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DEPRESSION- CURRENT APPROACHES FOR ITS CONVENTIONAL AND ALTERNATIVE TREATMENT

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Abstract:

Depression is a mood disorder that affects physical and mental health by altering a person's behaviour, feelings, and thoughts. Multiple neurotransmitters and part of brain (mainly amygdala, the thalamus and the hippocampus) are involved with disorder of depression. Main cause of depression is unknown but it may be due to neurohormonal or neurochemical imbalance. There are two main hypothesis involved in the pathophysiology of depression that is- monoamine hypothesis and neurotropic hypothesis. According to National Comorbidity Survey, lifetime prevalence of major depression and dysthymia are 16.9 and 2.5% respectively. Several type of intervention have been shown to be efficacious in treating depression including pharmacological and non-pharmacological approaches. Pharmacological approaches include conventional medical therapies and non-pharmacological approaches include complementary and alternative therapies. Conventional medical treatment involve antidepressant medications, they are relatively safe and effective for many patient. Electroconvulsive therapy is particularly effective for the most severe and resistant depressions, but it has some severe side effects on memory and cognition. There are various complementary and alternative medicines (CAM) like herbal, homeopathic, bright light therapy, traditional Chinese medication, aromatherapy, physical exercise etc. It was identified that complementary therapies have less side effects as compared to conventional therapies.

Keywords: *Depression, hypothesis, monoamines, serotonin, noradrenaline, dopamine, antidepressants, CAM.*

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1. INTRODUCTION

Depression is a mental illness with depressed mood, decreased energy, loss of interest, disturbed sleep or appetite, and poor concentration.[1] Depression is generally interconnected with poor self-care, increased mortality, adverse medical effects, and risk of suicide. In the language of clinical psychology, depression is a syndrome, a cluster of emotional, physical, and behavioral symptoms that are characterized by sadness, low confidence, loss of pleasure, and, sometimes, difficulty in functioning. [2]

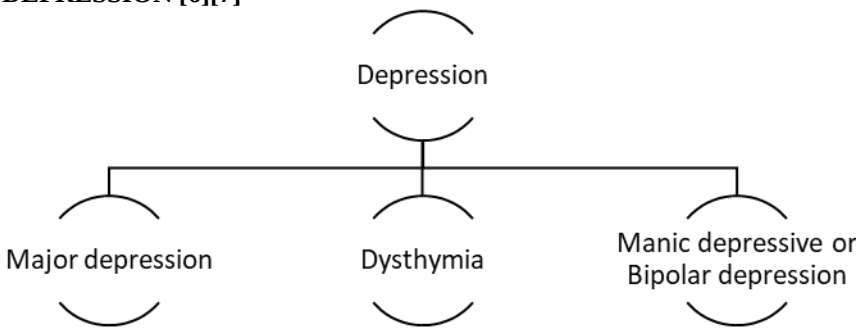
According to World Health Organization (WHO), depression will become the second largest illness in terms of morbidity by another decade in the world, already one out of every five women, and twelve men have depression. [3]

Problems which are common when someone is depressed [2] [4] [5]

A person may experience the following problems if depressed:

- Disrupted sleep
- Skipping days of work or not going to work.
- Difficulty concentrating during day
- Inability to study or pursue serious intellectual or creative interests.
- Avoiding friends or usual social activities, hobbies.
- Neglecting yourself physically (in terms of grooming and hygiene).
- Becoming upset or emotional for no specific reason.
- Feeling irritable and getting into arguments easily.
- Increased and excessive use of alcohol or other recreational drugs.
- Forgetfulness

2. TYPES OF DEPRESSION [6][7]



In major depression, a person may experience a combination of symptoms that affect the ability of a person to work, sleep, eat and enjoy. In this type of depression, person having symptoms of depression most of the day for 2 weeks that interfere with person's daily life style. These episodes of depression can occur many times in a person's lifetime.

In dysthymia, a person may experience long-term (two years or longer) but less severe symptoms that affect the normal functioning of the individual. Difference between dysthymia and major depression is that dysthymia is less severe but generally long lasting type of depression. People with dysthymia may also experience one or more episodes of major depression with less severe symptoms also.

Manic-depressive or bipolar depression is not as common as other forms of depression. Bipolar disorder used to be known as 'manic depression' because in this the person experiences periods of mania and periods of depression, with periods of normal mood in between. About 1% of the population will experience bipolar disorder at some time in their lives. In bipolar disorder cycles of mood swings from mania to depression occur over time. The mood change may have a psychotic basis with delusional thinking or occur in isolation and induce anxiety.

Apart from these three, there are other forms of depression like-

- **Perinatal depression or postpartum depression**- In this type of depression women experience major depression during pregnancy or after delivery.
- **Seasonal Affective Disorder (SAD)** - SAD is a type of depression in which person experience a feeling of depression at certain times of the year, usually starting in the autumn and early winter and going away during the spring and summer. Person with SAD generally want to eat foods rich in carbohydrate and want to sleep more.
- **Psychotic depression-** In this type of depression a person experience severe depression with some form of psychosis like having misbeliefs (disturbing false beliefs) or hearing or seeing

disturbing things that others cannot hear or see (illusions or hallucinations).

3. EPIDEMIOLOGY [8] [9]

National comorbidity survey exposed in detail the rates of subtypes of mood disorders: unipolar, bipolar, and the sub-threshold disorders. The lifetime prevalence of different types of depression was explained by National comorbidity survey.

Table 1- Lifetime prevalence calculated by National comorbidity survey.

	Lifetime Prevalence	Female %	Male %
Any Mood disorder	21.4%	24.9%	17.5%
Major depression	16.9%	20.2%	13.2%
Dysthymia	2.5%	3.1%	1.8%

According to Diagnostic and statistical manual of mental disorders:

Table 2- Lifetime prevalence calculated by Diagnostic and statistical manual of mental disorders.

