INTEGRATIVE HEALTH (IH) MODALITIES FOR MANAGING PAIN IN EHLERS-DANLOS RELATED SYMPTOMS.

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Presentation

- History and EDS definitions
- Differential diagnosis and characteristics
- Collagen
- 2 routes (audience decides order)
  - Mechanisms and models of pain
  - CAM interventions for Pain and Ehler Danlos
- Mechanisms of Action of IH Modalities
- Contact and references

HISTORY OF EDS

- The first known reference to joint laxity is attributed to Hippocrates who, in the 4th century BCE, described the Scythians as being "so loose-limbed that they were unable to draw a bow-string or hurl a javelin.
- "The Three Graces" (1638 to 1640) by Peter Paul Rubens, Clinical features suggestive of hypermobility syndrome
- 1657 A Dutch surgeon noted a case history of a boy with hyperextensible skin.
- 1892 Chernogubov published about the disease in Moscow
- 1901 Edvard Ehlers in defined it as a distinct disorder in a case history that included lax joints, hyperextensible skin and a tendency to bruise.
- In 1908, Henri-Alexandre Danlos published a second case history.
- In 1936, Frederick Parkes-Weber suggested the disorder be named Ehlers-Danlos syndrome.

What is EDS?

- Ehlers-Danlos syndrome (EDS) is the term used for a group of relatively rare genetic disorders of connective tissue that are characterized by skin hyperextensibility, joint hypermobility, and/or tissue fragility.
- The management of patients with EDS depends largely upon common principles and practices, with an emphasis on patient education for prevention and early recognition of injuries and complications.
- Management of EDS also includes monitoring and additional interventions tailored to the particular manifestations or complications that may occur with each form of EDS.
- No medical treatments that can reverse or "cure" EDS, most other interventions used in these patients have not been evaluated in randomized trials.
### Differential diagnosis

- **Other types of Ehlers-Danlos syndrome (EDS)**
- **Joint hypermobility syndrome** and other disorders of connective tissue (Hypermobility EDS)
- **Marfan Syndrome** — Marfan syndrome, like EDS, is typically characterized by joint laxity. It is inherited in an autosomal dominant pattern, due to mutations in the FBN1 gene.
- **Loeys-Dietz Syndrome** — Loeys-Dietz syndrome involves aortic and other arterial aneurysm and dissection, but also includes generalized arterial tortuosity, hypertelorism (widely-spaced eyes), cleft palate, or bifid uvula.
- **Osteogenesis imperfecta** — Osteogenesis imperfecta is a group of disorders whose main features are fragile osteopenic bones with recurrent injuries.
- **Larsen syndrome** — Larsen syndrome consists of dislocations of large joints (hips, knees, and elbows), specific craniofacial features.
- **Stickler syndrome** — Stickler syndrome is characterized by specific craniofacial features (flattened midface, cleft palate, micrognathia), high myopia with risk for retinal detachment, hearing loss, and spondyloarthropathy.

### Definitions: 3 basics

- **Joint hypermobility** — Joint hypermobility or laxity is the hallmark of most types of EDS. This can involve both proximal and distal joints or may be seen predominantly in distal joints (such as in vascular EDS). The assessment of the joints is done using the Beighton hypermobility scale.
- **Skin hyperextensibility** — Skin hyperextensibility is defined as the capacity to stretch the skin for 4 cm or more at a neutral site, such as the neck or ventral aspect of the forearm, until feeling resistance. This is particularly true of the classic form. The hyperextensibility increases with age, but is present in children.
- **Mitral valve prolapse** — Mitral valve prolapse has been reported as a feature of several forms of EDS. However, older estimates of the frequency of mitral valve prolapse should be interpreted with caution, as the criteria defining MVP have evolved, and studies prior to 1989 may have overestimated its prevalence.

### Classification of Ehlers-Danlos Syndromes

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</table>

*Classification of Ehlers-Danlos Syndromes (Revised Nosology, Villefranche, 1997)*
How does Ehlers-Danlos Syndrome manifest?

**Background** (be patient…we all need to be at a similar level)

- **PAIN**
  - Joint dislocations: sprains, loss of function; overly flexible joints, the connective tissue that holds joints together is looser, your joints can move far past the normal range of motion. Small joints are affected more than large joints.
  - Bruised skin. Wounded connective tissue allows your skin to stretch much more than usual. This may be able to stretch even when you don’t think it is under strain. For example, the eyes used to close a wound often will not only move when you apply more or less pressure, but will also move in directions more horizontal than you realize. The skin might also move and look shiny.
  - Stretchy skin. Weakened connective tissue allows your skin to stretch much more than usual. You may be able to pull a pinch of skin up away from your body, but it will snap back into place when you let go. Hair might also be more easily pulled and removed.
  - Ragged skin. Damaged skin will often heal very fast, but the result may look thin and soft. Fat lumps at pressure points. These small, harmless growths can occur around the knees or elbows and may show up in all ways.

