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CONTINUING EDUCATION ACTIVITY

Pain Management in Patients With Hypermobility Disorders: Frequently Missed Causes of Chronic Pain

Linda Stapleford Bluestein, MD

Learning Objectives/Outcomes: After participating in this CME/CNE activity, the provider should be better able to:

1. Describe the various types of hypermobility.
2. Identify signs and symptoms of hypermobility spectrum disorders.
3. Develop treatment plans for patients with hypermobility disorders that address their specific and unique needs.

Key Words: Chronic pain, Connective tissue disease, Ehlers-Danlos syndromes, Hypermobility, Musculoskeletal pain

Chronic musculoskeletal symptoms account for a vast amount of health care utilization and are a leading cause of impairment and deterioration of quality of life. Clinicians frequently observe the presence of musculoskeletal pain in patients with joint hypermobility, although in too many cases, the hypermobility goes unrecognized. Over the past few decades, more attention has been drawn to Ehlers-Danlos syndrome (EDS) and related disorders, although there has also been confusion over diagnostic labels and criteria. This article addresses some of the recommendations by the International Consortium on Ehlers-Danlos Syndromes, many of which were updated in March 2017. Chronic and acute

In This Issue

Dr. Bluestein is Assistant Professor, Medical College of Wisconsin–Central Wisconsin, 333 Pine Ridge Blvd, Ste 2-730, Wausau, WI 54401; E-mail: lbluestein@mcw.edu.

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pain are both common manifestations of many of the Ehlers-Danlos subtypes and other hereditary disorders of connective tissue (HDCT); however, the focus of this article is on pain management in patients with hypermobile EDS (hEDS) and those with hypermobility spectrum disorder (HSD), collectively referred to as hypermobility disorder (HD).

Overview and Incidence

Studies have demonstrated a high percentage of generalized joint laxity in the general population, with about 10% to 15% of males and 20% to 40% of females in young adulthood and adolescence affected.[1] Joint hypermobility (JH) may be localized to 1 to several joints (LJH), peripheral if occurring in the fingers and toes (PJH), or generalized (GJH). A goniometer is recommended for accurate assessment of joint range of motion. Not all patients with JH are symptomatic, and the appropriate terminology as recommended by the International Consortium on Ehlers-Danlos Syndromes is demonstrated in Table 1 and described in more detail below.[2]

In certain occupations, such as ballet dancing, GJH can be an asset, and GJH is highly prevalent among ballet dancers with estimates as high as 60% to 90%.[3,4] JH is more prevalent among females, dancers, gymnasts, musicians, and in Asians and West Africans, and decreases with age.

Joint hypermobility syndrome (JHS) was the earlier term used most commonly to describe symptomatic hypermobility. The prevalence of JHS was difficult to ascertain due to the variability of diagnostic criteria, although it was felt to be a common cause of widespread joint pain.[5] In a 2013 survey in

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Table 1. The Spectrum of Joint Hypermobility

Type	Beighton Score	Musculoskeletal Involvement	Notes
Asymptomatic GJH	Positive	Absent	
Asymptomatic PJH	Usually negative	Absent	JH typically limited to hands and/or feet
Asymptomatic LJH	Negative	Absent	JH limited to single joints or body parts
G-HSD	Positive	Present	
P-HSD	Usually negative	Present	JH typically limited to hands and/or feet
L-HSD	Negative	Present	JH limited to single joints or body parts
H-HSD	Negative	Present	Historical presence of JH
hEDS	Positive	Possible	

GJH, generalized joint hypermobility; hEDS, hypermobile Ehlers-Danlos syndrome; HSD, hypermobility spectrum disorder; JH, joint hypermobility; LJH, localized joint hypermobility; PJH, peripheral joint hypermobility. Adapted from Hakim.[9]

the United Kingdom, 3% of the general population reported the combination of JH and chronic widespread pain, typical of patients with JHS.[6] It was estimated that in the general population the frequency of symptomatic GJH was likely somewhere between 0.75% and 2%,[7] although these incidence rates may be underestimated due to the lack of awareness of the prevalence of JHS, especially among patients presenting to chronic pain and rheumatology clinics.[5] The true prevalence of hEDS is unknown, although recent estimates translate to 10 million affected in the United States, 2 million in the United Kingdom, 17 million in Europe, and 255 million worldwide.[8]

With the 2017 International Classification on EDS, clarity has been given to the criteria for all 13 subtypes including hypermobile EDS, by far the most common type. The term "JHS" and the numerous other older terms have been dropped and their use is highly discouraged. Patients with hypermobility-related problems not meeting the new, stricter criteria for hEDS, or other HDCT, will now most likely fall into the classification of HSD. Patients suspected of another HDCT should be referred for expert opinion, which may include genetic testing, vascular imaging, and ophthalmologic evaluation.[9]

HD, whether hEDS or HSD, may be associated with extra-articular manifestations occurring in such systems as cardiovascular, autonomic nervous system, gastrointestinal, ocular, gynecologic, neurologic, and psychiatric. Fatigue and sleep disturbances are also frequently associated.[9]

Patients with HD experiencing potentially debilitating symptoms of widespread joint pain with or without systemic manifestations, whatever the underlying cause, deserve prompt and appropriate intervention. Early diagnosis, albeit challenging, is essential and may eliminate unnecessary surgical procedures, prevent further functional decline, and avoid excessive financial and time expense and inappropriate therapies.[10] With proper recognition and treatment, severe disability may be avoided particularly in children, where late diagnosis might add to the severity of symptoms and level of disability later in life.[11]

Diagnostic Criteria

JH is genetically determined and is defined as an excessive range of movement within the joint(s) factoring in age, sex, and ethnic background and is most commonly identified using the Beighton score.[1,5,11,12] This scoring system (Figure 1), first introduced in 1973, is the most commonly used method to identify polyarticular hypermobility, although other scoring systems have been developed to address sites not included in the Beighton score (such as shoulders, cervical and thoracic spine, hips, ankles and mid-foot, and first metatarsophalangeal joint). A total of 9 points are collated from 5 maneuvers.

