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REVIEW ON DEPRESSION AND ITS CURRENT TREATMENT STRATEGIES

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Abstract: Depression is a devastating and prevalent disease, with profound effects on neural structure and function. It is reported as one of the most common psychiatric disorder in outpatient clinic population and in subjects seen in various medical and surgical setting. Different symptoms of depression observed for different age group person and severity of symptoms vary with individual. Single or combination of factors may be responsible for promoting depression. Several theories of depression do exist, including modulation of monoaminergic neurotransmission, alterations in neuroplasticity, and relation of hippocampus with depression are briefly mentioned in the review. Diagnosis is generally based on the symptom criteria spelled out in the Diagnostic and Statistical Manual of Mental Disorders (DSM). Several types of interventions have been shown to be efficacious in treating depression. The antidepressant medications are relatively safe and work for many patients. About half of all patients will respond to a given medication, and many of those who do not will respond to some other agent or to a combination of medications. Psychotherapies and somatic treatment also available for treatment of depression. Electro-convulsive therapy is particularly effective for the most severe and resistant depressions. Cognitive behaviour therapy also appears to be efficacious in treating depression, and recent studies suggest that it can work for even severe depressions in the hands of experienced therapists. Treatment combining Interpersonal therapy with medication retains the quick results of pharmacotherapy and boosting response in patients who are otherwise more difficult to treat.

Keywords: Depression, Monoamine, Neuroplasticity, Cognitive Behaviour Therapy

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INTRODUCTION

The term "depression" is still somewhat ill-defined covering a range of phenomena from a normal emotion - a natural response to loss or disappointment to an accompanying symptom common in a variety of physical conditions, up to a clinical psychiatric disorder. Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behaviour, feelings and sense of well-being. Depression is the most common of the affective disorders (defined as disorders of mood rather than disturbances of thought or cognition); it may range from a very mild condition, bordering on normality, to severe (psychotic) depression accompanied by hallucinations and delusions.[1] Depressed mood is not necessarily a psychiatric disorder. It may be a normal reaction to certain life events, a symptom of some medical conditions, or a side effect of some drugs or medical treatments. As estimated by WHO, depression shall 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. Not just adults, but two percent of school children, and five percent of teenagers also suffer from depression, and these mostly go unidentified. Depression has been the commonest reason why people come to a psychiatrist, although the common man's perception is that all psychological problems are depression.[2,3] Depressed mood is also a primary or associated feature of certain psychiatric syndrome such as clinical depression. Clinical depression (also known as a major depressive disorder) is a complex condition marked by sustained instances of a depressed mood and loss of interest in life. It differs from having a depressed mood in that a major depressive disorder lasts for more than two weeks, evolving into a mental illness. The primary clinical manifestations of major depression are significant depression of mood and impairment of function. Some features of depressive disorders overlap those of the anxiety disorders, including panic-agoraphobia syndrome, severe phobias, generalized anxiety disorder, social anxiety disorder, posttraumatic stress disorder, and obsessive-compulsive disorder.[4]

SYMPTOMS OF DEPRESSION[5]

People with depressive illnesses do not all experience the same symptoms. The severity, frequency and duration of symptoms vary depending on the individual and his or her particular illness.

- Emotional pain or sadness [6]
- Feelings of hopelessness or pessimism[7]
- Crying[8]
- Irritability, restlessness
- Loss of interest in activities or hobbies once pleasurable, including sex

- Fatigue and decreased energy
- Difficulty concentrating, remembering details, and making decisions
- Insomnia, early-morning wakefulness, or excessive sleeping
- Overeating, or appetite loss[9]
- Thoughts of suicide, suicide attempts
- Aches or pains, headaches, cramps, or digestive problems that do not ease even with treatment.

Symptoms in older adults

Symptoms of depression may be different for older adults. Depression can make older adults confused or forgetful or cause them to stop seeing friends and doing things. It can be confused with problems like dementia.

Symptoms in children and teens

A child may be depressed if he or she:

- Is grumpy, sad, or bored most of the time.
- Does not take pleasure in things he or she used to enjoy.
- A child who is depressed may also:
- Lose or gain weight.
- Sleep too much or too little.
- Feel hopeless, worthless, or guilty.
- Have trouble concentrating, thinking, or making decisions.
- Think about death or suicide a lot.

