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9. DEPRESSION

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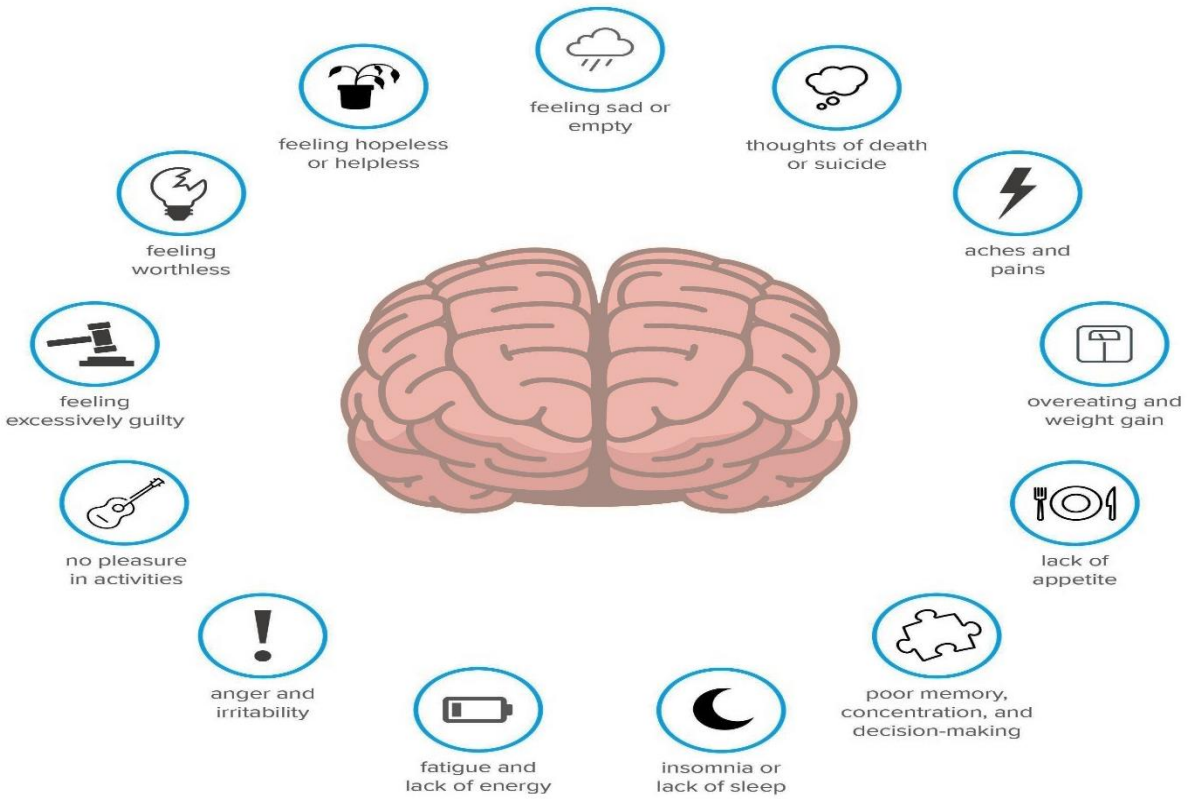
DEFINATION

- Depression is an illness marked by feelings of sadness, worthlessness, or hopelessness, as well as problems concentrating and remembering details.
- 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.

WHAT IS DEPRESSION?

- Depression is a common but serious illness.
- Pathologically depression refers to change in mood state.
- Depression means feelings of blue or extreme sadness that can last for a longer time.
- Depression is precipitated due to deficiency of monoamines neurotransmitters.
- Neurotransmitters: Noradrenaline, Serotonine, Dopamine, 5-Hydroxy tryptophan (5-HT.)
- Major depression is characterized by symptoms like sad mood, loss of interest and pleasure, low energy, worthlessness, guilt, psychomotor retardation, change in mode of sleep, Suicidal thought. (Tripathi K.D.)

SIGN & SYMPTOMS



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Depression symptoms can vary from mild to severe and can include:

- Persistent sad, anxious, or "empty" mood
- Feelings of hopelessness, or pessimism
- Irritability
- Feelings of guilt, worthlessness, or helplessness
- Loss of interest or pleasure in hobbies and activities
- Decreased energy or fatigue
- Moving or talking more slowly
- Feeling restless or having trouble sitting still
- Difficulty concentrating, remembering, or making decisions
- Difficulty sleeping, early-morning awakening, or oversleeping
- Appetite and/or weight changes
- Thoughts of death or suicide, or suicide attempts
- Aches or pains, headaches, cramps, or digestive problems without a clear physical cause and/or that do not ease even with treatment

TYPES OF DEPRESSION

1. **Bipolar disorder**
    - Major depressive disorder, and persistent depressive disorder are the primary types of depression.
    - A person who experiences alternating states of depression and mania (abnormal elevation of mood) or hypomania (distinct, though not necessarily abnormal, elevation of mood) is said to suffer from bipolar disorder.
2. **Major depressive disorder**
    - Major depressive disorder is characterized by severe symptoms that disrupt the individual's daily life, typically with effects on appetite, sleep, work, or the ability to enjoy life.
    - Episodes of major depression can occur at any age and may occur once or multiple times in an affected person's life.
3. **Persistent depressive disorder**
    - Persistent depressive disorder involves symptoms that last two or more years, sometimes marked by episodes of major depression.

