

- **Serotonin and norepinephrine reuptake inhibitors (SNRIs)** are a class of medications that are effective in treating depression. SNRIs increase levels of serotonin and norepinephrine in the brain by blocking or delaying their reuptake by nerves.
- SNRIs are also sometimes used to treat other conditions, such as anxiety disorders and chronic pain, especially nerve pain.

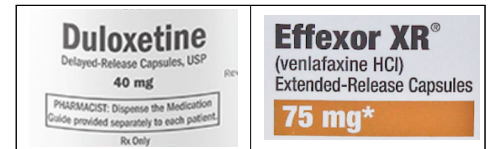
SSRI	SNRI
Inhibits the reuptake of <u>serotonin</u>	Inhibits the reuptake of both <u>serotonin</u> and <u>norepinephrine</u>



- Dual inhibition of these neurotransmitters can offer advantages over other antidepressant drugs by treating a wider range of symptoms.
- They can be especially useful in concomitant chronic or neuropathic pain.

Duloxetine (Cymbalta), Venlafaxine (Effexor), Milnacipran (Savella), and Mirtazapine (Remeron) are _____ and are used to treat depression and chronic neuropathic pain.

- Tricyclic antidepressants
- Benzodiazepines
- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors (SNRIs)

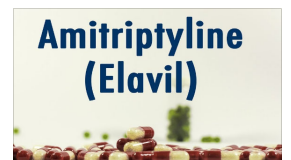


SSRIs	SNRIs
<ul style="list-style-type: none"> • Celexa (citalopram) • Fluvoxamine • Lexapro (escitalopram) • Paxil (paroxetine) • Prozac (fluoxetine) • Symbyax (olanzapine/fluoxetine) • Zoloft (sertraline) 	<ul style="list-style-type: none"> • Cymbalta (duloxetine) • Effexor (venlafaxine) • Meridia (sibutramine)*

- Tricyclic antidepressants (TCAs) are a class of medications that are used primarily as antidepressants. TCAs were discovered in the early 1950s and were marketed later in the decade.
- Although TCAs are sometimes prescribed for depressive disorders, they have been largely replaced in clinical use in most parts of the world by newer antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and norepinephrine reuptake inhibitors (NRIs).
- The TCAs show efficacy in the clinical treatment of a number of different types of chronic pain, notably neuralgia or neuropathic pain and fibromyalgia. The precise mechanism of action in explanation of their analgesic efficacy is unclear, but it is thought that they indirectly modulate the opioid system in the brain downstream via serotonergic and noradrenergic neuromodulation, among other properties. They are also effective in migraine prophylaxis, though not in the instant relief of an acute migraine attack. They may also be effective to prevent chronic tension headaches.

Amitriptyline (Elavil) and Nortriptyline (Pamelor) are _____ and are used to treat depression and neuropathic pain.

- Benzodiazepine
- Tricyclic antidepressant (TCA)
- Selective serotonin reuptake inhibitor (SSRI)
- Serotonin-norepinephrine reuptake inhibitor (SNRI)



<p>Fewest AEs</p> <p>↓</p> <p>Most AEs</p>	<ul style="list-style-type: none"> • Desipramine • Nortriptyline • Imipramine • Doxepin • Amitriptyline 	<ul style="list-style-type: none"> • Anticholinergic effects: dry mouth, blurred vision, urinary retention, constipation, dizziness, and vomiting. (TCA blocks the action of a neurotransmitter called acetylcholine. This inhibits nerve impulses responsible for involuntary muscle movements and various bodily functions.) • Cardiac effects: hypertension (early and transient, should not be treated), tachycardia, orthostasis and hypotension, arrhythmias (including ventricular tachycardia and ventricular fibrillation, most serious consequence) / ECG changes (prolonged QRS, QT, and PR intervals) 	<p>Cardiovascular system</p> <p>Sinus tachycardia Prolonged PR/QRS/QT ST/T-wave changes Heart block Vasodilatation Hypotension Cardiogenic shock Ventricular fibrillation/tachycardia Asystole</p>	<p>Central nervous system</p> <p>Drowsiness Coma Convulsions Pyramidal signs Rigidity Delirium Respiratory depression Ophthalmoplegia</p>	<p>Anticholinergic effects</p> <p>Dry mouth Blurred vision Dilated pupils Urinary retention Absent bowel sounds Pyrexia Myoclonic twitching</p>

What is the most accurate statement regarding neuropathic pain medications?

