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REVIEW

Pain in Ehlers-Danlos syndromes: manifestations, therapeutic strategies and future perspectives

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ABSTRACT

Introduction: Ehlers-Danlos syndrome (EDS) groups together an increasing number of hereditary soft connective tissue disorders. Among the most common variants, the hypermobility type emerges as the most problematic, due to clinical similarities with the joint hypermobility syndrome, strong association with pain and lack of molecular confirmatory tests. To date, chronic pain and the related physical disability are the most relevant clinical issues in the long-term management of EDS.

Areas covered: A literature review was carried out covering all known pain manifestations, i.e. musculoskeletal pain, neuropathic pain, central sensitization, headache and visceral pain, in EDS. The natural history of pain, as well as other critical issues, i.e. heterogeneity, clinical approach and evolving phenotype, of EDS are also addressed. All available data on therapeutic strategies for pain in EDS are extensively reported.

Expert opinion: Multidisciplinarity emerges as an undeniable prerequisite for the management of the complex EDS patient reporting pain. All available therapeutic resources, comprising painkillers, physical and psychological therapies, and surgery, show a low evidence of efficacy in the long-term treatment of pain. Education and early diagnosis are primary resources for secondary and tertiary prevention. Novel drug therapies could be developed considering the potential role of a dysfunctional extracellular matrix on pain modulation in EDS.

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Ehlers-Danlos syndrome; joint hypermobility; management; pain; treatment

1. Background

1.1. Disease definition and classification

Ehlers–Danlos syndrome (EDS) is an umbrella term for an increasing number of hereditary soft connective tissue disorders (HSCTDs) featuring generalized joint hypermobility (GJH) and related complications, abnormal skin texture often manifesting with hyperextensible and/or soft/velvety and/or translucent skin, and laxity and/or fragility of the internal organs and vessels. The Villefranche nosology identifies six well-defined types, namely classical, hypermobile, vascular, kyphoscoliotic, arthrochalasia, and dermatosparaxis, for which major and minor diagnostic criteria are defined [1]. These major forms of EDS can be differentiated by the presence of key clinical features (e.g. papyraceous scars for the classical type), inheritance pattern, and mutated gene(s). Among them, the hypermobile type (EDS-HT) is the most problematic one. In fact, it is the unique EDS variant still lacking a major causative gene, is regularly recognized by a combination of non-specific features, and shows marked overlap with the joint hypermobility syndrome (JHS).

JHS is a rheumatologic entity defined by a different set of diagnostic criteria (i.e. Brighton criteria) published 2 years after the Villefranche nolosogy [2]. It features GJH, widespread pain and additional findings. Similarly to EDS-HT, JHS is recognized by exclusion of partially overlapping conditions and lacks of any laboratory confirmatory test. Although the two sets of criteria are not exactly the same and emphasize different aspects of the diseases, many experts and recent segregation studies support a clinical identity between EDS-HT and JHS, with the delineation of a single entity (temporarily named JHS/EDS-HT) at least in the familial cases [3,4]. Not all researchers agree with such an assumption [5], and future research and international consensus are expected in order to shed more light on the issue.

In the last two decades, old and new additional rarer variants of EDS have been re-delineated or identified. The present nosology of EDS includes no less than 22 additional minor EDS variants with 18 different causative-genes identified (Table 1). Most EDS clinical variants are caused by mutations in genes involved in collagen biogenesis or other components of the extracellular matrix (ECM). An update of the EDS nosology is ongoing trying to merge the most recent discoveries on the molecular and pathophysiological bases of EDS.

1.2. Epidemiology

EDS has been considered a rare disorder with a presumed overall frequency of ~1/5000 in the general population [6]. An Eurordis survey on 12,000 patients with selected rare disorders showed that EDS is the disease suffering from the

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Article highlights

- Ehlers-Danlos syndrome comprises an under-diagnosed group of hereditary soft connective tissue disorders, sharing generalized joint hypermobility, abnormal skin texture, and fragility/dysfunctions of internal organs and vessels.
- Pain is common in Ehlers-Danlos syndrome, particularly in the hypermobility type, and it is strongly related to reduced quality of life and physical disability.
- In Ehlers-Danlos syndrome, pain has heterogeneous manifestations, including osteoarticular pain related to generalized joint hypermobility and its complications, neuropathic pain, headache and visceral pain.
- Pain sensitization has been recently emphasized as a source of symptom chronification in adults. Cardiovascular dysautonomia, sleep disturbance and psychological distress are further contributors to pain-related disability in Ehlers-Danlos syndrome.
- Contemporary therapeutic resources include painkillers, physical therapy, psychological support and surgery, but available literature does not support long-term efficacy and a tailored approach is lacking.
- Education and early diagnosis seem the most effective strategies for secondary and tertiary prevention, and reducing ineffective expenses in a- and oligo-symptomatic patients.
- Quality of life of the chronic patient with Ehlers-Danlos syndrome is poor and novel pain-reduction therapies are needed. Increasing evidence on the effects that various molecules highly expressed in the connective tissues (particularly in the extracellular matrix) have on pain, points out Ehlers-Danlos syndrome as a model for identifying novel therapeutic targets or drugs effective on chronic pain.

This box summarizes key points contained in the article.

Table 1. The nosology of Ehlers–Danlos syndromes.

Subtype	Inheritance	Gene(s)
Villefranche variants		
Classical	AD	*COL5A1, COL5A2*
Hypermobile	AD	Unknown*
Vascular	AD	*COL3A1*
Kyphoscoliotic	AR	*PLOD1*
Arthrochalasia	AD	*COL1A1, COL1A2*
Dermatosparaxis	AR	*ADAMTS2*
Other variants		
Brittle cornea syndrome type 1	AR	*ZNF469*
Brittle cornea syndrome type 2	AR	*PRDM5*
Cardiac-valvular	AR	*COL1A2*
Classical with vascular rupture	AD	*COL1A1*
FLNA-related/with periventricular heterotopias	XL	*FLNA*
Kyphoscoliotic with myopathy and deafness	AR	*FKBP14*
Musculocontractural type 1	AR	*D4ST1*
Musculocontractural type 2	AR	*DSE*
Myopathy overlap	AD, AR	*COL12A1*
Osteogenesis imperfecta overlap	AD	*COL1A1, COL1A2*
Progeroid type 1	AR	*B4GALT7*
Progeroid type 2	AR	*B3GALT6*
Spondylocheirodysplastic	AR	*SLC39A13*
Tenascin X-deficient	AR	*TNXB*
TNXB-CYP21A2 contiguous gene syndrome	AR	*TNXB, CYP21A2*
With periodontitis	AD	Unknown

*Single families with heterozygous mutations in *TNXB*.
AD: Autosomal dominant; AR: autosomal recessive; XL: X-linked.

greatest diagnostic delay, with significant impact on quality of life (QoL) of patients and families (*The Voice of 12,000 Patients*, at www.eurordis.org). This supports the hypothesis that EDS is a significantly underdiagnosed disorder, as proposed by Hakim and Sahota who suggest a frequency of 0.75–2% for any form of symptomatic GJH [7]. Similar results are obtained considering available epidemiological data. GJH, independently from the assessment procedure, has an estimated rate of 6–57% in females and 2–35% in males [8]. Presumably, 3.3% of females with GJH and 0.6% of males will develop some related symptoms in their life [9–11]. Therefore, nearly 0.19–1.9% of females (~1/50–500) and 0.012–0.21% of males (~1/500–8000) in the general population may present with GJH *plus* one or more related symptom. Nevertheless, it is likely that not all individuals with symptomatic GJH have a genetic syndrome, and not all cases of symptomatic and 'syndromic' GJH have EDS. Therefore, EDS remains a rare disorder unless more systemic clinical and molecular epidemiological studies will demonstrate the contrary.

