One in 5,000 people has Ehlers-Danlos syndrome — at least twice the number as have sickle cell anaemia, phenylketonuria or haemophilia A. EDS is a heritable disorder of collagen, which is a major component of connective tissue. Mutations of the genes involved in the structure, production and processing of collagen underlie the condition.

Since connective tissue is abundant throughout the body, EDS can affect the skin, ligaments, muscles, blood vessels and organs. (see Figure 1 for manifestations)

Subclassification

Although symptoms of hypermobility and skin scarring have been described for centuries, the first clinical description of EDS was made in 1892 and the condition was later named after two dermatologists, Edvard Ehlers and Henri-Alexandre Danlos. In 1998 the major subtypes of EDS were classified according to their clinical features and genetic findings.

The three most common subtypes, described in Panel 1, are:

- Classic
- Hypermobility
- Vascular

Clinical diagnosis is based on the presence or history of major and minor diagnostic criteria alongside family history. The vague and insidious onset of some symptoms means patients often go undiagnosed or are misdiagnosed for years.

All EDS subtypes tend to share common characteristics of:

- Soft skin
- Easy bruising
- Joint laxity

A genetic defect has been identified for all subtypes apart from hypermobility type (EDS-HT); this is the most common subtype and the focus of this article.

The classic and hypermobility subtypes together make up 90% of all EDS cases and men and women of all racial and ethnic backgrounds can be affected.

Life expectancy at birth for people with the classic and hypermobility subtypes is usually as for the general population although considerable morbidity and disability often result, particularly with EDS-HT.

Vascular EDS is thought to account for around 4% of EDS cases and is life-threatening. Vascular or organ rupture is a major cause of early death at a median age of 48 years. Pregnancy is particularly dangerous in vascular EDS.

EDS-HT in childhood. Diagnosis of EDS-HT is made on the basis of an individual showing all three major diagnostic criteria accompanied by minor diagnostic criteria listed in Panel 2.

There is overlap between EDS-HT and a condition known as joint hypermobility syndrome (JHS) and discrepancy among clinicians as to the relationship between them. EDS-HT tends to be viewed as more serious and the associated hypermobility occurs alongside other significant signs and symptoms which are the manifestations of faulty collagen.

Management of symptoms

Four potentially troublesome symptoms that can cause a patient with EDS-HT to present at the pharmacy are:

- Joint laxity
- Pain
- Gastric problems
- Dysautonomia

EDS-HT is a spectrum disorder — not all patients will suffer all of these symptoms and some will have additional symptoms.

Joint laxity

The term “joint hypermobility” is used when the range of movement of the joint goes beyond its normal range. Hypermobility is more common in females and those of Asian, African or Caribbean origin.
About 10% of the general population have a degree of hypermobility and may be described as “flexible” or “double jointed”. This can be advantageous, helping them excel at, for example, ballet or gymnastics. However, in someone with EDS-HT (or JHS) the weakness and laxity of ligaments and tendons supporting the joints results in frequent dislocations or subluxations (partial dislocation) and predisposes a person to sprains, tendonitis and bursts. Simple movements (such as changing direction when walking or turning over in bed) or light knocks can cause joint displacement. This impairs a person’s ability to carry out day-to-day activities such as walking, dressing and writing.

The EDS individual can usually return the dislocated joint to its natural position themselves, but the trauma of dislocation causes inflammation and pain, which can last for days, and a vicious circle of events that make it difficult to recover and regain muscle and joint strength (see Figure 2). Commonly affected joints are the knee, shoulder, hip and jaw.

Physiotherapy and occupational therapy is vital in EDS and patients require personalised exercise programmes to strengthen muscles and joints and remain mobile. Non-stress activities, such as swimming, are particularly beneficial. Weight bearing and contact activities should be avoided. Despite physiotherapy, some individuals need to wear braces to stabilise joints or use crutches or a wheelchair.

Pain
Joint hypermobility in EDS-HT tends to be followed by dislocations and then articular, muscular and back pain. These commonly begin during the second decade. Joint stiffness and osteoarthritis occur later, but at an earlier age than in the general population.

The chronic pain associated with EDS-HT may be myofascial (muscular pain, tenderness or spasm), neuropathic or arthralgic/osteoarthritic in origin. Back pain, abdominal pain and headache (including migraine) are also common. Chronic pain can be difficult to manage and helping patients develop relaxation and coping strategies is important alongside pharmacological measures.

There are no standardised guidelines for the assessment and treatment of pain in EDS-HT but it is important to manage it. Chronic pain is debilitating and can have severe psychological effects. In addition, those with EDS have an increased incidence of anxiety and depression compared with the general population.