4. **Postpartum depression**
    - Postpartum depression develops in women in the period following childbirth. Symptoms include anxiety, a lack of interest in caring for the infant, and feelings of sadness, hopelessness, or inadequacy.
    - Postpartum depression is longer-lasting and more severe than the "baby blues," a common condition among women after childbirth that typically involves mood swings, feelings of sadness, and crying spells.
5. **Psychotic depression**
    - Psychotic depression arises against a background of psychosis, which may involve symptoms of delusions, hallucinations, or paranoia.
6. **Seasonal affective disorder**
    - Seasonal affective disorder is characterized by the onset of depressive symptoms in autumn and winter, which are alleviated with increased exposure to natural light in spring and summer.
7. **Cyclothymic disorder**
    - Cyclothymic disorder is often described as a milder form of bipolar disorder.
    - The person experiences chronic fluctuating moods over at least two years, involving periods of hypomania (a mild to moderate level of mania) and periods of depressive symptoms, with very short periods (no more than two months) of normality between.
    - The duration of the symptoms are shorter, less severe and not as regular, and therefore don't fit the criteria of bipolar disorder or major depression.
8. **Dysthymic disorder**
    - The symptoms of dysthymia are similar to those of major depression but are less severe.
    - However, in the case of dysthymia, symptoms last longer.
    - A person has to have this milder depression for more than two years to be diagnosed with dysthymia.

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CAUSES

It's not known exactly what causes depression. As with many mental disorders, a variety of factors may be involved, such as:

- **Biological differences:** People with depression appear to have physical changes in their brains. The significance of these changes is still uncertain, but may eventually help pinpoint causes.
- **Brain chemistry:** Neurotransmitters are naturally occurring brain chemicals that likely play a role in depression. Recent research indicates that changes in the function and effect of these neurotransmitters and how they interact with neurocircuits involved in maintaining mood stability may play a significant role in depression and its treatment.
- **Hormones:** Changes in the body's balance of hormones may be involved in causing or triggering depression. Hormone changes can result with pregnancy and during the weeks or months after delivery (postpartum) and from thyroid problems, menopause or a number of other conditions.
- **Inherited traits:** Depression is more common in people whose blood relatives also have this condition. Researchers are trying to find genes that may be involved in causing depression.

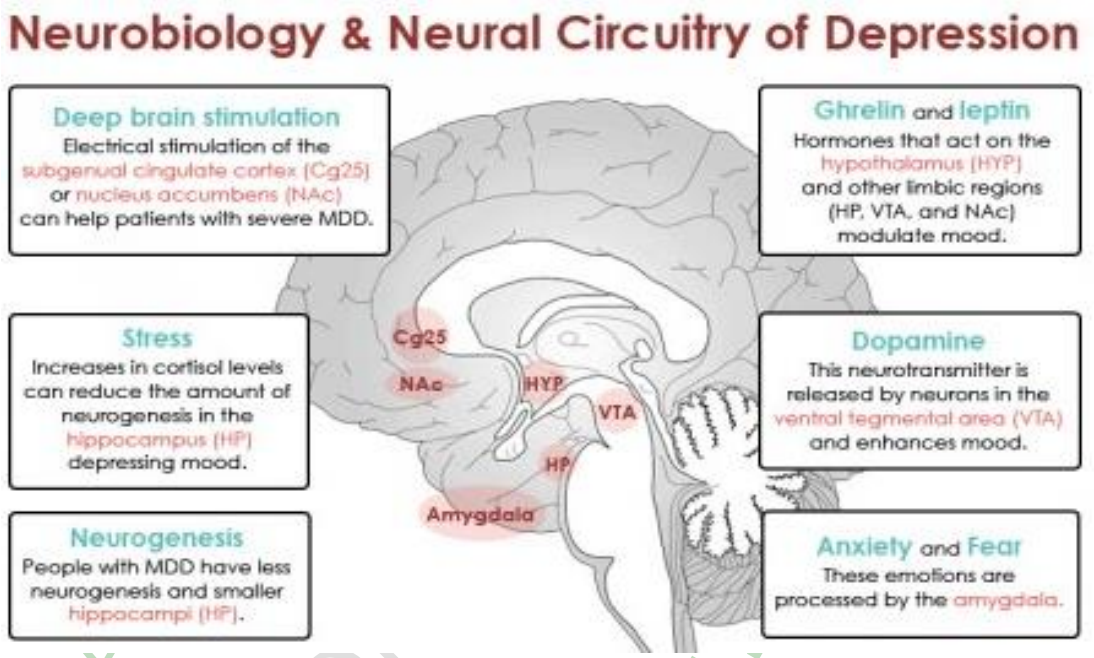
PATHOPHYSIOLOGY

Even though there are numerous studies attempting to shed light on the pathophysiology of depression, it still remains elusive. There are diverse theories on the pathogenesis of depression most based on measurement of indirect markers, post-mortem studies and neuro-imaging techniques.

A) Neural circuitry of depression:

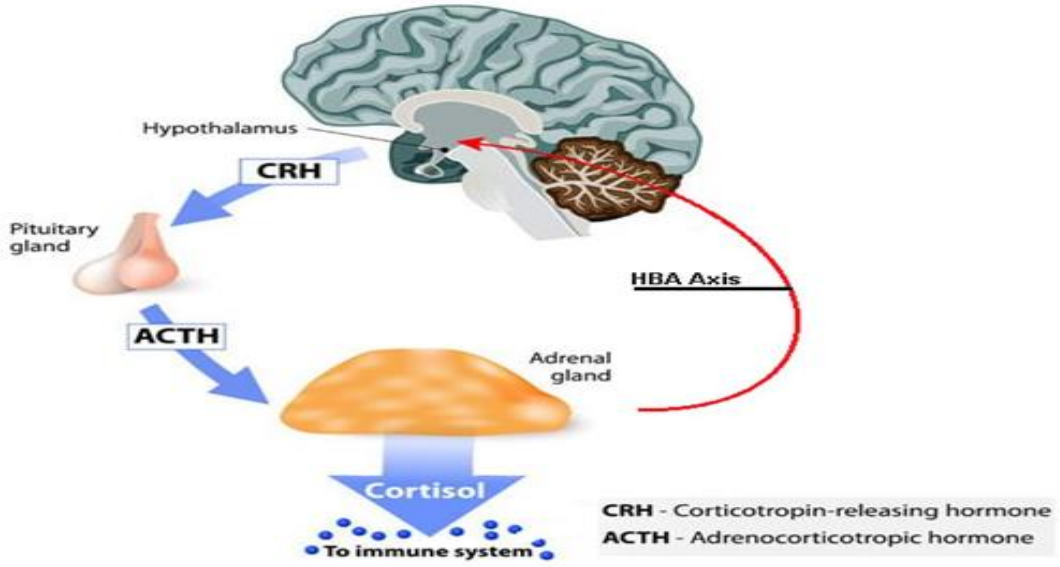
- Various structural and functional studies report abnormalities in the areas of the brain that are responsible for the regulation of mood, reward response and executive functions.
- Post-mortem and neuro-imaging studies have reported morphological changes indicated by reductions in grey-matter volume and glial density in the prefrontal cortex and the hippocampus.
- The decline in hippocampal function, which is believed to have an inhibitory effect on the hypothalamic-pituitary- adrenal (HPA) axis, could potentially be responsible for the hypercortisolemia seen in depression.