Two other tools rarely used are the Rose-Querol score and the Contompasis score; the Beighton score remains the only validated scoring system and is used the most often in both clinical settings and epidemiologic research.[13] One challenge with this scoring system is the natural decrease in joint motion that occurs with aging. For this reason, some authors have advocated using historical Beighton scores. In 2003, Hakim and Grahame[14] developed a 5-part questionnaire (5-PQ) to identify patients with GJH (Table 2) with 2 or more affirmative answers suggesting generalized JH with a sensitivity of 80% to 85% and a specificity of 80% to 90%.

The most common hereditary connective disorder is likely the hypermobile type of Ehlers-Danlos syndrome (hEDS) previously known as EDS type III. The Brighton criteria and Villefranche nosology were previously used to establish the diagnosis; however, current medical literature complicates differentiation and describes multiple different disorders and associated symptoms.[8] Because of this, a group of physicians with expertise in treating patients with EDS formed the International Consortium on Ehlers-Danlos syndromes in 2012 to update the nosology for EDS and related disorders, and to develop best-practice clinical guidelines.[15] With the 2017 Classification, there is now a clear set of diagnostic criteria for each EDS subtype. Of patients with EDS, 80% to 90% have hEDS.[8] However, many patients previously

The Beighton score is calculated as follows:

1. One point if while standing forward bending you can place palms on the ground with legs straight
2. One point for each elbow that bends backwards
3. One point for each knee that bends backwards
4. One point for each thumb that touches the forearm when bent backwards
5. One point for each little finger that bends backwards beyond 90 degrees.

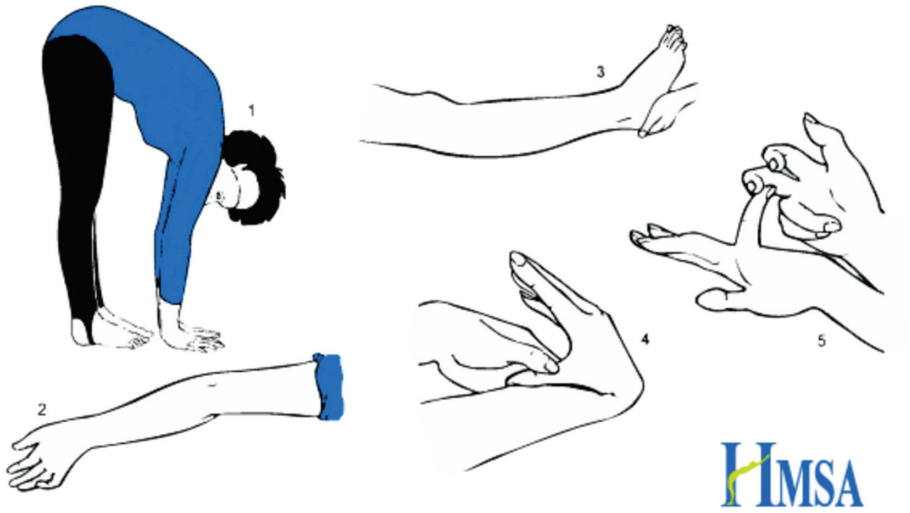

Figure 1. Calculation of the Beighton score. With permission from the Hypermobility Syndromes Association (http://hypermobility.org/help-advice/hypermobility-syndromes/beighton-score/).

diagnosed with EDS-HT/JHS will not meet the stricter set of criteria for hEDS under the new nosology. These patients with symptomatic JH may likely receive the updated diagnosis of HSD.[15] With the 2017 Classification, the previous terms in use—including EDS-HT, EDS-type III, JHS, hypermobility syndrome, and benign joint hypermobility syndrome—are now considered outdated and their use is discouraged.[15]

Table 2. Five-Part Questionnaire for Identifying Hypermobility

Ask the patient the following questions:

1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child did you amuse your friends by contorting your body into strange shapes *or* could you do the splits?
4. As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?
5. Do you consider yourself double-jointed?

Calculate score: Affirmative answers to 2 or more questions suggest hypermobility, with sensitivity 80%–85% and specificity 80%–90%.

Modified from Hakim and Grahame.[1]

All subtypes of EDS share the clinical hallmarks of JH, skin hyperextensibility, and tissue fragility. The definite diagnosis of all subtypes except hEDS relies on molecular confirmation of (a) causative variant(s) in the respective gene. The genetic basis of hEDS is still unknown, likely reflecting genetic heterogeneity, and therefore the diagnosis is based on clinical findings.[16] The hEDS diagnostic criterion is specifically defined in the new nosology and is dependent on a positive Beighton score plus 2 or more among musculoskeletal criteria, systemic involvement, and positive family history.[15]

Under the proposed 2017 Classification, the diagnosis of hEDS requires a patient to fulfill each of 3 separate domains. For Domain 1, GJH, the required Beighton score is 6 for prepubertal children and adolescents, 5 for pubertal men and women up to the age of 50 years, and 4 for those older than 50 years for hEDS. A diagnosis of GJH may also be made if the Beighton score is 1 point below these specific set points *and* the 5-PQ is positive (at least 2 affirmative answers).[16]

