


Multidisciplinary Approach to Treating Chronic Pain in Patients with Ehlers–Danlos Syndrome: Critically Appraised Topic

Kiley C Whalen, Wilson Crone 

Center for Physician Assistant Studies, Albany Medical College, Albany, NY, USA

Correspondence: Wilson Crone, Center for Physician Assistant Studies, Albany Medical College, MC-4, 47 New Scotland Avenue, Albany, NY, 12208, USA, Tel +1 518-262-5251, Fax +1 518-264-0484, Email CroneW@amc.edu

Abstract: The Ehlers–Danlos syndromes (EDS) are a group of 13 related connective tissue disorders with a combined prevalence of 1 in 5000 people, with the most common noted as hypermobile EDS (hEDS). The EDS genetic condition is thought to affect both males and females equally, although most symptomatic patients are female. EDS causes a myriad of symptoms, including skin hyperextensibility and fragility, easy bruising and bleeding, joint hypermobility, subluxation, dislocation, and chronic pain. Pain is one of the most common symptoms of EDS, leading to disability and decreased quality of life. Current guidelines for treating chronic pain in EDS are lacking. Clinicians focus on a conservative multidisciplinary approach in patients with EDS, which avoids surgical interventions and its accompanying risks of morbidity and mortality. The multidisciplinary approach includes physiotherapy, occupational therapy, cognitive behavioral therapy, and pharmacologic interventions to decrease pain. This review identifies literature examining the components of this conservative multidisciplinary approach and their effectiveness across the PubMed, EMBASE, CINAHL, Web of Science, and Trip databases, using the terms “Ehlers–Danlos Syndrome AND Pain Management” that was then subsequently evaluated. The evaluation of this current literature provides weak evidence to support the efficacy of the individual components of the conservative multidisciplinary approach. Lack of alternative approaches leaves medical providers with little choice but to suggest these pain control methods, despite low-grade evidence of weak evidence of their efficacy. More research into the pathophysiology of chronic pain in EDS could help identify additional modes and rationales for therapy.

Keywords: Ehlers–Danlos syndrome, conservative management, chronic pain, evidence-based medicine

Clinical Question

What components of a conservative multidisciplinary approach are best for treating chronic musculoskeletal pain in a young adult female with hypermobile Ehlers–Danlos syndrome (hEDS)?

Background

The Ehlers–Danlos syndromes (EDS) and hypermobility spectrum disorder (HSD) are connective tissue disorders that commonly cause skin hyperextensibility, joint hypermobility and tissue fragility.¹ The Ehlers–Danlos syndromes previously included six different subtypes. The subtypes were updated in the 2017 International Classification to 13 different subtypes.² The Ehlers–Danlos syndromes affect 1 in 5000 people, with hypermobile Ehlers–Danlos syndrome (hEDS) being the most common subtype.¹ Previous nomenclature for hEDS was EDS Type III or EDS-HT (hypermobile type).³ Most of these syndromes affect collagen synthesis and production and are inherited in autosomal dominant or recessive fashion. The genes affecting hEDS have not been discovered. The Ehlers–Danlos syndromes have similar pain patterns among types but may primarily affect different joints according to subtype.⁴ Hypermobile Ehlers–Danlos syndrome causes hypermobility in small and large joints, which result in frequent dislocations, chronic pain, and

osteoarthritis.¹ Other symptoms include mild skin hyperextensibility, GI symptoms, and autonomic nerve dysregulation, and possible cardiac involvement.¹

The 2017 International Diagnostic Criteria for hEDS are based on generalized joint hypermobility, which is assessed using the Beighton scale, manifestations of connective tissue disorders, marfanoid features, family history, and exclusion of other connective tissue disorders or disorders that may cause joint hypermobility.^{5,6} Symptomatic patients that have hypermobility, but do not match the diagnostic criteria of hEDS or other connective tissue disorders, are diagnosed with hypermobility spectrum disorder (HSD).² HSD has previously been referred to as Joint Hypermobility Syndrome and benign hypermobility syndrome.³

Pain in the Ehlers–Danlos Syndromes manifest in various forms including generalized body pain, soft-tissue pain, joint pain, neuropathic pain, headaches, GI pain, TMJ pain, dysmenorrhea, vulvodynia, and dyspareunia.⁴ In a more mechanistic approach, pain can be characterized as nociceptive, neuropathic, or nociplastic.⁷ Briefly, nociceptive pain stems from activation of pain receptors (nociceptors) from tissue damage. Neuropathic pain suggests a lesion within the somatosensory pain pathways. Nociplastic pain would then apply to issues of sensory processing without formal lesion identification. Recent reviews and small group studies have identified several pain components of interest. Malfait et al highlighted genetic bases for many of the types of EDS that then could be correlated with pain mechanisms, but note the lack of genes associated with hEDS.⁸ Malfait et al noted that dislocations and other laxity-based issues could directly lead to nociceptor pain involvement. A recent case–control study by De Wandele et al characterized possible nociplastic mechanisms, including temporal pain summation and exercise-induced hypoalgesia.⁹

Although musculoskeletal complications, joint hypermobility, and various forms of pain are hallmark features of hypermobile Ehlers–Danlos syndrome (hEDS), the lack of awareness of the Ehlers–Danlos syndromes and hEDS can result in poor management of chronic musculoskeletal pain in these patients. This lack of awareness can delay diagnosis of EDS and hEDS. As highlighted in the literature and publicized on the Ehlers–Danlos Society website, on average it takes between 10 and 12 years since the start of symptoms for someone to be diagnosed with EDS, which is congruent with published literature.^{6,10} Resources regarding management of chronic musculoskeletal pain in this population are scarce due to the difficulty in diagnosis and subsequent underdiagnosis of EDS. While evidence-based medicine (EBM) databases such as UpToDate and DynaMed briefly discuss pain management in these populations, the information in these databases offers generalized approaches that are not specific and lack supportive data. These EBM database entries identified multidisciplinary approaches including physical therapy, medications, self-management, and behavioral therapy, but failed to detail what modalities suggested were of most benefit.^{11,12} The UpToDate article by Grahame et al on treatment and prognosis of hEDS highlighted chronic pain management strategies based off studies in fibromyalgia patients, rather than patients with hEDS or EDS.¹² As suggested by the findings on EBM databases, research on chronic pain management in hEDS and EDS is limited and is generally lower-quality evidence.