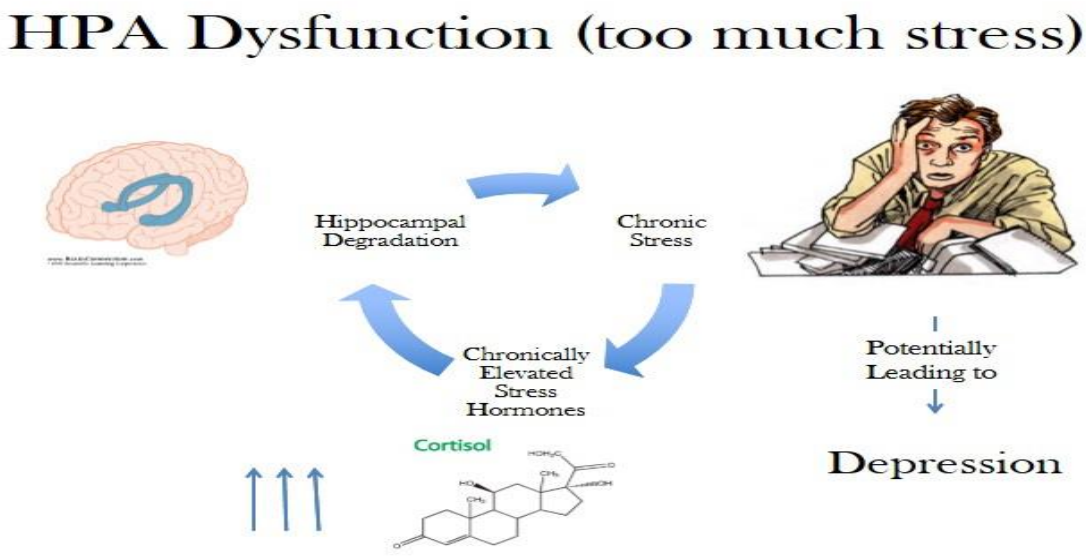
- The mesolimbic dopamine system that consists of the nucleus accumbens (NAc) and the ventral tegmental area (VTA) also are believed to play a role in the pathogenesis of depression.
- These brain regions mediate the reward response to pleasurable stimuli such as food, sex and even drugs. Therefore, a peculiar lack of pleasure in depressed patients can possibly be explained as a dysfunction in this brain reward circuit.



B) **Stress response circuits:**

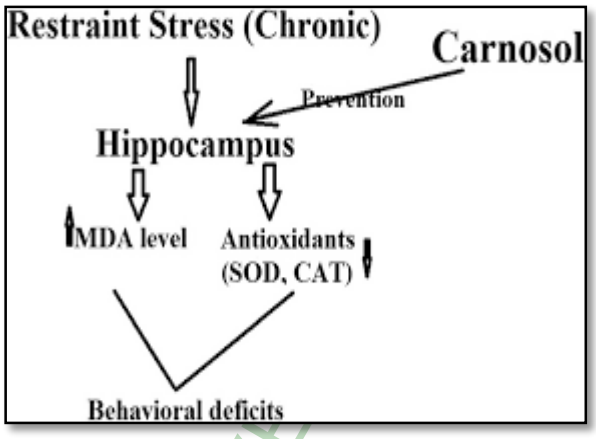
- Chronic stress and hyperactivity of the HPA axis (causing chronic hypercortisolemia) have been hypothesized to play a prominent role in the incidence of depression and even in recurrence after complete remission.
- Structural brain abnormalities have been documented in patients with elevated levels of corticosteroids.
- One of the brain structures affected is the amygdala, area of the brain involved in mainly regulating emotional reactivity and to some degree stress response.
- Another brain region shown to decrease in size with chronic administration of corticosteroids is the hippocampus, area of the brain that is believed to exert an inhibitory signal to the HPA axis.