Domain 2 addresses 3 distinct areas: systemic manifestations of a more generalized connective tissue disease, musculoskeletal complications, and family history. Among these 3 areas within Domain 2, patients must meet the strict specifications described for at least 2 of the 3. The final domain, Domain 3, essentially functions to eliminate the other EDS subtypes and other HDCT.[16]

Due to the highly specific diagnostic criteria for hEDS, many patients previously identified with JHS will no longer

fit the requirements for hEDS and will be most likely diagnosed with HSD. Four different HSD subtypes have been identified, with the first 3 being distinguished by type of JH involvement (GJH, LJH, or PJH) occurring in conjunction with 1 or more musculoskeletal manifestations (Table 1). Patients with GJH-HSD should be carefully assessed to rule out the possibility of full-blown hEDS. Most patients not meeting the full diagnostic criteria for hEDS will fall into this category. H-HSD, the fourth type, consists of patients with a negative Beighton score but having historical HSD (eg, by the 5-PQ). Clinically, a single continuous spectrum can be used to consider these disorders ranging from asymptomatic JH to full-blown hEDS, passing through the various HSDs.[9,15]

The diagnosis of hEDS or HSD is made clinically, as no laboratory test, imaging study, or genetic testing currently exists to definitively establish the diagnosis. Fatigue and sleep disturbances are commonly reported. Other extra-articular symptoms are dermatologic and gastrointestinal, with prior studies demonstrating 33% to 67% of patients with HD experiencing functional bowel disorders.[17] Patient symptoms have often been dismissed or misdiagnosed, with the most common being chronic fatigue syndrome, fibromyalgia, hypochondriasis, and/or malingering.

Imaging of the affected region may show degenerative disease, vertebral listhesis, or joint subluxation, although static images may also appear normal. Dynamic ultrasound and weight-bearing images may be more informative.

Clinical Picture

The clinical picture is often variable, involving many systems and pain perception.

Musculoskeletal

Hypermobile joints are at increased risk of acute and chronic dislocations, subluxation, and soft tissue injury due to joint instability. Patients with HD experience these injuries spontaneously or with minimal trauma, with frequent recurrence. Sometimes reduction of the dislocation occurs spontaneously or may be accomplished by the affected individual or a family member. The most common sites are the base of the thumb at the carpometacarpal joint, the shoulder, and the patella. Other "injuries" occur in hypermobile individuals during small everyday activities such as opening doors, changing from one position to another, or sustained posture at end-range joint motion. The onset of pain can be instantaneous or insidious, and if JH is not recognized, it may be hard to appropriately assess the cause of the problem, and the patient's symptoms are easily dismissed.

In HD, all or some joints can have a greater-than-expected range of motion with ankles, knees, hips, and the temporomandibular joint (TMJ) being common sites. Patients may experience iliotibial band syndrome ("snapping hip") and interpret this as hip joint instability. TMJ syndrome is relatively common and represents a specific example of early joint degeneration and osteoarthritis. Tendon and ligamentous injuries are common, as is bursitis, although inflammation is not usually a causative factor in the chronic symptoms these patients experience.

Overall, males report pain and major joint complications less frequently than females and clinical variability is significant, perhaps due to differences in pain perception, inherent joint stability, and/or the effects of sex hormones.[18] Reduced endurance and generalized muscle weakness have been demonstrated in patients with both asymptomatic and symptomatic hypermobility.

Pain

Chronic pain, distinct from that seen with acute injuries, is a frequent and serious complication of HD, with often physically and psychologically disabling results. Approximately 30% of children with HD experience arthralgias, back pain, and myalgias, with greater than 80% of adults older than 40 years having similar symptoms.[19] This evolution occurs despite a progressive decrease of the Beighton score, which, at a mean age of 33, tends to fall below a Beighton score of 4 even in highly symptomatic subjects.[19]

Several forms of pain have been described as more prevalent. Nociceptive pain presenting in or around joints may be attributable commonly to soft tissue injuries or myofascial spasm.[19] Symptoms are usually of acute arthralgias occurring mainly in the shoulders, knees, and hands. Foot pain is also common, likely due to multiple joint dysfunctions. Myofascial pain is frequent and may be a cause of temporomandibular dysfunction. Back pain may be due to a variety of causes, including palpable spasm with point tenderness (like that seen with fibromyalgia), especially in the paravertebral musculature. The distinction between fibromyalgia and hEDS is important, as the distinction will affect the treatment plans. However, they can be virtually impossible to distinguish from one another, due to significantly overlapping symptomatology.[8]

No less than one-third of patients report headaches, with migraine being the most common type.[20] Hypermobility of the cervical spine may also be an important factor in the patient with daily persistent headache, and cervical myofascial pain is frequent. Patients with HD may present with a Chiari malformation type I, due to instability at the occipitoatlantoaxial junction.[17] Pain due to osteoarthritis can occur earlier than in the general population and presents usually with aching/stiff joints with exacerbations due to stasis and/or highly repetitive activities. Osteoporosis and osteopenia have also been reported to occur with increased frequency in patients with HD. This lower bone mass may delay the repair of fractures, which can lead to pain amplification.[21]