TYPE OF DEPRESSION[10]

There are several different types of depression, and the diagnosis is mostly determined by the nature and intensity of the mental and physical symptoms, the duration of the symptoms, and the specific cause of the symptoms.

1. Major depression

Major depression disorder is one of many different types of depression. It is sometimes referred to as unipolar depression which basically means that the person who has it consistently feels down and depressed. This is of course converse to Bipolar depression which is when the person has mood swings going from a depressed mood to a hyper, energetic mood over time. Unipolar depression is commonly (about 75% of cases) non-familial, clearly associated with stressful life events, and accompanied by symptoms of anxiety and agitation; this type is sometimes termed reactive depression.[1]

2. **Chronic depression or dysthymia**

Chronic depression, or dysthymia, is characterized by a long-term (two years or more) depressed mood. There are also symptoms present that are associated with major depression but not enough for a diagnosis of major depression. Chronic depression is less severe than major depression and typically does not disable the person.

3. Manic depression

Manic Depression, also known as Bipolar Disorder, is a clinical depression. However, what makes this one different is that the person does not have long periods of sadness nearly every day for weeks at a time. Instead they have huge mood swings. Bipolar disorder is a complex genetic disorder. The mood swings associated with it can range from very mild to extreme and they can happen gradually or suddenly within a timeframe of minutes to hours. When mood swings happen frequently, the process is called rapid cycling. Mania is the defining feature of bipolar disorder. Mania is a distinct period of elevated or irritable mood, which can take the form of euphoria, and lasts for at least a week (less if hospitalization is required).[10]

4. Post partum depression

Postpartum depression is a complex mix of physical, emotional, and behavioural changes that happen in a woman after giving birth. Among men, in particular new fathers, the incidence of postpartum depression has been estimated to be between 1% and 25.5%.[11]According to the DSM IV, a manual used to diagnose mental disorders, PPD is a form of major depression that has its onset within four weeks after delivery. Postpartum depression is linked to chemical, social, and psychological changes associated with having a baby. The term describes a range of physical and emotional changes that many new mothers experience. This type of depression affects from 15% of new mothers. The symptoms can begin at any time within the first year after birth and usually include fatigue, loss of interest, feeling of worthlessness and excessive anxiety over their child's health.

5. Seasonal affective depression

Seasonal affective disorder(SAD), also known as winter depression, winter blues, summer depression, summer blues, or seasonal depression, was considered a mood disorder in which people who have normal mental health throughout most of the year experience depression during winter or summer.[12] In the Diagnostic and statistical manual of mental disorders DSM-IV and DSM-V, its status was changed. It is no longer classified as a unique mood disorder, but is a specifier for recurrent major depressive disorder with seasonal pattern that occurs at a specific time of the year and fully remits otherwise.[13]

6. Endogenous depression

Endogenous Depression is an atypical sub-class of the mood disorder and major depressive disorder (clinical depression). Endogenous depression includes patients with treatment-resistant, non-psychotic, major depressive disorder, characterized by abnormal behaviour of the endogenous opioid system but not the monoaminergic transmission.[14]

THEORY OF DEPRESSION

Monoamine theory

The main biochemical theory of depression is the *monoamine hypothesis*, proposed by Schildkraut in 1965, which states that depression is caused by a functional deficit of monoamine transmitters at certain sites in the brain, while mania results from a functional excess.[1] Another piece of evidence in support of the Monoamine Hypothesis is that levels of 5-HT, as measured by its metabolites, seem to be correlated with depression. For example, patients who have low levels of a 5-HT metabolite were found to be more likely to have committed suicide. The 'monoamine hypothesis' of depression, which posits that depression is caused by decreased monoamine function in the brain, originated from early clinical observations.[15,16] Two structurally unrelated compounds developed for non-psychiatric conditions, namely iproniazid and imipramine, had potent antidepressant effects in humans and were later shown to enhance central serotonin or noradrenaline transmission. Reserpine, an old antihypertensive agent that depletes mono amine stores, produced depressive symptoms in a subset of patients. Today's antidepressant agents offer a better therapeutic index and lower rates of side effects for most patients, but they are still designed to increase monoamine transmission acutely,[15] either by inhibiting neuronal reuptake (for example, selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine) or by inhibiting degradation (for example, mono amine oxidase inhibitors such as tranylcypromine). Although these mono amine-based agents are potent antidepressants[17] and alterations in central monoamine

function might contribute marginally to genetic vulnerability[18,19] the cause of depression is far from being a simple deficiency of central monoamines.