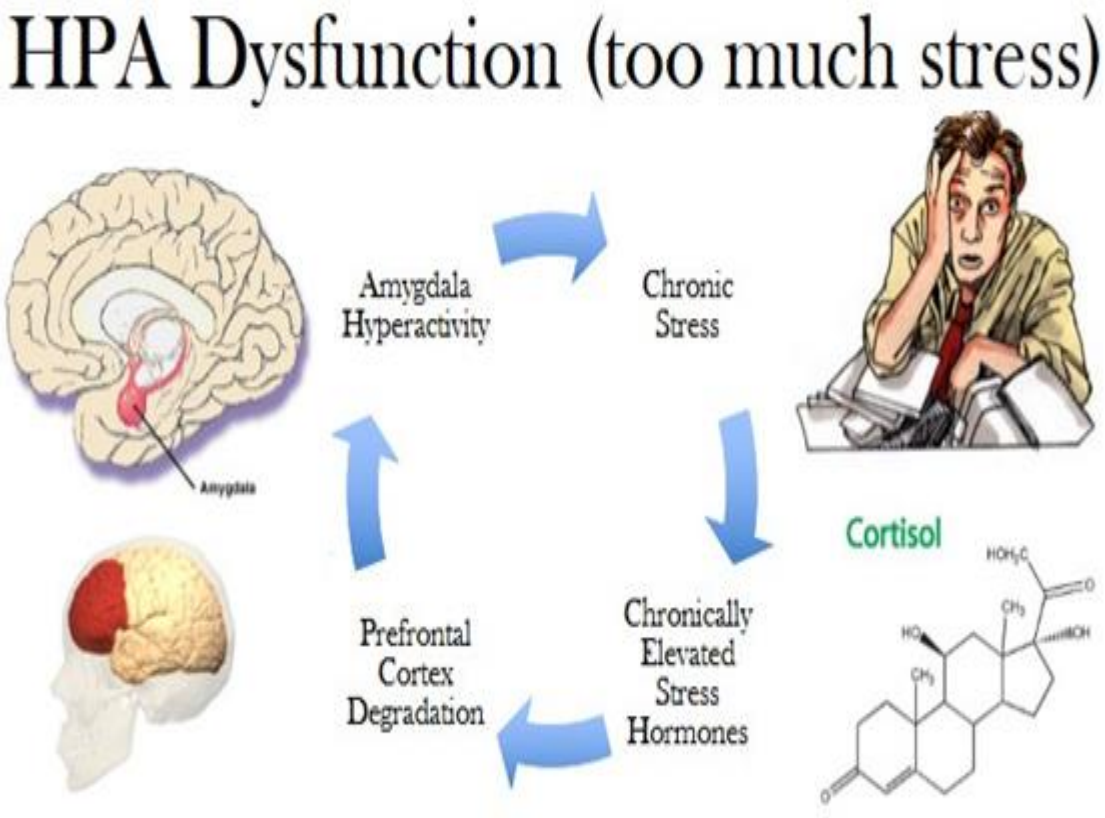


Chronic stress

- However, chronic stress has been shown to alter the expression of genes regulating antioxidant systems, such as superoxide dismutases (SODs), catalase, glutathione peroxidase, glutathione reductase and NADPH oxidase.



- Moreover, animal studies uncovered that treatment with glucocorticoids cause elevation in the level reactive oxygen species (ROS) both in vitro and in the brains of animals, while also down-regulating various antioxidant enzyme and inducing depression-like behavior.



C) <u>Genetic vulnerability and environmental interaction:</u>

- In depression there is a complex gene-environmental interaction occurs that alters an individual response to stressful life situations. No single gene polymorphism [having multiple forms] seems responsible for causing depression, it has been suggested that genetic factors make certain individuals susceptible to depression by increasing their vulnerability to stressful environmental factors.

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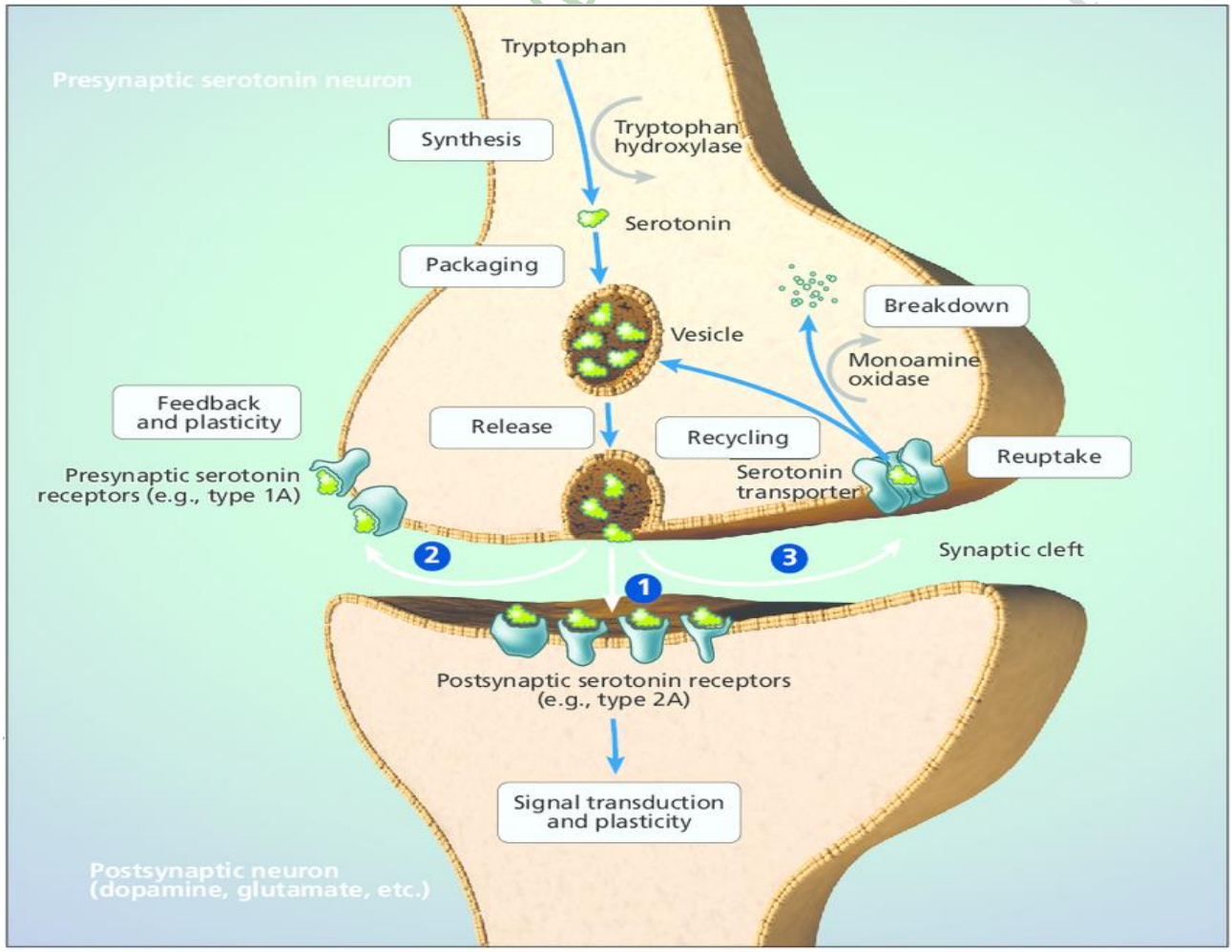
1. Serotonin Transporter