	Lifetime Prevalence	Female %	Male %
Major depressive disorder	1.5%	-	-
Dysthymia	0.5%	-	-
Bipolar Disorders	4.4%	4.5%	4.3%

4. RISK FACTOR[9]

- Gender (female at greater risk)
- History of suicide attempts.
- Age (18-44 years of age is at greater risk)
- Marital status (separated and divorced at greater risk)
- Family history (relatives with depression)
- Early parental death
- Life events (negative stressful events, chronic exposure to stress)
- Low confidence
- Urban environment

5. CAUSES OF DEPRESSION

The exact cause of depression is unknown. Depression may be caused due to neurohormonal and neurochemical imbalance. There are mainly three neurotransmitters in brain-norepinephrine (NE), serotonin (5-hydroxytryptamine [5-HT]), and dopamine (DA). Deficiency of these neurotransmitters may cause depression.

Other causes include:

- Physical illness (low blood sugar, hormonal problems especially thyroid and parathyroid problems, symptoms relating to menstrual cycle or menopause)
- Genetics
- Anxiety or stress
- Loss
- Diet
- Side effects of medication
- Result of unfortunate experience[4][10]

The physical illness that is associated with depression:[10]

Metabolic disturbances: Acid-base disturbance, dehydration, hypo and hypocalcemia, hypo and hyperglycaemia, and hypoxia.

Neurological disease: Brain tumours, cerebral arteriosclerosis, cerebrovascular disease, dementia, intracranial tumours, meningitis, neurosyphilis, Parkinson's disease, subarachnoid haemorrhage and temporal lobe epilepsy.

Pulmonary disorders: Chronic obstructive lung disease and malignancy.

Gastrointestinal disorders: Hepatitis, irritable bowel, malignancy, other organic causes of chronic and abdominal pain and ulcer.

Metal intoxications: Toxicity due to the metal like thallium and mercury.

Endocrine: Addison's disease, Cushing's disease, diabetes mellitus, hyper and hyperparathyroidism, hypo and hyperthyroid.

Respiratory infections: Brucellosis, hepatitis, influenza, pneumonia and tuberculosis.

Cancer: Occult carcinomas and pancreatic cancer.

Cardiovascular disorders: Congestive heart failure, endocarditis and myocardial infarction.

Musculoskeletal disorders: Degenerative arthritis, osteoporosis with vertebral compression or hip fracture and rheumatoid arthritis.

Anaemia's: Folate & iron deficiencies, megaloblastic anaemia and pernicious anaemia.

6. DIAGNOSIS

- Interleukin-6 levels can be used to predict the severity of depression. IL-6 is used as a biomarker in the diagnosis of depression. IL-6 may influence the pathophysiology of depression

like cytokine-induced changes in the metabolism of monoamines, such as dopamine, noradrenaline and serotonin, specifically in midbrain nuclei. IL-6 also induces cortisol hypersecretion, directly by stimulating the hypothalamic-pituitary-adrenal axis and indirectly by modifying the sensitivity of the glucocorticoid receptor.[11]

- Screening for other medical conditions should be based on clinical judgment. Medical conditions include cancer, coronary artery disease, diabetes mellitus, cerebral vascular accident, hypothyroidism, hyperthyroidism, chronic pain.[12]
- The dexamethasone suppression test (DST) - mainly used to differentiate severe melancholic depression, mania, or acute psychosis from chronic psychosis or dysthymia.
- By using genomic method – Measuring gene expression profile in blood cell is a disease classifier and risk marker for diagnosis of depression. [12]
- Patient health questionnaire may be used to screen for depression. [12]
- Laughter analysis is a new tool for clinical diagnostic and evaluation of depression. [13]

7. PATHOPHYSIOLOGY

There is two main hypothesis of depression:

- Monoamine hypothesis
- Neurotrophic hypothesis

7.1. Monoamine hypothesis or biogenic amine hypothesis

The main biochemical theory of depression is the monoamine hypothesis which is first proposed by **Schildkraut** in 1965 and according to this, depression is caused by a deficiency of the monoamine transmitters, noradrenaline (NE) and 5-hydroxytryptamine (5-HT) in the brain while mania results from an excess of these neurotransmitters.

It was noted that the antihypertensive drug reserpine depleted neuronal storage granules of NE, 5-HT and dopamine and produced clinically significant depression in 15% or more of patients.

Every compound that inhibits monoamine reuptake, leading to an increased concentration of monoamines in the synaptic cleft, was proven to be a clinically effective antidepressant. Inhibiting the enzyme monoamine oxidase, which induces an increased availability of monoamines in presynaptic neurons, also has antidepressant effects.

These above observations led to the pharmacologically most relevant theory of depression, referred to as the monoamine-deficiency hypothesis. [8][14][15][16]

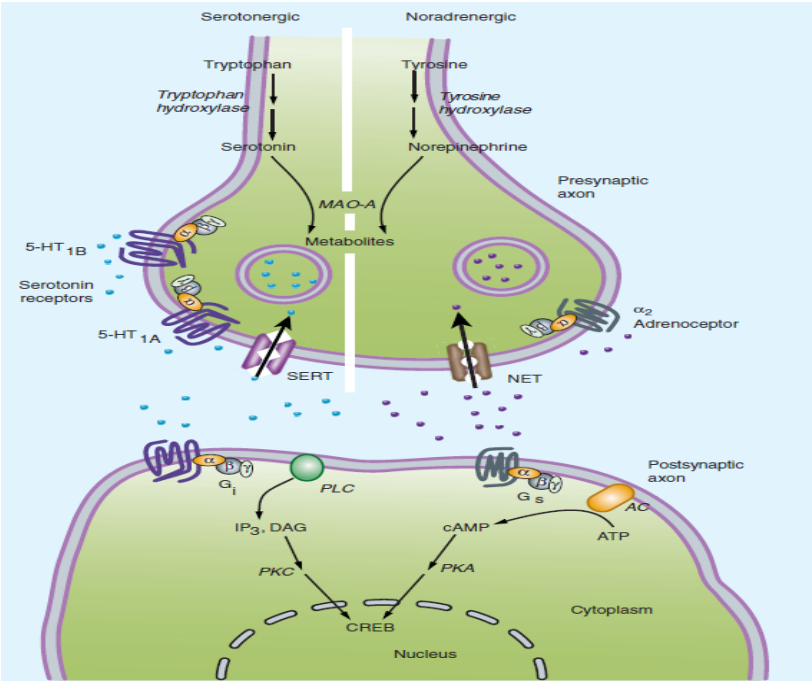


Figure 1. The amine hypothesis of major depression. [17]