- **BLOOD PRESSURE variations**

- **Pregnancy difficulties**

**Vascular Ehlers-Danlos syndrome** (One of the most severe forms of the disorder, vascular Ehlers-Danlos syndrome can weaken your heart’s largest artery (aorta), as well as the arteries that supply blood to your kidneys and spleen. The vascular subtype can weaken the walls of the aorta and large arteries.

*some material modified from Mayo clinic website

Why Pain? And what other symptoms can we treat?

EDS symptoms include in between others

- pain (musculoskeletal and neuropathic),
- cardiovascular autonomic disturbance,
- bowel disturbances,
- profound fatigue,
- Anxiety,
- problems related to connective tissue laxity

Prevention?

- 6 categories, different inheritance models, in

    (IASP, APS) (International Association for the Study of Pain, American Pain Society)

- **Collagen?** Large daily doses (1-4 g) of vitamin C may help rebuild collagen structure, therefore helping sprain treatment, wound healing, capillarity stability.

- Physical activity: Promote activity. Encourage your child to participate in physical activities with appropriate boundaries. Disallow contact sports while endorsing non-weight-bearing activities, such as swimming. Your child’s doctor or physical therapist also may have recommendations.

- Avoid injury (protect the body)

- Use mild soaps and sunscreens, (protect the skin)

- Pain is considered a protective mechanism meant to bring awareness of tissue damage that is occurring or about to occur.
Collagen and tenascin main components

- Can we rebuild (good quality) collagen or try to make it stronger?
  - It’s a protein
  - The triple helix is made of motifs in the amino acid sequence
    - glycine-proline-X and glycine-X-hydroxyproline, where X is any amino acid other than glycine, proline, or hydroxyproline.
  - Many supplements have a specific mixture of those amino acids and Vitamin C

Types of collagen

- Collagen occurs in many places throughout the body. Over 90% of the collagen in the body, however, is type I.
  - So far, 28 types of collagen have been identified and described. The five most common types are:
    - Collagen I: skin, tendon, vascular ligature, organs, bone (main component of the organic part of bone)
    - Collagen II: cartilage (main component of cartilage)
    - Collagen III: reticulate (main component of reticular fibers), commonly found alongside type I.
    - Collagen IV: forms basal lamina, the epithelium-secreted layer of the basement membrane.
    - Collagen V: cell surfaces, hair, and placenta

Some uses for (hydrolized) collagen supplementation

- Type II collagen for rheumatoid arthritis
- Hydrolyzed type II collagen for osteoarthritis
- Cosmetic surgery
- Bone grafts
- Tissue regeneration
- Reconstructive surgical uses
- Wound care management uses

- No successful studies with EDS and collagen supplementation,
Pain mimics other pathologies, treatments for similar conditions

- **Musculoskeletal pain** — In patients with joint hypermobility, preventive strategies and nonopioid pain management are important in the management of musculoskeletal pain before it becomes chronic.
- Pharmacologic treatment of joint pain involves the use of acetaminophen and, if necessary, nonsteroidal antiinflammatory drugs (NSAIDs); avoid in patients with easy bruising.
- **Chronic musculoskeletal pain** benefit from use of meditation or other relaxation techniques.
- Those with symptoms and findings compatible with fibromyalgia syndrome (chronic widespread pain, fatigue, nonrestorative sleep, and cognitive disturbances). Patients with refractory pain may require referral for further evaluation in a pain clinic.
- Symptoms of Raynaud phenomenon feel better in warmer, more humid climates and may benefit from medical therapy for Raynaud phenomenon.

Need to Individualize the treatment

- Each patient is unique in its biochemical/nutritional status and genetic component; unique nutrition and supplementation challenges.
- Many different components to EDS and clinical manifestations.
- No cure, but many palliative and prevention strategies can be used.
- EDS develops differently in different people; health practitioners need to follow their development and adjust treatment.
- Different psychological manifestations.

Traditional Chinese Medicine: different constitutions

CAM interventions
Integrative Medicine? Complementary and Alternative Medicine? Integrative Health Programs?

The Consortium of Academic Health Centers for Integrative Medicine defines integrative medicine as "the practice of medicine that reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, healthcare professionals and disciplines to achieve optimal health and healing."

- "Complementary" generally refers to using a non-mainstream approach together with conventional medicine. "Alternative" refers to using a non-mainstream approach in place of conventional medicine. (NIH)

NIH-NCCAM generally uses "complementary health approaches" when discussing the practices and products we study for various health conditions. These approaches fall into one of two subgroups—natural products or mind and body practices.