1.3. Introduction to pain

EDS is a highly variable disorder (Figure 1). For decades, practitioners' attention was focused on related mucocutaneous, articular, and vascular issues. This is easily explained by the closeness that these features have with the traditional medical approach that lays on the objective evidence and deadly potential of the diseases. For the first time, Lumley et al. [12] pointed out pain as a major determinant of QoL in EDS. Three years later, Sacheti et al. [13] explored pain in 51 patients with various EDS types and demonstrated its high rate. The awareness on pain definitely went up in 2010, when Dr Voermans and collaborators published a survey on 273 EDS patients (mainly, classical, hypermobile, and vascular types) and found pain as common, severe, and associated with functional impairment [14]. Since then, the number of publications exploring pain and disability in EDS, especially JHS/EDS-HT (which seems the EDS variant more commonly featuring these complications), dramatically increased, but the burden of affected individuals did not decrease.

This paper is intended to review pertinent literature on pain, and actual evidence-based and anecdotal resources for its treatment in the complex patient with EDS. Elements for the interpretation of the huge clinical variability, also comprising pain, of EDS are also presented together with possible future fields of therapeutic research.

2. Heterogeneity and diagnostic issues

EDS is a protean disorder with phenotypic ramifications in potentially all systems and organs. Clinical heterogeneity often reflects locus-specific patterns of altered histogenesis and morphogenesis. Therefore, although highly variable, such a heterogeneity is constrained within relatively well-defined genotype–phenotype correlations. For this reason, clinical-molecular subclassification of patients is crucial not only for genetic counseling, but also for appropriate management. To review the clinical manifestations of the various EDS variants is beyond the scope of this article. However, among the three most commonly encountered variants (i.e. classical EDS, JHS/EDS-HT, and vascular EDS), the prevalence and severity of the involvement of skin, musculoskeletal apparatus, and vessels is strongly influenced by the EDS subtype. Classical

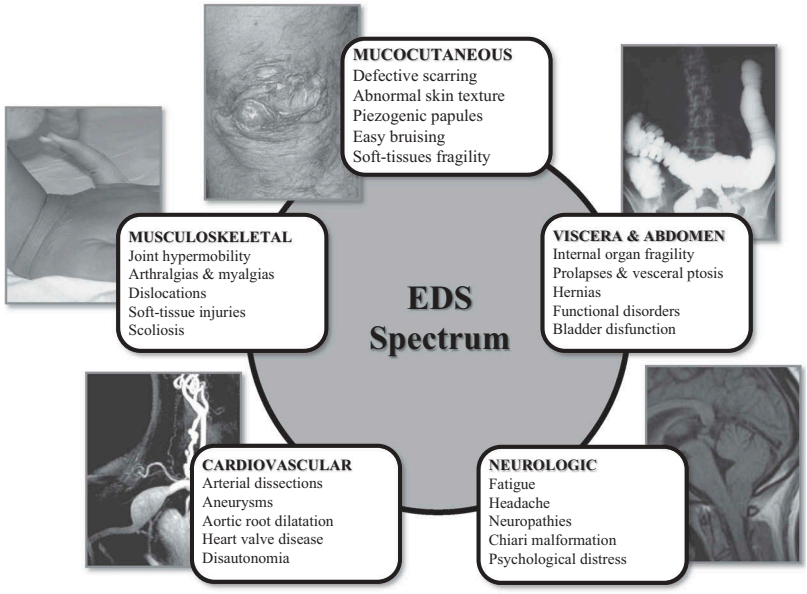

Figure 1. A summary of the clinical spectrum of the various Ehlers-Danlos syndromes (EDS). Many EDS variants manifest with possible mucocutaneous, musculoskeletal, cardiovascular, visceral and neurological features. The clinical variability distinguishing EDS variants and patients mostly lays on the frequency and severity of the involvement of these structures and organs.

EDS typically presents with a recognizable spectrum of cutaneous features, JHS/EDS-HT is usually dominated by GJH complications and pain, while vascular EDS features severe/extensive vascular manifestations.

Besides specific circumstances or rare EDS subtypes, the diagnosis of EDS is rarely straightforward for the untrained physician. It is often formulated after various consultations requested for apparently nonspecific manifestations (e.g. delayed wound healing, pain, extensive bruising). However, once EDS is suspected, reaching the most accurate diagnosis is not easy. Differential diagnosis with other conditions requests expertise and selected instrumental resources. Finally, the identification of the right EDS variant needs the support of an experienced genetics laboratory [15]. At present, not any National or International guidelines are available.

Heterogeneity is not only a matter of diagnosis, but also of clinical assessment. After EDS subtype establishment, first-line investigations useful to support clinical examination for management planning may include full vascular tree study, brain/spine MRI, investigation for small fiber neuropathy, head-up tilt-test, and gastrointestinal tract functional exams. Once the health status of the affected individual has been explored carefully, the patient may be referred to the pertinent specialists. A summary flow-chart for the diagnosis and initial assessment of the patient with (suspected) EDS is presented in Figure 2.

3. JHS/EDS-HT and the evolving phenotype

3.1. Nomenclature

In the past, JHS/EDS-HT has been considered the most benign variant of EDS. Accordingly, this definition was originally linked to JHS that was previously named 'benign joint hypermobility syndrome.' This inaccuracy still happens today in some published papers. However, since the publication of the 'revised' Brighton criteria in 2000, the adjective 'benign' was removed because it does not reflect the overall nature of the disorder [2]. To date, JHS/EDS-HT is considered a systemic disorder with common extra-musculoskeletal manifestations, such as fatigue [16], sleep disturbance [17], cardiovascular dysautonomia [18] and various functional gastrointestinal troubles [19,20]. This constellation of features often leads to periodic consultations with different specialists and sometimes associates with physical disability (see Section 4).

A further source of confusion is the nosologic conundrum between JHS/EDS-HT and isolated GJH, according to the Beighton score [21]. The Beighton score was first introduced in the medical literature as an epidemiological tool to estimate the rate of GJH in African children. Subsequently, it was successfully applied in other populations and, hence, introduced as a rapid screening also in the clinical practice [8]. Now, it is clear enough that GJH is a clinical sign that may be assessed by the Beighton score, while JHS/EDS-HT is a multisystem disorder that *always* features GJH *plus specific* additional anomalies. Unfortunately, the literature is full of reports diagnosing JHS/EDS-HT with the application of the Beighton score (or alternative screening methods for GJH) alone. This phenomenon is quite common in the psychiatric literature (for further details, see [22]).