Depression appears to be associated with changes in serotonin or norepinephrine signalling in the brain. Most antidepressants cause changes in amine signalling. AC [adenylyl cyclase]; 5-HT, serotonin ; CREB [cAMP response element-binding (protein)]; DAG [diacyl glycerol]; IP 3 [inositol trisphosphate]; MAO [monoamine oxidase]; NET [norepinephrine transporter]; PKC [protein kinase C]; PLC [phospholipase C]; SERT [serotonin transporter].[17]

7.2. Neurotrophic hypothesis

The neurotrophic hypothesis of depression states that a deficiency in neurotrophic factor causes the development of depression. Brain-derived neurotrophic factor (BDNF) is the most pervasive neurotrophic factor in the adult brain. Animal and human studies indicate that stress and pain are associated with the decrease in BDNF levels and this loss of neurotrophic support causes atrophic structural changes in the hippocampus and other areas such as the medial frontal cortex and anterior cingulate.

It was studied that acute and chronic stress decreases levels of BDNF in the hippocampus in rodents. This reduction of BDNF is mediated partly by stress-induced glucocorticoid and partly via other mechanism like stress-induced increases in serotonergic transmission. There is also evidence that antidepressant increases hippocampal BDNF levels in human. [8][14][15][16]

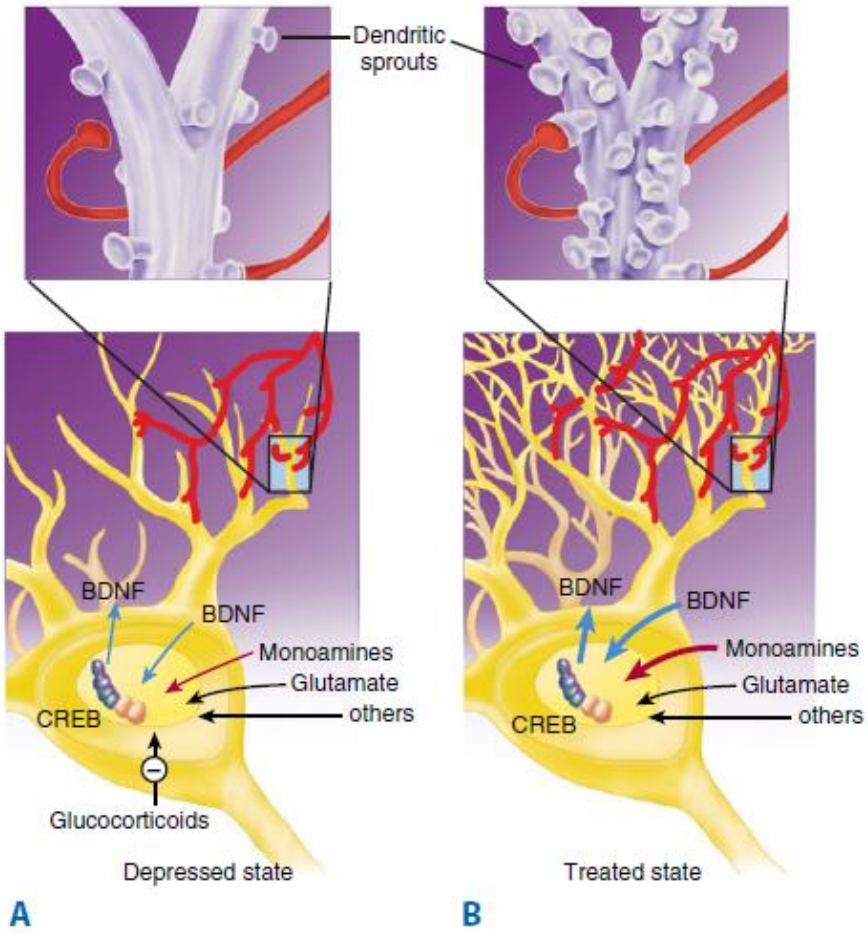


Figure 2. The neurotrophic hypothesis of major depression. [17]

Changes in trophic factors (especially brain-derived neurotrophic factor [BDNF]) and hormones appear to play a major role in the development of major depression

(A) Successful treatment results in changes in these factors

(B) cAMP response element-binding (protein) [CREB]. [17]

Other hypothesis include:

- Glutamate hypothesis
- Neuronal plasticity hypothesis
- Cholinergic/adrenergic balance
- Gamma-aminobutyric acid (GABA) hypothesis[15]