- A. Serotonin-norepinephrine reuptake inhibitors (SNRIs) are better tolerated than tricyclic antidepressants (TCAs).
- B. Selective serotonin reuptake inhibitors (SSRIs) are more efficacious than TCAs.
- C. The mechanism of action of TCAs is through modulation of calcium channels.
- D. Because TCAs have been studied extensively, they are considered a safe, first-line drug for treatment of the elderly.

- SNRIs are better tolerated than TCAs, which are contraindicated for patients with urinary retention, cardiac arrhythmias, congestive heart failure, recent myocardial infarction, and prolonged QTc interval.
- For these reasons and because they often cause sedation and cognitive problems, TCAs should be prescribed with caution for the elderly.
- SSRIs are not as efficacious as TCAs because they do not inhibit reuptake of norepinephrine, which is associated with analgesia.
- TCAs act at voltage-gated sodium channels and inhibit norepinephrine reuptake.

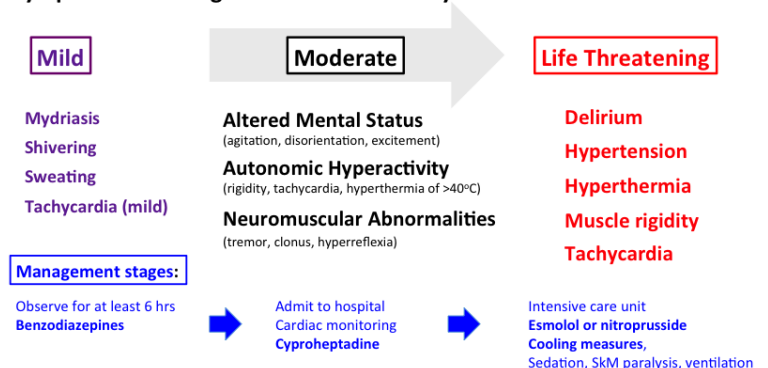
- **Tramadol**, sold under the brand name Ultram among others, is an opioid pain medication used to treat moderate to moderately severe pain. When taken by mouth in an immediate-release formulation, the onset of pain relief usually begins within an hour. It is also available by injection. It may be sold in combination with paracetamol (acetaminophen) or as longer-acting formulations.

Side effects of Tramadol		
↑dependence/withdrawal	↑seizure risk	↑serotonin syndrome

- **Serotonin syndrome** is typically caused by the use of two or more serotonergic medications or drugs. This may include selective serotonin reuptake inhibitor (**SSRI**), serotonin norepinephrine reuptake inhibitor (**SNRI**), monoamine oxidase inhibitor (**MAOI**), tricyclic antidepressants (**TCAs**), amphetamines, pethidine (meperidine), tramadol, dextromethorphan, buspirone, L-tryptophan, 5-HTP, St. John's wort, triptans, ecstasy (MDMA), metoclopramide, ondansetron, or cocaine. It occurs in about 15% of SSRI overdoses. It is a predictable consequence of excess serotonin on the central nervous system (CNS). Onset of symptoms is typically within a day of the extra serotonin.

- **Serotonin syndrome** occurs when you take medications that cause high levels of the chemical serotonin to accumulate in your body.
- Serotonin is an important chemical neurotransmitter in the human body that is needed for nerve cells and brain function. But too much serotonin causes signs and symptoms that can range from mild (shivering and diarrhea) to severe (muscle rigidity, fever and seizures). Severe serotonin syndrome can cause death if not treated.
- Milder forms of serotonin syndrome may go away within a day of stopping the medications that cause symptoms and, sometimes, after taking drugs that block serotonin.