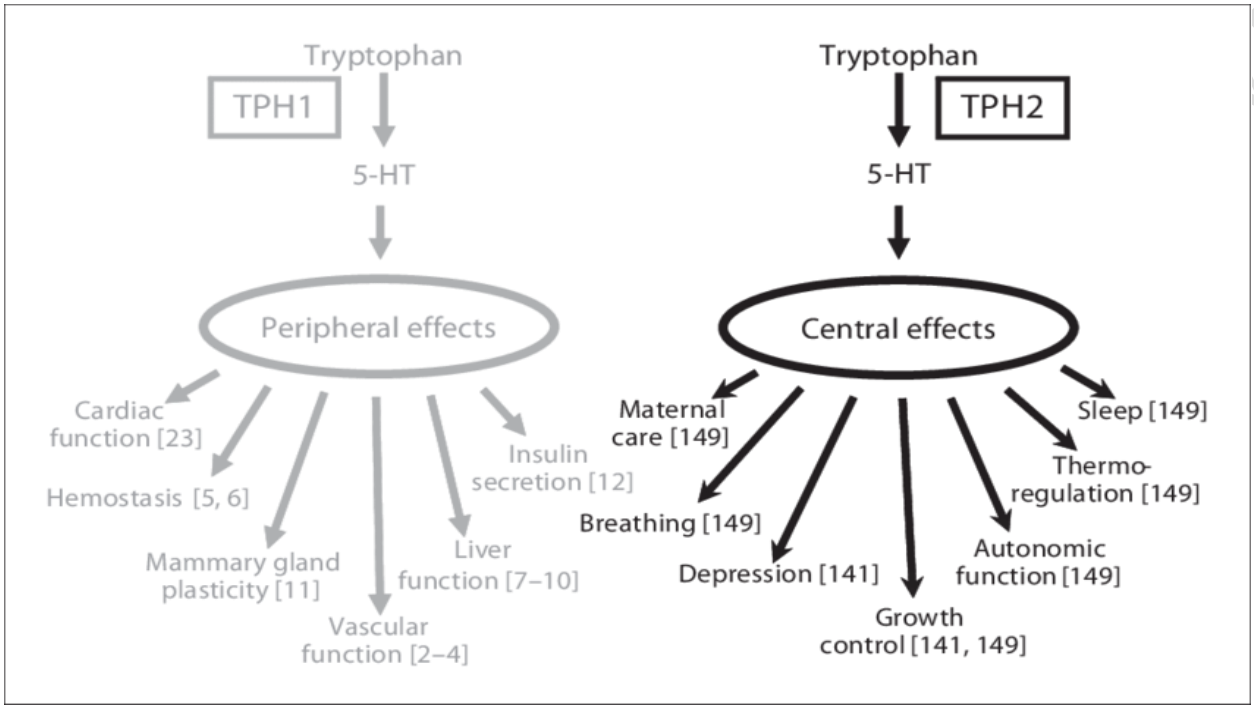
- In depression a genetic polymorphism that has been occur in the promoter region of the gene encoding the serotonin transporter (5- HTT). The promoter region of 5- HTT gene (5-HTTLPR-serotonin-transporter-linked polymorphic region) contains a functional polymorphism resulting in a long (L)/short(S) variant in the promoter region upstream of the transcription starting site.
- The short allele of 5-HTT has a low-activity and has been shown to put carriers at a greater risk of developing depression in response to stressful life events.



2. Tryptophan Hydroxylase

- The rate-limiting enzyme in serotonin biosynthesis, tryptophan hydroxylase (TPH), is encoded by two distinct genes *Tphl* and *Tph2* and has been proposed to play a role in pathogenesis of depressive disorders and suicide.
- Single nucleotide polymorphisms (SNPs) on *Tph2* gene have been linked with increased incidence of MDD and completed suicide attempts.

- Also, *Tph l gene*, which is dominantly expressed in the pineal gland, is thought to influence suicidal risk by disrupting the synthesis of melatonin a hormone responsible for regulation of circadian rhythm resulting in an increase in suicidal risk.



D) **The biogenic monoamine theory:**

- The monoamine hypothesis of depression came into the picture after the serendipitous discovery of the first antidepressant drugs that were otherwise developed for other medical conditions.
- These clinical observations have contributed greatly to the understanding of the pathophysiological changes that take place in the brains of depressed individuals.
    - The drugs were proposed to increase the amount of monoamine neurotransmitters in the brain either by blocking a monoamine degrading enzyme monoamine oxidase inhibitor (MAOI) or by blocking the reuptake of the neurotransmitters into the presynaptic neuron.
    - The Serotonin hypothesis:
    - Serotonin is a monoamine neurotransmitter with a wide range distribution throughout the central nervous system. It is involved in physiologic activities such as pain sensation, appetite regulation, aggression and mood.
    - Dysfunction in serotonergic system has been implicated in mood and anxiety disorders. The basis for this hypothesis is the fact that the first antidepressant

drugs worked by reviving the diminished monoamine activity in the brain. And later SSRIs alone were found to be sufficient to treat symptoms of depression effectively. This fact further strengthened the involvement of 5-HT in the pathogenesis of the disease.