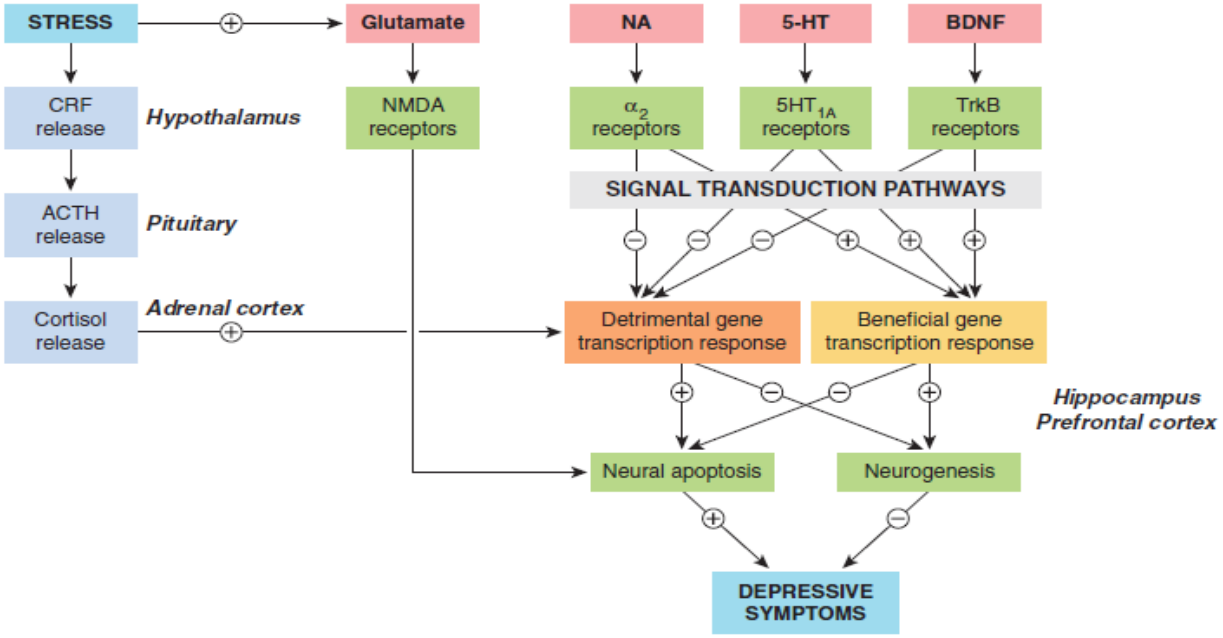


Figure 3. Simplified diagram showing mechanisms believed to be involved in the pathophysiology of depression. [14]

8. TREATMENT OF DEPRESSION

There are three phases of treatment to consider when treating patients with major depressive disorder:

8.1. Acute phase - from 6 to 10 weeks in which the goal is remission (i.e., the absence of symptoms). The main aim of acute treatment is to remove all signs and symptoms of the current episode of depression and to restore psychosocial and occupational functioning (a remission).

8.2. Continuation phase - 4 to 9 months after remission is achieved, in which the goal is to eliminate residual symptoms or prevent relapse (i.e., return of symptoms within 6 months of remission).

8.3. Maintenance phase - at least 12 to 36 months in which the main aim is to prevent recurrence (i.e. a separate episode of depression). [18][19].

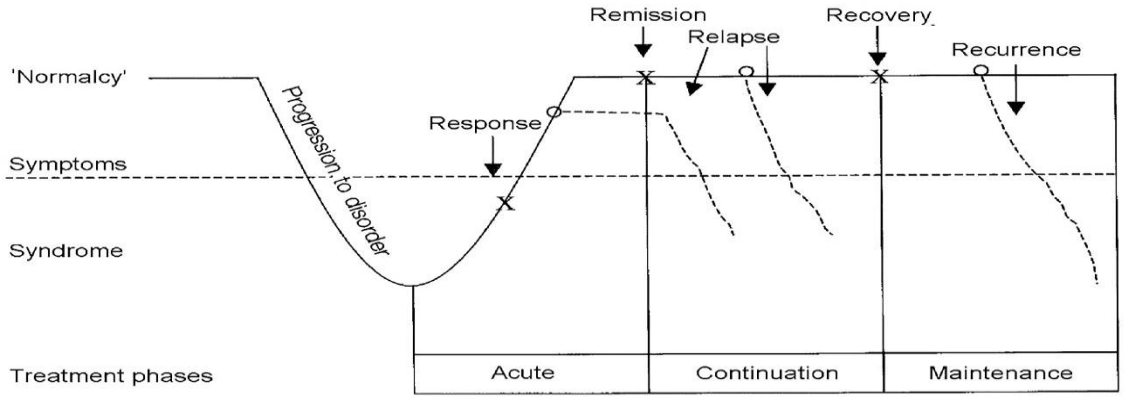


Figure 4: **Phases of treatment of major depression. [18][20]**

Treatment therapy for depression mainly divided into two:

- **Conventional medical treatment**
  It includes:
  - Antidepressants
  - Hormonal replacement
  - Counselling.

- **Complementary and alternative medicines (CAM)**
  It includes:
  - Ayurveda
  - Homeopathic
  - Herbalism
  - Electroconvulsive therapy
  - Bright light therapy
  - Traditional Chinese medication (acupuncture)
  - Aromatherapy
  - Massage
  - Physical exercise

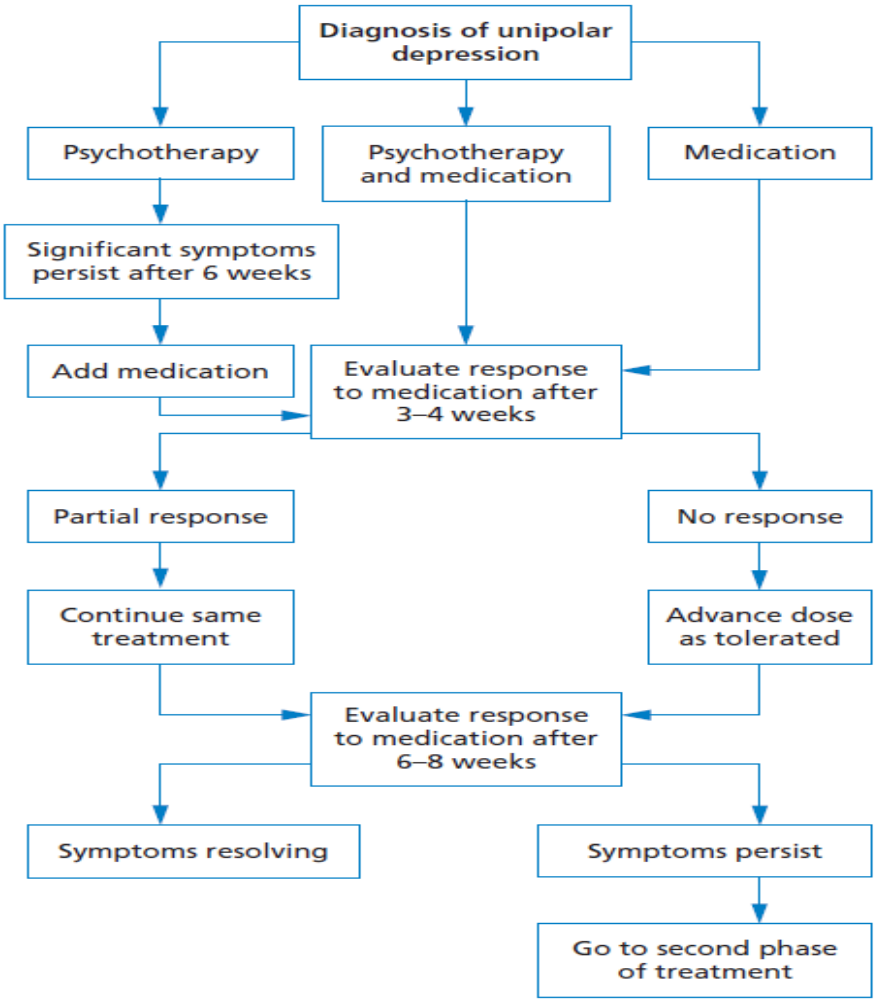


Figure 5. General algorithm for the initial phase of treatment of depression. [21][22]