A high incidence of neuropathic pain is seen in HD, with two-thirds of patients experiencing at least "probable" neuropathic pain.[22] Patients often describe the pain as burning, shooting, numb, electric, or with hot/cold intolerance. A radicular or peripheral nerve distribution may be present, or the pain may appear to localize to an area surrounding one or more joints. One hypothesis is that nerve compression causes

neuropathic pain via subluxations and/or osteoarthritis. Nerve compression could also occur within areas of myofascial spasm. HD has been associated with mild axonal polyneuropathy and compression neuropathies.[23] Differentiating between nociceptive and neuropathic is a crucial step in developing efficient treatment strategies, particularly because only 11% of Patients with HD are prescribed neuropathic pain medications whereas almost 90% take analgesic mediations regularly.[23]

Painful sensations may also assume dysfunctional features with widespread manifestations such as complex regional pain syndrome, fibromyalgia, functional abdominal pain, dysmenorrhea, vulvodynia, and dyspareunia. Recurrent abdominal pain is very frequent, occurring in up to 68% of patients. Symptoms of gastroesophageal reflux, gastritis, constipation, and diarrhea are very common as well.[17,19] Visceral pain and hypersensitivity may be due to excessive laxity of the hollow viscera, and autonomic nervous system dysfunction may contribute to abdominal symptoms as well.[24]

There is evidence for generalized hyperalgesia in adult patients with HD.[25] Even in asymptomatic areas of their body, patients with HD may have considerably lower pressure thresholds as compared with healthy controls.[25] It is hypothesized that central upregulation occurs in the central nervous system (CNS), which could cause the onset of chronicity. Central sensitization may also be the reason why patients with HD are more susceptible to pain and fatigue. The reduced effectiveness of lidocaine in some patients with HD is also supportive evidence of upregulation and can be distressing to the patient.[26] It is possible that central sensitization is a CNS adaptation helpful in countering adverse events due to joint instability (and the decreased proprioceptive feedback in patients with HD) and may even be protective.[27]

Other Manifestations

Hyperelasticity of the skin, easy bruising, striae, and abnormal scarring are valuable clues to the diagnosis of HDCT, although the severity varies greatly among the different disorders. Skin manifestations in HD are usually mild; if skin manifestations are severe, an HDCT other than HD should be considered. Cardiovascular autonomic dysfunction may be associated with HD; prompt referral to a cardiologist or neurologist with experience in dysautonomia is indicated, should potential autonomic symptoms appear. The most common signs and symptoms pointing to cardiovascular dysfunction include rapid heart rate (palpitations), presyncope or syncope, visual impairments, cognitive dysfunction (often described by patients as "brain fog"), chest pain, chronic fatigue, temperature dysregulation, tremulousness, orthostatic intolerance, peripheral vasoconstriction, sleep disturbance, exercise intolerance, and postexercise malaise.[28]

Anxiety is even more prevalent in patients with HD than in patients with other chronic pain states and can significantly contribute to increased pain, disability, depression, and kinesiophobia. The basis for this finding is not fully understood; however, there may be a relationship to dysautonomia. Hernias, rectal/uterine prolapse, and bladder dysfunction are more frequent in HD. Increased joint laxity is seen in all women during pregnancy, when symptoms of joint pain may rise. Fatigue is an extremely common manifestation and is likely related to poor sleep and/or autonomic nervous system dysfunction and suboptimal pain control. Up to 90% of patients with HD older than 40 years report fatigue.[19]

Neurologic manifestations may arise due to weakness of the ligaments of the craniocervical junction and spine and those of the epineurium and perineurium surrounding peripheral nerves. Early disc degeneration may also occur in addition to spinal segment instability and kyphosis. Although epidemiologic evidence is not yet available, an increased prevalence of migraine, idiopathic intracranial hypertension or hypotension, Tarlov cysts, tethered cord syndrome, Chiari malformation type I, and dystonia has been reported. Patients may experience early, chronic, and debilitating musculoskeletal pain, myelopathy, myalgia, and easy fatigability with impairment of mobility and daily activities.[29]

Pain Management in Patients With HD

Patients with HD, like those with other chronic pain syndromes, are likely to experience significant psychologic and physical disability. The major challenge facing patients with HD is pain management and associated physical limitations.[10] Pain management goals should address improving functional capacity, reducing symptomatology, and decreasing dependency on the health care system and caregivers. There is no "magic bullet" or cure. However, a combination of nonpharmacologic and pharmacologic intervention may greatly improve quality of life.

Due to a paucity of evidence-based studies, treatment recommendations are based largely on the clinical opinion of experts.[10,24,30] The lack of an evidence-based approach for treatment of pain in these patients also reflects the scant attention paid by health care providers to the needs of this group.[21] Scales and standardized questionnaires (eg, ID Pain, Neuropathic Pain Symptom Inventory, Pittsburgh Sleep Quality Index, and Central Sensitization Inventory) may be useful in guiding therapy.[21]

Pharmacologic

Pain in HD has various causes, including subluxation/dislocation, tendinopathies, neuromuscular tone, central and peripheral sensitization, and physiologic factors. Pharmacologic management should be directed at each of these contributing factors. Analgesics are often underprescribed and should be tailored to the patient's subjective symptoms, rather than to radiologic findings or physical examination. Pharmacologic treatment should be used in conjunction with physical rehabilitation and management of associated psychologic symptomatology.