The use of a standard terminology is essential for both clinics and research of JHS/EDS-HT. Clinics needs accurate patients' stratification for prognostic, management, therapeutic, and economic issues. Research must lay on well-defined phenotypes to realize successful studies deciphering the molecular and pathophysiological basis of the disorder. Practice suggests the existence of a phenotypic continuum among patients with isolated GJH, JHS, and EDS-HT (Figure 3). This spectrum also comprises all individuals who display GJH in association with single additional complaints (i.e. oligosymptomatic GJH) [23]. The existence

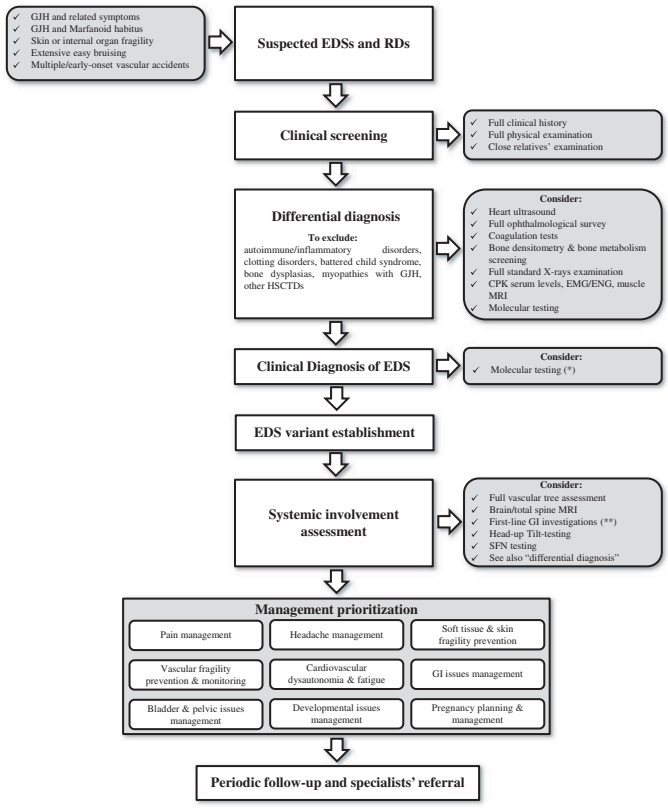

Figure 2. Flow-chart summarizing the diagnostic and initial assessment approach to the Ehlers-Danlos syndrome patient. In selected cases, the management schedule may include additional consultations, such as the ear-nose-throat specialist and the ophthalmologist. CPK, creatine phosphokinase; EDS, Ehlers-Danlos syndrome; EMG/ENG, electromyography/electroneurography; GI, gastrointestinal; GJH, generalized joint hypermobility; MRI, magnetic resonance imaging; RD, related disorder; SFN, small fiber neuropathy. (*): molecular testing is not indicated/available in all cases: e.g., the hypermobility type does not have any confirmatory test; hence, in this case, molecular testing is useful for differential diagnosis only in presence of doubtful clinical diagnoses. (**): fist-line gastrointestinal investigations might include Breath test for lactose intolerance, non-invasive and invasive testing for celiac disease and esophago-gastro-duodenal-scopy.

of this spectrum is derived by extended family studies [4] and the potential transition, that an individual may experience, from non-syndromic GJH to JHS/EDS-HT thanks to the appearing of specific acquired features (e.g. pain).

3.2. Metatropism (evolving phenotype)

The need of revising diagnosis in the absence of any confirmatory test and the changing pattern of emerging clinical manifestations require attention on the natural history of JHS/EDS-HT. As to date JHS/EDS-HT patients represent the prevalent population requesting specialistic consultation, the study of the natural history in JHS/EDS-HT will also help to better manage patients with the rarer EDS subtypes. Ideally, studying the natural history of a disorder implies longitudinal observations on a selected patients' cohort. JHS/EDS-HT is a slowly progressive, chronic disorder and the patients' changing needs usually manifest in decades. Therefore, at the moment, we can extrapolate data only from cross-sectional observations on large samples of patients at different ages [4,24–27].

In brief, patients with JHS/EDS-HT early experience GJH and some live this like an asset, a propensity to specific sports (e.g. ballet). In childhood, some patients develop recurrent/chronic pain usually at the lower limbs (i.e. 'growing' pain) and some coordination troubles, with or without attention and concentration problems. Dislocations may occur, as well as fatigue, recurrent headache and functional gastrointestinal issues, mostly constipation. Individuals, who regularly practice physical activity, have an optimal weight control and are predisposed to a 'confrontation' strategy to fear [28] since their teen are often those with the most successful adult life and overall better prognosis. This is not a rule and symptoms tend to become chronic and progressively affect patients' QoL in early adulthood. Dislocations may reduce in frequency, but soft-tissue injuries and arthralgias are more frequent and, eventually, may become habitual/chronic. In selected individuals, gastrointestinal issues affect multiple tracts of the gut with a mixture of intermittent or chronic complaints. Additional visceral manifestations may worsen in time, including symptoms related to cardiovascular dysautonomia, bladder dysfunction, and pelvic issues, especially in women. In the most advances stages, GJH progressively disappear and the Beighton score may turn negative. Joint hypermobility is slowly substituted by painful stiffness and dysfunctional or degenerative complications (e.g. tempormandibular joint dysfunction, premature osteoarthritis). The most severely patients are those showing widespread chronic pain syndrome and chronic physical disability.

4. QoL and disability

The possibility of a 'restricted life' in EDS was first introduced at the very end of the last millennium by Berglund and collaborators [29]. Ten years afterward, two independent studies formally demonstrated a poor health-related QoL in EDS, especially JHS/EDS-HT [30,31]. Subsequent works tried to dissect the various contributors to the poor QoL in EDS. Among them, there are oral issues [32], functional digestive symptoms [33], kinesiophobia [34], autonomic symptom burden [35], anxiety and depression [36,37], shoulder dysfunction [38], and iatrogenic injuries [39]. QoL seems affected also in children with JHS [40], and a survey shows that the diagnosis negatively affects the ability to work or attend school in more than half of the patients [41]. Taken together, these data recapitulate the multidimensional nature of QoL and testify for the need of a multidisciplinary approach to symptom chronification and disability in EDS.

Voermans and Knoop [42] suggested that pain and fatigue are major contributors to disability in EDS, particularly JHS/EDS-HT. A recent meta-analysis selected 16 papers to explore the disability potential of JHS/EDS-HT [43]. In this study, the disability levels of JHS/EDS-HT are higher than 'isolated' GJH. The authors also selected pain, fatigue, and psychological distress as the likely major contributors to disability. They found a strong relationship with fatigue and psychological distress, while the association with pain was moderate. This suggests a more complex relationship between pain and QoL in EDS and prompts to further research.