- We use "INTEGRATIVE HEALTH PROGRAMS" for our research.

Is There Evidence?

The National Center for Complementary and Alternative Medicine (NCCAM) and the NLM partnered to index articles on complementary medicine. This research data has been added to the larger PubMed database. CAM on PubMed is a subject database within the larger PubMed database with the following search terms:

- complementary alternative medicine: 12436
- integrative medicine: 8138
- complementary alternative medicine: 16363

- Yes: There is evidence, studies and funding.
Collagen health and Why?

- To from Collagen (hydroxyproline and hydroxylysine). The hydroxylase enzymes require Vitamin C and Iron as cofactors.
- Excess vitamin C à Scurvy
- The enzymes that catalyze the glycosylation step, galactosyl and glucosyl transferases, require the trace metal manganese (Mn+2). The glycosylation step imparts unique chemical and structural characteristics to the newly formed collagen molecule and may influence fibril size.
- Other trace metals: Copper, Silica, Zinc
- Vitamin E (might help with synthesis), prevents degradation.

Herbs and supplement combinations for collagen building → pain modulation

- Ginger, ginkgo biloba, Aesculus horse chestnut and sweet violet
- Calcium (readily for venous health)
- Hyaluronic Collagen Peptides
- Chinese patent formulas geared to treat constitution (Blood deficiency, spleen deficiency, stagnation + others)
- Gotu Kola herb & root (Centella asiatica)
- Horsetail (Equisetum arvense)
- MSM/Chondroitin
- B vitamins (6 and 12 for nervous system)
- Bioflavonoids (citrus)
- Bromelain 100 mg
- Butcher’s broom (ruscogenin, escin 20%)
- Grape seed extract (proanthocyanidin)
- Resveratrol (Polygonum cuspidatum)
- Horsetail (Equisetum arvense)
- Horse chestnut (Escin 20%)
- Arnica montana
- Capsicum frut.
- Hypericum perforatum
- Ricinus communis
- Cinnamomum camphora
- Larrea tridentata
- Mentha piperita
- Arnica montana
- Filipendula ulmaria
- Hamamelis lupulus
- Matricaria recutita
- Pycnogenol erythrina
- Salix alba/nigra
- Aconitum napellus
- Boswellia serrata
- Curcuma Longa

Herbal components to help pain (and Chinese medicine temperature correspondences)

### Topical
- Arnica montana
- Capsicum frut.
- Hypericum perforatum
- Ricinus communis
- Cinnamomum camphora
- Larrea tridentata
- Mentha piperita

### Internal
- Cooling:
  - Bryonia alba
  - Filipendula ulmaria
  - Hamamelis lupulus
  - Matricaria recutita
  - Pycnogenol erythrina
  - Salix alba/nigra
- Warming:
  - Aconitum napellus
  - Boswellia serrata
  - Curcuma Longa
### Nutritional/Homeopathy (for pain)

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<tr>
<th>Dietary Interventions</th>
<th>Selected Acute homeopathic remedies</th>
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<tr>
<td>Antiinflammatory diet</td>
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<td>Elimination diet</td>
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<td>Soft Detox diet</td>
<td>Hypericum</td>
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<td>NASH diet</td>
<td>Ignatia</td>
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<tr>
<td>Ketogenic diet (cases)</td>
<td>Sulphur</td>
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<tr>
<td>Paleo/body building diet</td>
<td>Others</td>
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</tbody>
</table>

### Pain and inflammation common supplements

- Fish oil
- Curcuma (turmeric)
- Magnesium
- Digestive enzymes (Bromelain/Papain/Proteases)
- Zyflamend
- Wobenzym
- Intenzyme (priority one)

### Prescriptive Medications

- **NSAIDs**
  - Acetaminophen, Aspirin, Ibuprofen, naproxen, diclofenac, celecoxib, others
  - Pure & receptor agonists: morphine, oxycodone, hydrocodone, codeine, fentanyl, hydromorphone, oxymorphone, methadone, meperidine, levorphanol
- **Dual action**
  -tramadol/naproxen
- **Partial agonist**
  -Buprenorphine (Buprenex injectable, Subutex and Suboxone sublingual tablets)
  -buprenorphine, pregabalin
  -dexamfetamine, lamotrigine
  -Topiramate
- **Tricyclics**
  -amitriptyline, desipramine, amitriptyline, desipramine, others
- **SNRIs**
  -duloxetine, milnacipran
Conventional Therapeutics

- Epidural steroid injections (ESI), facet joint injections, single nerve root blocks, peripheral nerve injections and sacroiliac joint injections.
- Prolotherapy (not that conventional but gaining momentum)
- Surgery, (laminectomy for example for discogenic pain)
- Long time medication

Mechanisms and Models of Pain

WHAT IS PAIN?