Acetaminophen (paracetamol in Europe), although the weakest analgesic, is considered first-line therapy for nociceptive pain in HD due to its safety profile. The maximum daily dose is 4 g per day, although with long-term use 3 g per day is recommended by some manufacturers. With heavy alcohol use or

significant liver disease, acetaminophen is relatively contraindicated and, if used, the maximum daily dose is thought to be 2 g per day. Other potential sources of acetaminophen must also be taken into consideration. Patients may find improved benefit with extended-release formulations (every 6- to 8-hour dosing) due to fewer peaks and troughs. Such dosing may be especially beneficial at night, as many of these patients experience sleep disturbances and subsequent fatigue.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the anti-inflammatory agents of choice and should be selected on the basis of individual patient risk profile and duration of action desired. NSAIDs can be particularly useful for the secondary inflammatory conditions (eg, bursitis or postdislocation pain), and for arthralgia and myalgia. Cyclooxygenase-2 inhibitors may be preferable for patients at increased risk of gastrointestinal and renal side effects. The small but appreciable cardiovascular risk with this class of drugs is also an important consideration.

Corticosteroids produce the greatest anti-inflammatory effect; however, they may increase skin bruising. The potential side effect from corticosteroids includes collagen-content reduction in joint capsules. This reduction of collagen can add to the magnitude of hypermobility and should be taken into consideration. Corticosteroids, either by the oral or intra-articular route, are rarely indicated and should be used at the lowest possible dose for the briefest possible time. However, short courses of corticosteroids can be very effective for controlling acute pain flares due to secondary inflammation. Chronic corticosteroid use is not appropriate as HD is not an intrinsically inflammatory disorder.[31]

Skeletal-muscle relaxants may be considered in combination with the above therapies to treat myofascial spasm, although caution should be exercised as there is a theoretic risk of increasing joint instability via reduced muscle tone. Increased fatigue and sedation may also occur even with metaxalone, the least-sedating agent. Benzodiazepines may reduce muscle spasm and provide anxiolysis, although they carry a high risk of tolerance, dependency, and addiction. Alternative muscle relaxants should be chosen, if they are used at all.[31]

Anticonvulsants such as gabapentin and pregabalin (often referred to as gabapentinoids) are effective for neuropathic pain and have been used to treat neuropathic pain in HD. These drugs should be started at a low dose, with gradual titration up to a maximum daily dose of 3600 mg for gabapentin (1200 mg thrice a day) and 300 mg for pregabalin (dosed twice a day or thrice a day). Sedation, dizziness, weight gain, and gastrointestinal side effects may limit use with either medication; however, gabapentin (the less expensive alternative) is less well tolerated than pregabalin. Topiramate and lamotrigine have also been tried with some success.[30]

Gabapentin and pregabalin can be used in combination with tricyclic and/or serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants. Antidepressants are useful for neuropathic pain with tricyclic antidepressants (TCAs) and SNRIs preferred. TCAs dosed in the evening provide the additional benefit of sedation, thereby decreasing sleep disturbances that commonly occur with patients with HD. The dose of amitriptyline is titrated to 10 and 150 mg approximately 2 hours before bedtime, although some patients develop side effects at doses ineffective at providing analgesia. Prolonged sedation, dizziness, tachycardia, dry mouth, constipation, and increased appetite are commonly observed. Nortriptyline (25–150 mg) causes less sedation and may therefore be better tolerated.[31] These drugs should be prescribed with caution in patients with ischemic cardiac disease or ventricular conduction abnormalities. Patients older than 40 years should have a screening electrocardiogram per guidelines from the International Association for the Study of Pain.

SNRIs, such as venlafaxine, desvenlafaxine, and duloxetine, and selective serotonin reuptake inhibitors (SSRIs, eg, fluoxetine) can be beneficial in treating neuropathic pain, depression, and anxiety that commonly coexist with HD.[31] Safety concerns with these drugs include headache, nausea, insomnia, dizziness, constipation, orthostatic hypotension, and hyponatremia, and rare instances of hepatic failure. Occasionally, TCAs and SSRIs are used in combination; in particular, the combination of amitriptyline and fluoxetine has been found to have enhanced benefits.[30] Each of these drugs should be titrated carefully, with close monitoring of side effects. Practitioners must also be aware that all antidepressants carry a warning from the FDA regarding an increased risk of suicide, particularly among children and young adults, often preceded by violent behaviors, mania, or aggression.[30] Caution should be exercised when prescribing anticonvulsants, TCA, and SSRI/SNRI medications, as they may worsen other symptoms of HD such as dysautonomia.[32]

Tramadol, with its combined μ-opioid activity and inhibition of serotonin/norepinephrine reuptake, has been shown to improve pain scores with good tolerability in fibromyalgia and has been used effectively as a second-line analgesic to treat neuropathic pain. The most common side effects are constipation and nausea. Enhanced effects are seen with the combination of tramadol with acetaminophen and/or NSAIDs. The maximum recommended daily dose of tramadol is 400 mg per day in divided doses.[30] Monitoring for signs and symptoms of serotonin syndrome is essential as many of the above medications raise serotonin levels.[8]

Opioids are currently the most effective analgesics in Western medicine and have some use in myofascial and/or neuropathic pain, although they are generally considered second- or third-line analgesics for these conditions. Opioids should be administered only after failing with the above medications or should be prescribed in conjunction with the above medications (except tramadol) to minimize opioid requirements. Risks of substance abuse and overdose are important considerations for chronic opioid use. Transcutaneous applications, such as fentanyl patches, may be effective.[30]

Cannabinoids can relieve muscle spasm and pain in patients with HD and represent an alternative class of drugs, although their use in chronic pain is controversial. The potential for dependency and/or psychoactive effects must be considered. Although several different types of pain may be improved

with dronabinol and marijuana, the latter is still considered illegal in many states and is still illegal under US federal law.[31] The long-term adverse effects are unknown, and side effects include dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination.[30]

It is important to educate patients about the half-life of each analgesic prescribed to optimize expectations and minimize report of "drug failure" when perhaps pain recurred due to expected pharmacokinetics.[30] Medication management should be directed at improving functional capacity through symptom control, as complete obliteration of pain is very unlikely. Patients should be informed of these goals. Polypharmacy is often employed as no single treatment is usually sufficiently effective. Most drugs used therapeutically in HD need to be tapered gradually upon cessation to avoid seizures and other side effects.