8.4. Conventional Medical Treatment

Antidepressants

These are drugs which can elevate mood in depressive illness. Practically all antidepressants affect monoaminergic transmission in the brain. There are different types of antidepressants:

- Reversible inhibitors of monoamine oxidase-A{RIMAs}
- Selective serotonin reuptake inhibitors {SSRIs}
- Tricyclic antidepressants{TCAs}
- Serotonin and noradrenaline reuptake inhibitors (SNRIs)
- Atypical antidepressants [23]

Table 3. Types of antidepressant drugs:[8][14][19][22][23]

Type and example	Action	Usual dose(mg/day)	Risk of overdose	Side Effects
SSRIs	· All highly selective for 5-HT.	-	Low risk in overdose.	• Headache • Nausea, • Insomnia and nervousness (trouble falling asleep or waking often during the night • Agitation (feeling jittery) • Sexual problems - both men and women can experience sexual problems including reduced sex drive, delayed ejaculation, erectile dysfunction.
➢ Fluoxetine	· SSRIs inhibit the reuptake of serotonin. As a result, the serotonin stays in the synaptic gap for more time than it normally would, and may repeatedly stimulate the receptors of the recipient cell. This leads to an increase in signalling across synapses in which serotonin serves as the primary neurotransmitter.	20-60		
➢ Fluvoxamine		50-300		
➢ Paroxetine		20-60		
➢ Citalopram		20-60		
➢ Escitalopram		10-20		
➢ Sertraline		50-200		
Classical TCA Group	· Inhibition of NA and 5-HT re-uptake. · TCAs increase levels of norepinephrine and serotonin and block the action of acetylcholine, another neurotransmitter.		Ventricular dysrhythmias.	• Dry mouth • Constipation • Bladder problems—emptying the bladder may be difficult. • Sexual problems—sexual functioning may change. • Blurred vision • Drowsiness
➢ Imipramine	· Non-selective · Converted to desipramine	100-300		
➢ Desipramine	Non selective	100-300		
➢ Amitryptiline	Non selective	100-300		
➢ Nortryptyline	Non selective	50-200		
➢ Clomipramine	Non selective	100-250		
Other 5-HT/NA uptake inhibitors				• Headache • Nausea, • Insomnia and nervousness • Agitation • Sexual problems - both men and women can
➢ Venlafaxine	· Venlafaxine inhibits the reuptake of both serotonin and norepinephrine at their respective presynaptic sites. · This drug does not have significant effects at	75-225	Ventricular dysrhythmias	

	muscarinic, histamine, or α-adrenergic receptors			experience sexual problems including reduced sex drive, erectile dysfunction, delayed ejaculation.
➢ Duloxetine	· Potent non-selective NA/5-HT uptake inhibitor. · No action on monoamine receptor.	30-90	Low risk in overdose.	
➢ Milnacipran	NA selective (slight)		Low risk in overdose.	
NA selective inhibitors				
➢ Bupropion	· Weak inhibitor of both dopamine and norepinephrine neuronal re-uptake. · It does not block muscarinic, histaminergic, or adrenergic receptors	150-300	Seizures at high doses.	• Headache • Dry mouth • Agitation • Insomnia
➢ Maprotiline	Selective NA inhibitor	75-150	Ventricular dysrhythmias	• Dry mouth • Constipation • Bladder problems • Blurred vision • Drowsiness during the day.
➢ Reboxetine	Selective NA inhibitor	10-12	Safe in overdose. Low risk of cardiac dysrhythmia.	• Dizziness • Insomnia • Anticholinergic effects
Monoamine receptor antagonists				
➢ Mirtazapine	Blocks α2, 5-HT2C and 5-HT3 receptors	15-45	No serious drug interaction.	• Dry mouth • Sedation • Weight gain
➢ Trazadone	· It blocks the neuronal reuptake of serotonin and is an antagonist at the 5HT2-receptor. · Blocks 5-HT2A and 5-HT2C receptors as well as H1 receptors.	150-300	Safe in overdose.	• Sedation • Hypotension • Cardiac dysrhythmias
➢ Mianserin	Blocks α1, α2, 5-HT2A and H1 receptors	30-40	-	• Milder antimuscarinic and cardiovascular effects than TCAs • Agranulocytosis • Aplastic anaemia
MAO inhibitors	Inhibit MAO-A and/or MAO-B			
➢ Phenelzine	Non selective	30-90	Many interactions (opioids, sympathomimetic drugs). Hypotension Insomnia Liver damage [rare]	• Cheese reaction to tyramine containing foods. • Anticholinergic side effects. • Hypotension

			Weight gain	• Insomnia • Weight gain • Liver damage (rare)
➢ Tranylcypromine	Non selective	20-60	Many interactions (opioids, sympathomimetic drugs). Hypotension Insomnia Liver damage [rare] Weight gain	
➢ Isocarboxazid	Non selective	20	Many interactions (opioids, sympathomimetic drugs) Hypotension Insomnia Liver damage [rare] Weight gain	
➢ Moclobemide	MAO-A selective	300	-	• Nausea • Insomnia • Agitation

8.5. Complementary and alternative medicines(CAM)

Pharmaceutical medication generally used when:

- There is immediate concern of harm to self or harm to other (suicidal ideation).
- When a patient is not able to perform a basic function like physical activity or other daily life function.