A previously published review by Chopra et al covered the incidence and types of pain in patients with EDS, as well as various methods of pain management. This review, authored by leading experts on EDS, took place under the 2017 International Consortium of Ehlers–Danlos Syndromes. The authors noted that pain was common across the different types of EDS, with the severity and incidence of pain highest among those with hEDS, such that generalized body pain was common in >90% of the patients with hEDS.⁴ Other common types of pain in this population included soft tissue pain (>90%), neuropathic pain (68%), and joint pain. Dislocations occurred in 78% of the hEDS patients. Chopra et al cited the lack of evidence regarding the pathophysiology of pain in hEDS patients, and noted most approaches to chronic pain are based on fibromyalgia in this population. Fibromyalgia was a common comorbidity, and hEDS was commonly misdiagnosed as fibromyalgia in these populations. The chronic pain in this population included a mixture of both nociceptive and neuropathic pain. The authors suggested various methods of pain management in these populations, emphasizing a multidisciplinary approach. The suggested approach included physiotherapy, cognitive behavioral therapy, pharmacologic agents, transcutaneous neuro stimulator (TENS), and special cushioning and mattresses. The authors acknowledged the lack of evidence for many of these pain management strategies.⁴

Given the above findings, this current review is intended to evaluate the various components of pain management in hypermobile Ehlers–Danlos syndrome. The goal is to identify which components are most effective to better identify a definition of a “multidisciplinary” approach in treating chronic pain in patients with hEDS.

Search Criteria and Results

A search of *Ehlers-Danlos Syndrome AND pain management* in the evidence-based medicine resource of UpToDate identified “Overview of the Management of Ehlers-Danlos Syndrome”. This was not specific to only pain management strategies but also detailed management of other EDS symptoms. The article featured suggestions about various management strategies but was fairly generalized and lacked data. Similar results were found when searching *Ehlers-Danlos Syndrome AND pain management* on the evidence-based medicine resource of DynaMed. Cochrane Library was searched with *Ehlers-Danlos Syndrome AND Pain Management* and utilizing the filter “Title, Abstract, and Key Word”. Seven results were found, but were not applicable to this research. None of the retrieved titles addressed pain management. A PubMed Clinical Queries search with *Ehlers-Danlos Syndrome AND Pain Management*, and the filters “Clinical Studies, Therapy, and Broad Scope”, retrieved 28 results. A follow-up search in PubMed with same terms *Ehlers-Danlos Syndrome AND Pain Management*, sorted by “Best Match”. This retrieved 154 results. Searches with the same terms in the Trip (386 results), Web of Science (81 results) Embase (19), and CINAHL databases (14 results), identified overlapping citations. The lack of extensive clinical trials regarding Ehlers–Danlos syndrome, and more specifically pain management in Ehlers–Danlos syndrome, made it difficult to further isolate the searches without excluding nearly all literature related to pain management in EDS. Nearly all literature would be considered lower-level evidence including case reports, and studies that have very small sample sizes. The retrieved articles were then evaluated by the level of evidence criteria established by the Centre for Evidence-Based Medicine, Oxford, with the rankings of preference for systematic review, clinical trial, cohort, and case series.¹³ The key inclusion criterion for included studies was identification of pain management as a clinical outcome.

The first piece of literature chosen for examination was a systematic review by Palmer et al published online in July 2020. This was chosen to provide a background on which strategies are considered most effective in management of Ehlers–Danlos syndrome.¹⁴ The next selection was a clinical trial by Celletti et al involving pain management in patients with hEDS and chronic back pain with neurocognitive exercises. This was one of the only clinical trials conducted regarding pain management and Ehlers–Danlos syndrome, and which was published subsequent to the Palmer et al systematic review.¹⁵ The next selection was identification of complementary and alternative therapies in a survey of EDS patients by Demes et al, as many patients with EDS turn to complementary and alternative treatments for pain management when current strategies fail to provide relief.¹⁶ This also was published subsequent to the Palmer et al systematic review. The final selection was a qualitative study of pain control methods and their perceived effectiveness in patients with EDS by Arthur et al. This study was used to compare how the methods suggested by other literature examined reached perceived levels of effectiveness by patients.¹⁷ This study was not included in the Palmer et al systematic review. The key outcomes of these four papers are summarized in Table 1.

Evaluating the Identified Literature Evidence

In the paper “The Effectiveness of Conservative Interventions for the Management of Syndromic Hypermobility: A Systematic Literature Review”, the authors analyzed multiple online databases to determine the effectiveness of conservative interventions on pain levels, physical function, psychological well-being, and quality of life in patients with syndromic hypermobility. Syndromic hypermobility referred to patients with hypermobile Ehlers–Danlos syndrome (hEDS), which was previously known as Ehlers–Danlos syndrome hypermobile type (EDS-HT); and, hypermobility spectrum disorders (HSD), which was previously known as joint hypermobility syndrome (JHS). The authors noted that little is known about syndromic hypermobility, and that it is likely underdiagnosed. The authors cited their background information that current medical management for syndromic hypermobility is not effective and requires a multi-disciplinary approach. The focus on conservative interventions stems from previous research that a larger percentage of syndromic hypermobility patients achieved benefit after physiotherapy when compared to surgery. Palmer et al focused on physiotherapy interventions in their literature review, therefore several articles featuring non-physiotherapy conservative interventions included in this review were not included in their systematic review. Increased risks of complications in surgery make conservative interventions more attractive.¹⁴

Table 1 Key Findings on Pain Control in Patients with Hypermobile Ehlers–Danlos Syndrome in Identified Literature

