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DEPRESSION: ETIOLOGY, PATHOPHYSIOLOGY, CLINICAL ASSESSMENT AND THERAPEUTIC APPROACHES IN VIEW OF RECENT STUDIES UPDATED REVIEW

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ABSTRACT

Depression is a common and disabling psychiatric disorder characterized by persistent low mood, loss of interest or pleasure, cognitive and emotional disturbances, and a range of somatic symptoms. Major depressive disorder (MDD) is a heterogeneous condition arising from complex interactions among genetic vulnerability, environmental stress, psychological factors, neurobiological abnormalities and social determinants. Contemporary research has moved beyond a simple monoamine-deficiency model toward an integrated understanding involving altered neural circuits, impaired neuroplasticity, hypothalamic-pituitary-adrenal-axis dysfunction, inflammation, immune signaling, metabolic abnormalities and the microbiota-gut-brain axis. Diagnosis remains primarily clinical, although standardized instruments such as the Patient Health Questionnaire-9 can support screening. Treatment includes pharmacotherapy, psychotherapy, exercise and other psychosocial interventions. Selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and other antidepressants remain important pharmacological options. Cognitive behavioral therapy is an established psychological intervention, while digital psychological interventions and exercise have increasing evidence. Treatment-resistant depression remains a major challenge and has stimulated development of rapid-acting and mechanistically novel interventions, particularly ketamine and esketamine, together with neuromodulation approaches. Emerging research is investigating neuroplasticity, inflammatory mechanisms, metabolic pathways and gut-brain interactions as potential therapeutic targets. An integrated, individualized and biopsychosocial approach is therefore central to contemporary depression research and management.

KEYWORDS: Depression, major depressive disorder, antidepressants, psychotherapy, neuroplasticity and inflammation, gut-brain axis treatment-resistant depression, ketamine, and esketamine.

1. INTRODUCTION

Depression is among the main causes of disability globally and it poses a serious health issue for the public at large. A major depressive episode includes symptoms lasting continuously for at least two weeks that affect mood, interest, pleasure, thinking, behavior and the body in combination of depressed mood and/or reduced interest or pleasure. Current reviews highlight that depression is very different and varied, there are differences among patients as to the nature of the disease, the body mechanisms, the course of illnesses and responses to treatments. In the past, depression was most commonly associated with the dysfunction of monoamine neurotransmitting mechanisms, especially serotonin, norepinephrine, and dopamine. While monoamine antidepressants are still effective, the latest research clearly shows that depression isn't merely a single neurotransmitter deficiency. Today, scientists are exploring neural circuits, neuroplasticity, stress response, inflammas, immune system, metabolism, and the gastrointestinal brain axis as the main factors. The main purpose of this review is to compile the latest knowledge about depression's characteristics, risk factors, mechanisms of illness, diagnostic techniques and treatment modalities. Novel ways of managing depression are also discussed.

2. EPIDEMIOLOGY AND DISEASE BURDEN

In most age groups and in different populations, depression can result in major effects. The occupational,

educational, interpersonal and social functioning areas may all be significantly affected by depression.

The prevalence of depression changes depending on which diagnostic criteria are used. Furthermore, changes in sampling method and questionnaire instrument used to identify patients with a depressed mood also affect prevalence estimates.

The review of Global Burden of Disease estimates emphasized that the method for diagnosing depression greatly affects the accuracy of prevalence numbers.

The heterogeneity of depression as a disease is an important aspect of its epidemiological study.

Variation in the severity of symptoms, age of onset, recurrence of episodes, comorbidities, and treatment response among patients may differ quite a bit. As a consequence, depression is better considered as a wide and varied syndrome and not as a single-biological disease disorder.

Physical illness can also bring about depression through a bidirectional relationship, in which depression not only makes a person more susceptible to physical illness but also causes a person to act in ways that will reduce their physical wellbeing through unhealthful lifestyle choices, neglecting treatment, etc.