CAM therapy is only used when the patient is stable with above two conditions. If the patient is not stable (with respect to above two conditions) then CAM should not be used as first line treatment. [24]

CAM include:

- Ayurvedic medication
- Aromatherapy
- Massage
- Traditional Chinese medication
- Homeopathy
- Hypnosis

8.5.1. Ayurvedic medication

In Ayurveda, the main aim to treat depression is by rebalancing the doshas. There are three doshas present inside human body according to Ayurveda, they are kapha, pitta, vata. According to the principles of Ayurvedic medicine, each and every person is born with a unique and distinctive combination and balance of doshas that can affect an individual's vulnerability to physical or mental diseases. Imbalances of the doshas may be caused by several factors, including poor sleep, overexertion or under exertion, poor diet, and exposure to seasonal changes.

- Imbalance in the vata dosha destroys mental sense and gives rise to distress and grief.
- Imbalance in the fire or 'pitta' gives rise to the production of mental states of excessive fear and grief.
- Imbalance in the kapha dosha causes lethargy, anxiety, and in discrimination.[25]

Table 4. Symptoms of depression and doshas responsible for that symptom. [26]

Symptoms of depression	Dosha
Sadness of mood	Vata
Lack of pleasure	Kapha
Sleep disturbances	Vata
Suicidal ideation	Vata
Easy fatigability	Vata
Psychomotor retardation	Kapha
Guilty feeling	Vata
Poor concentration	Vata
Appetite changes	Vata

Ayurvedic system of medicine includes:

- Panchakarma
- Yoga
- Aromatherapy
- Massage

8.5.1.1. Panchakarma

Ayurveda describes panchakarma as purification methods which detoxify the whole body. Panchakarma mainly helps to maintain the balance between the tri-doshas in the body.

Panchakarma involves:

- Shaman chikitsa {used for vitiated doshas}
- Shodhan chikitsa {used for detoxification purpose}

According to ayurveda, different approaches for the treatment of depression are:

- Daivavyapashraya
- Yuktivyapashraya
- Sattvavajaya chikitsa[26][27]

Daivavyapashraya chikitsa (spiritual healing)

In this type of approach by considering the faith, religion, educational levels of the patient, mantradi chikitsa is administered to attain better results. It creates confidence and reduces fear.

Yuktivyapasraya chikitsa (rationale therapy)

The approach is planning the treatment according to the condition of the factors like dosha, dhathu etc. This includes:

- Internal medications
- External therapeutic procedures
- Diet

In psychiatric diseases like depression, the treatment according to panchakarma is:

- Snehapana (intake of medicated ghee)
- Mridu sodhana (mild purification by emesis or purgation).
- Niruha vasti (enema with decoction)
- Sirovirechana (medicated errhines)
- Sajna prabodhana (medication for mood and intellect stabilization)

Sattvavajaya chikitsa (psychotherapy)

Sattvavajaya means to enhance sattva guna (goodness, constructive, harmonious). As depression is a tamo guna (darkness, destructive, confused) predominant disease, the psychotherapy can be preferred to treat depression.

Satvavajaya chikitsa corrects the negative cognition and promotes sattva by means of:

- Jnana (knowledge of self)
- Vijnana (analytic knowledge)
- Dhairya (confidence)
- Smriti (scriptural wisdom)
- Samadhi (concentration) [26][27][28]

Two main types of psychotherapies:

- Cognitive-behavioural therapy (CBT)
- Interpersonal therapy (IPT)

8.5.1.2. Yoga

Yoga is an integral part of ayurvedic medicine. It is a combination of movement, mindfulness, and relaxation and it is a traditional Indian spiritual practice originated around 5000 years ago.

Yoga has 3 basic component:

- Asanas (postures)
- Pranayama (breathing exercises)
- Dhyana (meditation).[29][30]

The yoga teachers agreed and believed that yoga classes should be on average 30- 40 min, [five times per week over six weeks]. For reducing depression, postures and breath regulation were considered essential. In a study comparing yoga alone,

antidepressant medication alone and yoga along with antidepressants, decrease in the level of cortisol observed in yoga patients and in the yoga alone group, the cortisol decrease correlated with decreased depression scores.[30][31]

Sudarshan kriya yoga (SKY) is proven to have the potential to treat depression. SKY involves four phases:

1) Ujjayi pranayama (victory breath) – it includes long and deep breathing {breathing in, breathing out and then holding}
2) Bhastrika pranayama (bellows breath) – it includes forced inhalation and exhalation {for 2-3 min}
3) SK (healing) – it includes slow, medium and fast breathing.
4) Yoga nidra (deep relaxation) – for 15min.

The entire procedure takes about 40-45 min.[32]

8.5.1.3. Herbal therapy

There are many herbs which are used in the treatment of depression and these herbs are clinically proved to possess antidepressant activity.

Examples of herbal medicine:

- *Hypericum perforatum* (St. John's wart)
- *Rhodiola rosea* (roseroot)
- *Crocus sativus* (saffron)

Some of the herbal medicine may show antidepressant activity by:

- Inhibiting Monoamine Oxidase re-uptake (like serotonin, dopamine, noradrenaline).
- Enhancing binding and sensitization of serotonin receptor.
- Inhibiting Monoamine oxidase (MAO).
- Neuroendocrine modulation.[33]

Table 5. Herbal drugs used for depression.

Herbal medicine	Major active constituent	Mechanism of action	Application
St. John's wart (*Hypericum perforatum*)[33][34][[35]	· Hyperfonin · Hypericin	· Non-selective inhibition of reuptake of serotonin, dopamine, norepinephrine. · Induction of the cytochrome P450 enzymes (CYP3A4 and CYP2C9) · Modulation of monoamine transmission via Na+ channel. · Reduces the degradation rate of acetylcholine. · Increased binding/ sensitivity/ density to 5-HT1A,B.	Depression, bipolar depression
Lavender (*Lavandula spp.*)[33]	· Linalool · Linayl acetate	GABA modulation (based on volatile constituent)	Depression, anxiety, somatic tension.
Brahmi (*Bacopa monniera*) [33]	· Bacoside A · Bacoside P	· 5-HT2C modulation. · Cholinestrase inhibition.	Depression, nervous exhaustion, anxiety, cognitive impairement
Borage (*Echium amoenum*) [33]	· Rosmarinic acid · Thesinine	Mechanism currently unknown.	Depression, anxiety
Korean ginseng (*Panax ginseng*) [33]	· Ginsenoside Rb1 · Ginsenoside Rg1	· Monoamine modulation · Nitric oxide synthase inhibition.	Fatigue, depression, poor cognition.
Roseroot (*Rhodiola rosea*) [33]	· Salidrosid · Tyrosol · Rosavin	· Neuroendocrine modulation · Monoamine Oxidase A inhibition · Monoamine modulation · Normalisation of 5-HT	Depression, fatigue, cognitive impairment.
Saffron (*Crocus sativus*) [33][34]	· Crocin · Safranal	· Increases reuptake inhibition of monoamines · GABA α agonism	Depression, anxiety.
Ginkgo (*Ginkgo biloba*) [33]	· Ginkolide · Bilobalide	· Modulation of cholinergic and monoamine pathways · GABAergic effect · Nitric oxide activity	Depression, anxiety, cognitive impairment.