Reference (LOE)	Population and Setting	Activity	N Involved	Key Outcomes
Palmer S et al (2021) ¹⁴ (1)	Systematic review of RCTs	Exercises; RCTs measuring pain	283 Total participants (140 with intervention)	32/140 with significant reduction in pain relief in study subjects with intervention
Celleti C et al (2021) ¹⁵ (3)	Chronic back pain patients with hEDS, Rome, Italy	Neurocognitive therapeutic exercises	18 Participants	Average decrease in pain, fatigue, and disability scores from before treatment to after treatment ($p < 0.05$)
Demes J et al (2020) ¹⁶ (3)	EDS and HSD patients, Aurora, CO	Complementary and alternative therapies	486 Participants	Statistically significant perceived effectiveness of intervention <ul style="list-style-type: none"> ● Acetaminophen: moderately to extremely helpful: 26.8% ● NSAIDs: moderately to extremely helpful: 55.9% ● Antidepressants: moderately to extremely helpful: 34.8% ● Opioids moderately to extremely helpful: 88.1% ● Physical therapy: moderately to extremely helpful: 60.6% ● TENS therapy: moderately to extremely helpful: 53.4%
Arthur K et al (2016) ¹⁷ (3)	Patients with EDS, Boone, NC	Pain control methods	179 Participants	Average perceived efficacy of intervention on a 5-point scale <ul style="list-style-type: none"> ● Chronic pain <ul style="list-style-type: none"> ● Antiseizure medications: 2.65 ± 1.29 ● Regular exercise: 2.76 ± 0.98 ● Counseling or Psychotherapy: 2.42 ± 1.12 ● Herbal remedies: 2.11 ± 0.89 ● Diet management: 2.51 ± 0.96

Abbreviations: EDS, Ehlers–Danlos syndrome; LOE, level of evidence^{(1),(3)}; N, Number; UK, United Kingdom; RCT, randomized controlled trial; hEDS, hypermobile Ehlers–Danlos syndrome; FSS, Fatigue Severity Scale; TSK, Tampa Scale of Kinesiophobia; NRS, Numerical Rating Scale; ODI, Oswestry Disability Index; CO, Colorado; NSAIDs, non-steroidal anti-inflammatory drugs; TENS, transcutaneous electrical nerve stimulation.

Palmer et al utilized PRISMA guidelines to conduct and report the systematic literature review. A librarian familiar with systematic reviews was consulted to aid in the selection process. The authors utilized a Boolean search strategy to ensure no articles of significance were left out of the literature review. Exclusion criteria were determined prior to the literature search, and the articles were then reviewed independently by two researchers. This was done to limit selection bias. The reference sections of the articles chosen for review were analyzed for additional articles to review, decreasing the likelihood that relevant articles were excluded. Eleven studies were included in the literature review. These included seven randomized controlled trials (RCTs), one pilot RCT, two cohort studies, and one pilot cohort study. The studies selected examined either the effectiveness of conservative interventions versus no treatment, or the effectiveness of conservative treatment in pre-treatment versus post-treatment. All of the studies featured exercise as a main component of their conservative treatments. The wide differences in complementary approaches, exercise regimens, and the various length of the studies included in the systematic review prevented meta-analysis.¹⁴

Only three of the eight controlled trials cited in the Palmer et al systematic review (Toprak Celenay and Ozer Kaya,¹⁸ Daman et al,¹⁹ and Reychler et al)²⁰ found statistically significant evidence that conservative intervention was more effective than no treatment controls. The authors of the systematic review highlighted that these studies had several

inconsistencies, including focusing on a single body part, lacking long-term follow-up, and only including women, which brings into question the generalizability of the studies. Two of the eight controlled trials (Pacey et al²¹ and Kemp et al)²² found inconsistent results regarding the effectiveness of conservative intervention versus no treatment. Bale et al²³ found no differences between groups. Palmer et al²⁴ was a pilot randomized controlled study from 2016 and did not analyze the effectiveness of conservative intervention versus no treatment. Therefore, the randomized controlled trials included in the systematic review only offered weak evidence that conservative interventions as defined as exercise therapy as the main component were more effective than no treatment.¹⁴

Several randomized controlled trials and cohort studies chosen to be analyzed in the systematic review by Palmer et al found statistically significant evidence that conservative interventions, with exercise as a main component, were very effective when comparing pre-treatment to post-treatment groups. In the randomized controlled trials where pain levels were measured (Bale et al,²³ Daman et al,¹⁹ Kemp et al,²² and Pacey et al,²¹ and Toprak Celenay and Ozer Kaya et al),¹⁸ a statistically significant decrease in pain was found between pre-treatment and post-treatment groups. Randomized controlled trials by Reychler et al²⁰ and Palmer et al²⁴ found significant improvement in exercise capacity, but did not measure the pain levels. Two of the three cohort studies found a significant decrease in pain from pre-treatment to post-treatment. In contrast, a cohort study by Bathen et al did not find a significant decrease in pain from pre-treatment to post-treatment.²⁵ The incongruity between the effectiveness of conservative intervention versus no treatment controls and reduction in pain from pre-treatment to post-treatment was somewhat unexpected.

In the systematic review, Palmer et al suggested that the decrease in pain from pre-treatment to post-treatment groups may be caused by time rather than the interventions of the conservative therapies. Overall, the review by Palmer et al provided weak evidence that conservative treatment with exercise as a main component is effective at managing pain in patients with syndromic hypermobility. The information presented by Palmer et al matches current literature regarding pain control in syndromic hypermobility. The authors identified a need for further studies on pain management in syndromic hypermobility. The lack of studies regarding conservative management of syndromic hypermobility severely limited the evidence found by Palmer et al as only 11 studies fit their criteria. The sizes of the 11 studies ranged from 12 to 119 participants. The heterogeneity of the studies further limited ability to draw definitive conclusions.¹⁴

The non-randomized controlled trial “Pain management through neurocognitive therapeutic exercises in hypermobile Ehlers-Danlos syndrome patients with chronic low back pain” by Celletti et al evaluated the effectiveness of neurocognitive therapeutic exercises in controlling pain in 18 patients with hEDS. There was a high female-to-male ratio, with 14 women to 4 men. This is not surprising, considering the EDS are diagnosed more frequently in female patients.¹⁷ The small size of this study also reflects the prevalence of EDS in the general population. In general, future studies that include a more equal ratio of females and males, and a larger population size, would strengthen the evidence.