“Pain is an unpleasant sensory and emotional experience associated with potential or actual tissue damage, described in terms of such damage”

- Pain is a multiple and complex phenomena.
- There is no predictable relationship between tissue injury and pain sensation.
- Pain is considered a protective mechanism meant to bring about awareness of tissue damage that is occurring or about to occur.
Pain and Tissue Injury

- **Acute**: Pain experience is less than expected given the amount of trauma observed.
- **Chronic pain**: Many times felt without noticeable tissue trauma (dysfunctions in neural integration process).
- **New definition**: “Pain is whatever the experiencing person says it is, existing wherever he says it does” → the most reliable indicator of pain is patient self-report.

Pain is Subjective

- Pain perception can be modified by past or present experiences.
  - Fear of re-experiencing painful stimuli: heighten the perceived pain.
  - Competitive event/Stress: reduce the perception of pain.

4 Stage Model of Pain Processing*

4 Stage Model of Pain Processing* (1 + 2)

Pain Sensation/Intensity

Pain Unpleasantness

Pain Emotion/Suffering

Pain Behavior

Response

Responsibility

Tell

Hurt

Acupuncture
Nutrition
PT


4 Stage Model of Pain Processing

Mind/body techniques interventions
supplementation

Pain Sensation/Intensity

Pain Unpleasantness

Pain Emotion/Suffering

Pain Behavior

Response

Responsibility

Tell

Hurt

PT/OT/Psy support

Safety-Efficacy Criteria for Modalities

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Different Pain Types with EB Support for Treatment with Integrative Health Modalities

- Fibromyalgia
- Headache, tension
- Migraine
- Osteoarthritis
- Pain, back, chronic
- Pain, cancer
- Pain, labor management
- Pain, neck
- Pain, postoperative
- Rheumatoid arthritis

Mechanisms of Action: IH Modalities

IH Therapies: Mechanisms of Action

- Most Mind/body therapies rely upon the Relaxation Response
- Acupuncture mechanisms have been studied in great detail and we can make a further presentation to explain this.
Mechanisms of Action: The Relaxation Response


Mechanisms of Action in Pain: Acupuncture


Figure 3: Acupuncture-induced robust axon reflex (a) and its involvement in the propagated sensation along meridians (PSM) (b). In (a), hyperemia (flare) was induced by acupuncture needling in acupuncture points including cutaneous receptors, pacinian corpuscles, small muscle spindles, and free nerve endings. (b) illustrates putative communication between adjacent branches of nerves from different neural tissue types. Neuroactive mediators from acupuncture stimulation were proposed to evoke mechanical sensations in the skin (Zhao et al., 2012).

Integrate!

“...the goal of integrating care should be the provision of comprehensive care that is safe and effective care, that is collaborative and interdisciplinary, and care that respects and joins effective interventions from all sources.”

From the Institute of Medicine

REFERENCES!

- UP TO DATE topics:
  - Susan P Pauker, MD, FACMG, Joan Stoler, MD, Peter H Schur, MD, Paul L Romain, MD
  Clinical manifestations and diagnosis of Ehlers-Danlos syndromes

- Susan P Pauker, MD, FACMG, Joan Stoler, MD, Peter H Schur, MD
Clinical manifestations and treatment of the hypermobility syndrome

- Rodney Grahame, MD, Alan J Hakim, BA MB BChir, Peter H Schur, MD, Paul L Romain, MD
Clinical manifestations and treatment of the hypermobility syndrome
Literature review current through: Mar 2014. | This topic last updated: Sep 13, 2013.

- Hoffman textbook of Natural Medicine

Presentation Title Goes Here
This study will assess the effectiveness of mind-body therapy in relieving pain in patients with Ehlers-Danlos syndrome. This syndrome is a hereditary condition caused by a connective tissue defect and is often associated with chronic pain poorly controlled by medication or physical therapy. Mind-body therapy comprises various complementary or alternative medicine techniques such as meditation, guided imagery, stress management, and group psychotherapy.

Adult patients with Ehlers-Danlos syndrome who have chronic pain may be eligible for this 4 1/2 to 5-month study. Patients not already enrolled in NHGRI's protocol 97-HG-0089 will undergo a history, physical examination, and brief interview before being accepted. Participants will attend 2-hour group sessions of mind-body therapy at NIH each week for at least 10 weeks. They will receive training in meditation, yoga breathing, guided imagery, and stress management in these sessions and will be asked to also practice the treatments at home each day. Patients may continue their medications and pain treatment with their own physicians during the course of the study.

National Human Genome Research Institute (NHGRI)
Bethesda, Maryland, United States, 20892

http://clinicaltrials.gov/show/NCT00001966

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