Drugs recommended by the National Institute for Health and Care Excellence for osteoarthritis and fibromyalgia are good starting points. However, use of these drugs in EDS presents challenges because their side effects may exacerbate other EDS symptoms.

Paracetamol
Patients with EDS routinely use Paracetamol for pain relief. NICE and the Medicines and Healthcare products Regulatory Agency is

**Panel 1: Common EDS Subtypes and Their Symptoms**

<table>
<thead>
<tr>
<th>Hypermobility type</th>
<th>Classic type</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Joint laxity of large and small joints (dislocation and subluxation of shoulder, patella, jaw, hip and fingers is common and frequent)</td>
<td>• Joint laxity</td>
</tr>
<tr>
<td>• Chronic joint pain develops</td>
<td>• Velvety, hyper-elastic, fragile skin that splits easily, heals slowly and leads to atrophic scars; easy bruising</td>
</tr>
<tr>
<td>• Soft, smooth skin, moderate skin elasticity, no scarring, easy bruising</td>
<td>Other features can include:</td>
</tr>
<tr>
<td>• Blue sclera</td>
<td>• Other skin features (piezogenic papules on sides of feet and molluscoid pseudotumors, cystlike nodules on bony prominences)</td>
</tr>
<tr>
<td>• Fatigue and sleep disturbances</td>
<td>• Blue sclerae</td>
</tr>
<tr>
<td>Other features can include:</td>
<td>• Hernias and prolapses (uterine, anal)</td>
</tr>
<tr>
<td>• Gastrointestinal dysfunction (eg, delayed gastric emptying, constipation, irritable bowel syndrome)</td>
<td>• Scoliosis</td>
</tr>
<tr>
<td>• Autonomic dysfunction, including postural orthostatic tachycardia syndrome (POTS)</td>
<td>Vascular type</td>
</tr>
<tr>
<td>• Irregular menstrual cycle (and worsening symptoms around menstruation)</td>
<td>• Spontaneous rupture of medium or large arteries at any age from mid-teens onwards</td>
</tr>
<tr>
<td>• Urinary dysfunction and incontinence</td>
<td>• Skin shows only mild hyperextensibility but is fragile. It is also thin, appearing translucent (showing underlying veins and capillaries) especially on the chest and abdomen</td>
</tr>
<tr>
<td>• Other skin manifestations (eg, keratosis pilaris [tiny red “goose bump” type rash seen on the upper arms or thighs more commonly in EDS than in the general population], piezogenic papules on bony prominences, petechiae [pinpoint red/purple haemorrhages], keratosis pilaris can be a feature of EDS-HT [CID/ISM/SPL])</td>
<td>• Easy bruising</td>
</tr>
<tr>
<td>Other features can include:</td>
<td>• Scars are numerous</td>
</tr>
<tr>
<td>• Vascular type</td>
<td>• Perforation of hollow organs such as bowel or uterus</td>
</tr>
<tr>
<td>• Fatigue and sleep disturbances</td>
<td>Other features can include:</td>
</tr>
<tr>
<td>• Other skin features (piezogenic papules on sides of feet and molluscoid pseudotumors, cystlike nodules on bony prominences)</td>
<td>• Distinctive facial appearance (prominent eyes, thin face, lips and nose, lobelless ears)</td>
</tr>
<tr>
<td>• Blue sclera</td>
<td>• Small fingers and toes, which may be hypermobile, but no large joint hypermobility</td>
</tr>
<tr>
<td>• Fatigue and sleep disturbances</td>
<td>• Early onset varicose veins</td>
</tr>
<tr>
<td>Other features can include:</td>
<td>• Premature aging of the skin on the hands and feet</td>
</tr>
<tr>
<td>• Vascular type</td>
<td>• Bleeding or receding gums</td>
</tr>
</tbody>
</table>

**Figure 1: Could it be EDS?**
(COURTESY OF EHLERS-DANLOS SUPPORT UK)
conducting a review into the safety of over-the-counter analgesics following some evidence relating to the cardiovascular, gastrointestinal and renal side effects of paracetamol. The results will be relevant because EDS patients commonly take pain-relieving medicines for many years, often starting in young adulthood.

Topical NSAIDs Topical non-steroidal anti-inflammatory drugs (eg, ibuprofen gel) are advocated by NICE ahead of oral NSAIDs, cyclo-oxygenase-2 inhibitors and opioids for pain management in osteoarthritis associated with the knee and hand joints.3 After topical application, therapeutic drug levels can be detected in synovial fluid. Plasma concentrations, however, are 15% of those seen after oral NSAIDs, so it can be expected that side effects are reduced by topical use. This is relevant in EDS because gastric symptoms associated with the condition are frequently troublesome.