The pathophysiology of depression involves both external social stressors and internal genetic vulnerability. Among all biological theories postulated about MDD, an impairment of neuroplasticity and cellular resilience has been suggested.

Neuralplasticity

Neural plasticity may be defined as the ability of neurons and neural elements to adapt in response to intrinsic and extrinsic signals. It is also called brain plasticity, is the process in which brain's neural synapses and pathways are altered as an effect of environmental, behavioural and neural changes. As such, our ability to process and synthesize information, ultimately producing behaviour, is dependent upon this neural plasticity.[20] Dysregulation or disruption of neural plasticity is associated with neuropsychiatric and neurodegenerative disease. Dynamic processes such as adult neurogenesis, the development of dendritic spines, and synaptic adaptations are included under the umbrella of neural plasticity and are essential to normal functioning. Aberrant neural production, connectivity, or transmission is invariably present under disease states, such as Alzheimer's disease, schizophrenia, or depression.[21]Researchers have discovered that depression, chronic stress (which can worsen depression) and other mood disorders may cause decreases in neuroplasticity. In such cases, decreased plasticity results in a reduced number of synaptic connections. This, in turn, can lead to lower chances of cell survival as well as decreased efficiency of neural synapses. Conversely it's been found that antidepressant treatment creates the opposite effect - it increases neuroplasticity. It is now thought that acute increases in the amount of synaptic monoamines induced by antidepressants produce secondary neuro plastic changes that are on a longer time scale and involve transcriptional and translational changes that mediate molecular and cellular plasticity.[16,22]

Hippocampus relationship to depression[23]

The hippocampus should show a special relationship to depression. A number of different pieces of evidence link clinical depression to changes in the hippocampus.

Clinical evidence supports an important role for the hippocampus in depression.

- The brains of depressed patients have smaller hippocampi than the brains of control subjects.

- Patients with Cushing's Syndrome (elevated levels of adrenal hormones in plasma) have a high incidence of depression. Additionally, patients administered such hormones for other medical reasons frequently become depressed.

- Temporal lobe epilepsy, which involves massive cell loss in and around the hippocampus, is often accompanied by depression.

- Reduced hippocampal volume is most common finding in depressed subjects and longer duration of depressive episodes is known to be closely related to modifications in hippocampal volume.[24]

CAUSES OF DEPRESSION

There are a number of factors that may increase the chance of depression, including the following:

- **Abuse:** Past physical, sexual, or emotional abuse can cause depression later in life.

- **Certain medications:** For example, some drugs used to treat high blood pressure, such as beta-blockers or reserpine, can increase your risk of depression.

- **Conflict:** Depression may result from personal conflicts or disputes with family members or friends.

- **Death or a loss:** Sadness or grief from the death or loss of a loved one, though natural, can also increase the risk of depression.

- **Genetics:** A family history of depression may increase the risk. It's thought that depression is passed genetically from one generation to the next. Most of the published genetic association studies of mood disorders have focused on functional polymorphisms (DNA sequence variations that alter the expression and/or functioning of the gene product) in the loci encoding the serotonin transporter (SLC6A4), serotonin 2A receptor (5HTR2A), tyrosine hydroxylase (the limiting enzyme for dopamine synthesis), tryptophan hydroxylase 1 (serotonin synthesis), and catechol -o- methyltransferase (COMT) (dopamine catabolism).[25]

- **Other personal problems:** Problems such as social isolation due to other mental illnesses or being cast out of a family or social group can lead to depression.

- **Stress:** Stress is cited as the leading cause of depression by depressed patients.[25] Most researchers believe that for some people there is a direct relationship between a stressful event and the development of depression. Stress can be negative or positive. Examples of negative stress are loss of a loved one, loss of a job, loss of a relationship and divorce.