Transcutaneous medication delivery may be useful in addition to the oral route. Topical application of NSAIDs and/or lidocaine (gel, creams, patches, etc) may be applied directly to the affected area and provide some symptom relief. It is important to remember that drug distribution still occurs throughout the body, so systemic side effects are not avoided. (eg, topical NSAIDs still carry the risk of gastrointestinal side effects).[30] Some patients may derive psychologic benefits from local drug application, whereas others find the procedure cumbersome. Individualization is key. Topical lidocaine, in particular, has shown efficacy in patients with neuropathic pain, with gel (5%) being substantially less expensive than the 5% lidocaine patch.[30]

Capsaicin may be useful for neuropathic pain treatment. Patient education is essential as meticulous hand washing is required to avoid the accidental spread to other parts of the body such as mucous membranes or the genital area. Up to one-third of patients will discontinue therapy due to intolerance.[30] Capsaicin is available over-the-counter in several forms, and the 8% patch has been recommended as a second-line analgesic in the treatment of neuropathic pain.

Hormonal fluctuations may influence pain with a flare-up of symptoms occurring during the progesterone-dominated portion of the menstrual cycle. Symptoms may improve during the estrogen-dominant portion. Therefore, progesterone-only contraceptives may be contraindicated and estrogen formulations may be somewhat protective. Patients may also experience a change in symptoms with hormonal therapy for a concomitant medical condition such as antiestrogen therapy or the use of male sex hormone agonists or antagonists.[30] Many patients with HD report mucosal issues with their genital area and painful intercourse. Topical estrogens may be beneficial for dyspareunia. In severe cases, lidocaine gel just before intercourse may be tried.[8]

Custom-compounded formulations can be used topically and may be beneficial. Commonly included drugs are gabapentin, ketamine, diclofenac, baclofen, cyclobenzaprine, and tetracycline. Some limitations include variations in insurance coverage, potential difficulties locating compounding pharmacies, and patient-compliance issues (eg, messiness and frequency of application required).

Magnesium may be effective in reducing muscle spasm and pain with various forms being useful (Epsom salt baths, oral or topical formulations). Glucosamine and chondroitin may provide benefit to some patients.[31] Other supplements considered potentially useful to combat fatigue include L-carnitine (250 mg daily) and coenzyme Q10 (100 mg per day).[21]

Additional treatment considerations for complex regional pain syndrome may include calcitonin, bisphosphonates, and spinal cord stimulation, and mirror visual feedback and hand laterality recognition physiotherapy.[21] Neuropathic pain may also respond to neural mobilization, neuromodulation, or radiofrequency therapy.[21]

Nonpharmacologic

Physical therapy is a critical component in the management of pain in hypermobile patients and should be focused on the whole body rather than on a single joint.[33] Ideally, patients are referred to a physical therapist with appropriate expertise and experience working with patients with HD. Once patients understand that their pain is due to hypermobility and associated musculoskeletal insufficiencies, they will likely be more motivated to take an active role in the rehabilitation program. Education is essential, so that patients understand that participation in therapy will enable more appropriate joint motion, stronger muscles, and better joint protection, all of which will aid in the lessening of pain, although patience is required, as it is a slow and gradual process.[33] Sometimes having patients keep a journal with brief entries during rehabilitation can assist in tracking improvement in functional capacity, as changes are so gradual that they might otherwise be missed.

Patients with hypermobility derive benefits from postural training and working with a therapist on proprioception, as joint-position sense is often impaired. Retraining exercises using neutral positions and often involving taping should be performed with the eyes open and then closed to improve proprioception.[33] Due to the lack of joint awareness, poor posture is common and postural taping, corsets, or pressure garments may be helpful. Support can also be provided as needed to hypermobile areas via tight garments such as compressive sleeves, form-fitting underwear, Lycra cycling shorts, or specific splints and braces.[33]

Hypermobile patients benefit from education regarding stretching to regain and/or maintain muscle length and relieve muscle tension. Stretching safely, without overstretching into hypermobile or vulnerable areas, will help improve function.[33] Patients should be encouraged to practice good postural and ergonomic hygiene during sleep, at school, and in the workplace.[21]

Kinesiophobia, a maladaptive cognitive process, commonly occurs in hypermobile patients and other chronic musculoskeletal

pain disorders. This fear of movement amplifies muscular deconditioning and increases catastrophizing of physical impairment and fatigue. If patients are informed that biomechanical dysfunction can be improved, they are likely to have less kinesiophobia and lower levels of disability.