Topical capsaicin Topical capsaicin is an adjunct for treating pain in osteoarthritis for hand and knee joints. It is also used in EDS, although there is no evidence to support its efficacy. It may need to be applied for one to two weeks before any effect is experienced.

Oral NSAIDs Oral NSAIDS (eg, ibuprofen or naproxen) and COX-2 inhibitors (eg, celecoxib) are commonly prescribed to manage acute symptoms. The skeletal muscle relaxant baclofen acts centrally and is occasionally used for muscle related pain thought to have a neurological component. There are a number of cautions related to its use.1 Doses should be carefully titrated to reduce the likelihood of side effects and the medicine should be withdrawn carefully by gradual dose reduction over one to two weeks.

Gastric problems Collagen abnormalities in the extracellular matrix surrounding the gastrointestinal tract can alter the way it stretches and affect gut transit time. In addition, autonomic dysfunction can aggravate symptoms. Gastrointestinal symptoms such as dyspepsia and reflux, nausea, dysphagia, abdominal pain and altered bowel habit are common for patients with EDS. Reflux and dysphagia are usually managed with proton pump inhibitors (eg, lansoprazole). However, patients can still have symptoms despite maximum doses and H2-receptor antagonists (eg, ranitidine) and antacids or alginates. Patients taking PPIs long term (ie, for more than one year) and in high doses have an increased risk of bone fracture although the relationship may not be causal. EDS patients are already at risk of osteoporosis and should be advised to maintain an adequate calcium intake and take supplements if necessary. Calcium and vitamin D supplements may be useful particularly when PPIs are taken, patients are inactive, their exposure to sun is limited or dietary intake is lacking. Further, hypomagnesaemia may also result from PPI treatment (usually after a year but sometimes after just three months).

Prokinetic agents can help with symptoms of nausea and early satiety due to delayed gastric emptying. Domperidone increases gastric emptying and motility; new guidelines limit its use to the relief of nausea and vomiting, and it should no longer be used for heartburn, bloating or relief of stomach discomfort.4 Metoclopramide has also been used, but new guidelines now further restrict this due to unacceptable neurological risks.5 Concurrent opioid analgesics can antagonise the effects of these drugs.

Symptoms akin to irritable bowel syndrome (IBS) are common in EDS. Patients can experience abdominal discomfort, bloating, constipation or diarrhoea. As in IBS, exclusion diets can be of benefit, including avoiding gluten, lactose and high FODMAP foods. FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) are short-chain carbohydrates that are poorly absorbed from the gut and rapidly fermented by gut bacteria, producing gas and bloating. A low FODMAP diet is

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**Panel 2: Diagnosis of EDS-HT2**

**Major diagnostic criteria**
- Joint hypermobility (score ≥5 on Beighton scale*)
- Soft skin with normal or only slightly increased extensibility
- Absence of skin fragility or other skin or soft tissue abnormalities such as poor healing, hernias, translucent skin, atrophic scars

**Minor diagnostic criteria**
- Positive family history
- Recurrent joint dislocations or subluxations
- Chronic joint, limb or back pain
- Easy bruising
- Functional bowel disorders (reflux, irritable bowel syndrome)
- Autonomically mediated hypotension or postural orthostatic tachycardia syndrome (POTS)
- High narrow palate
- Dental crowding

* Beighton score (out of a maximum score of 9 points) to assess degree of hypermobility by:
  - Bending small finger back more than 90 degrees (1 point per finger)
  - Bending thumbs to touch forearm (1 point per thumb)
  - Hyperextending elbows and knees beyond the straight line (1 point for each joint [maximum 4 points])
  - Putting hands flat on the floor without bending knees (1 point)

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**Figure 2: Joint trauma and laxity cycle**

- Dislocation
- Increased joint laxity
- Trauma and inflammation
- Muscle wasting
- Pain and immobility

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one of avoidance (or limitation) and excludes, for example, some dairy products, wheat and certain fruits and vegetables that are rich in fructose or polyols, such as apples, cherries, mushrooms.6

Dietary supplements Taking vitamin and mineral supplements in addition to calcium and vitamin D to help symptoms and avoid long-term complications of EDS is sometimes proposed.8 Vitamin C is involved in collagen synthesis and repair and is often recommended. Doses higher than 500mg are probably excreted and so offer no additional benefit. Magnesium deficiency can affect calcium and vitamin D levels and it is involved in collagen synthesis. Magnesium supplementation has been proposed in EDS as deficiency is thought to be common in the general population and in patients taking PPIs long term.9

There is some evidence that certain probiotics can be beneficial in IBS in reducing bloating. With all these dietary supplements, specific studies relating to EDS are lacking.