This non-randomized controlled trial recruited patients from the outpatient rehabilitation clinic for hypermobility disorders at the Umberto I University Polyclinic Hospital of Rome. The limited geographical spread of this study and non-randomized population makes it difficult to generalize the findings of this study to other populations. To participate in the study, patients had to be diagnosed with hEDS by a clinical geneticist using the 2017 International Classification of Ehlers–Danlos syndromes, and have chronic lower back pain. These patients were recruited from March 2017 to February 2018, and the study took place over 3 months. This study featured limited follow-up, and future studies would benefit from longer follow-up.¹⁵

The neurocognitive exercises aimed to allow the patients to identify the differences between painful and non-painful stimuli. Over-sensitization is one of the proposed pathophysiologic mechanisms of chronic pain in patients with EDS.¹ These exercises also aimed to increase proprioception and to allow patients to better understand which physical maneuvers cause them pain, and how to avoid or replace them with other physical maneuvers. The patients enrolled in the study completed these neurocognitive exercises with the help of a physiotherapist once a week, for 60 minutes. The neurocognitive exercises included five phases. The phases included recognition of local contact at the trunk, recognition of positions through lumbopelvic rhythm, recognition of two sponges of different consistency at the pelvic level, recognition of tilting of the pelvis and the laterolateral and anteroposterior relationship of the trunk, and finally recognition of the symmetrization of the load. These learned skills allow the patients to develop ergonomic and symmetrical movements, therefore decreasing factors that contribute chronic back pain.¹⁵

While the systematic review by Palmer et al also looked at conservative interventions with exercise as a main component of treatment, this study by Cellitti et al was unique in its neurocognitive approach, vs strength building common in many of the articles analyzed by Palmer et al.^{14,15} Celletti et al used various clinical outcome scales to quantify changes in patient pain levels. Their use of the McGill Pain Questionnaire, the Tampa Scale of Kinesiophobia (TSK), Fatigue Severity Scale (FSS), Oswestry Disability Index (ODI), and the Numerical Rating Scale (NRS) for pain ensured that differences in pain level were not only due to the potential bias of any one scale used. Celletti et al utilized median and range, as well as Wilcoxon tests for paired samples with a significance level of $p < 0.05$. All scales found significant reductions in scores, which correlates with decreased pain, fatigue, kinesiophobia, and pain associated disability.¹⁵ These findings are similar to the findings of Palmer et al that found statistically significant decreases in pain from pre-treatment to post-treatment groups after conservative interventions of syndromic hypermobility. The lack of control group makes it difficult, however, to determine if the reduction in pain in the trial by Celletti et al was due to neurocognitive therapy, or instead due to the effect of time, as suggested by the systematic review by Palmer et al.^{14,15}

The study, “Use of complementary therapies for chronic pain management in patients with reported Ehlers-Danlos syndrome or hypermobility spectrum disorders”, by Demes et al surveyed 500 patients with self-reported EDS or HSD on their use of complementary and alternative therapies for pain.¹⁶ The study took place from November 2017 to November 2018. The participants included a self-selecting audience recruited through the EDS Society newsletter and Facebook page. The survey included five sections, including Baseline Pain, Pain Management Strategies, Overall Health Demographics, and Additional Comments, for a total of 188 questions. The Pain Management Strategy Section included traditionally recommended therapies, traditional Chinese therapy, herbal medications, and marijuana. Pain intensity was measured using modified National Institutes of Health Patient-Reported Outcomes Measurement Information Systems (NIH PROMIS) Pain Intensity Short Form 3a V1.0 and NIH PROMIS Pain Interference Short Form 6b V1.0. The relatively large population size of the study helps to strengthen the quality of evidence drawn from this study, although stricter definition of EDS and HSD through clinical diagnosis by medical professionals would strengthen the level of evidence.¹⁶

Demes et al used means and 95% confidence intervals to analyze the data. This study found no significant gender differences between males and females, allowing for more generalized application of the findings of this study. Pain scores were analyzed using frequencies and percentages, with Fisher’s exact tests to analyze the differences between average pain intensity. The perceived effectiveness of therapy was also measured, which is perhaps the most important factor in determining patient satisfaction and pain control. The perceived effectiveness was analyzed using frequencies and percentages. The association between perceived effectiveness and average pain rating was also examined using Fisher’s exact test or Chi square tests depending on the cell frequencies.¹⁶

Therapy use in relation to pain intensity was analyzed for association. The therapy categories, including traditionally recommended therapies, traditional Chinese therapy, and herbal medications, all showed significant association with p -values < 0.05 . Participants were considered to have utilized a therapy if they had ever used the therapy for pain management, regardless of current use. Use of traditionally recommended therapies had a p -value of 0.039. As the average pain level of participants increased, the use of traditionally recommended therapy increased. One hundred percent of those participants who rated their pain as “very severe” (12 participants) utilized traditionally recommended therapy. Overall, 92.5% of the participants surveyed utilized traditionally recommended therapies. The differences in the therapy category of marijuana had a p -value of < 0.01 . The prevalence of marijuana use was lowest in the no pain category at 20.0%, and highest in the very severe pain category at 50.0%, with increased pain correlating with increased use of marijuana. Of the participants studied, a total of 195 participants (36.9%) utilized marijuana to cope with pain. Levels of use of traditional Chinese therapy also demonstrated statistical significance, with a p -value of 0.023. Increased use of traditional Chinese therapy by participants correlated with increased pain levels. Overall, a total of 303 participants (56.3%) utilized traditional Chinese therapy. Finally, the differences in use in the category of herbal medications had a p -value of 0.047. Participants utilizing herbal medications were most common in the mild, moderate, and severe pain level groups. A total of 290 participants (54.2%) utilized herbal medications.¹⁶

Therapy use by patients in the Demes et al study was further broken down into the categories of acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, antidepressants, opioids, lidocaine, cognitive

behavioral therapy, physical therapy, TENS, acupuncture, cupping/scraping, Tai Chi, arnica, capsaicin/capsicum, fish oil, ginger, glucosamine/chondroitin, turmeric, smoked marijuana, vaporized marijuana, edible marijuana, topical marijuana, and marijuana concentrate. These categories were also used to evaluate the prevalence of therapy use in relation to pain intensity, as well as frequency of therapy use in relation to pain intensity. The frequency of therapy use included the categories of ever used, used in the past year, used in the past month, and used in the past week. Of the statistically significant categories, increased percentage of use among the population generally correlated with increased average pain severity.¹⁶ Of the therapies used in the past week, only the correlation of average pain severity and frequency of acetaminophen use was significant, with a *p*-value of 0.012. The percentage of patients utilizing acetaminophen in the past week with no pain was 0%, and very severe pain at 33%. The combined cohort included 42.6% of the participants using acetaminophen in the past week.¹⁶