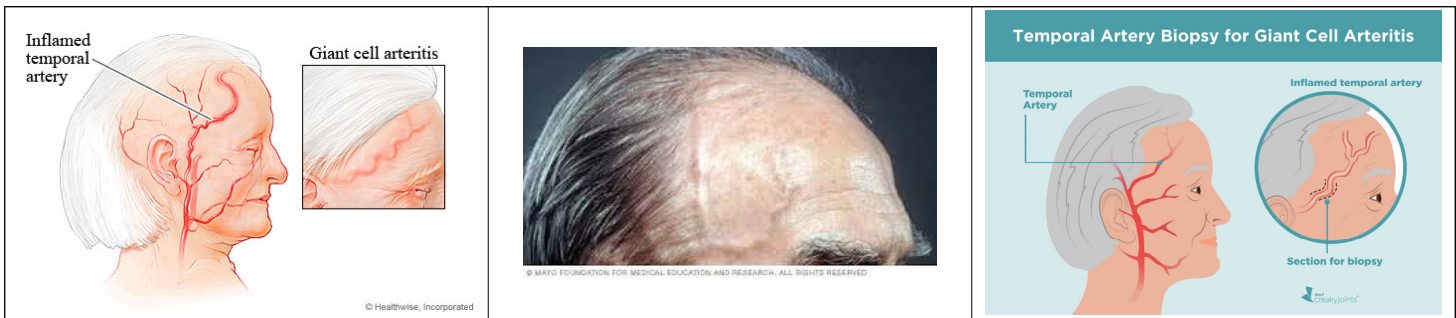
Symptoms & Management in Serotonin Syndrome:



You recently prescribed Tramadol (Ultram) and Pregabalin (Lyrica) to an 80-year-old male with Parkinson's disease, IDDM, anxiety, and painful peripheral diabetic neuropathy. One week later you see him for new-onset confusion and agitation. He has a fever, his pulse and blood pressure are elevated, and his pupils are dilated. Also, he is much stiffer despite his compliance with his usual dose of levodopa. Chest X-ray, fingerstick, CBC, and urinalysis are all normal. The following information best explains his new symptoms:

- A. His primary care doctor abruptly stopped his tramadol.
- B. His primary care doctor added lorazepam to treat his anxiety.
- C. His primary care doctor added paroxetine to treat his anxiety.
- D. He has a urinary tract infection.

- In addition to increasing seizure risk, tramadol also increases the risk of serotonin syndrome, particularly when combined with antidepressant therapy. The addition of paroxetine is the most likely explanation.
- Lorazepam can cause cognitive changes in the elderly, but it is not associated with the abnormal vital signs or dilated pupils. Tramadol withdrawal usually does not include severe cognitive symptoms, significant alterations in vital signs or pupillary changes. Furthermore, tramadol withdrawal would be unusual after only one week of treatment. Urinary tract infection may cause cognitive changes in the elderly, but it is also associated with elevated white blood cells in serum and urine, and it is not associated with an elevated blood pressure or dilated pupils.



CASE: A 68-year-old female patient states that she has jaw pain when she is chewing food. She also complains that the right side of her scalp aches when she combs her hair. After completion of your physical exam, you note tenderness on the scalp just above the right ear.

♠ What is the most likely diagnosis?

- A. Giant cell arteritis
- B. Tension headache
- C. Migraine headache
- D. Cluster headache

- Giant cell arteritis is another name for temporal arteritis. It is more commonly seen in people over the age of 50 and more often in women.
- Temporal arteritis (giant cell arteritis) will present with headache, tenderness on the scalp in the temporal region, jaw claudication and visual abnormalities.
- When suspicious of temporal arteritis, start the patient on high dose prednisone and obtain a temporal artery biopsy

Temporal arteritis

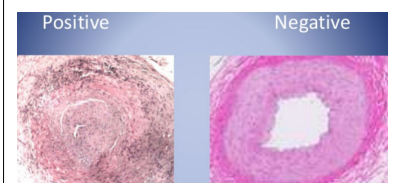
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Giant cell arteritis

♠ Which of the following is most likely to confirm the diagnosis?

- A. Erythrocyte sedimentation rate
- B. Temporal artery biopsy
- C. Visual acuity test
- D. Monitor response to NSAID

- The best confirmatory test for temporal arteritis is a temporal artery biopsy. It will reveal mononuclear infiltration or granulomatous infiltration with giant cells. These findings can be seen up to 14 days after starting treatment.
- Erythrocyte sedimentation rate (ESR) is useful because it is almost always increased, oftentimes over 100. However, ESR is elevated in a variety of inflammatory states and is therefore not very specific.
- Visual acuity test should be done because temporal arteritis can cause visual irregularities and ultimately blindness. However, it does not provide a diagnosis.