Dysautonomia People with EDS-HT can experience dysautonomia and autonomic dysfunction. These affect involuntary functions relating to heart rate, breathing, digestion, balance and temperature regulation, and cause symptoms that are difficult to recognise and diagnose because of vague or lacking outward signs. Misdiagnoses of anxiety disorders can add to the stresses that sufferers face.

One of the manifestations of autonomic dysfunction is orthostatic intolerance and POTs. The autonomic nervous system is unable to adapt to changes in body position, for example from lying down to sitting or standing. POTs is diagnosed by either an increase in pulse of more than 30 beats/min, or greater than 120 beats/min, 12 minutes after standing from being supine, without any further exertion other than that required to change position.

When an individual with normal autonomic function and no joint hypermobility syndrome stands from lying or sitting there is a brief pooling of blood in the lower parts of the body, which, in turn, reduces blood pressure and cerebral blood flow. This results in sympathetic nervous system activation to compensate, and causes an increase in heart rate, force of contraction and vasoconstriction of blood vessels. In an EDS-HT individual with POTs, standing causes the pooling of blood in the lower body, heart rate is increased, but the blood vessels do not adjust in the same way. As a consequence the blood pressure can remain low, the heart rate remains fast and dizziness, confusion and fainting result. Excess adrenaline can also result as the body attempts to compensate, producing additional symptoms (eg, tremor, feelings of fear, flushing). These symptoms of dysautonomia can be as disabling as the joint laxity.

The strategy for managing symptoms starts with non-pharmacological measures and then a number of drug treatments can be tried. Non-pharmacological measures include:

- Maintaining adequate hydration by increasing fluid intake (isotonic drinks can be helpful) and salt consumption in the absence of contraindications
- Eating small frequent meals to divert less blood volume to the intestine for digestion
- Avoidance of alcohol and its vasodilating and dehydrating effects
- Tilting the head of the bed with bed raisers or bricks to an angle of around 30 degrees (may also help with night-time reflux)
- Wearing compression hosiery (ideally full length) to give support to lower limb vessels and reduce the venous pooling
- Low resistance exercise to suit the individual is also beneficial

No drugs are currently licensed for managing orthostatic hypotension and POTs in the UK, but the following medicines are sometimes used:

- Fludrocortisone where hypovolaemia is a problem, to encourage salt and water retention and aid vasoconstriction. Doses should be as low as possible to avoid adrenal suppression. Note also the tendency to increase risk of gastric bleeding and ulceration when given with NSAIDs and to cause calcium loss.

PRACTICE POINTS

Reading is only one way to undertake CPD and the regulator will expect to see various approaches in a pharmacist’s CPD record.

1 Help increase awareness of Ehlers-Danlos syndrome by sharing your learning with others. Leaflets are available from www.ehlers-danlos.org
2 Find out more about the patient experience of Ehlers-Danlos syndrome — a number of videos are available on YouTube
3 Be aware of the type of symptoms described in this article in your teenage/young adult population. Might someone with these symptoms have undiagnosed EDS?

Consider making this activity one of your nine CPD entries this year.

Learning & development

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- Low doses of beta-blockers, (eg, labetolol, propranolol) are sometimes used to control tachycardia where hypotension is not a factor. They are useful where hyperadrenergic symptoms are troublesome.
- Ivabradine is used to control tachycardia by its action on the sinus node and it improves diastolic filling. It has advantage over beta-blockers since it does not have their vasodilating effects.
- The parasympathomimetic agent pyridostigmine has been used with some benefit in POTs to restrain the heart rate rise on standing. It has also been shown to increase intestinal motility which may have additional benefits to some EDS patients.
- The alpha agonist midodrine (unlicensed in the UK) has been used, where there is no hypertension, with some success in maintaining blood pressure on standing by causing vasoconstriction. Side effects include tingling and goose bumps and the more severe supine hypertension.10
- Selective serotonin reuptake inhibitors and selective noradrenaline reuptake inhibitors, eg, sertraline and venlafaxine, are sometimes used because serotonin is implicated in autonomic control of blood pressure. They have been shown to be especially useful where syncope is a significant symptom and also in treating chest pain associated with POTs.

Pharmacist’s role

Pharmacists can play a key role in recognising EDS symptoms and referring those with signs of EDS who may present in the pharmacy with queries about joint dislocations, gastrointestinal problems, central nervous system symptoms, fatigue, bruising or other skin symptoms. In addition, they can make a difference by understanding diagnosed EDS patients and supporting and advising on medication and complementary measures. Pharmacists can also signpost patients to support groups such as Ehlers-Danlos Support UK (www.ehlers-danlos.org) and the Hypermobility Syndromes Association (hypermobility.org).

References available online.

http://bit.ly/1jSg4J

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