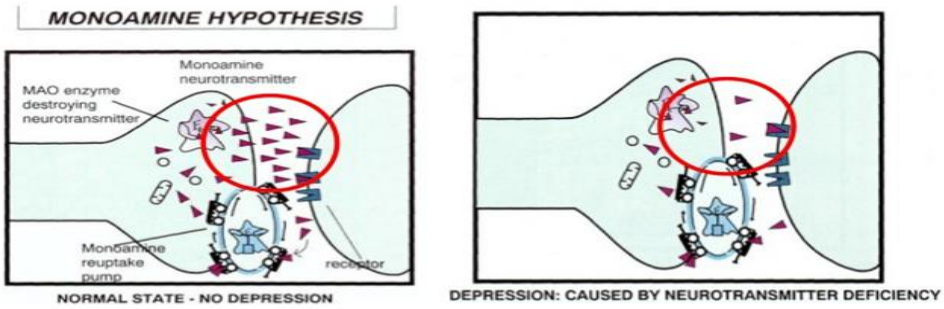
- There is also a decreased availability of 5-HTT in midbrain and brainstem regions. But this serotonergic dysfunction associated in depression is debated whether it is an etiologic factor or increases susceptibility.

i) The catecholamine hypothesis:

- The catecholamine hypothesis of depression emerged in the 1960s after the observation that reserpine; an antihypertensive drug depletes central and peripheral amine storage in the nervous system, induced depression. However, there are no consistent findings on the alteration in the levels of Norepinephrine metabolites in the CSF of depressed individuals.

BIOCHEMICAL BASIS OF DEPRESSION

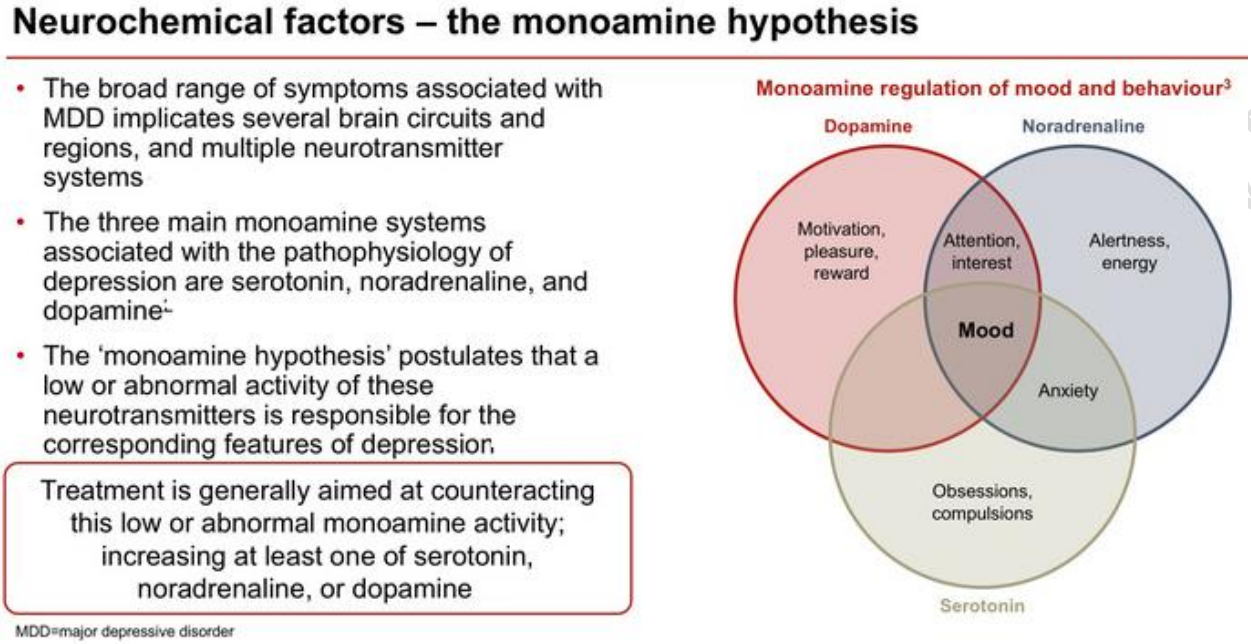
Monoamine Hypothesis: depression was due to a deficiency of monoamine neurotransmitters, notably nor-epinephrine (NE) and serotonin (5-hydroxytryptamine [5HT])



ii) Dopamine Hypothesis

- Additionally, some symptoms of depression including anhedonia [inability to feel pleasure in normally pleasurable activities] and psychomotor retardation are better explained by a derangement in the brain DA systems.
- These systems include the substantia nigra -basal ganglia motor system and the reward circuitry involving the NAc[nucleus accumbens] and VTA[ventral tegmental area].
- There is a decreased DA activity in the NAc specifically which corresponds to the inability to experience pleasure which is one of the hallmarks of depression.

- The concentration of the dopamine metabolite homovanillic acid (HVA) in CSF is reported to be lower in depressed patients as well.



E) **Inflammation and depression:**

- The claim that depression is an inflammatory disorder is gaining popularity nowadays. This is supported by the fact that many pro-inflammatory marker levels are reported to be elevated in depressed patients.
- Examples of these markers are C-reactive protein (CRP), interleukin (IL)-6, IL-1 and tumor necrosis factor alpha (TNF-α). In fact depressive like behaviors can be induced in the laboratory by administration of (IFN)-α, a powerful inflammatory cytokine, that has also been shown to produce depression like symptoms in patients taking it for the treatment of hepatitis C.
- An increase in reactive oxygen and nitrogen species generation and damage by oxidative and nitrosative stress (ONS), including lipid peroxidation, damage to deoxyribonucleic acid (DNA) and proteins is also seen. Even though a complete understanding of the mechanisms involved remains unclear.