Pacing is an essential part of the educational component of pain management in hypermobile patients.[33] As in other chronic pain conditions, deconditioning is often the result of cycles of overactivity, resulting in a flare-up of pain and then periods of rest and underactivity. These cycles can lead to feelings of inadequacy and weakness but can be lessened by teaching pacing skills. Alteration between active and sedentary tasks, high-intensity muscle work with low-intensity work, and balancing flexibility with muscular strength, can assist with increasing activity levels and reducing flare-ups. Caution should be exercised when engaging in activities involving repetitive motion, and patients should avoid excessive weight lifting or carrying.[21] Educational efforts should be directed at avoiding further soft-tissue injuries while maintaining as much activity as possible. Education regarding the beneficial effects of regular aerobic fitness and healthy weight control is essential and may improve mood and reverse some of the deconditioning that often occurs.[21] Prolonged sitting or recumbence and sudden head-up posture changes should be avoided.[21]

Symptoms can be improved after several months of strengthening exercises. Low-resistance exercises with a gradual increase in repetition are often recommended. Determining the zone in which patients are "safe but sore" requires practice and an appropriate level of vigilance. Although resistance bands can be beneficial, caution should be used with such devices.

Specialized physical therapy may be required, such as occupational therapy for hand and upper extremity symptoms or pelvic physical therapy for symptoms in the areas of the hips and pelvis. Hydrotherapy, especially in warm water, can be particularly useful for muscle spasm and maintaining muscle tone without aggravating symptoms. Myofascial release, a massage therapy designed to reduce tension in muscles and fascia, may be beneficial in reducing pain, anxiety, and lactic acid build-up in some patients. With participation and awareness, patients may learn how to release muscles that have developed an overactive and dominant pattern. Yoga can be helpful in reducing symptoms; however, patients should be instructed in modification when appropriate to reduce the likelihood of symptom exacerbation through overstretching. Other adjuncts such as Pilates, the Alexander Technique, and Tai Chi may be particularly helpful as they use slow, controlled movements.[33] At least initially, patients may find more benefit from class exercises rather than unsupervised sessions at the gym, where they may perform movements incorrectly, overexercise or exercise into their hypermobile range of joint motion.

Assistive devices may be useful, such as seat pads and specialized mattresses that may increase comfort in sitting and supine positions, respectively. Crutches should be used with great caution, if at all, due to the strain placed on the upper extremities. If offloading of the lower extremities is necessary, a wheelchair or scooter may be more beneficial.[31] Hard foods and excessive jaw movements (chewing ice, gum, etc) should be avoided and malocclusion should be treated early.[21]

Psychologic

Patients with HD have often experienced symptoms for a long duration with severe deconditioning, kinesiophobia and psychologic effects. They may hold detrimental beliefs about their pain and disability. The lack of recognition and knowledge of the disease may further add to the patient's distress before a diagnosis is established. Education about hypermobility should be geared toward addressing their fears and concerns about weakness and vulnerability of their tissues while encouraging paced exercises and activity to improve confidence. Patients with chronic pain frequently experience depression and anxiety. Pain catastrophization is also common and may result in a poorer prognosis. Referral to a psychologist and/or psychiatrist may be appropriate, as cognitive behavioral therapy, in addition to pharmacotherapy directed at psychologic symptoms, produces optimal results. Guided imagery and meditation are 2 other adjuncts that may dramatically improve symptoms.

Prevention of Disability

Screening in certain populations with a high prevalence of GJH, such as dancers, gymnasts, athletes, and musicians, may be beneficial, with educational approaches directed at maintaining muscle strength to maximize joint protection. Psychologic effects should be carefully assessed in patients with symptomatic hypermobility and those with other causes of chronic pain, as earlier treatment of comorbid depression, anxiety, and catastrophizing may improve outcome.

Conclusion

HDs are underappreciated causes of both acute and chronic pain and should be considered when treating any patient with polyarthralgias. Individualized treatment encompassing pharmacologic management, physical therapy, and psychologic support is essential. With the 2017 International Classification on Ehlers-Danlos syndromes, there is a new standard for the diagnosis of EDS and related disorders, which should greatly advance future research and allow significant improvements in quality of care.

Patients should be encouraged to take an active role in their care, particularly regarding physiotherapy and the management of psychologic concerns. Further education, self-help and supportive advice are available through such organizations as the Hypermobility Syndromes Association (hypermobility.org) in the United Kingdom and the International Ehlers-Danlos Society (Ehlers-Danlos.com). Patients with

hypermobility syndromes can have a much better quality of life and be more productive members of society if their needs are addressed in effective and comprehensive ways. ■

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Topics in Pain Management CE Quiz

To earn CME credit using the enclosed form, you must read the CME article and complete the quiz and evaluation assessment survey on the enclosed form, answering at least 70% of the quiz questions correctly. **Select the best answer and use a blue or black pen to completely fill in the corresponding box on the enclosed answer form.** Please indicate any name and address changes directly on the answer form. If your name and address do not appear on the answer form, please print that information in the blank space at the top left of the page. Make a photocopy of the completed answer form for your own files and mail the original answer form in the enclosed postage-paid business reply envelope. Your answer form must be received by Lippincott CME Institute by **June 30, 2018**. Only two entries will be considered for credit.