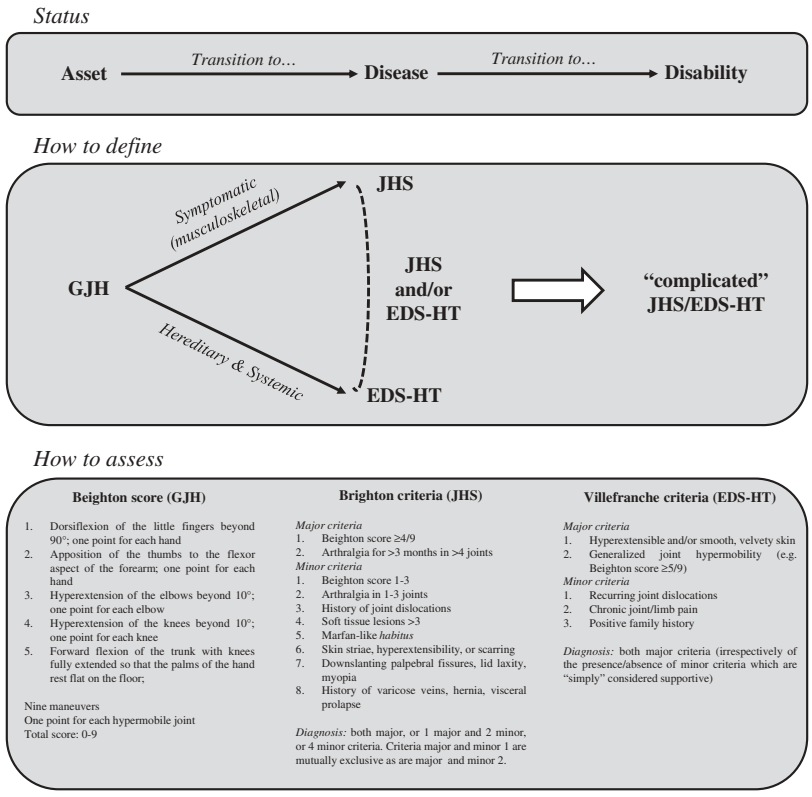

Figure 3. A summary of the Beighton score for assessing generalized joint hypermobility, the Brighton criteria for the joint hypermobility syndrome and the Villefranche criteria for the Ehlers-Danlos syndrome hypermobility type. To date, the joint hypermobility syndrome and Ehlers-Danlos syndrome hypermobility type are considered not distinguishable at the clinical level by many experts according to the available diagnostic criteria. A spectrum comprising individuals with generalized joint hypermobility alone on one end and those fulfilling the Brighton and/or Villefranche criteria on the other is proposed. This spectrum also comprise patients with generalized joint hypermobility and single associated manifestations (i.e. oligosymptomatic) not sufficient for a 'syndromic diagnosis' in the middle, as well as those with chronic physical disability at the extreme right. EDS-HT, Ehlers-Danlos syndrome hypermobility type; GJH, generalized joint hypermobility; JHS, joint hypermobility syndrome.

5. Pain

5.1. Overview

To date, pain is considered a common manifestation of EDS [14]. Available data on pain manifestations and mechanisms usually derive from studies on relatively small patients' samples and most enrolled patients are affected by JHS/EDS-HT. These limitations origin from the rarity of the disorder and the overt predominance of JHS/EDS-HT. Furthermore, very preliminary data and practice suggest that JHS/EDS-HT features musculoskeletal manifestations more frequently than the other 'common' EDS variants. The spectrum of pain manifestations in EDS and JHS/EDS-HT is still incompletely understood [26,44]. Different mechanisms intervene at different ages and/or disease phases with variable, often unpredictable outcomes. The various possible contributors to pain in EDS are summarized in Figure 4 and more extensively described in the following sections.

5.2. Musculoskeletal pain

Nociceptive, joint pain is usually the first manifestation of pain in EDS [44]. It is likely related to the widespread joint instability which may manifest with both macro- and microtraumatism. Macrotraumatism presents with occasional, habitual, or intentional dislocations and increased propensity to soft-tissue traumatisms, especially at the lower limbs and fingers. Propensity to traumas might be amplified by poor proprioception, as repeatedly demonstrated in GJH and JHS/EDS-HT especially in the lower limbs [45]. Accordingly, fear of falling and kinesiophobia are common complaints among women with JHS/EDS-HT [34,46]. The combination of joint laxity and poor proprioception/coordination can lead to a restricted movement with consequent hypotonia and amplification of joint instability. Microtraumatism is probably the background mechanism producing recurrent pain not related to overt traumas and, eventually, contributing to chronic joint pain in EDS. The role of biomechanics and gait in triggering, maintaining, or exacerbating pain in EDS is hypothesized by the predominance of pain at lower limbs, especially in children and in the early phases of pain progression in JHS/EDS-HT. In line with this, many studies demonstrated abnormal gait patterns in adults and children with GJH and JHS/EDS-HT [46–53]. Recurrent myalgias, myofascial pain, and muscle cramps are further common types of musculoskeletal pain in EDS [54].

Early observations suggested a causal relationship between joint hypermobility and osteoarthritis [55], but available data are contrasting to date. In fact, two studies proposed GJH as a protective, rather than predisposing factor to osteoarthritis in apparently non-syndromic adults [56,57]. No further study

