Lupus, Anxiety and Depression

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Introduction

- Systemic lupus erythematosus (SLE) is a chronic autoimmune disease of unknown cause that can affect virtually any organ of the body.
- Immunologic abnormalities, especially the production of several antinuclear antibodies (ANA), are a prominent feature of the disease.
- Patients present with variable clinical features ranging from mild joint and skin involvement to life-threatening kidney, hematologic, or central nervous system involvement.
- The diagnosis of SLE is generally based on clinical and laboratory findings after excluding alternative diagnoses.
- In the absence of SLE diagnostic criteria, SLE classification criteria are often used by clinicians as guidance to help identify the clinical features when making the diagnosis.
- Serologic findings are important in suggesting the possibility of SLE, with some antibodies (eg, anti-dsDNA and anti-Smith) highly associated with this condition.

https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-systemic-lupus-erythematosus-in-adults

Clinical Manifestations

- **Constitutional symptoms** — such as **fatigue, fever, and weight loss** are present in most patients with SLE at some point during the course of the disease.
  - **Fatigue** is the most common complaint, occurring in 80 to 100 percent of patients, and is frequently associated with **depression**, sleep disturbances, and concomitant fibromyalgia [2].
  - **Fever** – can be a manifestation of active disease and is seen in over 50 percent of patients with SLE [3].
  - **Myalgia** – Muscle pain is also common among patients with SLE.
  - **Weight changes** – frequent in patients with SLE and may be related to the disease or to its treatment.
    - Unintentional weight loss may be due to decreased appetite, side effects of medications (particularly diuretics and occasionally hydroxychloroquine, and gastrointestinal diseases)
    - Weight gain in SLE may be due to salt and water retention or increased appetite associated with the use of glucocorticoids.

2. Tench CM, McCurdie I, White PD, D'Cruz DP. The prevalence and associations of fatigue in systemic lupus erythematosus. Rheumatology (Oxford) 2000; 39:1249.
3. Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore) 2003; 82:299.

Arthritis and Arthralgias

- Arthritis and arthralgias occur in **over 90 percent of patients with SLE** and are often one of the earliest manifestations [4].
- Arthritis, with demonstrable inflammation, occurs in 65 to 70 percent of patients and tends to be migratory, polyarticular, and symmetrical.
- The arthritis is moderately painful, usually does not cause erosion, and is rarely deforming.
- However, occasionally patients with SLE also develop a deforming erosive arthritis, which is similar to that of rheumatoid arthritis (RA).

American College of Rheumatology Image Library, Copyright 2022 ACR

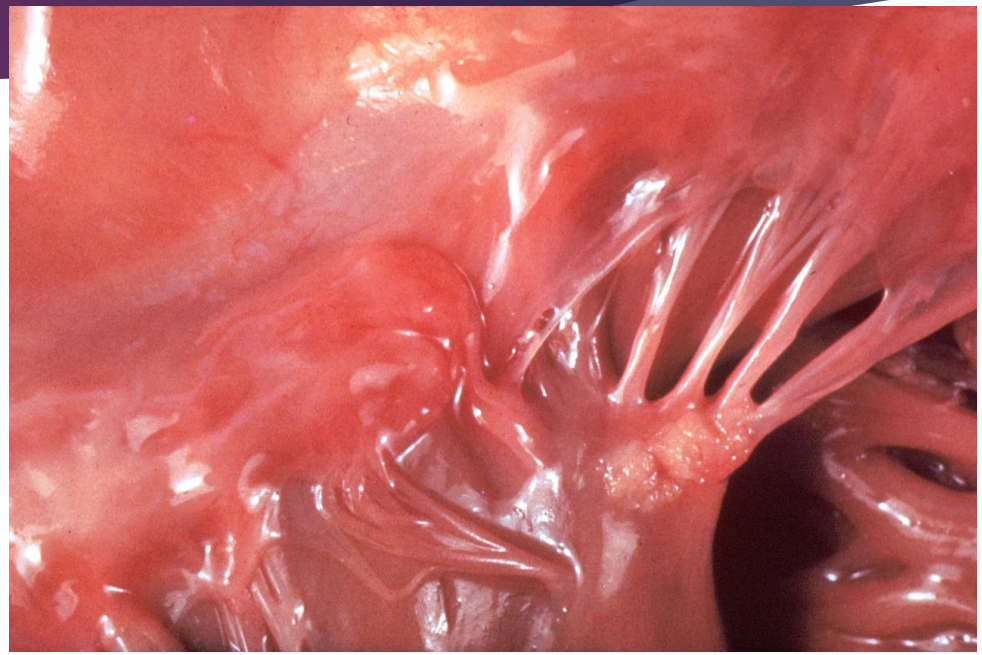
4. Greco CM, Rudy TE, Manzi S. Adaptation to chronic pain in systemic lupus erythematosus: applicability of the multidimensional pain inventory. Pain Med 2003; 4:39.

Mucocutaneous Involvement

- Most patients develop **skin and mucous membrane lesions** at some point during the course of their disease.
- The most common lesion is a facial rash known as a ”**malar rash”** or **“butterfly rash**" that presents as a flat or raised red rash over the **cheeks and nose** (but sparing the nasolabial folds) that appears after sun exposure.
- Some patients may develop **discoid lesions**, which are more inflammatory and tend to **scar**.
- **Photosensitivity** is also a common theme for skin lesions associated with SLE.
- Many patients develop **oral and/or nasal ulcers.**
- Nonscarring **alopecia** is also observed in many SLE patients at some point during the course of their disease.
- Scarring alopecia can occur in patients with discoid lupus erythematosus.

Cardiac Involvement

- Cardiac disease is common in SLE and can involve the pericardium, myocardium, valves, conduction system, and coronary arteries.
- **Pericarditis**, with or without an effusion, is the most common cardiac manifestation of SLE, occurring in approximately 25 percent of patients at some point during their disease course [5].
- Verrucous (Libman-Sacks) endocarditis is usually clinically silent, but it can produce valvular insufficiency and can serve as a source of emboli.
- Myocarditis is uncommon but may be severe.
- Patients with SLE also have an increased risk of coronary artery disease.
- Neonatal lupus, which can occur in babies of women with SLE expressing anti-Ro/SSA and anti-La/SSB, can cause **congenital heart block** of varying degrees.



5. Miner JJ, Kim AH. Cardiac manifestations of systemic lupus erythematosus. Rheum Dis Clin North Am 2014; 40:51.

Vascular Manifestations

- **Raynaud phenomenon** – common in SLE, induced by cold that occurs in up to 50 percent of patients [6]. Characterized by intermittent acral pallor (white) followed by cyanosis (blue) and erythroderma (red).
- **Vasculitis** – Inflammation of blood vessels. Estimates of the prevalence of vasculitis in SLE patients range from 11 to 36 percent [7]. Can involve vessels of all sizes. Small vessel involvement is the most common, often as cutaneous lesions.
- **Thromboembolic disease** – Blood clots can complicate SLE, particularly in the context of antiphospholipid antibodies. Can affect both the venous and arterial circulations.

6. Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore) 2003; 82:299.
7.Barile-Fabris L, Hernández-Cabrera MF, Barragan-Garfias JA. Vasculitis in systemic lupus erythematosus. Curr Rheumatol Rep 2014; 16:440.

Kidney Involvement

- Kidney involvement is clinically apparent in approximately 50 percent of SLE patients and is a significant cause of morbidity and mortality [8].
- Thus, periodic screening for the presence of **lupus nephritis** with urinalyses, quantitation of proteinuria, and estimation of the glomerular filtration rate is an important component of the ongoing management of SLE patients.
- Several forms of glomerulonephritis can occur, and **kidney biopsy** is useful to define the type and extent of kidney involvement.
- The clinical presentation of lupus nephritis is highly variable, ranging from asymptomatic hematuria and/or proteinuria to nephrotic syndrome and rapidly progressive glomerulonephritis with loss of kidney function.

8. Danila MI, Pons-Estel GJ, Zhang J, et al. Renal damage is the most important predictor of mortality within the damage index: data from LUMINA LXIV, a multiethnic US cohort. Rheumatology (Oxford) 2009; 48:542.

Gastrointestinal Involvement

- Gastrointestinal symptoms are common in SLE patients, occurring in up to 40 percent of patients [9].
- The majority of gastrointestinal symptoms are caused by adverse medication reactions and viral or bacterial infections.
- SLE-related gastrointestinal abnormalities can involve almost any organ along the gastrointestinal tract and include esophagitis, intestinal pseudo-obstruction, protein-losing enteropathy, lupus hepatitis, acute pancreatitis, mesenteric vasculitis or ischemia, and peritonitis.

9. Tian XP, Zhang X. Gastrointestinal involvement in systemic lupus erythematosus: insight into pathogenesis, diagnosis and treatment. World J Gastroenterol 2010; 16:2971.