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1. **It is important to recognize and understand HD because**
   A. it is often misdiagnosed and inadequately managed
   B. there may be significant extra-articular manifestations that need to be addressed and treated
   C. late diagnosis may add to the severity of symptoms and disability later in life
   D. all of the above
2. **Joint hypermobility**
   A. is always symptomatic
   B. does not affect proprioception
   C. may be an asset in some populations, such as dancers
   D. never causes muscular weakness in asymptomatic patients
3. **Which one of the following patients presenting to your clinic is *least* likely to have an HD?**
   A. A 50-year-old woman with a Beighton score of 1/9, chronic widespread pain, and fatigue
   B. A 32-year-old retired ballet dancer with anxiety, arthralgia, and symptoms suggesting autonomic disorder
   C. A 40-year-old man with hypertension, chronic pain, and obstructive sleep apnea
   D. A 22-year-old woman with a Beighton score of 6/9, chronic migraine headaches, and recurrent subluxations of both shoulders
4. **Extra-articular manifestations that may be associated with hEDS include**
   A. obstructive sleep apnea
   B. autonomic nervous system abnormalities
   C. decreased skin elasticity
   D. inflammatory bowel disease
5. **The diagnosis of hEDS or HSD**
   A. is usually made by laboratory testing
   B. should be made clinically using the 2017 Classification
   C. always depends on the Beighton score regardless of the patient's age
   D. can be determined by genetic testing and imaging
6. **All of the following are signs and symptoms of HD *except***
   A. hyperextensible skin
   B. chronic widespread pain, fatigue, and anxiety
   C. impaired glucose tolerance
   D. uterine or rectal prolapse
7. **Medications *most likely* to be useful to treat pain in patients with HD include**
   A. SNRIs, TCAs, NSAIDs, topical lidocaine, acetaminophen
   B. corticosteroids
   C. extended-release opioids
   D. none of the above
8. **Recommendations for physical therapy for patients with HD include**
   A. stretching into the patient's hypermobile range of motion
   B. high-load and high-repetition exercises
   C. high-load and low-repetition exercises
   D. treatment by a physical therapist with expertise in HD when possible
9. **Joint hypermobility can cause**
   A. increased muscular strength
   B. dislocation and subluxation of peripheral and central joints
   C. increased stability of joints and surrounding soft tissues
   D. decreased risk of soft-tissue injury
10. **Individualized management of patients with HD should include**
    A. the use of orthotics and splints with referral to podiatry for foot symptoms
    B. rehabilitative physiotherapy and addressing psychologic needs
    C. pharmacotherapy directed at symptom control
    D. all of the above

ICYMI: IN CASE YOU MISSED IT

Notes from recent studies related to pain management, compiled by Elizabeth A. M. Frost, MD.

Intraoperative Methadone Reduces Postoperative Hydromorphone

Pain after spinal fusion surgery is often severe for several days. The authors of this blinded study—in which anesthetic care was standardized—randomized 120 patients to receive either methadone 0.2 mg/kg at the start of surgery or hydromorphone 2 mg at surgical closure. The primary outcome measured IV hydromorphone consumption on postoperative day 1. Pain scores and satisfaction with pain management were measured at postanesthesia care unit admission, 1 and 2 hours postadmission, and on the mornings and afternoons of postoperative days 1 to 3.

Median hydromorphone use was reduced in the methadone group on postoperative day 1 (4.56 mg vs 9.90 mg), and on postoperative days 2 (0.60 mg vs 3.15 mg) and 3 (0 mg vs 0.4 mg; all $P < 0.001$). Pain scores at rest, with movement, and with coughing were less in the methadone group at 21 of 27 assessments (all $P = 0.001$ to < 0.0001). And overall satisfaction with pain management was higher in the methadone group until the morning of postoperative day 3 (all $P = 0.001$ to < 0.0001).

Murphy GS, Szokoi JW, Avram MJ, et al. Clinical effectiveness and safety of intraoperative methadone in patients undergoing posterior spinal fusion surgery: a randomized, double-blinded, controlled trial. *Anesthesiology.* 2017;126(5): 822-833. doi:10.1097/ALN.0000000000001609.

New Requirement in New York to Train in Pain, Palliative, Addiction Care

A new statutory mandate in New York required all licensed health care prescribers in that state who are registered with the US Drug Enforcement Administration to complete 3 hours of training in pain management, palliative care, and addiction. The requirement had to be satisfied by July 1, 2017, with courses such as the 2017 New York Mandatory Prescriber Education Course.

Ketamine Study Finds Risk of Incontinence Even at Low Dose

In a study of 262 patients treated with low-dose ketamine infusions for pain relief associated with cancer, 2 patients developed urinary urgency and incontinence. Although this effect has been described after anesthetic or in abuse cases, it has not been reported to date in low-dose usage.

Vickers BA, Lee W, Hunsberger JA. Case report: Subanesthetic ketamine infusion for treatment of cancer-related pain produces urinary urge incontinence. *A&A Case Reports*. 2017;8(9):219-221. doi:10.1213/XAA.0000000000000472.

Persistent Opioid Use After Surgery in the United States

The authors reviewed 36,177 US adults (66.1% women; 72.1% white) who had filled an opioid prescription in the month before surgery or within 2 weeks after discharge, but not in the year before surgery. Two groups were identified: patients who had undergone either minor (80%) or major (20%) elective procedures. The sample was compared with 492,177 age-matched patients who had not undergone surgery or filled an opioid prescription during a 12-month period. These individuals were assigned a random fictitious surgery date.

The 2 groups showed similar rates of new persistent opioid use, defined as a prescription filled between 90 and 180 days after surgery: 5.9% in the minor surgery group versus 6.5% in the major surgery group. The rate was 0.4% in the nonsurgical comparison group.

The finding of similar rates of use between the minor and major surgery groups suggests "persistent opioid use may be less associated with postsurgical pain than addressable patient-level factors," the authors stated. The factors identified included preoperative tobacco use, alcohol and substance abuse, mood disorders, anxiety, and preoperative pain.

Brummett CM, Waljee JF, Goesling J, et al. New persistent opioid use after minor and major surgical procedures in US adults [published online April 12, 2017]. *JAMA Surg*. doi:10.1001/jamasurg.2017.0504.