Withania (*Withania somnifera*) [33]	· Withanolide · Withaferin	GABA-mimetic activity	Anxiety, insomnia, fatigue, nervous exhaustion.
Kava (*Piper methysticum*) [33]	· Kawain · Dihydrokawain	· GABA channel modulation (lipid membrane structure and sodium channel function). · Weak GABA binding (increased synergistic effect of [3H] muscimol binding to GABA-α receptors) . · β-adrenergic downregulation. · MAO-B inhibition. · Re-uptake inhibition of norepinephrine in the prefrontal cortex.	Anxiety, comorbid depression, anxious insomnia.
Passionflower (*Passiflora spp.*) [33]	• Harman • Chrysin	• GABA-system mediated anxiolysis • Benzodiazepine receptor partial agonist • Animal behavioural models have shown non-sedative anxiolytic effects(elevated-plus maze, light/dark box choice tests)	Anxiety, insomnia
Valerian (*Valeriana spp.*) [33]	· Valepotriate · Valerenic acid	· Adenosine (A1 receptor) interactions GABA modulation (increased binding and decreased degradation of GABA) · Valerenic acid from valerian has demonstrated GABA-A receptor (β3 subunit) agonism · 5-HT5a partial agonism · Animal models have shown anxiolytic effects (elevated plus maze)	Insomnia, anxiety, somatic tension, CNS stimulant withdrawal.

8.5.1.4. Supplemental Therapies

Many nutritional ingredients have confirmed efficacy for the treatment of mild to moderate depression.

Table 6. Supplements used for the treatment of depression.

Supplement	Mechanism	Dose	Side effect
Chromium [24]	· Glucose balance, therefore, balances insulin level. · Serotonin modulation	200 µg per day	None known at therapeutic dosages
Fish oil (omega-3-fatty acids)[24][35][36]	· Platelet clotting ability · Inhibits sympathoadrenal activation and normalizes membranes	1 tablespoon of fish oil per day or 2 g docosahexanoic acid (DHA) per day	Side effects of mild reflux and gastrointestinal disturbances.
Folic acid[24][35]	· Lowers homocysteine · Folate may modulate serotonergic or catecholaminergic functions	0.5–1.0 mg per day	Contraindicated with methotrexate for cancer treatment or anti-seizure medications.

Inositol [24]	Serotonin and acetylcholinergic modulation	4–12 g per day	None known at therapeutic dosages
Melatonin [24]	· Circadian rhythm restoration in people with insomnia and jet lag. · Antioxidant	0.5–5 mg at bedtime	Side effects of some waking drowsiness. Contraindicated in nocturnal asthmatics.
Selenium [24]	· Antioxidant helps convert T4 to T3 · Enhances immunity	200 µg per day	Can cause brittle nails in high doses.
L-tryptophan [24][34]	Serotonin precursor	0.5–1.0 g per day	Side effect of possible serotonin syndrome when used with other SSRIs or St. john's wort.
Vitamin B[36]	B-vitamins play a central role in energy metabolism, mitochondrial function, and neurotransmitter production.	1.5 mg per day	None known at therapeutic dose
Vitamin C[36]	· Neuromodulator in the brain, modulating both dopamine and glutamate-mediated neurotransmission · Antioxidant · Influences5-HT1A receptor activity	75 and 90 mg	None known at therapeutic dose
Vitamin D[36]	· Vitamin D can regulate serotonin synthesis by activating the transcription of the serotonin-synthesizing enzyme, tryptophan hydroxylase 2. · It can influence dopamine production via its effect on the expression of the enzymes catechol-O-methyltransferase and tyrosine hydroxylase.	400-1,100 IU	None known at therapeutic dose
Vitamin E [24]	Antioxidant	400 IU per day	None known at therapeutic dose
Zinc [24][36]	Neurologic and immune modulator.	25 mg per day	Long-term supplementation may deplete copper

8.5.1.5. Aromatherapy massage

In aromatherapy massage, essential oils are used and it was earlier identified that essential oils have some active constituents which help in the treatment of depression and anxiety also. The exact mechanism of action of aromatherapy is not yet understood but it has some functions which help in the reduction of symptoms of depression. [37] The main purpose of aromatherapy massage is to induce the release of physical and emotional tension. [35]

Table 7. Essential oils used for the treatment of depression and their function. [37]

Essential oil	Function
Bergamot	· Light, fresh, citrus fragrance boost the mind, lifting one out of depression. · It can stimulate or sedate the nervous system according to the individual needs, relieving anxiety and calming fear problem.
Clary sage	· It has a relaxing effect, thus it is helpful in dealing with muscular stress and tension. · It was also used for treating hormone related mood disorders.
Lavender	· It helps to calm feelings of depression. · Help in getting good night sleep.

Rose	· The scent of rose has a powerful effect on the emotions. · It is also a mild sedative and anti-depressant, excellent for emotional shock, and grief.
Lemon	· Tangy, bright fragrance of lemon is refreshing. · It has a psychologically strengthening effect on usually depressed fearful patients. · Lemon has used to boost the immune system and fight infection.
Roman chamomile	· It has a calming effect on an emotional level. · It is mild sedating without being depressive. · It is generally used for hypersensitive individuals who are deeply affected by emotional upsets and those who are prone to allergies.
Geranium	· It has a relaxing effect, thus it is helpful in dealing with muscular stress and tension. · It was also used for treating hormone related mood disorders. · It has an excellent regulatory effect on the body including the nervous system. It is soothing yet reviving and revitalizing.
Sandalwood essential oil	· It is used for depression, anxiety, and stress-related problems as it has an effect on the psyche. · Its heavy scent is gently sedating and antiseptic in nature
Jasmine	· It boosts a person's sense of self-trust and thus confidence.