Several categories only had significant data in the ever-used frequency categories. These included use of NSAIDs, anticonvulsants, lidocaine, cognitive behavioral therapy, and physical therapy. Any prior use of NSAIDs was the only frequency that had a significant *p*-value (0.013). The percentage of patients utilizing NSAIDs without pain included 60%, while the percentage of patients with severe pain utilizing NSAIDs was 100%. The combined cohort included 92.5% of the patients ever using NSAIDs. Prior use of anticonvulsants had a *p*-value of 0.002. The percentage of the population ever utilizing anticonvulsants without pain included 20%, while the percentage of the population with severe pain utilizing anticonvulsants was 50%. The combined cohort included 36.9% ever using anticonvulsants. Prior use of lidocaine had a *p*-value of 0.020. The percentage of the population ever utilizing lidocaine without pain included 0%, while the percentage of the population with severe pain utilizing lidocaine was 50%. The combined cohort included 44.2% ever using lidocaine. Prior use of cognitive behavioral therapy had a *p*-value of 0.002. The percentage of the population ever utilizing cognitive behavioral therapy without pain included 20%, while the percentage of the population with severe pain utilizing cognitive behavioral therapy was 58.3%. The combined cohort included 46.0% ever using cognitive behavioral therapy. Prior use of cognitive behavioral therapy had a *p*-value of 0.002. The percentage of the population ever utilizing physical therapy without pain included 40.0%, while the percentage of the population with severe pain utilizing physical therapy was 75%. The combined cohort included 88.9% ever using physical therapy. In general, the prevalence of use in the ever-used categories of NSAIDs, anticonvulsants, lidocaine, cognitive behavioral therapy, and physical therapy correlated with increased average pain level. These overall trends highlight the lack of effective treatments for patients with EDS and HSD, and the increased demand for patients to find an effective pain control method as their pain levels increase.¹⁶

Within the Demes et al study, antidepressant use, opioid use, and transcutaneous electric nerve stimulation use were statistically significant in the ever used and the used in the past year frequency categories. Prior use of antidepressants had a *p*-value of <0.001. The percentage of the population ever using antidepressants without pain was 0.0%, while the percentage of the population with severe pain ever using antidepressants was 66.7%. The combined cohort included 57.5% ever using antidepressants. Use of antidepressants in the last year had a *p*-value of 0.036. The percentage of the population using antidepressants within the last year without pain was 0.0%, while the percentage of the population with severe pain utilizing antidepressants in the last year was 58.3%. The combined cohort of patients utilizing antidepressants in the last year was 69.4%. The comparative percentages between the combined cohorts of participants ever-using antidepressants (66.7%) and participants using antidepressants in the past year (69.4%) suggested that antidepressants were beneficial to the participants. Demes et al did not determine if the patients remained on antidepressants due to decreased pain, or due to other benefits such as amelioration of depression or anxiety, both of which are common in patients with EDS and HSD.

In the Demes et al population, the differences in prior use of opioids had a *p*-value of <0.001. The percentage of the population ever using opioids without pain was 0.0%, while the percentage of the population with severe pain utilizing opioids was 83.3%. The combined cohort included 70.1% ever using opioids. Use of opioids in the last year had a *p*-value of 0.016. The percentage of the population using opioids within the last year without pain was 0.0%, while the percentage of the population with severe pain utilizing opioids in the last year was 25%. The combined cohort of patients utilizing opioids in the last year was 54.5%. The decrease in the percentage of participants utilizing opioids in the past year (54.5%), compared to the percentage of participants utilizing opioids ever (70.1%), was likely due to opioids

being prescribed for acute pain at a higher rate than prescribed for chronic pain. Many of the patients ever utilizing opioids to control pain may have been prescribed opioids after orthopedic injuries, or acute episodes due to EDS or HSD.¹⁶

Similarly, variations in the prior use of TENS in the Demes et al study population had a *p*-value of 0.001. The percentage of the population ever using TENS without pain was 0.0%, while the percentage of the population with severe pain utilizing TENS was 66.7%. The combined cohort included 66.9% ever using TENS. Use of TENS in the last year had a *p*-value of 0.004. The percentage of the population using TENS within the last year without pain was 0.0%, while the percentage of the population with severe pain utilizing TENS in the last year was 33.3%. The combined cohort of patients utilizing TENS in the last year was 75.4%. The higher rate of participants utilizing TENS in the last year (75.4%) compared to participants ever utilizing TENS (66.7%), suggested that TENS may have been a useful pain management technique in EDS and HSD. The decrease in percentage of participants with an average severe pain level in the group utilizing TENS in the past year (33.3%), compared to the percentage of participants utilizing TENS ever with an average severe pain level (75.4%), suggest that TENS therapy is less effective in patients with severe pain.¹⁶

Demes et al also looked at perceived effectiveness of therapy use by average pain rating. Acetaminophen, NSAIDs, antidepressants, opioids, physical therapy, and TENS therapies were the only ones with statistically significant effect differences. Most participants (73.1%) reported acetaminophen to be rarely or not at all helpful. Only 3.3% of the participants reported acetaminophen to be mostly or extremely helpful. NSAIDs were rated slightly higher, with 14% of the participants rating them to be mostly or extremely helpful, and 41.9% of the participants rating them to be moderately helpful. There was still a large percentage of participants reporting NSAIDs to be rarely or not at all helpful at 44.1%. The majority of participants reported antidepressants to be rarely or not at all helpful at 65.2%. Only 12.7% of the participants found antidepressants to be moderately or extremely helpful, which contrasted with the comparative percentages between the combined cohorts of participants ever-using antidepressants (66.7%) and participants using antidepressants in the past year (69.4%). One would expect the percentage of participants taking antidepressants to decrease from the ever-use to the past-year category if they were not helpful for pain control. As discussed above, this may be due to other non-pain control benefits of the antidepressants in survey participants, such as enhancing the mood of the participants. Opioids were reported to be the most effective in the statistically significant groups. Only 13.9% of the participants found opioids to be rarely or not at all helpful, with 29.2% of the participants rated opioids to be moderately helpful, and 58.9% of the participants rated them as mostly or extremely helpful.