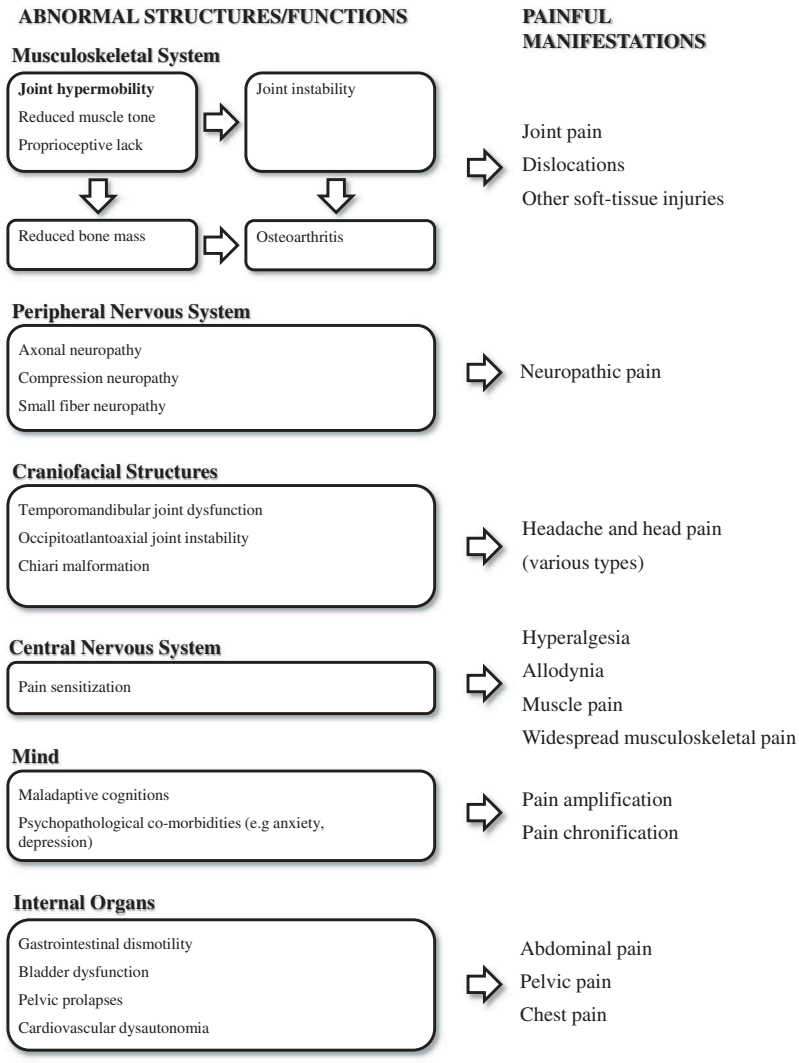

Figure 4. Schematic representation of the various likely contributors to pain in EDS. The different functional and structural factors are listed on the left, while the potentially linked forms of pain are summarized on the right.

explored the issue and focused on patients with syndromic GJH or EDS. In a single work, EDS with periodontitis was associated with premature osteoarthritis [58]. Anyway, practice suggests an increased rate of premature and multisite osteoarthritis in EDS patients, at least in those with JHS/EDS-HT, and this may contribute to the transition to chronic joint pain with morning stiffness in adults. Osteoporosis with propensity to fractures is exceptional in EDS and likely confined to the rare kyphoscoliotic EDS, arthrochalasia EDS, and *osteogenesis imperfecta* overlap. Fractures might also occur with an increased rate in adults with common EDS variants *plus* other factors predisposing to osteoporosis (e.g. premature ovarian failure). An increased rate of fractures in children is not a presentation of EDS [59]. Conversely, some studies pointed out an increased rate of mild reduction of bone density in patients with GJH, EDS, and JHS [60–65]. The reason for this association is unclear and the evidence is preliminary due to the very small patients' samples. Practice again supports the association and a mildly reduced bone mass, while does not significantly predispose to fractures, may still contribute to degenerative joint changes in adults.

5.3. Neuropathic pain

Joint instability is not the unique peripheral mechanism contributing to pain in EDS. Patients often report paresthesias, numbness, and dysesthesias that are hardly explained by the abovementioned processes [26,44]. Accordingly, neuropathic pain explored by a questionnaire study resulted common in JHS/EDS-HT [66]. Compression and axonal neuropathies have been evoked as possible explanation [67]. Accordingly, subluxations and luxations of the ulnar nerve occur more commonly in JHS/EDS-HT [68], and this phenomenon could explain occasional/recurrent manifestations of neuropathic pain. However, many patients describe neuropathic pain also at rest and with strikingly bilateral presentation, a combination that is unlikely related to compression neuropathies. Axonal neuropathies are possible but rare manifestations in EDS [69] and cannot account for a so commonly reported symptom. Recently, small fiber neuropathy was found in 24 adults with EDS (1 with classical EDS, 3 with vascular EDS, and 20 with JHS/EDS-HT) [70]. A case report further supports this evidence [71]. This preliminary finding may represent an entirely novel

approach for understanding pain and, perhaps, other chronic clinical manifestations of EDS. Complex regional pain syndrome may be a rare form of neuropathic pain in EDS [72].

5.4. Pain sensitization

Chronification of pain is a dreadful complication of EDS, especially JHS/EDS-HT [24]. The process leading the transition is incompletely understood. However, as previously speculated [44], some recent studies highlight the existence of pain sensitization in JHS/EDS-HT. The first study demonstrated lower pressure pain thresholds in symptomatic and asymptomatic body areas in 23 women with JHS/EDS-HT compared to controls [73], while lowered cold and heat pain thresholds and increased wind-up ratio were found in a second study on 27 adults with the same condition [74]. A further study confirmed lower pressure pain thresholds in JHS/EDS-HT compared to controls. Interestingly, in this work hyperalgesia was also used to distinguish JHS/EDS-HT from 'asymptomatic' GJH [75]. These researches point out the existence of mechanisms of central sensitization in JHS/EDS-HT. Accordingly, fibromyalgia, a widespread musculoskeletal pain syndrome commonly associated with central sensitization, occurs in 42% of adults with JHS/EDS-HT [41] and shows a significant association with GJH [76].

5.5. Headache and head pain

Headache is an apparently underestimated manifestation of EDS. An early study pointed out a rate of 30–40% out of 51 adults [13]. Another smaller case series reported nine EDS patients presenting with various forms of headache, comprising migraine with or without aura, tension-type headache, a combination of tension-type headache and migraine, and post-traumatic headache [77]. A high rate of headache is reported also by Castori et al. [24] and Rombaut et al. [31]. Migraine appears the most common type of headache in JHS/EDS-HT [78,79]. However, the type(s) of head pain reported by patients is wider and, presumably, different pathophysiological mechanisms may lead to the same overall symptom. In a recent work, a survey of the various processes potentially leading to headache and head pain in EDS was presented [80].

Single studies point out associations between GJH, JHS, or EDS and other types of headache, including new daily persistent headache [81], headache attributed to spontaneous cerebrospinal fluid leakage [82–84], and headache secondary to Chiari malformation [24]. Milhorat et al. [85] suggests a link between Chiari malformation and occipitoatlantoaxial joint instability in patients with recurrence of symptoms after surgery and, among them, found a high rate of features comparable with HSCTDs. Di Palma and Cronin [86] report a 27-year-old woman with classical EDS with a long-lasting pulsating headache associated with C2 dislocation. An early report describes two out of three vascular EDS patients with radiologically evident at lantoaxial subluxation [87]. Although a causal relationship between EDS, occipitoatlantoaxial joint instability, Chiari malformation (type 0), and some headache patterns is a fascinating field of research, definite data are still lacking.

In a cohort of 31 EDS patients (comprising classical EDS, vascular EDS, and JHS/EDS-HT), De Coster et al. [88] demonstrate temporomandibular joint dysfunction in all, unilateral myofascial pain in 83%, and unilateral and bilateral temporomandibular joint arthralgia in 28% and 51%, respectively. Finally, in vEDS, ipsilateral headache may occur together with additional neurologic features, such as ophthalmoplegia and tinnitus, due to vascular accidents, including spontaneous direct cavernous-carotid fistula (see, e.g. [89] or [90]).

5.6. Visceral pain

In EDS, pain does not seem limited to the musculoskeletal system and head. A wide range of visceral forms of recurrent pain are reported by patients with EDS.

Recurrent abdominal pain is reported in 57.1–85.7% of the patients [19,24,25,91]. The highest frequencies are observed among adults and JHS/EDS-HT patients [19,25]. It usually occurs in association of various functional gastrointestinal disorders [20]. The mechanisms leading to abdominal pain are obscure. It was speculated that an increased hollow viscera compliance can facilitate visceral sensitivity and hence generate abdominal pain [26]. Intra-abdominal ligamentous laxity and visceral prolapses are occasionally reported in JHS/EDS-HT and may contribute to abdominal pain [92,93].