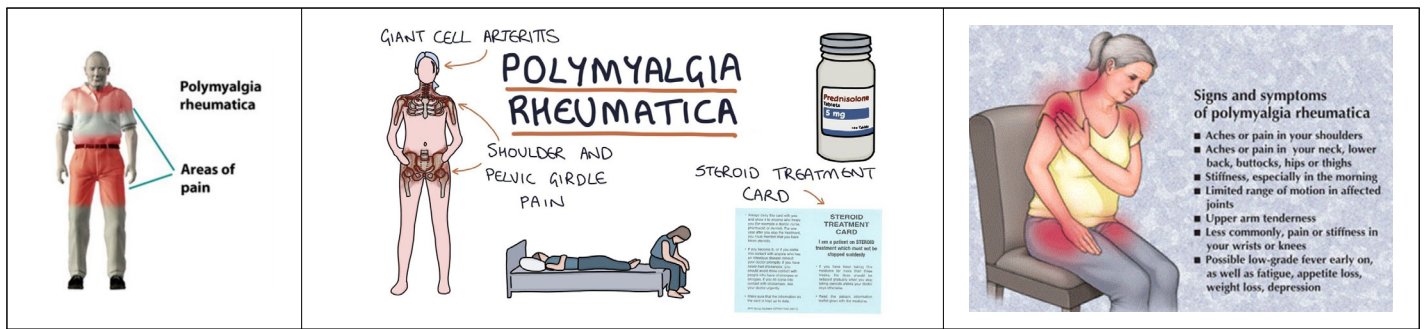


♠ What is the appropriate treatment?

- A. 100% oxygen
- B. Craniosacral treatment
- C. High-dose corticosteroids
- D. Low-dose corticosteroids

- It is extremely important to start therapy with **high dose prednisone** (60mg) for 1-2 months before tapering. You may start this treatment before obtaining a biopsy because the urgency of this diagnosis cannot be stressed enough as it may lead to irreversible blindness.
- Low dose corticosteroids** would not be ideal as the initial treatment in a newly diagnosed temporal arteritis case.

Temporal arteritis	Polymyalgia rheumatica
high-dose prednisone	low-dose prednisone



- Polymyalgia rheumatic (PMR) is an idiopathic inflammatory condition which results in pain and stiffness in the neck, upper arms, shoulders, hips, and pelvis. Physical examination will reveal tenderness without signs of objective weakness.
- PMR often affects the same population as giant cell arteritis (GCA), particularly older females. Both diseases show preference for the same HLA type and thus they often coexist.
- Symptoms of GCA include headache, jaw claudication, and visual disturbance. PMR and GCA both classically show an elevation in erythrocyte sedimentation rate.
- It is important to remember, however, that suspected giant cell arteritis should be treated immediately with high-dose systemic glucocorticoid therapy without waiting for results of serum analysis or temporal artery biopsy. Early treatment is crucial to avoid permanent vision loss.

With which of the following is polymyalgia rheumatica most commonly associated?

- A. Rheumatoid arthritis
- B. Statin-induced myositis
- C. Spondyloarthritis
- D. Temporal arteritis

- No pathogenic associations with polymyalgia rheumatica (PMR) have been confirmed. 5-15% of patients with PMR will have temporal arteritis.

Which of the following is the treatment of choice for polymyalgia rheumatica?

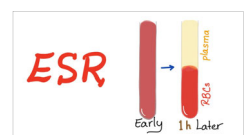
- A. High dose prednisone
- B. Low dose prednisone
- C. Intra-articular steroid injections
- D. Etanercept

- High-dose prednisone is used to treat temporal arteritis. Intra articular steroids are not the treatment of choice, though they can be adjunctive to oral therapy. Etanercept is not commonly used to treat polymyalgia rheumatica.

Temporal arteritis	Polymyalgia rheumatica
high-dose prednisone	low-dose prednisone

A 63-year-old woman presents to the clinic with joint and muscle pain. She complains of symmetric pain and stiffness in her shoulders and hips which is usually worse in the mornings. These symptoms began abruptly one month earlier. For the past week, this pain and stiffness has been so severe that she has been unable to dress herself without assistance. She denies any associated fevers but has noticed increased fatigue and general malaise. Past medical history is significant for hypertension. In addition, she describes an incident six months earlier during which she experienced headache and transient loss of vision in her right eye. She was treated with two months of corticosteroid therapy and has not had any recurrent symptoms. The patient denies alcohol, tobacco, or illicit drug use. Physical examination reveals tenderness to palpation along the shoulders and hips bilaterally. Range of motion is limited significantly by pain. Which of the following laboratory values is most likely to be elevated?