Pulmonary Involvement

- During the course of their disease, many patients develop symptoms secondary to pulmonary involvement of SLE.
- Pulmonary manifestations of SLE include **pleuritis** (with or without effusion), pneumonitis, interstitial lung disease, pulmonary hypertension, shrinking lung syndrome, and alveolar hemorrhage.
- Respiratory symptoms must also be distinguished from infection, particularly in patients on immunosuppressive therapy.
- The risk of thromboembolic involvement is increased in those with antiphospholipid antibodies or with lupus anticoagulant.

Hematologic Abnormalities

- Hematologic abnormalities are common in SLE, and all three blood cell lines (WBC, RBC, PLT) can be affected.
- **Anemia** (low RBCs or hemoglobin) is common.
  - Anemia of chronic disease (or anemia of inflammation) is the most common type of anemia among patients with SLE.
  - Autoimmune hemolytic anemia is relatively rare but can be severe, requiring immediate therapy.
- **Leukopenia** (low WBCs) is common in SLE patients, occurring in approximately 50 percent of patients [10].
  - **Leukopenia** can be due to lymphopenia and/or secondary neutropenia and generally correlates with clinically active disease.
  - Neutropenia may also result from toxicity due to immunosuppressive medications.
- **Thrombocytopenia** is also a common hematologic abnormality.
  - Rarely, severe thrombocytopenia can occur and requires treatment.

10. Newman K, Owlia MB, El-Hemaidi I, Akhtari M. Management of immune cytopenias in patients with systemic lupus erythematosus - Old and new. Autoimmun Rev 2013; 12:784.

Ophthalmologic Involvement

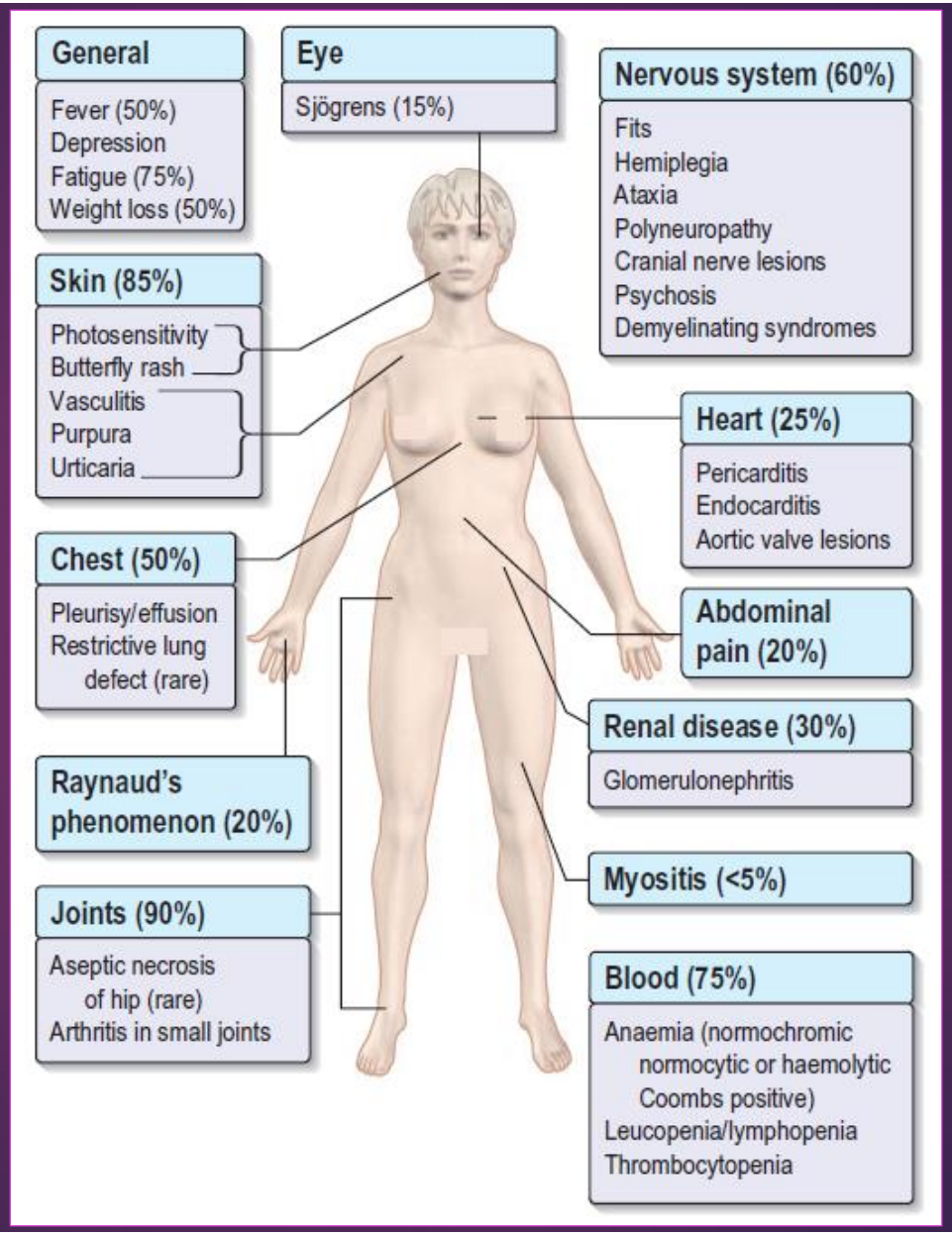
- Any structure of the eye can be involved in SLE, with keratoconjunctivitis sicca (**dry eyes**) being the most common manifestation as a result of secondary **Sjögren's syndrome** [11]
- The next most common pathologic condition involving the eye in lupus patients is retinal vasculopathy in the form of cotton wool spots.
- Other less common ophthalmologic manifestations of SLE include optic neuropathy, choroidopathy, episcleritis, scleritis, and anterior uveitis (iritis, iridocyclitis).

11. Silpa-archa S, Lee JJ, Foster CS. Ocular manifestations in systemic lupus erythematosus. Br J Ophthalmol 2016; 100:135.

Neurologic and Neuropsychiatric Involvement

- Neuropsychiatric involvement of SLE consists of a broad range of neurologic and psychiatric manifestations, including stroke, seizures, cognitive dysfunction, delirium, psychosis, depression, and/or peripheral neuropathies.
- Other less common problems are movement disorders, cranial neuropathies, myelitis, and meningitis.
- Thromboembolic events, often in association with antiphospholipid antibodies or with lupus anticoagulant, may occur in a substantial minority (20 percent) of patients with SLE [12].
- Arterial thromboemboli may cause focal neurologic problems, such as stroke or seizures and/or more diffuse cognitive defects.

12. Romero-Díaz J, García-Sosa I, Sánchez-Guerrero J. Thrombosis in systemic lupus erythematosus and other autoimmune diseases of recent onset. J Rheumatol 2009; 36:68.


General
Fever (50%)
Depression
Fatigue (75%)
Weight loss (50%)
Eye
Sjögrens (15%)
Nervous system (60%)
Fits
Hemiplegia
Ataxia
Polyneuropathy
Cranial nerve lesions
Psychosis
Demyelinating syndromes
Skin (85%)
Photosensitivity
Butterfly rash
Vasculitis
Purpura
Urticaria
Heart (25%)
Pericarditis
Endocarditis
Aortic valve lesions
Chest (50%)
Pleurisy/effusion
Restrictive lung defect (rare)
Abdominal pain (20%)
Renal disease (30%)
Glomerulonephritis
Raynaud's phenomenon (20%)
Myositis (<5%)
Joints (90%)
Aseptic necrosis of hip (rare)
Arthritis in small joints
Blood (75%)
Anaemia (normochromic normocytic or haemolytic Coombs positive)
Leucopenia/lymphopenia
Thrombocytopenia

Laboratory Testing

- Complete blood count (CBC) and differential may reveal leukopenia, mild anemia, and/or thrombocytopenia.
- Elevated serum creatinine may be suggestive of kidney dysfunction.
- Urinalysis with urine sediment may reveal hematuria, pyuria, proteinuria, and/or cellular casts.
- Serum protein electrophoresis may demonstrate a hypergammaglobulinemia that is suggestive of a systemic inflammatory process.

Lab Testing Continued

- Antiphospholipid antibodies
  - lupus anticoagulant [LA], immunoglobulin [Ig] G and IgM anticardiolipin [aCL] antibodies, and IgG and IgM anti-beta2-glycoprotein [GP]
- **C3** and **C4** or CH50 complement levels
- Erythrocyte sedimentation rate (**ESR**) and/or C-reactive protein (**CRP**) levels
- Urine protein-to-creatinine ratio

More Lab Testing Continued

- **Anti-dsDNA** and **anti-Sm antibodies** are highly specific for SLE, but anti-Sm antibodies lack sensitivity.
  - Anti-dsDNA and anti-Sm antibodies are seen in approximately 70 and 30 percent of patients with SLE, respectively [13].
- **Anti-Ro/SSA and anti-La/SSB antibodies** are present in approximately 30 and 20 percent of patients with SLE, respectively; however, both antibodies are more commonly associated with **Sjögren's syndrome** [13].
- Anti-U1 RNP antibodies are observed in approximately 25 percent of patients with SLE, but they also occur in patients with other conditions, and high levels are almost always present in patients with mixed connective tissue disease (MCTD) [13].
- Antiribosomal P protein antibodies have a high specificity for SLE but low sensitivity for SLE. They also lack specificity for involvement of a particular organ system or disease manifestation.