In fertile women, dysmenorrhea is common and occasionally associated with polycystic ovaries, endometrial cysts, uterine leiomyomas, endometrial hypertrophy, and endometriosis, but it remains 'idiopathic' in most cases [94]. Pelvic prolapse is a common soft-tissue attribute of EDS, particularly in women with JHS/EDS-HT [95–97], and its presence may contribute to pelvic discomfort and pain especially during exertions. Atypical thoracic pain is another anecdotally reported pain in EDS. Although a musculoskeletal origin (i.e. thoracic cage and respiratory muscles) should be first excluded, thoracic pain may be a presenting feature of postural orthostatic tachycardia syndrome, a common complication of EDS [18,98].

5.7. Comorbidities influencing pain

Psychological distress, fatigue, and sleep disturbances are common comorbidities and their presence may negatively affect pain manifestations and evolution, and ultimately contribute to pain chronification and disability.

Extrapolating homogeneous data on psychological distress in EDS is a hard task due to the extensive use of the single Beighton score for attributing a diagnosis of JHS/EDS-HT in the psychiatric literature [22]. Psychosocial functioning in EDS was selectively assessed by Lumley et al. [12] and Murray et al. [41]. In the first study on 41 adults and 7 children with various EDSs, anxiety, depression, anger, and interpersonal concerns were significantly elevated. The second paper reported the results of a questionnaire study on 466 adults with JHS/EDS-HT, who showed anxiety and depression in 73% and 69% of the cases, respectively. Whether psychological distress is secondary to the preexistent pain, or rather is an independent primary feature amplifying each other with pain, remains to be clarified. A recent work extracted

data from the Swedish national registries and presented epidemiological psychiatric findings in 1780 EDS and 11,082 JHS individuals, as well as on 1722 EDS siblings and a control group [37]. The authors confirmed the association with depression and demonstrate a statistically significant link with bipolar disorder, autism spectrum disorder, attention deficit hyperactivity disorder, and suicide attempt. An excess of depression, suicide, suicide attempt, and attention deficit hyperactivity disorder was also found in nonaffected siblings. A finding that introduces a role for shared environmental and background genetic factors for psychiatric comorbidities in EDS.

Though largely ignored in the past, severe fatigue is now considered a common accompanying feature of EDS, particularly JHS/EDS-HT, as it is reported in up to 84% of the patients [16]. The frequency of fatigue is influenced by age with a rate of 28% in the first decade of life to 90% in adults over 40 years of age [25]. In JHS/EDS-HT, the impact of fatigue on daily life is often equal or more dramatic than the impact of pain [16] – a fact that underscores the importance of fatigue for both assessment and treatment planning in these patients. A complex presentation of fatigue resembling chronic fatigue syndrome according to Fukuda et al. [99] is commonly reported in adults with JHS/EDS-HT [100]. A recent study highlighted the link between fatigue and orthostatic intolerance in JHS/EDS-HT and, therefore, the primary role of cardiovascular dysautonomia on this disability contributor [101].

Two studies explored sleep disorders in EDS. The first work was entirely based on questionnaires, and excluded sleep apnea in EDS but found a high rate of restless leg syndrome [102]. The second paper, reporting the results of polysomnography in 34 EDS patients, demonstrated flow limitation, apneas and hypopneas with a decrease in flow limitation and an increase of apnea and hypopnea events with age. Rhinomanometry also showed increased nasal resistance [17].

Taken together all the fragmented data on pain manifestations and its possible underlying mechanisms in EDS indicate a complex pathogenesis. The slow progression from episodic, low-moderate, and treatment-responsive pain at single joints to chronic, severe, and disabling pain affecting the entire body is probably the sum of various contributors. Some of these factors are directly related to the underlying disorder, while others are disguised under the deceptive cloak of human variability. Following the natural history of pain in EDS, the very first forms of pain are simple in origin and presumably derived by joint instability complications. Subsequently, pain becomes recurrent and progressively extent onto the entire body. Some patients are still able to localize pain and experience a satisfactory life, while others feel defeated and live a very restricted existence (Figure 5).

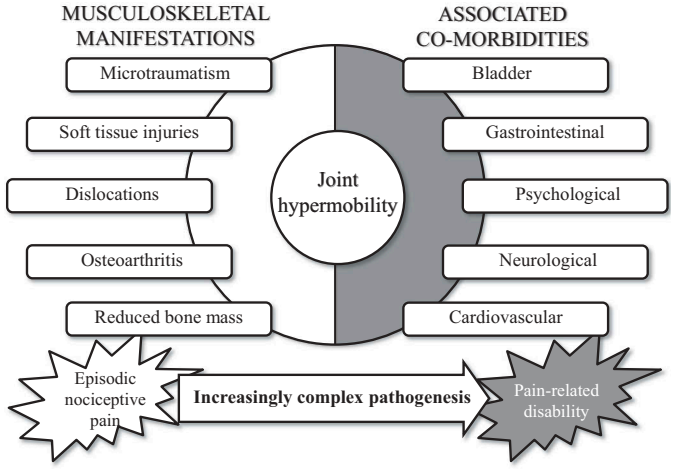

Figure 5. Possible natural history of pain in EDS. Pain usually originates as a simple symptom confined to single joints and episodic. In some people, pain worsens and progressively affects the entire body. In these cases, musculoskeletal pain is widespread and its often combined with other forms of pain, such as different visceral pains and headache. At this stage, multiple factors are contributing to the eventual symptom and related functional consequences.

6. Therapeutic resources for pain

6.1. Drugs

Painkillers and other pain medications are commonly used in EDS, but no clinical trial has been published to date. Two children with JHS/EDS-HT were treated with tramadol hydrochloride (50–150 mg/day). Pain intensity decreased and physical activity improved within days of starting therapy, and these results remained for 30 months [103]. Injections of a solution of equal parts betamethasone and bupivacaine resolved local pain in a man with JHS/EDS-HT and painful peizogenic papules at heels [104]. Resistance to local anesthetics (e.g. EMLA cream) is a well-known manifestation of JHS/EDS-HT [105–107]. These are the unique reports on drug use in EDS published to date.

Acetaminophen and nonsteroidal anti-inflammatory drugs at full dosage are usually effective to control episodic and recurrent musculoskeletal pain of mild–moderate intensity, either spontaneous or related to minor traumas. These drugs are usually effective at the beginning of the natural history of pain in EDS. Acute phases of articular and/or inflammatory pain may be successfully managed by short curses of steroids. Chronic use of steroids is contraindicated due to the related side-effects that are usually amplified in HSCTDs. Recurrent muscle cramps and myalgias might be treated with muscle relaxant drugs that should be managed with care due to the theoretical risk of increasing joint instability and consequently worsening joint pain and predisposing to dislocations. Muscle pain might also improve or be prevented by a regular intake of magnesium that can be taken orally or topically (e.g. Epsom salt baths). Coenzyme Q10 and L-acetyl-carnitine are possible co-adjuvants to consider for the treatment of recurrent myalgias.