- A. Rheumatoid factor
- B. Antinuclear antibody
- C. Erythrocyte sedimentation rate
- D. White blood cell count



- Polymyalgia rheumatica is characterized by an elevated erythrocyte sedimentation rate (ESR). Affected patients usually present with symmetric pain and stiffness in muscles and joints, especially in the shoulders and pelvic area.
- Elevated ESR is commonly seen in polymyalgia rheumatica. Polymyalgia rheumatica shares the same HLA type and affects the same patient population as giant cell arteritis.

Breast-Conserving Surgery

Lumpectomy Wide Excision Quadrantectomy

Breast Removal

Mastectomy

- After having breast cancer surgery, some women have problems with nerve (neuropathic) pain in the chest wall, armpit, and/or arm that doesn't go away over time. This is called **post-mastectomy pain syndrome (PMPS)** because it was first noticed in women who had mastectomies, but it can also happen after other types of breast-conserving surgery (such as a lumpectomy).
- The classic symptoms of PMPS are pain and tingling in the chest wall, armpit, and/or arm. Pain may also be felt in the shoulder or surgical scar. Other common complaints include: numbness, shooting or pricking pain, or unbearable itching. Most women with PMPS say their symptoms are not severe.
- Studies have shown that between 20% and 30% of women develop symptoms of PMPS after surgery. It's most common after operations that remove tissue in the upper outside portion of the breast or the underarm area.

A 60-year-old female with history of left breast cancer underwent chemotherapy followed by left mastectomy and axillary node dissection. Six months later, the patient continues to experience pain around the left chest wall and medial arm. Which nerve is most likely to have been injured during the mastectomy surgery?

- A. Intercostobrachial nerve
- B. Long thoracic nerve
- C. Thoracodorsal nerve
- D. Axillary nerve

- The **intercostobrachial nerve (ICBN)** is a sensory nerve that arises from the lateral collateral branch of the second intercostal nerve (T2). From the chest wall, the ICBN courses through the axilla and upper arm to then join with the medial cutaneous nerve of the arm. Sensory innervation is thus provided to the skin along this route.
- The ICBN is often sacrificed during mastectomy surgery and is thought to be a major contributor to **Post Mastectomy Pain Syndrome (PMPS)**. PMPS is a diagnosis of exclusion referring to chronic pain that develops after breast cancer surgery at or near the operative site and persists beyond 3 months after surgery.
- The long thoracic nerve is a motor nerve that supplies the serratus anterior. The thoracodorsal nerve is a motor nerve that supplies the latissimus dorsi. The axillary nerve is a sensorimotor nerve that supplies the deltoid and teres minor, but also sensation to part of the shoulder area.

Post Mastectomy Pain Syndrome (PMPS)

- Can occur after mastectomy or breast conservation surgery
- Defined as pain in the area of surgery or arm at least 4 days/week with severity at least 3 on a 0-10 pain scale
- Occurs in 23-68% of patients

Table 1: Common medications used to treat PMPS.^{25,26}

Class	Medication name
Antiepileptics	Gabapentin, pregabalin
Tricyclic antidepressants	Amitriptyline, imipramine, nortriptyline
Serotonin–norepinephrine reuptake inhibitors	Duloxetine, venlafaxine
Topical compounds	Lidocaine, capsaicin

PMPS, postmastectomy pain syndrome.

YIN-YANG BALANCING ACUPUNCTURE (PYUNG CHIM, 平針, 평침)

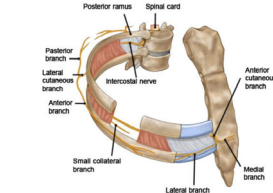
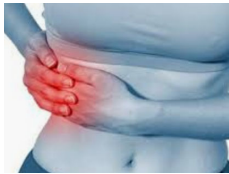
		System 1	System 2	System 3	System 4
IPSI LATERAL	FIRE				
	WATER				
CONTRALATERAL	FIRE				
	WATER				