13. Riemakasten G, Hiepe F. Autoantibodies. In: Dubois' Lupus Erythematosus and Related Syndromes, 8th ed, Wallace DJ, Hahn BH (Eds), Elsevier, Philadelphia 2013. p.282.

Diagnosis

- The diagnosis of SLE is based upon the judgment of an experienced clinician who recognizes characteristic constellations of symptoms and signs in the setting of supportive serologic studies after excluding alternative diagnoses.
- This is often challenging due to the great variability in the expression of SLE.
- Although the classification criteria were designed for research purposes, many clinicians refer to aspects of these criteria when making the diagnosis of SLE.
- After excluding alternative diagnoses, we diagnose SLE in the patient who fulfills the 1997 ACR criteria, the 2012 SLICC criteria, or the 2019 EULAR/ACR criteria.
- The **ACR criteria** require that a patient satisfy at least **4 of 11 criteria**.
- The **SLICC criteria** require either that a patient satisfy at least **4 of 17 criteria**, including at least 1 of the 11 clinical criteria and one of the six immunologic criteria, **or** that the patient has **biopsy-proven nephritis** compatible with SLE in the presence of antinuclear antibodies (**ANA) or anti-double-stranded DNA** (anti-dsDNA) antibodies.
- According to the **EULAR/ACR criteria**, a patient can be classified as having SLE if they have a **positive ANA ≥1:80 and score 10 or more points**.

Diagnostic criteria in SLE

S	• Serositis [pleuritis, pericarditis]
O	• Oral ulcers
A	• Arthritis
P	• Photosensitivity
M	Malar rash

B	• Blood [all are low - anemia, leukopenia, thrombocytopenia]
R	• Renal [protein]
A	• ANA
I	• Immunologic [DS DNA, etc.]
N	• Neurologic [psych, seizures]
D	Discoid rash

knowmedge
MEDICAL MNEMONICS

Mnemonic: "SOAP BRAIN MD"

2012 SLICC Classification Criteria for

SYSTEMIC LUPUS ERYTHEMATOSUS

Biopsy proven LUPUS NEPHRITIS and ANA or anti-DNA

CLINICAL

- Acute cutaneous LE
- Chronic cutaneous LE
- Oral ulcer
- Alopecia
- Synovitis
- Serositis
- Renal
- Neurologic
- Hemolytic anemia
- Leucopenia/ lymphopenia
- Thrombocytopenia

IMMUNOLOGIC

- ANA
- Anti-dsDNA
- Anti-Sm
- aPL antibodies
- Low complement
- Direct Coomb's test

AT LEAST 4 CRITERIA
(1 Needs to be IMMUNOLOGIC)

Petri M, Orbai AM, Alarcon GS, et al. Arth & Rheum 2012; 64 (8): 2677-86.

New EULAR/ACR criteria for the classification of SLE

Clinical domains	Points
Constitutional domain	
Fever	2
Cutaneous domain	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Arthritis domain	
Synovitis or tenderness in at least 2 joints	6
Neurologic domain	
Delirium	2
Psychosis	3
Seizure	5
Serositis domain	
Pleural or pericardial effusion	5
Acute pericarditis	6
Hematologic domain	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Renal domain	
Proteinuria > 0.5 g/24 hr	4
Class II or V lupus nephritis	8
Class III or IV lupus nephritis	10

Immunologic domains	Points
Antiphospholipid antibody domain	
Anticardiolipin IgG > 40 GPL *or* anti-β2GP1 IgG > 40 units *or* lupus anticoagulant	2
Complement proteins domain	
Low C3 *or* low C4	3
Low C3 *and* low C4	4
Highly specific antibodies domain	
Anti-dsDNA antibody	6
Anti-Sm antibody	6

REFERENCE: Aringer et al. Abstract #2928. 2018 ACR/ARHP Annual Meeting

- ✓ **Classification criteria are not diagnosis criteria**
- ✓ All patients classified as having SLE must have ANA ≥ 1:80 (entry criterion)
- ✓ Patients must have ≥ 10 points to be classified as SLE
- ✓ Items can only be counted for classification if there is no more likely cause
- ✓ Only the highest criterion in a given domain counts
- ✓ SLE classification requires points from at least one clinical domain

@Lupusreference

Suspicion of SLE		
ACR	SLICC	EULAR/ACR
any 4 of 11	Histology compatible with lupus nephritis and ANA or anti-dsDNA OR any 4 of 17 (at least one immunological)	ANA positive 10 points weighted items (highest in each domain counted only)