Examples of positive stress are planning for a wedding, preparing for a new job, and moving to a new city. Both negative and positive stress from environmental events can precede the development of depression.[26]

- **Serious illnesses:** Sometimes depression co-exists with a major illness or is a reaction to the illness.
- **Substance abuse:** Nearly 30% of people with substance abuse problems also have major or clinical depression.
- **Synthetic Chemicals:** Every day we take in synthetic chemicals from all over. From preservatives, additives and hormones that are found and added to so many of our foods, pesticides that are sprayed and air and water pollution as well. Synthetic chemicals and pollutants are now being more closely looked at as a link to depression and major depressive episodes.[27]
- **Noise Pollution:** Noise pollution has been linked to aggression, hypertension, increased stress levels, tinnitus, hearing loss and disruptions in sleep. Specifically, tinnitus is linked to severe depression, panic attacks and forgetfulness. A person with possible depressive tendencies will become even more susceptible to depression with continual, prolonged exposure to noise pollution.[28]
- **Natural and Catastrophic Disasters:** Natural and catastrophic disasters, such as hurricanes, earthquakes, or fires, and even manmade disasters such as bombings and war can push an already susceptible person into a severe major depression.[29]

Medical causes of depression include:

- Low thyroid function.
- Brain injuries and diseases (e.g. stroke, head injury, epilepsy, Parkinson's disease).
- Some forms of cancer.
- Infectious diseases.
- Blood vessel disease in the brain due to diabetes and/or hypertension.
- Some steroid and hormonal treatments.
- Chronic pain and Poor physical health due to smoking, obesity, lack of exercise.

DIAGNOSIS[10]

Because depression is common and often goes undiagnosed, some doctors and health care providers may ask questions about your mood and thoughts during routine medical visits. When doctors suspect someone has depression, they generally ask a number of questions and may do medical and psychological tests. These exams and tests generally include:

Physical exam: This may include measuring your height and weight; checking your vital signs, such as heart rate, blood pressure and temperature; listening to your heart and lungs; and examining your abdomen.

Laboratory tests: For example, your doctor may do a blood test called a complete blood count (CBC) or test your thyroid to make sure it's functioning properly.

Psychological evaluation: To check for signs of depression, doctor or mental health provider will talk with person about thoughts, feelings and behaviour patterns.

Diagnostic criteria for depression

To be diagnosed with major depression, the person must meet the symptom criteria spelled out in the Diagnostic and Statistical Manual of Mental Disorders (DSM). This manual is published by the American Psychiatric Association and is used by mental health providers to diagnose mental conditions and by insurance companies to reimburse for treatment.

TREATMENT

A large number of different treatments are available for depression and new treatments (particularly medications) regularly appear.

1.Antidepressants [1,4]: Antidepressant drugs fall into the following categories:

Selective serotonin reuptake inhibitors: Citalopram, Escitalopram, Paroxetine, Fluxotetine, Sertraline.

MAO Inhibitors: Selegiline, Isocarboxzaid, Phenelzine, Tranylcypromine

Tricyclic antidepressants: Amitriptyline, Amoxapine, Desipramine, Doxepin, Impiramine, Nortriptyline, Triimpiramine, Clomipramine.

Atypical antidepressants: Maprotiline, Trazodone, Nefazodone, Mirtazapine, Bupropion, Venlafaxine, Duloxetine, Desvenlafaxine.

2. **Psychotherapies:** There are a wide range of psychological treatments for depression. The main ones include:

- Cognitive behaviour therapy
- Interpersonal therapy

Cognitive behaviour therapy:

Cognitive behavioural therapy (CBT) is an effective treatment for depression. At the heart of CBT is an assumption that a person's mood is directly related to his or her patterns of thought. Negative, dysfunctional thinking affects a person's mood, sense of self, behaviour, and even physical state. The goal of cognitive behavioural therapy is to help a person learn to recognize negative patterns of thought, evaluate their validity, and replace them with healthier ways of thinking. Many CBT treatment programs for specific disorders have been evaluated for efficacy; the health-care trend of evidence-based treatment, where specific treatments for symptom-based diagnoses are recommended, has favoured CBT over other approaches such as psychodynamic treatments.[30]

- CBT is based on two specific tasks: Cognitive restructuring, in which the therapist and patient work together to change thinking patterns.
- Behavioural activation - in which patients learn to overcome obstacles to participating in enjoyable activities. CBT focuses on the immediate present: what and how a person thinks more than why a person thinks that way.
- CBT has six phases:

1. Assessment phase.
2. Reconceptualization.
3. Skills acquisition.
4. Skills consolidation and application training.
5. Maintenance phase.
6. Post-treatment assessment follow-up.