The effectiveness of physical therapy effectiveness was not particularly clear in the Demes et al population, with 39.5% of the participants rating it rarely or not at all helpful. Thirty-five percent of the participants rated physical therapy to moderately helpful, and 25.6% of the participants found it to be mostly or extremely helpful. In summary, TENS therapy appeared to be slightly more effective than acetaminophen use, although 46.5% of the participants rated TENS therapy as rarely or not at all helpful. Moreover, 41.4% of the participants rated TENS therapy to be moderately effective. Only a small portion of participants rated TENS therapy mostly or extremely helpful at 12%.¹⁶

The perceived lack of effectiveness of many of the therapies identified by Demes et al is troubling, considering the frequency at which these therapies are suggested or prescribed to persons with EDS. Physical therapy is often regarded as a mainstay of treatment in these patients, but its perceived effectiveness by patients was not as strong as one would expect.¹⁴ Pharmacological treatments often focus on acetaminophen, NSAIDs, and antidepressants due to the apprehension of many providers to prescribe opioids. The poor response to antidepressants coupled with the high percentage of participants utilizing antidepressants illustrates the need for further research to be done studying the pathophysiology of pain in patients with EDS. Many of the current recommendations are developed from fibromyalgia and other chronic pain disorders.⁴ Fibromyalgia patients typically respond to antidepressants with a decrease in pain, whereas this study shows that patients with EDS typically do not.²⁶ The poor response to acetaminophen is also concerning, given how often it is recommended to these patients for control of pain. The slightly better pain reduction achieved with NSAIDs may be limited in practice due to increased bleeding tendencies in patients with EDS. The current climate surrounding the use and prescription of opioids in the US is likely harming patients with EDS. While opioids are not benign medications, they were one of the only therapies that provided quality pain relief in these participants, with only 13.9% of the participants

reporting them as rarely or not at all helpful. Further research including larger sample sizes, and randomized controlled trials must be done to look at the effectiveness of these therapies.¹⁶

In “Pain control methods in use and perceived effectiveness by patients with Ehlers-Danlos syndrome: a descriptive study”, Arthur et al surveyed 1179 adults with Ehlers–Danlos syndrome (EDS). The survey took place between August 2013 and January 2014; because of this, the diagnosis of EDS and its subtypes were based on the 1997 Villefranche diagnostic criteria instead of the current 2017 International Classification of the Ehlers–Danlos syndromes. The incongruity between the two diagnostic criteria may limit the generalizability of this study’s findings to patients diagnosed with the updated 2017 criteria. The vast majority (75.1%) of patients surveyed had Hypermobility Type EDS (EDS-HT). The participants were self-selected as participants were notified of the survey through various EDS websites, online support groups, conferences, and patients on the mailing list for a prominent EDS specialist. The authors noted that the method of distributing the survey among these channels could impact the types of EDS patients surveyed and exclude a large portion of EDS patients. In general, underdiagnosis of EDS likely impacts the population of this and other studies, as many patients reported having to see several medical professionals prior to diagnosis with EDS. This could exclude patients that do not have the financial resources or have such severe disability that they cannot seek out diagnosis from multiple medical professionals. The study had a large sample size, which gives more weight to the level of evidence from this study. The population was heavily female predominant at 93.9%, which is similar to the population prevalence of females diagnosed with EDS versus males. The authors noted that this could still impact the types of pain control methods used by females vs males, and their efficacy. The survey relied on self-reporting of EDS diagnosis, which may impact the reliability of the participants’ diagnoses.¹⁷

Arthur et al utilized the Pain Management Strategies Survey to look at the prevalence and efficacy of various pain control methods in both acute and chronic pain associated with EDS. The pain control methods included a total of 42 strategies, which were chosen based off the then current EDS management guidelines. Effectiveness of the pain control strategies were graded on a 1–5 scale, with 1 being “not helpful at all”, and 5 being “helpful all of the time”. The authors combined the participants scores for effectiveness of the pain control strategies into a mean and standard deviation. The number of acute and chronic pain control strategies used by each patient in the last 6 months were combined. The number of pain control strategies and their perceived effectiveness were examined using Pearson’s correlations.¹⁷

Acute pain control strategies used most frequently by EDS patients in the last 6 months included ice therapy, creams or ointments, acetaminophen, NSAIDs, and heat therapy. Acetaminophen use was reported in 12.5% with a mean efficacy score of 2.11 ± 0.95 of patients in the past 6 months, while NSAIDs were reported in 11.5% of the patients in the last 6 months with a mean efficacy score of 2.64 ± 0.89 . Ice therapy was the most utilized treatment for acute pain management in the last 6 months at 20.1% with a mean efficacy score of 2.74 ± 0.94 . Heat therapy was utilized by 11.3% with a mean efficacy score of 2.84 ± 0.93 of participants. Creams and ointments were utilized by 12.6% of the participants in the past 6 months, with a mean efficacy score of 2.42 ± 0.89 . The comparable efficacy scores and ranges between acute pain control strategies indicate that none of these methods are particularly more effective than one another at managing acute pain.¹⁷

Chronic pain control strategies used most frequently by EDS patients in the last 6 months included anti-seizure medication, regular exercise, counseling or psychotherapy, herbal remedies, and diet management. The percentage of participants utilizing these strategies was reported along with the mean efficacy and standard deviation. Anti-seizure medications were utilized by 9.3% of the patients for chronic pain control in the last 6 months, with a mean efficacy score of 2.65 ± 1.29 . Regular exercise was the most utilized chronic pain management strategy in the last 6 months at 19.35%, and mean efficacy score of 2.76 ± 0.98 . Counseling or psychotherapy was utilized by 7.7%, with a mean efficacy score of 2.42 ± 1.12 . Herbal remedies were utilized by 9.0% with a mean efficacy score of 2.11 ± 0.89 . Diet management was utilized by 10.6% with a mean efficacy score of 2.51 ± 0.96 for chronic pain management in the past 6 months. Much like many of the acute pain control strategies, the similar efficacy scores and ranges between chronic pain control strategies indicate that none of these methods are particularly more effective than one another at managing chronic pain.¹⁷

The most utilized pain control strategies in the past 6 months for both chronic and acute pain in the Arthur et al survey included avoidance of potentially damaging strategies, heat therapy, splints or braces, physical therapy, and opioids. Opioids were utilized in the past 6 months by 34.1% of the participants with a mean efficacy score of $3.55 \pm$