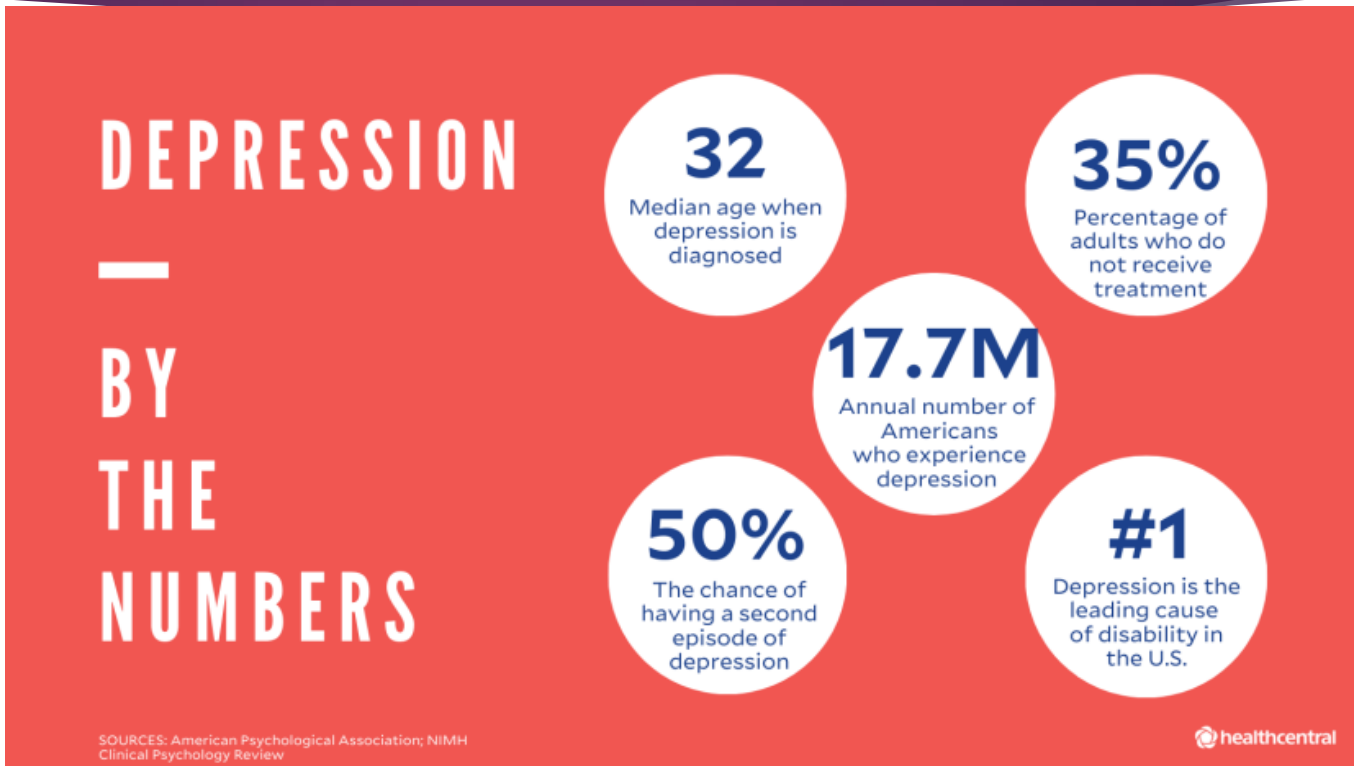
Lupus Medications

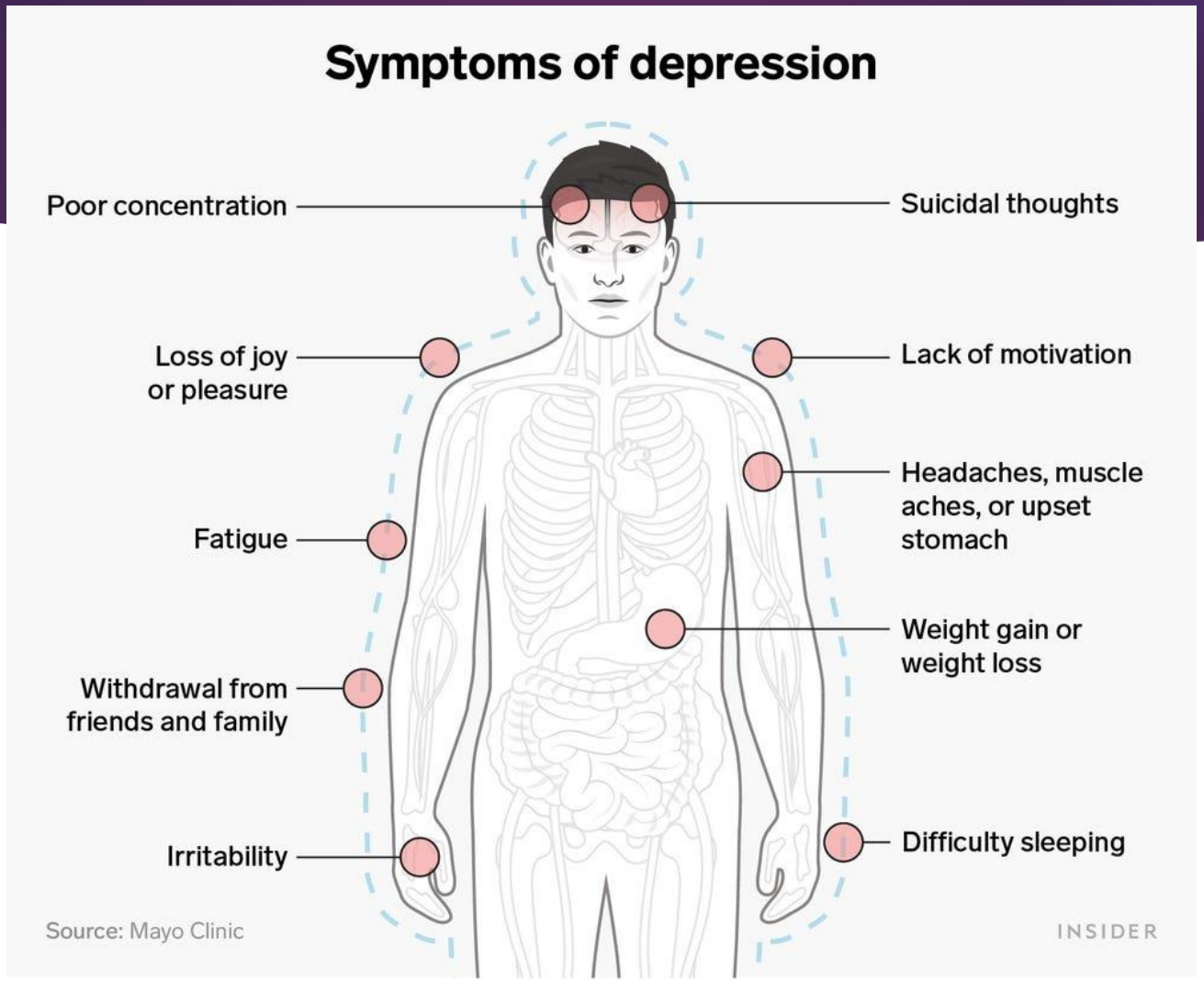
- NSAIDs
- Antimalarial drugs
  - hydroxychloroquine
- Corticosteroids
  - prednisone
- Immunosuppressants
  - azathioprine, mycophenolate, methotrexate, cyclosporine, voclosporin, etc.
- Biologics
  - Belimumab
  - Rituximab
  - anifrolumab

Depression

- Depression is a mood disorder that causes a persistent feeling of sadness and loss of interest.
- Also called major depressive disorder or clinical depression, it affects how you feel, think and behave and can lead to a variety of emotional and physical problems.
- You may have trouble doing normal day-to-day activities, and sometimes you may feel as if life isn't worth living.
- Most people with depression feel better with medication, psychotherapy or both.

https://www.mayoclinic.org/diseases-conditions/depression/symptoms-causes/syc-20356007


DEPRESSION
—
BY
THE
NUMBERS
32
Median age when depression is diagnosed
35%
Percentage of adults who do not receive treatment
17.7M
Annual number of Americans who experience depression
50%
The chance of having a second episode of depression
#1
Depression is the leading cause of disability in the U.S.
SOURCES: American Psychological Association; NIMH
Clinical Psychology Review
healthcentral


Symptoms of depression
Poor concentration
Suicidal thoughts
Loss of joy or pleasure
Lack of motivation
Headaches, muscle aches, or upset stomach
Fatigue
Weight gain or weight loss
Withdrawal from friends and family
Difficulty sleeping
Irritability
Source: Mayo Clinic
INSIDER

Symptoms of Depression

- Feelings of **sadness**, tearfulness, emptiness or hopelessness
- Angry outbursts**, irritability** or frustration, even over small matters
- Loss of interest or pleasure in most or all normal activities, such as sex, hobbies or sports
- **Sleep disturbances**, including insomnia or sleeping too much
- **Fatigue** or lack of energy, so even small tasks take extra effort
- Reduced appetite and **weight loss or** increased cravings for food and **weight gain**
- **Anxiety**, agitation or restlessness
- Slowed thinking, speaking or body movements
- Feelings of worthlessness or guilt, fixating on past failures or self-blame
- **Difficulty concentrating**, making decisions and remembering things
- Frequent or recurrent thoughts of death, suicidal thoughts, suicide attempts or suicide
- Unexplained physical problems, such as **back pain or headaches**

https://www.mayoclinic.org/diseases-conditions/depression/symptoms-causes/syc-20356007

Diagnosis

- A diagnosis of depression is based on:
- **Physical exam**
- **Lab tests**
- **Psychiatric evaluation.** Your mental health professional asks about your symptoms, thoughts, feelings and behavior patterns. You may be asked to fill out a **questionnaire** to help answer these questions.
- **DSM-5.** Your mental health professional may use the criteria for depression listed in the Diagnostic and Statistical Manual of Mental Disorders (**DSM-5**), published by the American Psychiatric Association.

https://www.mayoclinic.org/diseases-conditions/depression/symptoms-causes/syc-20356007

PHQ-9: 9 Item Patient Health Questionnaire

Over the last 2 weeks, how often have you been bothered by any of the following problems?	**Not at all**	**Several Days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3

Total Score: 1-4 Minimal depression; 5-9 Mild depression; 10-14 Moderate depression; 15-19 Moderately severe depression; 20-27 Severe depression

Types of Depression

- **Major depressive disorder (MDD):** Major depression (clinical depression) has intense or overwhelming symptoms that last longer than two weeks. These symptoms interfere with everyday life.
- **Bipolar depression:** alternating periods of low mood and extremely high-energy (manic) periods.
- **Perinatal and postpartum depression:** "Perinatal" means around birth. Many people refer to this type as postpartum depression. Perinatal depression can occur during pregnancy and up to one year after having a baby.
- **Persistent depressive disorder (PDD):** PDD is also known as dysthymia. Symptoms of PDD are less severe than major depression. But people experience PDD symptoms for two years or longer.
- **Premenstrual dysphoric disorder (PMDD):** a severe form of premenstrual disorder (PMS). It affects women in the days or weeks leading up to their menstrual period.
- **Psychotic depression:** People with psychotic depression have severe depressive symptoms and delusions or hallucinations. Delusions are beliefs in things that are not based in reality, while hallucinations involve seeing, hearing, or feeling touched by things that aren't actually there.
- **Seasonal affective disorder (SAD):** Seasonal depression usually starts in late fall and early winter. It often goes away during the spring and summer.

https://my.clevelandclinic.org/health/diseases/9290-depression

What Causes Depression?

- **Brain chemistry:** Abnormalities in brain chemical levels may lead to depression.
- **Genetics:** If you have a relative with depression, you may be more likely to become depressed.
- **Life events:** Stress, the death of a loved one, upsetting events (trauma), isolation and lack of support can cause depression.
- **Medical conditions:** Ongoing physical pain and illnesses can cause depression. People often have depression along with conditions like diabetes, cancer, heart disease, arthritis and lupus.
- **Medication:** Some medications have depression as a side effect. Recreational drugs and alcohol can also cause depression or make it worse.
- **Personality:** People who are easily overwhelmed or have trouble coping may be prone to depression.

https://my.clevelandclinic.org/health/diseases/9290-depression

How is Depression Treated?