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	LU	LI	ST	SP	HT	SI	UB	KD	PC	SJ	GB	LV
FIRE POINT	10	5	41	2	8	5	60	2	8	6	38	2
WATER POINT	5	2	44	9	3	2	66	10	3	2	43	8

- **Intercostal neuralgia** is neuropathic pain involving the intercostal nerves. These are the nerves that arise from the spinal cord, below the ribs. Intercostal neuralgia tends to cause thoracic pain, which affects your chest wall and upper trunk.
- Intercostal neuralgia is often associated with injury or inflammation of the nerves, muscles, cartilage and ligaments in the rib cage and middle spine area. **Common causes** of intercostal neuralgia include pregnancy, tumors, chest or rib injury, surgery to the chest or organs in the chest cavity, and shingles. Shingles can attack nerves in the chest and upper back.
- The **main symptom** of intercostal neuralgia is pain in the rib cage area, often described as stabbing, sharp, spasm-like, tearing, tender, aching or gnawing. The pain may wrap around your chest or radiate from the back toward the front of your chest in a band-like pattern. Sometimes you may feel pain uniformly along the length of your ribs.

Neuralgia = Neuron ("nerve") + Algos ("Pain")



- **Neuralgia** is more difficult to treat than other types of pain because it does not respond well to normal pain medications.
- Special medications have become more specific to neuralgia and typically fall under the category of membrane stabilizing drugs or antidepressants such as Duloxetine (Cymbalta). The antiepileptic medication (AED) Pregabalin (Lyrica) was developed specifically for neuralgia and other neuropathic pain as a successor to Gabapentin (Neurontin).

A 48-year-old female presents with pain radiating across the left flank that started eight weeks ago after she fell on her back. Upon examination, you find tenderness along the left T9 distribution. She denies any history of vesicular lesions. MRI of the thoracic spine shows mild thoracic spondylosis with absence of disc disease. Which of the following is the most likely diagnosis?

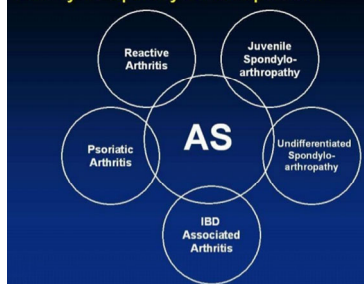
- Pott's disease
- Radiculopathy
- Intercostal neuralgia
- Post-herpetic neuralgia

- **Intercostal neuralgia** is a condition caused by trauma or impingement resulting in burning pain in a thoracic dermatomal distribution.
- **Pott's disease** is tuberculosis infection of a vertebral body, which would be seen on MRI.
- **Thoracic radiculopathy** would present with disc herniation on MRI.
- By eight weeks **post-herpetic neuralgia** vesicular lesions, consistent with a herpetic outbreak, would have occurred, although a rare entity of post-herpetic neuralgia without vesicular lesions does exist ("zoster sine herpete").

SERONEGATIVE SPONDYLOARTHRITIDIES

- These comprise a group of related inflammatory joint diseases, which show considerable overlap in their clinical features and a shared immunogenetic association with the HLAB27 antigen. They include:
 - ankylosing spondylitis
 - axial spondyloarthritis
 - reactive arthritis, including Reiter's syndrome
 - psoriatic arthritis
 - arthropathy associated with inflammatory bowel disease.

Family of Spondyloarthropathies



Five subgroups of spondyloarthritis:

- Ankylosing spondylitis
- Psoriatic arthritis
- Reactive arthritis (Reiter syndrome)
- Enteropathic arthritis (i.e. extra-intestinal manifestation of IBD)
- Undifferentiated spondyloarthritis

Seronegative	Spondyloarthropathies
negative rheumatoid factor and ANA	joint disease of the vertebral column

- **Seronegative spondyloarthropathies (SpA)** are a family of rheumatologic disorders that classically include: **Ankylosing spondylitis**, **Psoriatic arthritis**, **Inflammatory bowel disease (IBD) associated arthritis**, **Reactive arthritis** (formerly Reiter syndrome).

Which is the most commonly associated genetic marker with seronegative spondyloarthropathies?