In more advanced stages, musculoskeletal pain may relate to an underlying osteoarthritis and/or combine with neuropathic features. Osteoarthritis takes advantage from the use of Cox-2 inhibitors (e.g. celecoxib). Chronic pain with neuropathic features can be treated with pregabalin and gabapentin. Tricyclic antidepressants, serotonin/norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors are further resources to consider for neuropathic pain and/or fibromyalgia, especially in presence of significant psychiatric comorbidities. To date, pregabalin, duloxetine, and milnacipran are the unique FDA-approved medications for

fibromyalgia. The use of antiepileptics and other drugs for neuropathic pain should be managed with care due to the risk of amplifying dysautonomic symptoms. Among them, venlaxafine may rise blood pressure of a few points and could also improve manifestations related to cardiovascular dysautonomia [54]. Minor opioids (e.g. tramadol and codein) may be used alone or in association with acetaminophene or any nonsteroidal anti-inflammatory drug for the treatment of moderate pain. Prolonged use of opioids should be avoided due to the risk of narcotic bowel syndrome and the progressive exhaustion of the analgesic effect.

Experience indicates that pharmacological analgesia is often without benefit in the chronic EDS patient. Acetaminophen and nonsteroidal anti-inflammatory drugs are sometimes effective in children reporting occasional/recurrent articular pain and to mitigate acute pain associated with joint dislocation. Their use in the chronic patient is without effect. All other drugs reported above have a very little chance to be effective at the medium and long term, while show a high risk of side effects.

Headache and visceral pain should be treated following standard procedures.

6.2. Physical therapy and psychological support

Physical therapy and psychological support are considered the mainstay of a successful treatment of pain in EDS [108,109]. After the identification of proprioception as a common feature in joint hypermobility, early studies pointed out amelioration of musculoskeletal symptoms by the enhancement of proprioception in JHS [110]. However, Palmer et al. [111] reviewed four papers in order to explore therapeutic exercise effectiveness in JHS/EDS-HT and found clinical improvement over time in all. There is no convincing evidence that joint-specific and generalized exercise differ in effectiveness. The benefit of a mixed approach is emphasized by a pilot study on 12 adults with JHS/EDS-HT who demonstrated reduction of kinesiophobia and small improvement of self-perceived pain by using a combination of general exercise and cognitive-behavioral therapy [112]. Cognitive-behavioral therapy seems efficacious also in isolation for the medium-term treatment of chronic pain in JHS/EDS-HT [113]. The presumed efficacy of physical therapy in JHS/EDS-HT was confirmed also in children but only two papers focused the issue [11]. Despite these promising results, a recent meta-analysis considering all eligible studies published to date stated that 'although evidence is available that physical and psychological treatment modalities can induce significant pain reduction, the evidence regarding disability reduction is lacking' [43]. Therefore, more work is needed in order to identify the optimal nonpharmacological approach to the long-term management of pain in EDS and the treatment schedule including, but not limited to proprioceptive improvement and cognitive-behavioral therapy.

Chiropratic was used as a therapeutic resource in two EDS adults, one with a postsurgical thoracolumbar spinal fusion for scoliosis and osteoporosis, and the other with moderate anterior head translation. Both patients were able to reduce pain and painkillers use during the chiropractic care [114]. Recently, multimodal chiropratic was successfully applied in a further 23-year-old woman with JHS/EDS-HT [115]. Although scientific data are not yet available, EDS patients perceive the use of splints and braces, and massage therapies efficacious for the management of acute and chronic pain [116].

6.3. Surgery

Available data and practice offer contrasting evidence on the efficacy of orthopedic surgery in the medium- and long-term management of musculoskeletal pain in EDS. In a seminal paper on pain in 273 Dutch patients with EDS, Voermans et al. [14] highlight that pain severity correlate with previous surgery. A high rate of iatrogenic joint injuries in JHS/EDS-HT was also registered by Bovet et al. [39]. In a survey of 79 adults with JHS/EDS-HT, 92.4% used medications, especially analgesics, 70.9% underwent surgery at extremities or abdomen, and 51.9% were enrolled in a physical therapy program. Surprisingly, patients who had a high drug consumption or underwent surgery and/or physical therapy showed a higher dysfunction. Positive outcome was registered in 63.4% of the cases for physical therapy but in 33.9% only for surgery [117].

However, there are some exceptions to the rule. In 15 EDS adolescents who failed nonoperative intervention, open inferior capsular shift seemed to improve local pain and stability in >80% of the patients [118]. Trapezial opening wedgebosteotomy with volar ligaments reconstruction was successful in the treatment of thumb carpometacarpal ligament laxity in an 18-year-old man with EDS, who was pain-free after 2 years [119]. Meticulous capsular plication, arthroscopic correction of femoroacetabular impingement, and labral preservation led to symptom improvement and subjective stability without any iatrogenic dislocations in 16 hips from patients with JHS/EDS-HT [120]. Surgical reconstruction of ligamentum teres of the hip reduces symptoms related to hip instability for 1 year in a 43-year-old woman with EDS [121]. Surgical repair and augmentation of the hamstring tendon for treating spontaneous patellar tendon rupture was effective in a 27-year-old man with EDS. One year after the surgery, the patient was able to move his knee joint without pain [122]. Lumbar artificial disc replacement was used to treat lumbar back pain and radicular symptoms in a 52-year-old woman with JHS/EDS-HT but without extreme lower spine hypermobility. Improvement of symptoms and absence of surgical complications were registered 1 year afterward [123].

Taken together these data indicate that orthopedic surgery may be a pain-relief resource but in highly selected cases only, and must be carried out by expert practitioners and after multispecialistic consultation. Other invasive strategies to consider with a tailored approach comprise prolotherapy, anesthetic/corticoid injections, and anesthetic nerve blocks [54].

6.4. Education

In a focus group study involving 25 patients with JHS/EDS-HT and aimed at examining the patients' lived experience, the general lack of awareness of JHS/EDS-HT and the slow access to appropriate health-care services were emerging issues, a fact that points out the crucial role of education for patients

and health professionals for improving QoL [124]. Concerning pain management, patients' and families' education should include a basic understanding of the pathophysiology and natural history of pain, general strategies for joint protection (e.g. regular physical exercise), optimal weight control, and nonpharmacological recommendations for the treatment of pain-contributing comorbidities (i.e. cardiovascular dysautonomia and sleep disturbance) [26,44].