- **Self-help:** Regular exercise, getting enough sleep, and spending time with people you care about can improve depression symptoms.
- **Counseling:** Counseling or psychotherapy is talking with a mental health professional. Your counselor helps you address your problems and develop coping skills. Sometimes brief therapy is all you need. Other people continue therapy longer.
- **Alternative medicine:** People with mild depression or ongoing symptoms can improve their well-being with complementary therapy. Therapy may include massage, acupuncture, hypnosis and biofeedback.
- **Medication:** Prescription medicine called antidepressants can help change brain chemistry that causes depression. Antidepressants can take a few weeks to have an effect. Some antidepressants have side effects, which often improve with time. If they don't, talk to your provider. A different medications may work better for you.
- **Brain stimulation therapy:** Brain stimulation therapy can help people who have severe depression or depression with psychosis. Types of brain stimulation therapy include electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS) and vagus nerve stimulation (VNS).

https://my.clevelandclinic.org/health/diseases/9290-depression

Medications

- **Selective serotonin reuptake inhibitors (SSRIs).** Doctors often start by prescribing an SSRI. These drugs are considered safer and generally cause fewer bothersome side effects than other types of antidepressants. SSRIs include citalopram (**Celexa),** escitalopram **(Lexapro),** fluoxetine **(Prozac),** paroxetine **(Paxil),** sertraline **(Zoloft**) and vilazodone (Viibryd).
- **Serotonin-norepinephrine reuptake inhibitors (SNRIs).** Examples of SNRIs include duloxetine (**Cymbalta**), venlafaxine (Effexor XR), desvenlafaxine (Pristiq, Khedezla) and levomilnacipran (Fetzima).
- **Atypical antidepressants.** These medications don't fit neatly into any of the other antidepressant categories. They include bupropion (**Wellbutrin** XL, Wellbutrin SR, Aplenzin, Forfivo XL), **mirtazapine** (Remeron), nefazodone, **trazodone** and vortioxetine (Trintellix).
- **Tricyclic antidepressants.** These drugs — such as imipramine (Tofranil), nortriptyline (Pamelor), **amitriptyline,** doxepin, trimipramine (Surmontil), desipramine (Norpramin) and protriptyline (Vivactil) — can be very effective, but tend to cause more-severe side effects than newer antidepressants.
- **Monoamine oxidase inhibitors (MAOIs).** MAOIs — such as tranylcypromine (Parnate), phenelzine (Nardil) and isocarboxazid (Marplan) — may be prescribed, typically when other drugs haven't worked, because they can have serious side effects.
- **Other medications.** Other medications may be added to an antidepressant to enhance antidepressant effects. Your doctor may recommend combining two antidepressants or adding medications such as mood stabilizers or antipsychotics. **Anti-anxiety** and stimulant medications also may be added for short-term use.

https://www.mayoclinic.org/diseases-conditions/depression/diagnosis-treatment/drc-20356013

Psychotherapy

- Psychotherapy is a general term for treating depression by talking about your condition and related issues with a mental health professional.
- Psychotherapy is also known as **talk therapy** or psychological therapy.
- Different types of psychotherapy can be effective for depression, such as **cognitive behavioral therapy** or interpersonal therapy.
- Psychotherapy can help you:
  - Adjust to a crisis or other current difficulty
  - Identify negative beliefs and behaviors and replace them with healthy, positive ones
  - Explore relationships and experiences, and develop positive interactions with others
  - Find better ways to cope and solve problems
  - Identify issues that contribute to your depression and change behaviors that make it worse
  - Regain a sense of satisfaction and control in your life and help ease depression symptoms, such as hopelessness and anger
  - Learn to set realistic goals for your life
  - Develop the ability to tolerate and accept distress using healthier behaviors

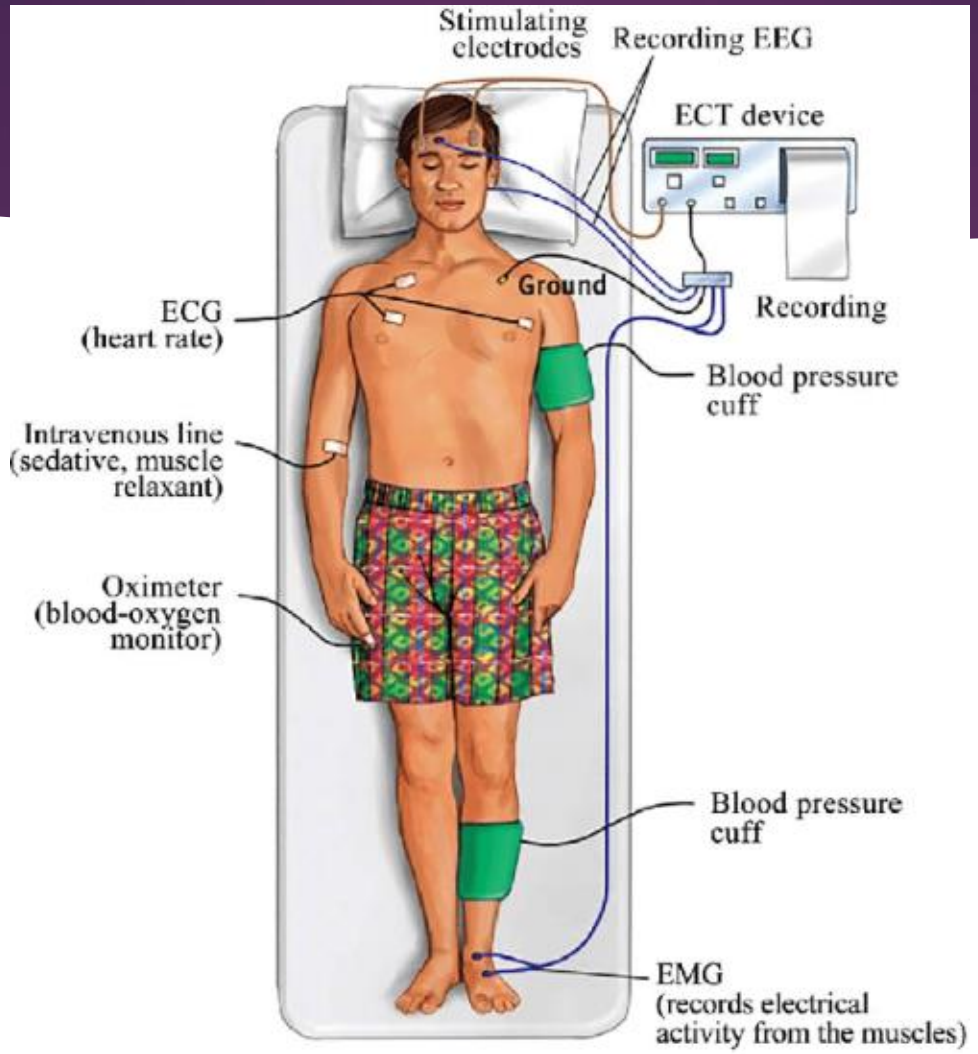
https://www.mayoclinic.org/diseases-conditions/depression/diagnosis-treatment/drc-20356013

Other Treatment Options

- **Electroconvulsive therapy (ECT)**
  - In ECT, electrical currents are passed through the brain to impact the function and effect of neurotransmitters in your brain to relieve depression.
  - ECT is a medical treatment that has been most commonly reserved for patients with severe major depression who have not responded to other treatments or are at high risk of suicide.
- **Transcranial magnetic stimulation (TMS)**
  - TMS may be an option for those who haven't responded to antidepressants.
  - During TMS, a treatment coil placed against your scalp sends brief magnetic pulses to stimulate nerve cells in your brain that are involved in mood regulation and depression.

https://www.mayoclinic.org/diseases-conditions/depression/diagnosis-treatment/drc-20356013

ECT



https://www.carenity.co.uk/condition-information/magazine/advice/severe-depression-what-is-electroconvulsive-therapy-ect-1086

Anxiety

- Anxiety is a normal reaction to stress and can be beneficial in some situations.
- It can alert us to dangers and help us prepare and pay attention.
- Anxiety disorders differ from normal feelings of nervousness or anxiousness and involve excessive fear or anxiety.
- Anxiety disorders are the most common of mental disorders and affect nearly 30% of adults at some point in their lives.

https://psychiatry.org/patients-families/anxiety-disorders/what-are-anxiety-disorders

Signs of an Anxiety Disorder

Frequent worry that interferes with daily life

Withdrawal from social life

Fixation on fear of next panic attack

Irrational fear and avoidance of a harmless object, place, or situation

Out-of-the-blue panic attacks

Recurring nightmares, flashbacks, or numbing of past trauma

How Common Are Anxiety Disorders?

- In any given year the estimated percent of U.S. adults with various anxiety disorders are:
  - Specific Phobia: 8% - 12%
  - Social Anxiety Disorder: 7%
  - Panic Disorder: 2% - 3%
  - Agoraphobia: 1-2.9% in Adolescents and Adults
  - Generalized Anxiety Disorder: 2%
  - Separation Anxiety Disorder: 0.9% - 1.9%
- Women are more likely than men to experience anxiety disorders.

https://psychiatry.org/patients-families/anxiety-disorders/what-are-anxiety-disorders

Anxiety Diagnosis

- To help diagnose an anxiety disorder:
- **Physical exam** to look for signs that your anxiety might be linked to medications or an underlying medical condition
- **Blood or urine tests** or other tests, if a medical condition is suspected
- Detailed interview and medical history
- Use psychological **questionnaires** to help determine a diagnosis
- Use the criteria listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)

https://www.mayoclinic.org/diseases-conditions/generalized-anxiety-disorder/diagnosis-treatment/drc-20361045

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Total Score ___ = Add Columns ___ + ___ + ___

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Score	Anxiety Severity
0 - 4	None – Minimal
5 - 9	Mild
10 - 14	Moderate
15 - 21	Severe