F) **Neurothrophic hypothesis:**

- Significant atrophy of certain prefrontal cortex areas and hippocampus observed in depression as well as decreased levels of nerve growth factors (NGF) such as BDNF(Brain-derived neurotrophic factor) has led to the neurotrophic hypothesis.

- BDNF is an important molecular regulator of neuronal development and plasticity. It increases survival of neurons, stimulates the growth of dendrites and increases the spine density and also involved in maturation of excitatory synapses, processes that are important in learning and adaptation process which seems to be deficient in depression.
- The expression of BDNF is believed to be halted by chronic stress.
- Vascular endothelial growth factor (VEGF) is another NGF that promotes proliferation of neuronal cells in some brain regions like the hippocampus.

G) **Neuropeptides and depression:**

- There is increasing evidence that this **neuropeptides** are involved in the modulation of stress- related behaviors and mood by acting on neurokinin type-1 receptors (NK- 1).
- Substance P (SP) is one of these neuropeptides known for its wide spread distribution in the brain and its co-localization with 5-HT and NE neurons.
- Elevated CSF SP concentrations have been reported in depressed

H) Hormones and depression

- **Thyroid hormones:** Thyroid hormones (TH) imbalances are implicated in the pathophysiology of **neurodegenerative** and psychiatric conditions. These hormones are very essential for brain development, maturation and have been shown to promote neurogenesis, in particular, in the hippocampus. Hypothyroidism has been linked to depressive -like behavior in that it impaired hippocampal neurogenesis which resolved with hormone replacement.
- **Estrogen involvement:** Increased female susceptibility to depression mostly overlaps periods of low estrogen levels in the menstrual cycle, postpartum and after the onset of menopause.
- **Vasopressin and** depression: Arginine vasopressin (AVP) is a hypothalamic hormone that influences some key symptoms pertinent to major depressive disorder. Its level is reported to be elevated in patients suffering from this mental disorder. AVP has been linked to play a role in the regulation of stress response, one of the prominent features of depression.

H) Implications of the circadian rhythm in depression:

- Melatonin, a hormone secreted by the pineal gland, in a circadian fashion, regulates the rhythm of various biological parameters like body temperature, cortisol secretion, and sleep cycles by acting on receptors in the suprachiasmatic nucleus (SCN) of the hypothalamus.

- Delayed circadian rhythm in patients with depression has been linked to diminished level of melatonergic signaling in the brain.
- Patients may manifest with delayed onset of sleep, difficulty in maintaining sleep and early morning awakening.

DIAGNOSIS

Physical Exam

- The goal with a physical exam is usually to rule out another medical cause for depression.
- When performing the physical exam, the doctor may focus primarily on the neurological and endocrine systems.
- The doctor will try to identify any major health concerns that may be contributing to symptoms of clinical depression.
- For example, hypothyroidism -- caused by an underactive thyroid gland -- is the most common medical condition associated with depressive symptoms.
- Other endocrine disorders associated with depression include hyperthyroidism -- caused by an overactive thyroid -- and Cushing's disease -- a disorder of the adrenal gland.
- Many central nervous system illnesses and injuries can also lead to depression. For example, depression might be associated with any of the following conditions:
  - Central nervous system tumors
  - Head trauma
  - Multiple sclerosis
  - Stroke
  - Syphilis
  - Various cancers (pancreas, prostate, breast)
- Corticosteroid medications such as prednisone, which people take for diseases such as rheumatoid arthritis or asthma, are also associated with depression.
- Other drugs, including illegal steroids and amphetamines and over-the-counter appetite suppressants, may cause depression on withdrawal.

Lab Tests

- Blood tests to check for medical conditions that may cause depressive symptoms.
- He or she will use the blood tests to check for such things as anemia as well as thyroid or possibly other hormones, and sometimes calcium and vitamin D levels.

Other Testing Methods

- The doctor may include other standard tests as part of the initial physical exam.

- Among them may be blood tests to check electrolytes, liver function, toxicology screening, and kidney
- function. Because the kidneys and liver are responsible for the elimination of depression medications, impairment to either of these two organs may cause the drugs to accumulate in the body.
- Other tests may sometimes include:
    - CT scan or MRI of the brain to rule out serious illnesses such as a brain tumor
    - Electrocardiogram (ECG) to diagnose some heart problems
    - Electroencephalogram (EEG) to record electrical activity of the brain

Depression Screening Tests

- Questions that are used specifically to screen for depression.
- It's important to keep in mind that the inventories and questionnaires the doctor may use are just one part of the medical process of diagnosing depression.
- Depression screening instruments that measure the presence and severity of depression symptoms. Examples include:
    - The Patient Health Questionnaire-9 (PHQ-9) -- a 9-item self-administered diagnostic screening and severity tool based on current diagnostic criteria for major depression
    - Beck Depression Inventory (BDI), -- a 21-question multiple-choice self-report that measures the severity of depression symptoms and feelings
    - Zung Self-Rating Depression Scale -- a short survey that measures the level of depression, ranging from normal to severely depressed
    - Center for Epidemiologic Studies-Depression Scale (CES-D) -- an instrument that allows patients to evaluate their feelings, behavior, and outlook from the previous week
    - Hamilton Rating Scale for Depression (HRSD), also known as the Hamilton Depression Rating Scale (HDRS) or abbreviated to HAM-D -- a multiple choice questionnaire that doctors may use to rate the severity of a patient's depression

TREATMENT

Psychotherapy

- Psychotherapy (or talk therapy) has an excellent track record of helping people with depressive disorder A good relationship with a therapist can help improve outcomes.
- A few examples include:
  - **Cognitive behavioral therapy (CBT)** has a strong research base to show it helps with symptoms of depression. This therapy helps assess and change negative thinking patterns associated with depression. The goal of this structured therapy is to recognize negative thoughts and to teach coping strategies. CBT is often time-limited and may be limited to 8–16 sessions in some instances. Learn more about CBT.
  - **Interpersonal therapy (IPT)** focuses on improving problems in personal relationships and other changes in life that may be contributing to depressive disorder. Therapists teach individuals to evaluate their interactions and to improve how they relate to others. IPT is often time-limited like CBT.
  - **Psychodynamic therapy** is a therapeutic approach rooted in recognizing and understanding negative patterns of behavior and feelings that are rooted in past experiences and working to resolve them. Looking at a person's unconscious processes is another component of this psychotherapy. It can be done in short-term or longer-term modes. Learn more about psychodynamic therapy.