- HLA-B27
- CD4
- COMT
- MOR

- The most commonly known genetic factor associated with these maladies is the **HLA-B27 (human leukocyte antigen B-27)**. This antigen is particularly strongly associated with the most widely recognized seronegative spondyloarthropathy, ankylosing spondylitis.
- **CD4** is a T cell marker, associated with innate immunity. **COMT** (Catechol-O-methyltransferase) and **MOR** (mu-opioid receptors) may be linked with chronic pain.

P	Psoriatic arthritis	skin psoriasis, pencil-in-cup deformity of DIP
A	Ankylosing spondylitis	sacroiliac joints fusion, bamboo spine
I	Inflammatory bowel disease	crohn's disease or ulcerative colitis
R	Reactive arthritis	conjunctivitis, urethritis, arthritis

Which of the following is a typical feature of seronegative spondyloarthropathies?

- A. Symmetric arthritis
- B. Enthesitis
- C. Bursitis
- D. Vasculitis

- Seronegative spondyloarthropathies are commonly asymmetric and have familial patterns. Less than 5% of patients are HLA-B27 negative. In order to identify patients with SpAs, symptoms of LBP lasting > 3months should be present, and occur before age 45 years.
- In addition, the following criteria should be met: Sacroiliitis on imaging plus one or more of the SpA features listed below. Or, alternatively, HLA-B27 positivity plus two or more of the following SpA features listed: inflammatory back pain; arthritis; enthesitis (e.g., heel); uveitis; dactylitis; Psoriasis; Crohn's/colitis; good response to NSAIDs; family history of SpA; ↑C-reactive protein (CRP).

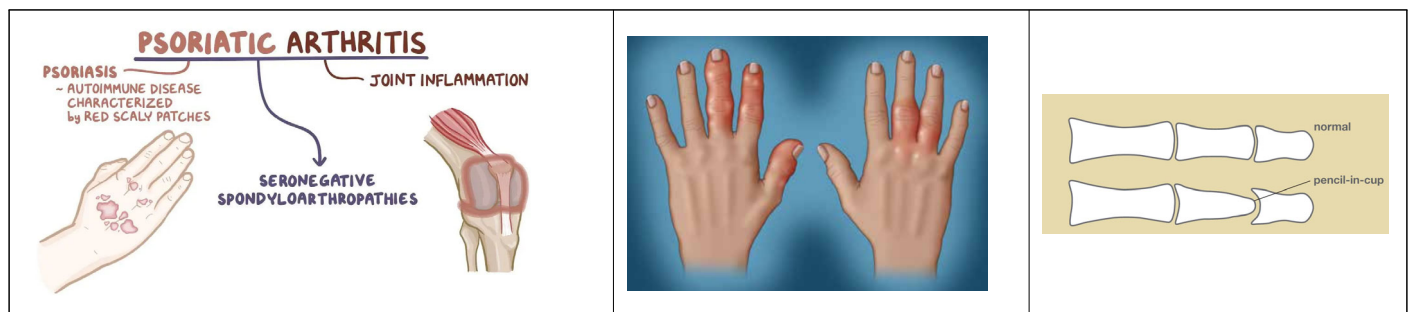
HLA-B27		2 or more of the following SpA features
Positive	+	inflammatory back pain / arthritis / enthesitis (e.g., heel) / uveitis / dactylitis / psoriasis / crohn's or colitis / good response to NSAIDs / family history of SpA / ↑C-reactive protein (CRP).

Enthesitis	Uveitis	Dactylitis
inflammation of the entheses, the sites where tendons or ligaments insert into the bone	inflammation of the uvea, the middle layer of tissue in the eye wall	inflammation of a digit (either finger or toe)

Which of the following is a poor prognostic indicator for seronegative spondyloarthropathies?

- A. Lack of uveitis
- B. Low peripheral joint involvement
- C. Low erythrocyte sedimentation rate
- D. Poor response to non-steroidal anti-inflammatory drugs

- Poor prognostic indicators include a younger age of onset, greater peripheral than axial joint involvement, uveitis, and elevated erythrocyte sedimentation rate (ESR), and poor response to non-steroidal anti-inflammatory drugs (NSAIDs).



Dactylitis is a common finding in which of the following conditions?

- A. Psoriatic arthritis
- B. Rheumatoid arthritis
- C. Systemic lupus erythematosus
- D. Osteoarthritis

Daktylos = "Finger"	• Dactylitis (commonly known as sausage digits) is seen in psoriatic arthritis.
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