8.5.2. Acupuncture

Most of the research on acupuncture for depression has been carried out in China. Acupuncture is the practice of inserting needles into specific body points. When acupuncture combined with conventional medical treatments such as anti-depressants, then it helps in reducing the side effects and enhance their pharmacological and therapeutic effects. [38]

8.5.3 Electroconvulsive therapy (ECT)

In ECT, electrical stimulation is delivered to the brain which causes seizures and it was observed that these seizures help to relive the symptoms of depression. ECT is a very effective and quicker method for the treatment of depression as compared to other methods.

The procedure of ECT involves delivery of up to 800 milliamperes of the pulse current to the brain for a time period of 1-6 seconds. [39]

According to a research, animal studies suggested that ECT acts via neuroplasticity effects on limbic structures as ECT increases neuroplasticity in the hippocampus by inducing neurogenesis [40] and endothelial cell proliferation [41] but in vivo confirmation at the human system level is not sufficient.

Candidates for ECT include:

- Patient with severe or major depression.
- Patient with any psychological emergency such as harming self or other like suicidal ideation.
- Patients who refuse to take medicines.[42]

Side effects of ECT include:

- Headache
- Upset stomach
- Memory loss
- Muscle ache

8.5.4. Homeopathic Treatment

Homeopathy is based on the principle of ''like cures like''. Homeopathy has been practiced worldwide for the past 200 years. Preparation of homeopathic medicines involves a specific process of successive dilutions and potentization.[43] Hahnemann claimed that 'in the process of shaking, or potentization of a substance, essential or spirit-like nature of the substance was extracted' which can be used to treat some disease.[44]

Homeopathic treatment is effective because of the following reasons:

- High patient acceptability
- Lack of adverse effects
- Safety in overdose[45]

Dr. Masi in her private practice reported that use of certain flower tinctures (*approved by the US Homeopathic Pharmacopeia*) have the potency to heal emotional disturbances, such as hopelessness, unhappiness, and fear, and she described two cases of major depression in which flower remedies produced a considerable improvement.[44]

In traditional homeopathic remedies for depression, Ullman mentioned such substances as:

- Arnica Montana (mountain daisy) - Arnica Montana is used for depression and anxiety caused by financial loss or a business failure

- Kali phosphoricum (phosphate of potassium) - Kali phosphoricum is advised to patients with depression who are in need of strengthening their motivation, determination, or bravery.
- Sepia (cuttlefish) - Sepia is indicated for people who feel chronically fatigued and socially withdrawn
- Natrum muriaticum (salt) -Natrum muriaticum is given to patients who have difficulty revealing or showing their emotions in public but become overloaded by feelings of sadness and disappointment when alone.[44]

Homeopathic medications available for use in the trial:[44]

- Arsenicum album
- Argentum nitricum
- Aurum metallicum
- Calcarea sulphurica
- Calcarea carbonica
- Causticum
- Cimicifuga racemosa
- Ignatia amara
- Kalium bromatum
- Kalium carbonicum
- Kalium phosphoricum
- Lac caninum
- Lilium tigrinum
- Lachesis mutus
- Lycopodium clavatum
- Natrum carbonicum
- Natrum muriaticum
- Natrum sulphuricum
- Nitricum acidum
- Nux vomica
- Opium phosphorus
- Phosphoricum acidum
- Platina
- Pulsatilla nigricans
- Sepia officinalis
- Silicea
- Staphysagria
- Sulphur
- Thuja occidentalis

8.5.5. Bright light therapy for depression (BLT)

According to clinicians and physicians, exposure of the eyes to light (appropriate intensity and duration), at an appropriate time of day, have marked effects on the symptoms of depressive illness. [46] Bright light therapy is widely used for seasonal major depressive disorder, but if BLT is used with antidepressant it may be used for the non-seasonal major depressive disorder.

Exposure to artificial light (2500-10,000 lux) in the morning or at night is assumed to prolong photoperiod and generally helps to reinstate a synchronization of the biological clock which is disturbed in depression. Another reason for the incorporation of BLT in the treatment of depression is the involvement of serotonergic transmission in the human brain. [47]

However, the exact mechanism of action of BLT in the treatment of depression remains unclear. [48]

It was observed in various studies that therapeutic effect of bright light therapy was found in 50% of the patients with the major depressive disorder. For non-seasonal major depressive disorder, improvements in mood observed in patients after bright light exposure (2000-3000 lx) as compared to dim light exposure (<50 lux) in the evening.[49]

According to a review of Michael Terman, it was noticed that the antidepressant effect is stronger when patient is exposed to morning rather than evening light. This may be because of the diurnal variation in retinal photoreceptor sensitivity, with greater sensitivity to morning light. [50]

In a Randomized Clinical Trial, patients were randomly assigned to:

(1) Light monotherapy (active 10 000-lux fluorescent white light box for 30 min/d in the early morning plus placebo pill).

(2) Antidepressant monotherapy (inactive negative ion generator for 30 min/d plus Fluoxetine Hydrochloride, 20mg/d).

(3) Combination light and antidepressant.

(4) Placebo (inactive negative ion generator plus placebo pill).

A total of 122 patients were randomized. From the above trial, it was concluded that bright light treatment, both as monotherapy and in combination with fluoxetine, was efficacious and well tolerated in the treatment of adults with nonseasonal major depressive disorder (MDD) and the combination treatment had the most consistent effects.[51]

9. CONCLUSION:

Depression is a serious mental illness with depressed mood, disturbed sleep or appetite, and poor concentration. Depression is among the leading causes of ill health, loss of productivity and disability worldwide, therefore, treatment of depression is necessary. There are various approaches for the treatment of depression. Complementary and Alternative Medication remains the treatment of choice as compared to conventional Medical treatment although evidence on the efficacy of CAMs is sometimes poor but they have a good safety record as they have lesser side effects. ECT is one of the

effective treatment in case of emergency and research is increasingly refining its practice and safety.

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