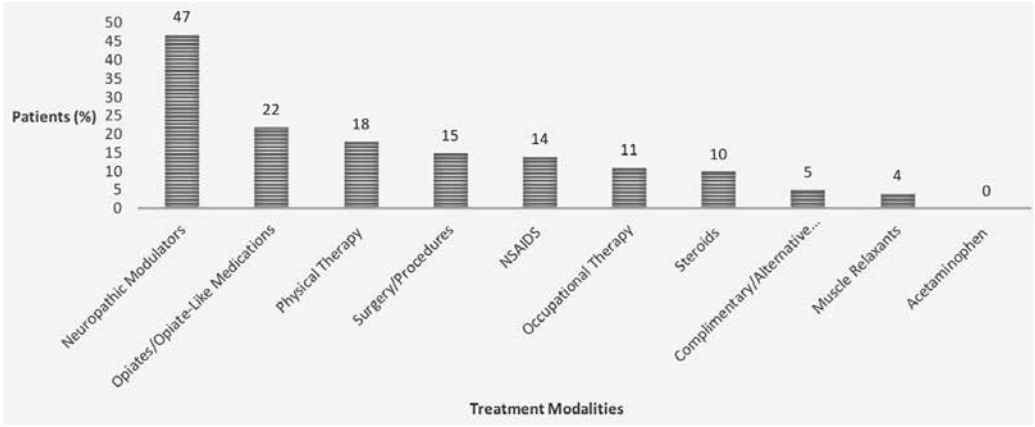

Fig. 3. *Percentage of patients with adverse symptoms from each treatment modality. Treatments were graphed with reference to percentage of patients citing "worsened symptoms" from each treatment and ordered from highest to lowest.*

and another 29% reporting adverse symptoms. Although helpful for some other joint pathologies, surgery is generally not recommended for the EDS population. This is due to poor pain relief and likelihood for postsurgical complications due to abnormal connective tissue healing, as well as muscle deconditioning (15). It is important to consider that many patients consider surgery only as a last resort. Despite this, surgery may be a reasonable option for certain specific conditions, such as thumb or wrist instability (13). Even in these circumstances, surgery should be used cautiously as sometimes the laxity can be so severe that surgery is unlikely to succeed (13).

Pain interventions, such as nerve blocks and radiofrequency procedures, are other options that may be beneficial mostly during the acute phase, but with unclear long-term efficacy (5). Other injections with anesthetics and dry needling techniques have also been effective, especially when combined with other modalities, such as PT and stretching (15). A 10% dextrose prolotherapy has also been shown to be helpful for various joint conditions, most notably temporomandibular joint syndrome (15).

Opioids and Opioid-Like Medications

Opioid and opioid-like pain medications are some of the most popular analgesic options currently for all types of pain. In our study, this class of medications showed moderate efficacy with 40% of patients reporting improvement with use. Of these, hydrocodone/acetaminophen demonstrated the most statistically significant benefit, relieving pain in 60% of patients. Although notorious for its side effects, opioids can be especially risky in EDS by causing constipation through decreased GI motility, orthostasis through peripheral vasodilation and reduced peripheral resistance, dysautonomia, proprioceptive deficits, hyperalgesia, and psychiatric side effects (10,16). Thus, they are not indicated for chronic musculoskeletal pain and should be reserved for acute exacerbations or pain refractory to other treatments (6). One other consideration is that central pain sensitization can result with prolonged opioid use (5,8,13). Although tramadol, with a slightly safer side effect and addiction profile, has been used as a viable alternative, its benefit in our population was debatable given only 29% of patients reporting improvement (5).

Muscle Relaxants

Muscle relaxants demonstrated moderate efficacy with 42% of patients reporting improvement. Interestingly, these medications were some of the most well tolerated after acetaminophen, with only 4% of patients reporting adverse effects. Of these, Botulinum toxin injections were most effective, benefiting 67% of patients. As a whole, muscle relaxants can also be helpful for spasm-related pain (6). However, they can worsen joint stability and are susceptible to loss of efficacy, addiction, and sedation (6).

Complimentary/Alternative Treatments

We found that many patients with EDS considered complementary and alternative treatments because of the perceived safety compared with adverse risk profiles

associated with medications and surgeries and when conventional treatments failed to address their pain. As a whole, these treatments helped 48% of patients. Of these, heat and massage were most effective, relieving pain in 58% and 60% of patients, respectively. Other treatments, such as chiropractic manipulations, should also be considered when other types of stretching or therapy is contraindicated due to tissue laxity (15). Transcutaneous electrical nerve stimulation units can also be helpful by using electrical stimulations to disrupt pain transmissions and pathways (8). Lidocaine can be effective either when topically applied or injected into localized painful areas after subluxations (8).