1.09. Opioids were perceived as the most effective pain control method. Physical therapy was utilized by 34.9% of the participants with a mean efficacy score of 2.81 ± 1.20 . Heat therapy was utilized by 40.7% of the participants with a mean efficacy score of 3.11 ± 1.08 . Splints or braces were utilized by 38.8% of the participants with a mean efficacy score of 3.18 ± 1.10 . The most used pain control strategies in the last 6 months included avoiding potentially dangerous activities at 60.2% with a mean efficacy score of 3.00 ± 1.14 . Similar to acute and chronic pain control strategies, the combined category of both chronic and acute pain control strategies had comparable efficacy scores and ranges, indicating that none of these methods were particularly better or worse at controlling pain in the participants. Arthur et al found opioids to be the most effective method for controlling pain, similar to the conclusions of Demes et al.¹⁷

The diverse acute and chronic pain control strategies in EDS patients highlight the lack of efficacy of any one treatment option, and the diversity of symptoms and experiences of patients with EDS. The support for one specific acute and chronic pain control method was weak. The pain control management strategies perceived as the most effective were not the most widely used methods of pain control. Examples of this include the use of opioids in acute pain management strategies, chronic pain management strategies and the combined acute and chronic pain management strategies. This is likely due to the inaccessibility of opioids compared to other interventions. As mentioned previously, opioids are not benign medications, which is illustrated by the current opioid epidemic. While it was necessary for providers to decrease the number of opioids prescribed nationally, the pendulum may have very well swung too far in the other direction. The current climate regarding opioid prescriptions may harm patients with chronic, lifelong conditions that have tried various other methods of pain control without real relief. More research needs to go into developing safe prescribing guidelines for opioids in patients with EDS to better find a balance between prescribing opioids too frequently and too little.¹⁷

The data in the Arthur et al paper with other modalities showed similar trends. The slightly higher efficacy of NSAIDs in comparison to acetaminophen comes with a drawback of the increased risk of NSAIDs and their adverse effects in patients with EDS. Ice and heat therapy were utilized commonly by patients and provided decent pain relief. Heat was slightly more effective in both the acute and chronic pain categories. This therapy is easily accessible and provides few to no adverse effects.¹⁷ Regular exercise was the most utilized chronic pain management strategy, with a mean efficacy score of 2.73 ± 1.19 .¹⁷ This is expected, considering the weak evidence of exercise regimens providing a benefit to pain control, as identified by other authors. Regular exercise should be done under the supervision of a physical therapist or medical professional to ensure that it does not negatively impact the patient's pain level and condition. The use of anti-seizure medication to control chronic pain was not surprising, considering current guidelines for treating chronic pain and chronic pain in relation to EDS often suggest anti-seizure medications or antidepressants, particularly for neuropathic pain as suggested by Chopra et al.⁴ Their efficacy in patients was weak at 2.20 ± 1.33 in the combined acute and chronic categories.¹⁷ The large standard deviation shows the variability in efficacy person to person in patients with EDS, although, anticonvulsants and antidepressants typically work well in patients with fibromyalgia.^{4,17,26} Much of the current pathophysiology of pain in EDS is presumed to be similar to pain in fibromyalgia, but the decreased effectiveness of fibromyalgia treatments (such as antidepressants and anticonvulsants) brings into question how similar the pathophysiology of the two conditions are.^{4,17,26} More research needs to be done to discover the pathophysiology of pain in EDS to better formulate treatments for pain.⁸

Clinical Bottom Line

Given the prevalence of chronic pain in patients with hEDS, it is important to find effective pain control methods for this population. Current literature suggests a multidisciplinary approach including physiotherapy, cognitive behavioral therapy, and pharmacological interventions.⁴ Lack of literature regarding the EDS and the hEDS subtype makes it difficult to ascertain that the key pieces of literature identified in the search and reviewed and analyzed here demonstrated weak evidence to support physiotherapy as an effective pain control method in EDS. There were lower levels of evidence to suggest the efficacy of cognitive behavioral therapy in pain control for patients with EDS, and this evidence was weaker than the intervention of physiotherapy.¹⁶ Pharmacological interventions had similar levels of evidence, with opioids being the most commonly perceived effective medication by patients with EDS.¹⁶ There was not significant evidence to support the pharmacological treatment of one category over another, with NSAIDs, acetaminophen,

anticonvulsants, and antidepressants also being suggested as therapy.¹⁶ Other pain control methods with weak evidence of their efficacy included braces, splints, heat therapy, and cold therapy.¹⁶ The mechanisms of nociceptive pain that appear to accompany dislocations and soft-tissue trauma in patients with hEDS may be responding to those modalities. Based on this information, the management of chronic musculoskeletal pain in a patient with hEDS should proceed with the various components suggested above. In addition, the patient should be referred to physiotherapy to strengthen the musculature to support weak joints.

Cognitive behavioral therapy may be suggested to assist with desensitization of pain, given the possible nociplastic pain mechanisms identified by studies such as De Wandele et al.⁹ Cold therapy, and heat therapy should be recommended, as well as avoidance of activities that may cause increased pain. Pharmacological interventions may begin with the addition of over-the-counter acetaminophen, and discontinuation of ibuprofen or other NSAIDs due to bleeding risk. If these recommendations are not effective, splinting and braces may be recommended.¹⁶ Other pharmacological therapies may include the addition of anticonvulsants or change of antidepressants. The re-addition of NSAIDs may be done with careful monitoring. In the case of severe breakthrough pain, or acute episodes of pain opioids may be necessary to provide relief of symptoms. There is weak evidence to support current practices, but little to no evidence at this point in time to suggest alternative pain control methods, thus demonstrating the need for further research.