Anxiety Treatment

- **Psychotherapy**
  - Also known as talk therapy or psychological counseling, psychotherapy involves working with a therapist to reduce your anxiety symptoms.
  - **Cognitive behavioral therapy** is the most effective form of psychotherapy for generalized anxiety disorder.
  - Generally a short-term treatment, cognitive behavioral therapy focuses on teaching you specific skills to directly manage your worries and help you gradually return to the activities you've avoided because of anxiety.
- **Medications**
  - Several types of medications are used to treat generalized anxiety disorder.

https://www.mayoclinic.org/diseases-conditions/generalized-anxiety-disorder/diagnosis-treatment/drc-20361045

Anxiety Medications

- **Antidepressants.** Antidepressants, including medications in the selective serotonin reuptake inhibitor (SSRI) and serotonin and norepinephrine reuptake inhibitor (SNRI) classes, are the first line medication treatments.
- **Buspirone.** An anti-anxiety medication called buspirone may be used on an ongoing basis. As with most antidepressants, it typically takes up to several weeks to become fully effective.
- **Benzodiazepines.** In limited circumstances, your doctor may prescribe a benzodiazepine for relief of anxiety symptoms.
  - These sedatives are generally used only for relieving acute anxiety on a short-term basis. Because they can be habit-forming, these medications aren't a good choice if you have or had problems with alcohol or drug abuse.

https://www.mayoclinic.org/diseases-conditions/generalized-anxiety-disorder/diagnosis-treatment/drc-20361045

Chronic Illness and Depression

- An estimated one-third of people diagnosed with a serious, life-changing chronic illness or disease will experience symptoms of depression.
- After a diagnosis of a serious illness, feelings of sadness and despair are normal.

https://my.clevelandclinic.org/health/articles/9288-chronic-illness-and-depression

Why is Depression Common in People Who Have a Chronic Illness?

- Depression is one of the most common complications of chronic illness.
- People who have chronic illnesses must adjust to both the illness and its treatment.
- The illness may affect a person's mobility (ability to move) and independence, and change the way they live, see themselves and/or relate to others.
- These changes can be stressful and cause a certain amount of despair or sadness.
- In some cases, having a chronic illness can trigger depression.
- The doctor and patient must decide whether symptoms of depression are just a normal reaction to the stress of having a chronic medical condition — or are so intense or disabling that they require additional treatment with an antidepressant.

https://my.clevelandclinic.org/health/articles/9288-chronic-illness-and-depression

Lupus, Anxiety and Depression

- **It has been reported that there were 2 times higher prevalence of depression in SLE patients compared to the general population** [19].
- In addition, previous study reported that the anxiety disorders were twice as prevalent among SLE patients as compared to the controls [20].
- Depression and anxiety often have profound impacts on SLE patients' health and well-being including increased incidence of cardiovascular diseases, myocardial infarction, suicidal ideation, physical disability, decreased quality of life, and a higher risk of premature mortality.
- Therefore, depression and anxiety may be useful targets for interventions aimed at improving subjective health and quality of life in individuals with SLE.

19. Bachen EA, Chesney MA, Criswell LA. Prevalence of mood and anxiety disorders in women with systemic lupus erythematosus. *Arthritis Rheum.* 2009;61(6):822–9. doi: 10.1002/art.24519
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Lupus, Anxiety and Depression

- **SLE patients are at high risk for depression and anxiety.**
- Depression and anxiety are common in SLE and appear to be more prevalent in SLE than in the general population.
- In one meta-analysis, **the prevalence of major depression in SLE was 24 percent and anxiety was 37 percent** [21].

21. Zhang L, Fu T, Yin R, Zhang Q, Shen B. Prevalence of depression and anxiety in systemic lupus erythematosus: a systematic review and meta-analysis. BMC Psychiatry. 2017 Feb 14;17(1):70.

Prevalence of Depression and Anxiety in Systemic Lupus Erythematosus: a Systematic Review and Meta-analysis

- Zhang, et al. BMC Psychiatry, 2017
- Methods:
  - Systematically reviewed studies presenting data on depression and/or anxiety in adult SLE patients and having a sample size of at least 60 patients were included.
- Results:
  - A total of 59 identified studies matched the inclusion criteria, reporting on a total of 10,828 adult SLE patients.
  - Meta-analyses revealed that the prevalence of **major depression was 24% and anxiety was 37%.**
- Conclusion:
  - The prevalence of depression and anxiety was high in adult SLE patients.
  - It indicated that rheumatologists should screen for depression and anxiety in their patients, and refer them to mental health providers in order to identify effective strategies for preventing and treating depression and anxiety among adult SLE patients.

Zhang L, et al. Prevalence of depression and anxiety in systemic lupus erythematosus: a systematic review and meta-analysis. BMC psychiatry. 2017 Dec;17(1):1-4.

Prevalence and Metric of Depression and Anxiety in Systemic Lupus Erythematosus: A Systematic Review and Meta-analysis

- Moustafa, et al. Seminars in Arthritis and Rheumatism, Feb **2020**
- **Objective**: to systematically review and synthesize literature on the overall prevalence of depression and anxiety in SLE patients
- **Results:**
- Prevalence of depression was **35.0%**
- Prevalence of anxiety was **25.8%**

Moustafa AT, et al. Prevalence and metric of depression and anxiety in systemic lupus erythematosus: a systematic review and meta-analysis. Seminars in arthritis and rheumatism 2020 Feb 1 (Vol. 50, No. 1, pp. 84-94).

Prevalence and Predictors of Depression in Patients with Systemic Lupus Erythematosus: a Cross-sectional Study

Neuropsychiatric Disease and Treatment, 2013

- **Rates of depression and anxiety in SLE patients were 45.2% and 37.1%, respectively** [23].
- The findings suggest that depression and anxiety are very common in SLE patients.
- In addition, higher levels of anxiety and a younger age may increase the risk of depression.

23. Maneeton B, Maneeton N, Louthrenoo W. Prevalence and predictors of depression in patients with systemic lupus erythematosus: a cross-sectional study. Neuropsychiatr Dis Treat. 2013;9:799-804

Study Conclusions

- SLE affects multiple organ systems including the central nervous system.
- Therefore, it can cause several neuropsychiatric syndromes, including depression, anxiety.
- In addition, the burden of SLE comorbid with depression may increase the risk of suicide.
- Mood disorder in those patients, especially in depression, may come from several causes, including pathology in CNS or psychological reaction of the disease.

Maneeton B, Maneeton N, Louthrenoo W. Prevalence and predictors of depression in patients with systemic lupus erythematosus: a cross-sectional study. Neuropsychiatr Dis Treat. 2013;9:799-804.

Depression in other Chronic Diseases

- A higher prevalence rate of depression is found in patients with a chronic medical illness.
  - Study of patients with systemic sclerosis showed that 1-year and lifetime prevalence rates of MDD were 11% and 23% respectively.[24] Those rates are approximately twice that of the general population.
  - Similarly, recent evidence suggests that the prevalence of depression in cancer patients is as high as 30% and depressive severity is associated with severity of physical pain.[25]

24. Jewett LR, Razykov I, Hudson M, Baron M, Thombs BD, on behalf of the Canadian Scleroderma Research G. Prevalence of current, 12-month and lifetime major depressive disorder among patients with systemic sclerosis. *Rheumatology*. 2013;52(4):669–675.

25. Maneeton B, Maneeton N, Mahathep P. Prevalence of depression and its correlations: a cross-sectional study in Thai cancer patients. *Asian Pacific Journal of Cancer Prevention: APJCP*. 2012;13(5):2039–2043.

Author	Year of publication	Diagnostic method	*n*	Point prevalence %
Miguel et. al.[8]	1994	HAM-D	43	44
Ainiala et. al.[9]	2001	Beck Depression Inventory	46	39
Brey et. al.[10]	2002	SCIDs-I, Calgary Depression Scale	128	28
Hanly et. al.[11]	2005	HADS	53	11
Lapteva et. al.[12]	2006	Beck Depression Inventory II	60	31
Harrison et. al.[13]	2006	Center for Epidemiological Studies Depression Scale	93	16
Waheed et. al.[14]	2006	Aga Khan University Anxiety and Depression Score	111	65.8
Bachen et. al.[15]	2009	Composite international Diagnostic interview/DSM IV criteria	326	47
Petri et. al.[16]	2010	Calgary Depression Scale	111	31
Julian et. al.[17]	2011	Center for Epidemiological Studies Depression Scale	150	26
Julian et. al.[18]	2011	Center for Epidemiological Studies Depression Scale	663	17
Jarpa et. al.[19]	2011	Mini-International Neuropsychiatric Interview - Plus, HADSs	83	22
Karol et. al.[20]	2013	Beck Depression Inventory II	127	41.7
Sehlo and Bahlas[21]	2013	SCID-I - Clinical Version; HADS - Depression subscale	80	18.75
Maneeton et. al.[22]	2013	HAM-D17	62	45.2
van Exel et. al.[23]	2013	Beck Depression inventory	102	16.6
Shen et. al.[24]	2013	Self-Rating Depression Scale	170	32.9

HAM-D: Hamilton Depression Rating Scale, SCID-I: Structured clinical interview for DSM-IV Axis I Disorder, HADS: Hospital Anxiety and Depression Scale

Pathogenesis of Depression in Lupus

- Two theories:
  - Depression in SLE is due to psychosocial factors due to the stress of being diagnosed with a chronic disease at a very young age.
  - Depression in lupus patients is due to organic damage taking place in the CNS.
  - This damage is most likely thought to be immune mediated.