Steroids

Steroids were effective in both oral and injectable form in 52% of patients. All 3 modalities (oral, intraarticular, trigger points) were similar in efficacy in our study. Their role is especially prominent in the acute phase by decreasing inflammation (5). Trigger points are common in EDS, the pathophysiology of which revolves around skeletal muscle fibers causing both local and referred pain when compressed (2). These have been shown to be relieved with steroid injections into these trigger points. Although oral steroids were the most effective formulation, they were also the least well tolerated. This is consistent with the literature indicating that the oral steroids have a greater systemic absorption than the injectable options, and thus have a higher chance for systemic side effects, such as hyperglycemia and weight gain, among others. It is also important to note that steroids should be used with caution especially in this population given the well-known side effect of impaired wound healing (17).

Neuropathic Pain Modulators

Tricyclic antidepressants, anticonvulsants, and selective norepinephrine reuptake inhibitors have all been shown to be effective for patients with generalized neuropathic pain. Interestingly, we noted that neuropathic modulators had the least efficacy of any treatment, with only 14% of patients reporting improvement. Additionally, they were also not tolerated well with 47% of patients reporting adverse effects. Historically, they have not been shown to be effective in patients with EDS with the additional side effect of worsening dysautonomia (8). Gabapentin and pregabalin are 2 commonly used medications for neuropathic pain that serve dual purposes as anxiolytics but can cause weight gain (13). As some of these neuropathic medications have different indications, there is also a possibility that separate patients were using the medications for different diagnoses, such as migraine versus neuropathic pain.

NSAIDs

NSAIDs are first-line medications that are especially helpful in reducing inflammation-related pain (8). Some 40% of patients in our study reported relief, with another 46.7% reporting no relief. Of these, ibuprofen was the most effective and best tolerated. Diclofenac, available in both an oral and topical formulary, was least effective with 68% of patients reporting no effect. Similar to the general population, NSAIDs should be used with caution to avoid GI, renal, and hematologic side effects (8). In patients with EDS specifically, NSAIDs can exacerbate mast cell symptoms (8).

Acetaminophen

Like NSAIDs, acetaminophen is another first-line analgesic medication. Although usually well tolerated, side effects, including hepatotoxicity, should be considered at high dosages (8,13). Interestingly, we observed a surprisingly low usage rate (n = 8), which could be explained by several reasons. It is possible that patients had used acetaminophen previously during the acute phase and did not report use. It is also possible that the relatively low efficacy (benefit in 25% of patients) also contributed to the low reported rate of usage. Furthermore, another theory is that it was not commonly prescribed by providers in our study.

Psychotherapy

Psychotherapy techniques, such as cognitive behavioral therapy (CBT), require thorough evaluation by a psychologist and psychiatrist prior to initiation (5). There are no clinical trials to indicate efficacy of CBT, but it may be a viable alternative for patients with refractory pain (5). None of the patients in our study underwent any psychotherapy.

Limitations

Men were only a small percentage of the study, comprising only 4% of patients. These data are consistent with the fact that the vast majority of patients with EDS are women, but nonetheless could affect pain reporting owing to differences in pain perception between men and women. The study was also limited by a relatively small sample size of 98 patients. Another limitation was that patients were not randomized, and

pain score reporting was subjective. Patient data were extracted from a single clinic setting, and thus could be skewed by individual provider practice model and preferences. Additionally, we were unable to isolate when in the disease progression certain treatments were attempted, that is, for acute versus chronic pain. Further research can be beneficial in categorizing the treatments that help in certain phases of pain.

Conclusions

There is limited literature on the different treatment modalities used to treat pain in the EDS population. EDS is a systemic condition that can cause widespread, debilitating pain. Because of the complexity and variability of this condition, there is no one single treatment that works for every patient. These patients often consult with multiple providers and are prescribed many treatments without subjective improvement. Most times, they will require a combination of treatments. Thus it is important for each patient to undergo a comprehensive evaluation and to create a dynamic, individualized treatment plan.

Pain physicians are unique in their ability to advocate for this patient population. As experts in neuromusculoskeletal medicine and diagnosis, pain medicine physicians are better positioned to more accurately identify EDS and its characteristics. In addition, their specialized training in therapeutic options, such as pain medication management and interventional approaches, make them best suited for managing this debilitating disease.

We found that in addition to prescribing the various treatments seen in our study, providers often spend a sizeable fraction of clinic visits counseling the patient. Specifically, patients should be educated on the common pain generators, including joint dislocation, subluxation, overuse pain, nerve hypersensitivity, arthritic changes, and central hypersensitivity to pain. Developing a close physician-patient relationship can facilitate trust and help patients understand that sometimes multiple treatments will be attempted before obtaining relief. They should also be advised to undergo genetic and clinical testing both themselves and for their children.

Future Directions

Although our study showed some promising data with some treatments, there is potential for larger scale studies to involve a greater number of patients in the future with even more treatment modalities. There is also potential for randomized clinical trials in comparing treatments with placebo.

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