CBT has been applied in both clinical and non-clinical environments to treat disorders such as personality conditions and behavioural problems.

CBT is time limited. Typically, treatment with CBT lasts 14 to 16 weeks.

Interpersonal therapy (IPT)

IPT is based on the so-called common factors of psychotherapy: a treatment alliance in which the therapist empathically engages the patient, helps the patient to feel understood, arouses affect, presents a clear rationale and treatment ritual, and yields success experience. IPT makes a practical link between the patient's mood and disturbing life events that either trigger or follow from the onset of the mood disorder.[31]

3. Somatic treatment

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is a procedure used to treat severe depression. It may be used in people with symptoms such as delusions, hallucinations, or suicidal thoughts or when other treatments such as psychotherapy and antidepressant medicines have not worked. It is also used for other psychiatric and neurological conditions, such as schizophrenia and Parkinson's disease. ECT probably works by altering brain chemicals (similarly to medicines), including neurotransmitters like serotonin, natural pain relievers called endorphins, and catecholamines such as adrenaline. ECT treatments are usually done 2 to 3 times a week for 2 to 3 weeks. Maintenance treatments may be done one time each week, tapering down to one time each month.[32,33]

Vagus nerve stimulation

Vagus nerve stimulation (VNS) appears to be effective for treatment-resistant depression and may induce changes in brain metabolism weeks or even months before patients begin to feel better, new imaging research suggests. In 1997, the US FDA approved the use of VNS as an adjunctive therapy for partial onset epilepsy. In 2005, the FDA approved the use of VNS for treatment resistant depression. [34] Two methods are widely used for stimulation:

- **Direct vagus nerve stimulation:** This is currently the only widely used method of therapeutic VNS. It requires the surgical implantation of a stimulator device.
- **Transcutaneous vagus nerve stimulation (t-VNS):** This method allows for the stimulation of the vagus nerve without surgical procedure. Electrical impulses are targeted at the aurical (ear), at points where branches of the vagus nerve have cutaneous representation. One such t-VNS device is cerbomed's NEMOS.

4. Investigational treatment [35]: Following treatments are not approved by the FDA for treatment of depression in the United States.

- Repetitive transcranial magnetic stimulation (rTMS)

- Deep brain stimulation (DBS)
- Magnetic seizure therapy (MST)
- CRF1 receptor antagonists
- N-Methyl-D-aspartic acid receptor antagonists
- NK1 receptor antagonists
- Triple (5HT, NE, DA) reuptake inhibitors
- Melatonin receptor agonists

Alternative therapies for depression: There is no evidence that any alternative treatment or home remedy is effective in treating moderate to severe depression. However, some people with mild depression may find benefit from home remedies through increased relaxation. Relaxation can provide relief from depressive symptoms. It can also help cope with some of the causes of depression, such as grief, anxiety, changing roles, and even physical pain. If you have depression and are considering using an alternative form of therapy, it is important to seek the advice of the health care provider.

Examples of alternative therapies include: Acupuncture, Aromatherapy, Biofeedback, Chiropractic treatments, Guided imagery, Herbal remedies, Hypnosis, Massage therapy, Meditation, Relaxation, Yoga, etc.[36]

CONCLUSION

Depression is a serious health condition and it is the leading cause of death worldwide. It is mental disorder that affects the mind and can have noticeable affects on physical and social wellness. It may affect person of any age group at any stages of life. For the well being of the person determination of factors, triggers and treatment is essential as soon as possible. Good medical management of depression can be hard to find, and the empirically supported psychotherapies are still not widely practiced. As a consequence, many patients do not have access to adequate treatment. Despite the known effectiveness of treatment for depression, the majority of people in need do not receive it. The prevention of depression is an area that deserves attention.

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