26. Jennekens FG, Kater L. The central nervous system in systemic lupus erythematosus. Part 1. Clinical syndromes: a literature investigation. *Rheumatology (Oxford)* 2002;41(6):605-18.

Pathogenesis of Depression in Lupus

- **Proinflammatory cytokines** released from monocytes/macrophages (tumor necrosis factor-alpha [**TNF-α**], interleukin-1 beta [IL-1β], IL-1, IL-6, IL-8, etc.,) may play an important role in the development of depression in lupus patients. [27]
- **Blood–brain barrier disruption** is an essential component.
- Once blood–brain barrier is compromised, **other autoantibodies may gain access to intrathecal space**.
- Depression in SLE patients is also reported to be associated with **central blood flow reductions** in discrete temporal and frontal regions [28]. It is not clearly understood if this reduction in central blood flow is caused by cytokines/autoantibodies/or some other unknown factor.

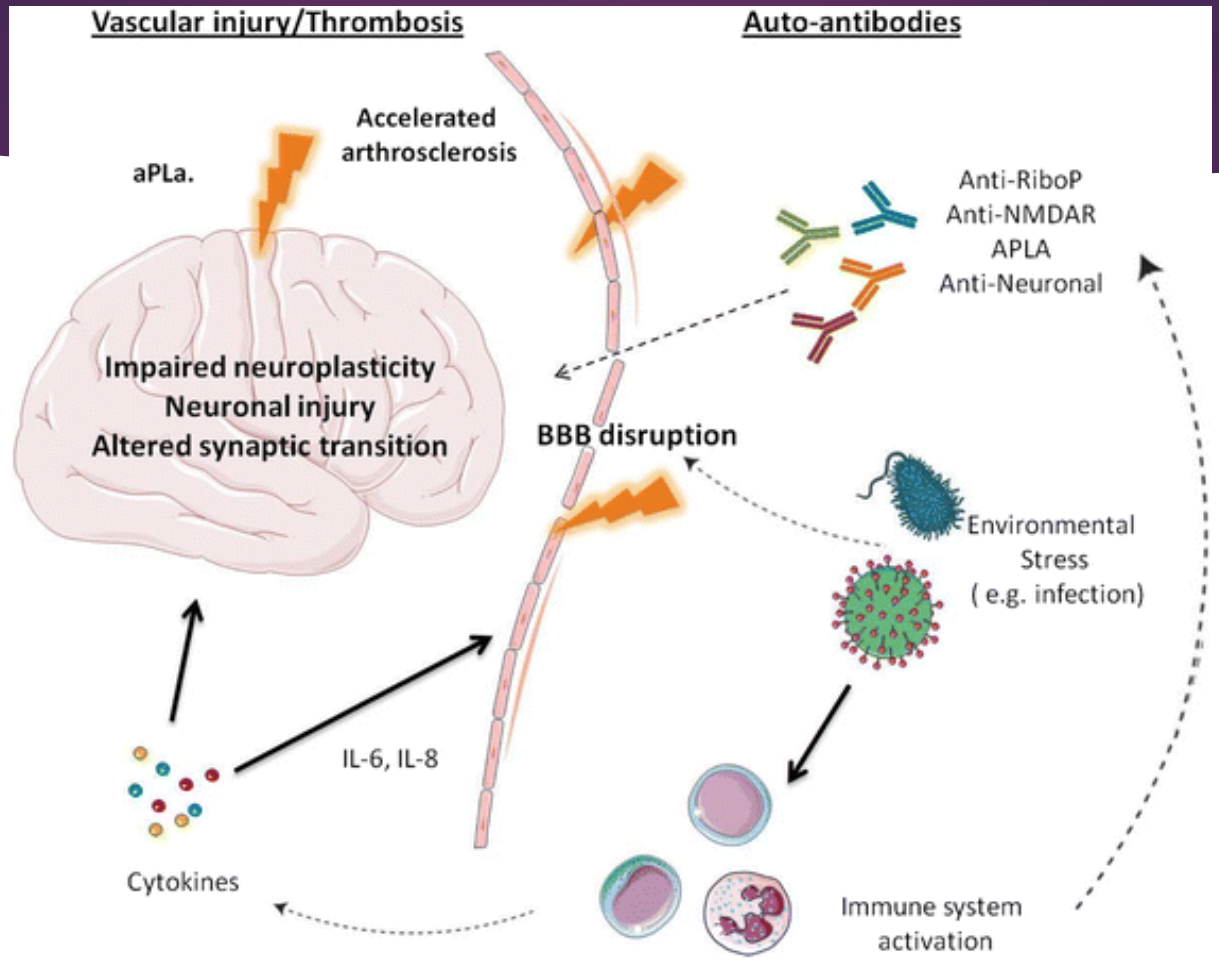
27. Mak A, Tang CS, Ho RC. Serum tumour necrosis factor-alpha is associated with poor health-related quality of life and depressive symptoms in patients with systemic lupus erythematosus. *Lupus* 2013;22(3):254-61.
28. Giovacchini G, Mosca M, Manca G, et. al. Cerebral blood flow in depressed patients with systemic lupus erythematosus. *J Rheumatol* 2010;37(9):1844-51.

Pathogenesis of Depression in Lupus continued

- Depression can also be caused by treatment with **corticosteroids** through downregulation of the brain-derived neurotrophic factor.
- The role of various **environmental factors** (retrovirus, ultraviolet light, stress, medicines) can also not be ruled out.
- **Hereditary predisposition** can also be present in lupus patients for developing depression.
- Cannot be explained by a single theory/mechanism.
- Mechanism for this disease is essentially **multifactorial**, which involves complex interactions between cytokines, antibodies, genetic factors, and environmental factors.

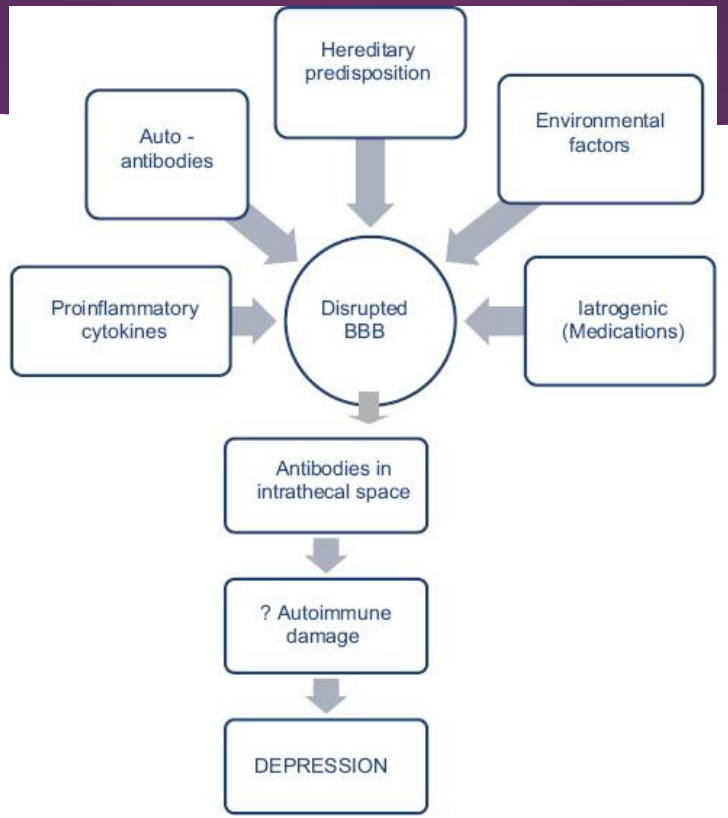
27. Mak A, Tang CS, Ho RC. Serum tumour necrosis factor-alpha is associated with poor health-related quality of life and depressive symptoms in patients with systemic lupus erythematosus. *Lupus* 2013;22(3):254-61.
28. Giovacchini G, Mosca M, Manca G, et. al. Cerebral blood flow in depressed patients with systemic lupus erythematosus. *J Rheumatol* 2010;37(9):1844-51.