Psycho education And Support Groups

- Psycho education involves teaching individuals about their illness, how to treat it and how to recognize signs of relapse. Family psycho education is also helpful for family members who want to understand what their loved one is experiencing.
- Support groups, meanwhile, provide participants an opportunity to share experiences and coping strategies. Support groups may be for the person with the mental health condition, for family/friends or a combination of both. Mental health professionals lead some support groups, but groups can also be peer-led.
- Explore NAMI's nationwide offerings of free educational programs and support groups that provide outstanding education, skills training and support.

Medications

Here are some antidepressants commonly used to treat depression:

- **Selective serotonin reuptake inhibitors (SSRIs)** act on serotonin, a brain chemical. They are the most common medications prescribed for depression.

- Fluoxetine (Prozac)
- Sertraline (Zoloft)
- Paroxetine (Paxil)
- Citalopram (Celexa)
- Escitalopram (Lexapro)

➢ **Serotonin and norepinephrine reuptake inhibitors (SNRIs)** are the second most common antidepressants. These medications increase serotonin and norepinephrine.

- Venlafazine (Effexor)
- Desvenlafazine (Pristiq)
- Duloxetine (Cymbalta)

➢ **Norepinephrine-dopamine reuptake inhibitors (NDRIs)** increase dopamine and norepinephrine. Bupropion (Wellbutrin) is a popular NDRI medication, which causes fewer (and different) side effects than other antidepressants. For some people, bupropion causes anxiety symptoms, but for others it is an effective treatment for anxiety.

- **Mirtazapine** (Remeron) targets specific serotonin and norepinephrine receptors in the brain, thus indirectly increasing the activity of several brain circuits. Mirtazapine is used less often than newer antidepressants (SSRIs, SNRIs and bupropion) because it is associated with more weight gain, sedation and sleepiness. However, it appears to be less likely to result in insomnia, sexual side effects and nausea than the SSRIs and SNRIs.
- Bupropion (Wellbutrin)
- Mirtazapine (Remeron)

➢ **Second-generation antipsychotics (SGAs)**, or "atypical antipsychotics," treat schizophrenia, acute mania, bipolar disorder and bipolar mania and other mental illnesses. SGAs can be used for treatment-resistant depression.

- Aripiprazole (Abilify)
- Quetiapine (Seroquel)

➢ **Tricyclic antidepressants (TCAs)** are older medications, seldom used today as initial treatment for depression. They work similarly to SNRIs but have more side effects. They are sometimes used when other antidepressants have not worked. TCAs may also ease chronic pain.

- Amitriptyline (Elavil)
- Desipramine (Norpramin)

- Doxepin (Sinequan)
- Imipramine (Tofranil)
- Nortriptyline (Pamelor, Avantyl)
- Protriptyline (Vivactil)

➢ **Monoamine oxidase inhibitors (MAOIs)** are less used today because newer, more effective medications with fewer side effects have been found. These medications can *never* be used in combination with SSRIs. MAOIs can sometimes be effective for people who do not respond to other medications.

- Phenelzine (Nardil)
- Isocarboxazid (Marplan)
- Tranylcypromine Sulfate (Parnate)
- Selegiline patch (Emsam)

➢ **Brain Stimulation Therapies**

For some, brain stimulation therapies may be effective, typically after other treatments have not been effective.

- **Electroconvulsive Therapy (ECT)** involves transmitting short electrical impulses into the brain. ECT does cause some side effects, including memory loss. Individuals should understand the risks and benefits of this intervention before beginning a treatment trial.
- **Repetitive Transcranial Magnetic Stimulation (rTMS)** is a relatively new type of brain stimulation that uses a magnet instead of an electrical current to activate the brain. It is not effective as a maintenance treatment.
- **Vagus Nerve Stimulation (VNS)** has a complex history. For a fuller understanding of this treatment, read the NIMH summary of this and other brain stimulation interventions.

➢ **Complementary And Alternative Medicine (CAM)**

- **Exercise.** Studies show that aerobic exercise can help treat mild depression because it increases endorphins and stimulates norepinephrine, which can improve a person's mood.
- **Folate**. Some studies have shown that when people with depression lack folate (also called folic acid or vitamin B9), they may not be receiving the full benefit from any antidepressants they may be taking.

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RISK FACTORS :

- Life events: These include bereavement, divorce, work issues, relationships with friends and family, financial problems, medical concerns, or acute stress.
- Personality: Those with less successful coping strategies, or previous life trauma are more susceptible.
- Genetic factors: Having first-degree relatives with depression increases the risk.
- Childhood trauma.
- Some prescription drugs: These include corticosteroids, some beta-blockers, interferon, and other prescription drugs.
- Abuse of recreational drugs: Abuse of alcohol, amphetamines, and other drugs are strongly linked to depression.
- A past head injury.
- Having had one episode of major depression: This increases the risk of a subsequent one.
- Chronic pain syndromes: These and other chronic conditions, such as diabetes, chronic obstructive pulmonary disease, and cardiovascular disease make depression more likely.

PREVENTION

- Depression isn't generally considered to be preventable. It's hard to recognize what causes it, which means preventing it is more difficult.
- But once you've experienced a depressive episode, you may be better prepared to prevent a future episode by learning which lifestyle changes and treatments are helpful.
- Techniques that may help include:
  - regular exercise
  - getting plenty of sleep
  - maintaining treatments
  - reducing stress
  - building strong relationships with others