7. Expert opinion

Pain, fatigue, and physical disability are the leading health-care issues in EDS. Although the risk of vascular accidents and potentially life-threatening complications represent an awful emergency, this issue involves a relatively small number of patients (i.e. those affected by EDS variants with increased arterial fragility). To date, the chronic issues mostly reported in specialized settings refer to the musculoskeletal manifestations and, among them, pain is the most common. The EDS patient reporting chronic or recurrent pain represents a challenge for the contemporary resources. In fact, EDS is slowly progressive and rarely affects the quantity of life. The etiopathology of pain is intimately related to the developmental nature of EDS and pain course will likely affect the entire patient's lifespan. Therefore, assessing patients with EDS and chronic musculoskeletal complaints needs a wider perspective that should range from available treatment strategies to the intricate pathophysiology of EDS. Evaluation of the *pros* and *cons* of all treatment decisions should rest on the natural history of the disorder and available knowledge updates. Dissecting the reported pain phenotype, prioritizing pain symptoms, quantifying the intensity of pain and its consequences on QoL consider the full spectrum of available therapeutic resources and scheduling follow-ups are undeniable steps for appropriate management of the EDS patient with pain (Table 2). Accomplishing these steps is a time-consuming activity which needs expertise, and the support of a wide range of examination tools, also comprising clinical questionnaires. Therefore, it is a highly specialistic procedure that should, ideally, took place in dedicated services.

Table 2. Approach to the management of the EDS patient with chronic musculoskeletal pain.

Recommendation
1. Identify specific chronic musculoskeletal pain conditions (neuropathies, fibromyalgia, osteoarthritis)
2. Identify additional chronic pain conditions (FGIDs, headaches, pelvic disorders)
3. Prioritize pain symptoms
4. Quantify pain symptoms (NRS, questionnaires, etc.)
5. Screen for pain-amplifying conditions (cardiovascular dysautonomia, sleep disorders, psychological distress)
6. Personalize drug use to the type(s) of presenting pain
7. Avoid chronic opioids use
8. Consider propensity to side-effects related to neuropathic painkillers
9. Consider psychiatric/psychological assessment
10. Consider physical medicine/therapy assessment
11. Consider dietary coadjuvants to painkillers
12. Plan periodic follow-ups
13. Identify appropriate tools (e.g. questionnaires) to apply at follow-ups
14. Avoid hyper-medicalization and promote patients' autonomy

FGIDs: Functional gastrointestinal disorders; NRS: numerical rating scale.

Table 3. List of specialists/professionals involved in the management of pain of EDS.

Professionals
Rheumatologist
Specialist in rehabilitation medicine
Specialist in pain medicine
Neurologist
Clinical psychologist
Physical therapist
Occupational therapist
Osteopath
Neurogastroenterologist
Neurourologist
Gynecologist

Multidisciplinarity is often requested, especially for the complex patient with intermingling pain, fatigue, and physical disability. To date, there is not any consensus on the optimal multidisciplinary team for the EDS patient with pain. The list of professionals potentially involved in the pain management of EDS is reported in Table 3. Contemporary treatment of chronic-recurrent pain in EDS is based on five pillars, i.e. education, painkillers, physical therapy, psychotherapy, and monitoring and prevention of pain-modulating comorbidities (Figure 6).

To date, not all health-care systems make feasible such an approach, given the excessively high number of requested professionals with competences on the various clinical aspects of EDS. The establishment of regional, national, and, perhaps, international working groups gathering the experiences and interests of different disciplines and able to offering expert consult to patients, families, and other professionals is probably a more achievable goal. It is one of the missions of the few ongoing initiatives in the field.

The scenario in which the complex EDS patient lives is frustrating. The lack of appropriate education among families and professionals leads to worsen QoL of affected individuals due to inappropriate and sometimes deleterious therapies or

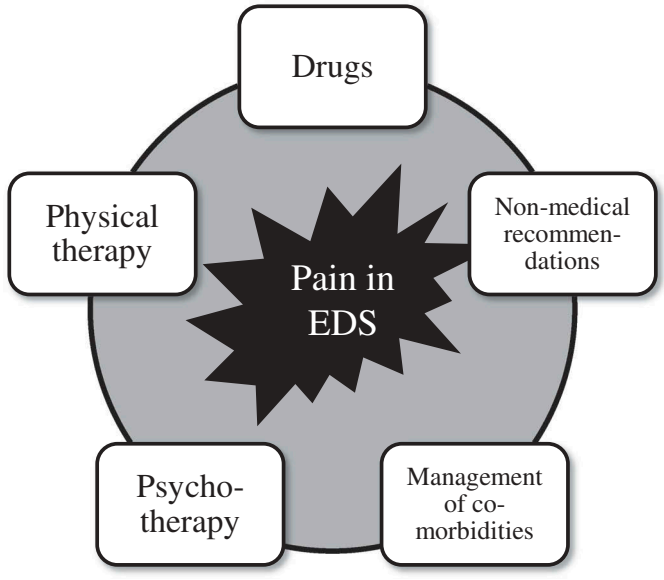

Figure 6. Schematic representation of the five pillars of the contemporary management of pain in EDS.

diagnostic investigations, ineffective monetary and time expenses, scepticism, and loss of confidence in the healthcare system. Patients often need dozens of consultations before obtaining the right diagnosis. After diagnosis certification, many patients, especially those with JHS/EDS-HT, do not receive respect by relatives, friends and untrained professionals, who do not recognize their unmet needs. This can force patients to face by themselves the symptom burden with the concrete risk of amplifying disability due to wrong decisions. Education emerges as the most effective way to improve patients' QoL, reduce redundant costs and limit disease progression. Early diagnosis is a further support to these efforts and is mostly based on a better definition of the (early) pediatric presentation of the various EDSs and on a deeper understanding of the molecular basis of such protean disorders.

Education and early diagnosis are the strongest resources for prompt patients' recognition and cost-effective management. However, more research is needed in order to identify the optimal therapeutic strategy(ies) for the chronically symptomatic patient. The medium- and long-term effects of available painkillers are overall scarce and the risk of side effects significant. Although physical and psychological therapies are considered effective, therapeutic standards are still lacking and the number of professionals with experience in HSCTDs is too low in most countries. Pain in EDS has not a simple explanation, but it is reasonable that a congenital disorder of the connective tissue structure plays a prominent role in pain onset and/or progression. Therefore, future pharmacological research could explore the pathophysiological and therapeutic connections between pain and the ECM. Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases belonging to the metzincin superfamily. MMP are involved in the degradation of various ECM components, as well as of cytokines, chemokines, and growth factors. Such a wide spectrum of tissue-specific functions prompted the study of the role of MMPs in various non-neoplastic diseases [125], also comprising neuropathic pain and migraine [126]. MMPs have been recently considered a potential therapeutic target for neuropathic pain in diabetes [127] and another work demonstrated the effects of AQU-118, a MMP-2 and -9 inhibitor, in a rat model of spinal and trigeminal neuropathic pain [128]. Intriguingly, *N*-acetylcysteine was demonstrated to inhibit MMP-2 and -9 and to reduce chronic constrictive injury-induced neuropathic pain in rats [129]. Hence, EDS may represent a biopathological model for studying novel pathways of pain modulation and for identifying new therapeutic targets or drugs. On this perspective, the achievements of such a research will not be limited to ameliorate life of the small group of EDS patients, but could be extended to the much wider population suffering by musculoskeletal chronic pain disorders, such as osteoarthritis, fibromyalgia, and autoimmune disorders.

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Declaration of interest

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