Acknowledgments

The lead author thanks S. Lahey, Schaffer Library of Health Sciences, for assistance with initial searches.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Parker SP, Stoler JM. Clinical manifestations and diagnosis of Ehlers-Danlos syndrome. In Post TW, ed. UpToDate; 2021. Available from: <https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-ehlers-danlos-syndromes>. Accessed May 1, 2022.
2. Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet.* 2017;175(1):8–26. doi:10.1002/ajmg.c.31552
3. Ehlers-Danlos Support UK. Types of EDS; 2017. Available from: <https://www.ehlers-danlos.org/what-is-eds/information-on-eds/types-of-eds/>. Accessed November 4, 2021.
4. Chopra P, Tinkle B, Hamonet C, et al. Pain management in the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet.* 2017;175(1):212–219. doi:10.1002/ajmg.c.31554
5. Grahame R, Hakim AJ, Tofts L. Clinical manifestations, and diagnosis of hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorder. In Post TW, ed. UpToDate; 2021. Available from: <https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-hypermobile-ehlers-danlos-syndrome-and-hypermobility-spectrum-disorder>. Accessed November 4, 2021.
6. Callewaert B, Malfait F, Loeys B, De Paepe A. Ehlers-Danlos syndromes and Marfan syndrome. *Best Pract Res Clin Rheumatol.* 2008;22(1):165–189. doi:10.1016/j.berh.2007.12.005
7. International Association for the Study of Pain (IASP). Terminology. Washington DC: International Association for the Study of Pain (IASP); 2021. Available from: <https://www.iasp-pain.org/resources/terminology/>. Accessed August 10, 2022.
8. Malfait F, Colman M, Vroman R, et al. Pain in the Ehlers-Danlos syndromes: mechanisms, models, and challenges. *Am J Med Genet C Semin Med Genet.* 2021;187(4):429–445. doi:10.1002/ajmg.c.31950
9. De Wandele I, Colman M, Hermans L, et al. Exploring pain mechanisms in hypermobile Ehlers-Danlos syndrome: a case-control study. *Eur J Pain.* 2022;26(6):1355–1367. doi:10.1002/ejp.1956
10. The Ehlers-Danlos Society. Why do we need awareness? Available from: <https://www.ehlers-danlos.com/may-awareness/why-we-need-awareness/>. Accessed November 4, 2021.
11. Roberts J. Ehlers-Danlos Syndrome (EDS). DynaMed. EBSCO Information Services; 2021. Available from: <https://www.dynamed.com/condition/ehlers-danlos-syndrome-eds>. Accessed November 4, 2021.
12. Grahame R, Hakin AJ, Tofts L. Treatment and prognosis of hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorder. In Post TW, ed. UpToDate; 2021. Available from: <https://www.uptodate.com/contents/treatment-and-prognosis-of-hypermobile-ehlers-danlos-syndrome-and-hypermobility-spectrum-disorder>. Accessed November 4, 2021.
13. OCEBM Levels of Evidence Working Group. The Oxford levels of evidence 2. Oxford Centre for Evidence-Based Medicine. Available from: <https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebml-levels-of-evidence>. Accessed August 10, 2022.
14. Palmer S, Davey I, Oliver L, Preece A, Sowerby L, House S. The effectiveness of conservative interventions for the management of syndromic hypermobility: a systematic literature review. *Clin Rheumatol.* 2021;40(3):1113–1129. doi:10.1007/s10067-020-05284-0
15. Celletti C, Paolucci T, Maggi L, et al. Pain management through neurocognitive therapeutic exercises in hypermobile Ehlers-Danlos syndrome patients with chronic low back pain. *Biomed Res Int.* 2021;2021:6664864. doi:10.1155/2021/6664864
16. Demes JS, McNair B, Taylor MRG. Use of complementary therapies for chronic pain management in patients with reported Ehlers-Danlos syndrome or hypermobility spectrum disorders. *Am J Med Genet A.* 2020;182(11):2611–2623. doi:10.1002/ajmg.a.61837

17. Arthur K, Caldwell K, Forehand S, Davis K. Pain control methods in use and perceived effectiveness by patients with Ehlers-Danlos syndrome: a descriptive study. *Disabil Rehabil*. 2016;38(11):1063–1074. doi:10.3109/09638288.2015.1092175
18. Toprak Celenay S, Ozer Kaya D. Effects of spinal stabilization exercises in women with benign joint hypermobility syndrome: a randomized controlled trial. *Rheumatol Int*. 2017;37(9):1461–1468. doi:10.1007/s00296-017-3713-6
19. Daman M, Shiravani F, Hemmati L, Taghizadeh S. The effect of combined exercise therapy on knee proprioception, pain intensity and quality of life in patients with hypermobility syndrome: a randomized clinical trial. *J Bodyw Mov Ther*. 2019;23(1):202–205. doi:10.1016/j.jbmt.2017.12.012
20. Reyckler G, Liistro G, Piérard GE, Hermanns-Lê T, Manicourt D. Inspiratory muscle strength training improves lung function in patients with the hypermobile Ehlers-Danlos syndrome: a randomized controlled trial. *Am J Med Genet A*. 2019;179(3):356–364. doi:10.1002/ajmg.a.61016
21. Pacey V, Tofts L, Adams RD, Munns CF, Nicholson LL. Exercise in children with joint hypermobility syndrome and knee pain: a randomised controlled trial comparing exercise into hypermobile versus neutral knee extension. *Pediatr Rheumatol Online J*. 2013;11(1):30. doi:10.1186/1546-0096-11-30
22. Kemp S, Roberts I, Gamble C, et al. A randomized comparative trial of generalized vs targeted physiotherapy in the management of childhood hypermobility. *Rheumatology*. 2010;49(2):315–325. doi:10.1093/rheumatology/kep362
23. Bale P, Easton V, Bacon H, et al. The effectiveness of a multidisciplinary intervention strategy for the treatment of symptomatic joint hypermobility in childhood: a randomised, single Centre parallel group trial (The Bendy Study). *Pediatr Rheumatol Online J*. 2019;17(1):2. doi:10.1186/s12969-018-0298-x
24. Palmer S, Cramp F, Clark E, et al. The feasibility of a randomised controlled trial of physiotherapy for adults with joint hypermobility syndrome. *Health Technol Assess*. 2016;20(47):1–264. doi:10.3310/hta20470
25. Bathen T, Hångmann AB, Hoff M, Andersen LØ, Rand-Hendriksen S. Multidisciplinary treatment of disability in Ehlers-Danlos syndrome hypermobility type/hypermobility syndrome: a pilot study using a combination of physical and cognitive-behavioral therapy on 12 women. *Am J Med Genet A*. 2013;161(12):3005–3011. doi:10.1002/ajmg.a.36060
26. Moret C, Briley M. Antidepressants in the treatment of fibromyalgia. *Neuropsychiatr Dis Treat*. 2006;2(4):537–548. doi:10.2147/ndt.2006.2.4.537

Journal of Pain Research

Dovepress

Publish your work in this journal

The Journal of Pain Research is an international, peer reviewed, open access, online journal that welcomes laboratory and clinical findings in the fields of pain research and the prevention and management of pain. Original research, reviews, symposium reports, hypothesis formation and commentaries are all considered for publication. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/journal-of-pain-research-journal>