Pathogenesis of Neuropsychiatric Lupus



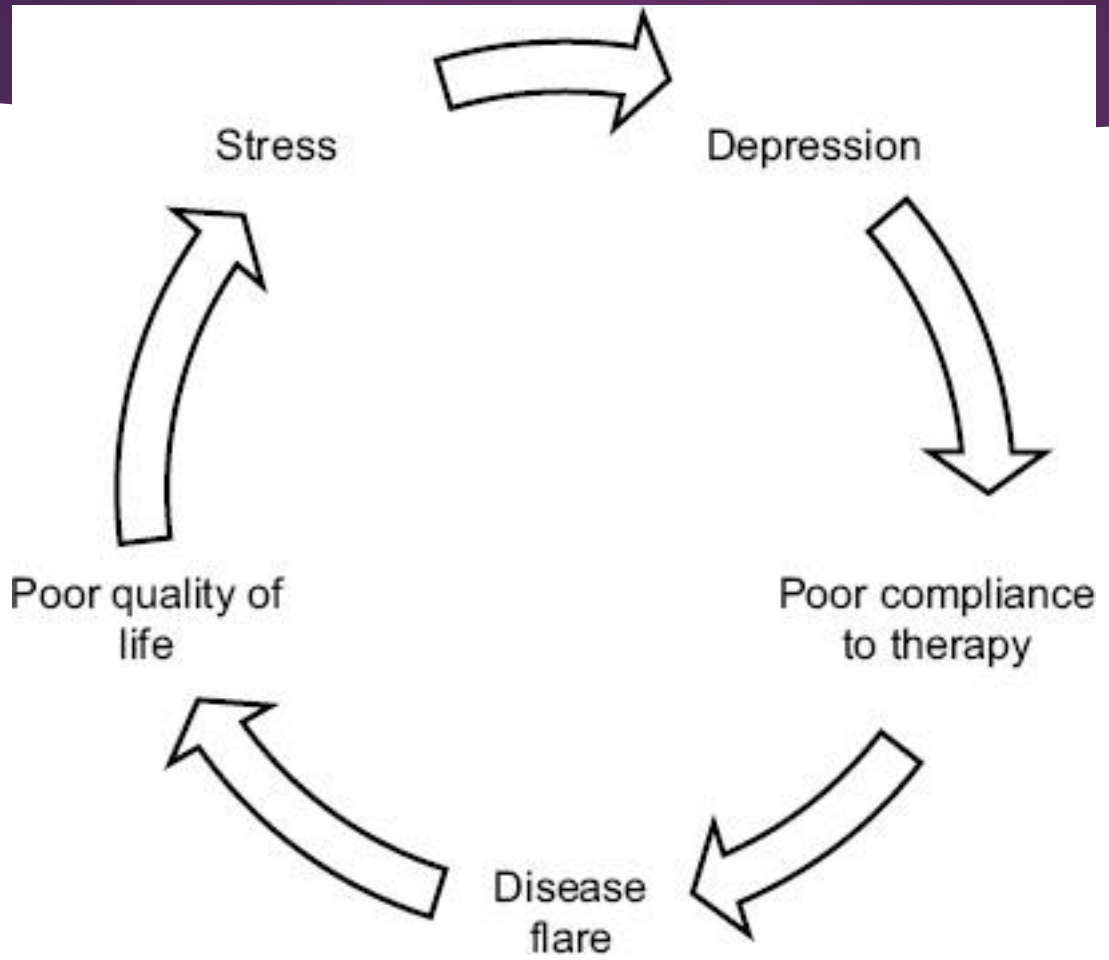
29. Kivity, S., Agmon-Levin, N., Zandman-Goddard, G. *et al.* Neuropsychiatric lupus: a mosaic of clinical presentations. *BMC Med* **13**, 43 (2015)

Pathogenesis of Depression in SLE



Gupta M. Depression in systemic lupus erythematosus: A systematic review. Int J Stud Res [serial online] 2015 [cited 2022 Oct 13];5:21-7

Stress and Depression Cycle



Gupta M. Depression in systemic lupus erythematosus: A systematic review. Int J Stud Res [serial online] 2015 [cited 2022 Oct 13];5:21-7

Management of Depression in SLE

- The management of depression in SLE depends on whether the physician thinks that the depression has a neurological basis (inflammation of the brain, a stroke, seizure, perhaps the presence of autoantibodies, elevated cytokines) versus a psychological cause (where signs of neurological basis are absent).
- One can differentiate neurological from psychological causes by imaging (MRI), EEG, CSF analysis, and psychometric testing.
- Patients with only **psychological** causes are treated with **antidepressants** while in case of organic disease, one treats with **glucocorticoids, immunosuppressants,** and **antidepressants.**
- In a study, combination of celecoxib (anti-inflammatory) and fluoxetine (antidepressant) has been reported to have greater antidepressant effect than fluoxetine alone [31]
- **EULAR recommends treatment of depression in SLE patients with a combination therapy of glucocorticoids, immunosuppressant, and antidepressant** [32].

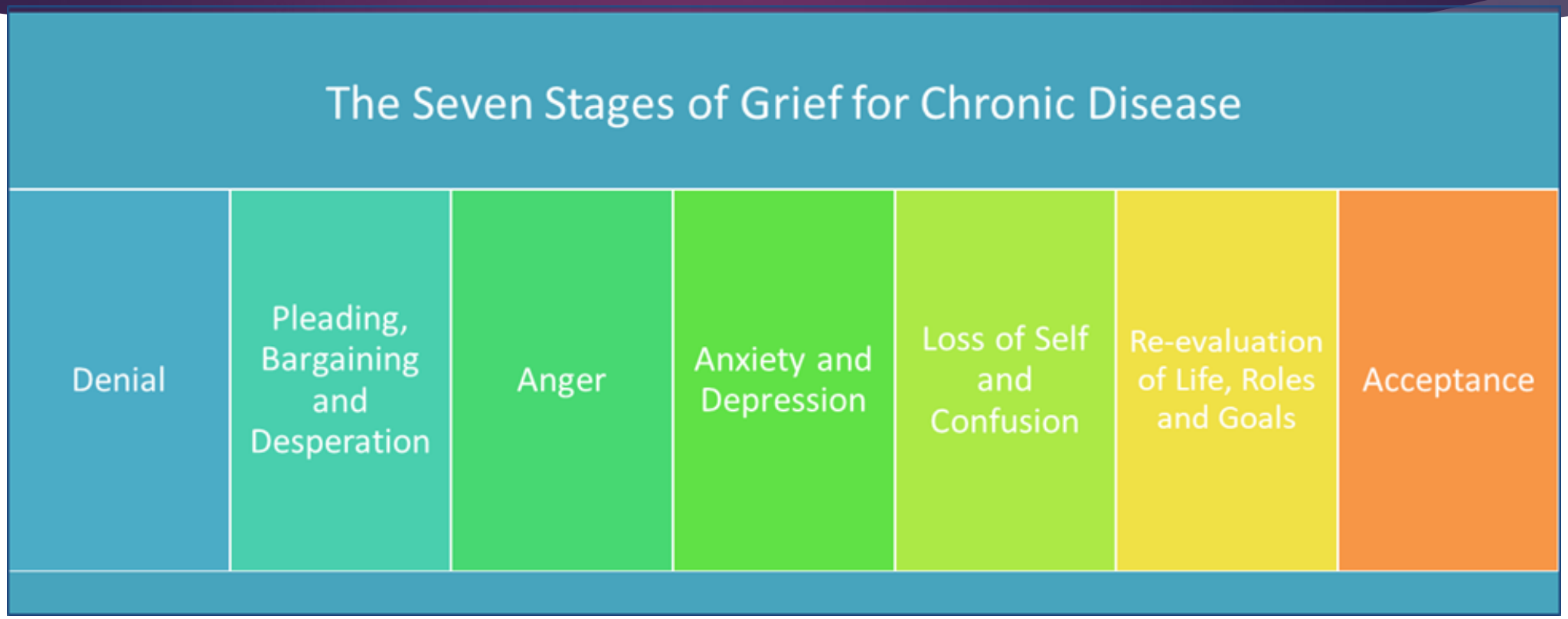
31. Akhondzadeh S, Jafari S, Raisi F, et. al. Clinical trial of adjunctive celecoxib treatment in patients with major depression: a double blind and placebo controlled trial. *Depress Anxiety* 2009;26(7):607-11.
32. Bertsimas GK, Boumpas DT. Pathogenesis, diagnosis and management of neuropsychiatric SLE manifestations. *Nat Rev Rheumatol* 2010;6(6):358-67.

Study on Medication Adherence and Depression

- Heiman, et al, Journal of Clinical Rheumatology, 2018.
- Study looked at low medication adherence and depression in SLE.
- Low adherence is a highly prevalent, multidimensional problem associated with poor outcomes in people with SLE.
- Study found that depression was a strong correlate of low medication adherence.
- Mental health interventions aiming to address and treat depression may increase medication adherence.

Heiman E, Lim SS, Bao G, Drenkard C. Depressive Symptoms Are Associated With Low Treatment Adherence in African American Individuals With Systemic Lupus Erythematosus. J Clin Rheumatol. 2018 Oct;24(7):368-374.

Kubler-Ross model of Five Stages of Grief



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Best Treatment Advice

- **Find a good rheumatologist to manage your lupus**
- **Find a good psychiatrist/therapist to manage your depression/anxiety**
- **Take care of your mind and body**
  - **Yoga, Tai Chi, massage, pilates, acupuncture, meditation, etc.**
  - **Exercise regularly**
  - **Get good sleep**
  - **Healthy balanced diet**

- If you or someone you know has thoughts of hurting themselves, please call the National Suicide Prevention Lifeline at 800.273.8255.
- This national network of local crisis centers provides free, private emotional support to people in suicidal crisis or emotional distress 24 hours a day, seven days a week.

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