3. ETIOLOGY AND RISK FACTORS

Depression is the result of interactions between a natural predisposition to the condition (i.e., having a biological vulnerability to a condition) and environmental exposures to a person's surroundings.

Major risk factors are

- Genetic Susceptibility
- Childhood Adversity
- Chronic Psychological Stress
- Social Isolation
- Trauma
- Chronic Medical Illness
- Sleep Disturbance
- Substance Use
- Hormonal and Endocrine Abnormalities
- Inflammatory Conditions
- Adverse Social and Socioeconomic Circumstances

There is really no single factor or cause that has been able to explain depression in more than the rarest cases.

3.1 GENETIC FACTORS

Genetic research has shown that for most major depression diseases, polygenetic factors are mainly responsible.

A paper review from 2021 put the proportion of the genes responsible for a given trait called heritability around approximately 30–50%. It was also mentioned in the paper that the effect of many gene variations on depression is minor or negligible rather, unlike a "gene for depression."

Some major discoveries in genome-wide association studies have led to identification of many loci at risk of developing an illness, but in reality it is still a very hard feat to change genetic information to a biological process (like what the gene controls is actually happening in the body). It also remains clear that the presence of genetic risk factors does not alone decide whether or not an individual will experience depression, which highlights once again that genetics alone do not play the primary role. That gene-environment depression model still exists.

4. PATHOPHYSIOLOGY OF DEPRESSION

Depression's pathophysiology is complex involving more than just psychological factors and has been referred to by some as a multi factorial illness.

Simplified integrated model

The interaction of the following elements leads to the development of the symptoms of the disorder:

1. The existence of genetic vulnerability
2. Environmental stress / adverse experiences

=HPA-axis dysregulation + inflammatory activation
=Neurotransmitter and glutamatergic abnormalities
=Impaired neuroplasticity and synaptic function
=Altered neural circuits
=Changes in mood, cognition, motivation and behavior
=Depressive symptoms

4.1 MONOAMINE NEUROTRANSMITTERS

In regard to regulating the emotional and cognitive functions of the body, monoamines such as serotonin, norepinephrine and dopamine are key players.

Historically considered a monoamine hypothesis of depression is that an imbalance caused the deficiency of these major neurotransmitters leads to a state of depression. However new studies suggest that the antidepressant effects work not at the level of monoamines or serotonin but at the level of plasticity and functional organization of the brain networks.

This also explains one limitation of the monoamine hypothesis, which, is that even if you can achieve higher neurotransmitter concentrations by some means (say, using drugs that increase the availability of certain neurotransmitters), this may not necessarily relieve the symptoms of depression and hence, cannot explain completely the biological and medical complexity of the disease state of depression.

4.2 NEUROPLASTICITY

Neuroplasticity is the ability of the nervous system to change structurally and functionally in accordance with lived experiences.

Research findings indicate that depression is related to

changes at synapses (between neurons) as well as in neurotrophic factor (e.g., BDNF) signaling. Many authors have emphasized how neuroplasticity is an important key to understanding both how disease is caused and how a treatment can be a medicine.

A great deal of investigation has focused on the role of brain-derived neurotrophic factor (BDNF) and the associated pathways.

The concept of neuroplasticity also offers a new way of looking at the different interventions which affect brain networks through similar or overlapping adaptations.

4.3 DYSFUNCTION OF HPA-AXIS

The hypothalamic-pituitary-adrenal (HPA) axis is our internal regulator for dealing with stressful situations.
A schematic view of its functioning is as follows.
Stress → Hypothalamus → Released CRH → Pituitary →Released ACTH → Adrenal cortex
→ Released cortisol

Repeated studies have found HPA-axis disturbance in some depressed patients as one possible cause. The presence of excess cortisol and altered feedback regulation has been connected with continued stress and depression. It remains, therefore, a possible biological factor that could be used to differentiate depressed individuals in a diagnostic framework.

On the other hand, HPA-axis dysfunctions are not equally prevalent among depressed individuals. The different ways they are expressed further illustrate the biological plurality of depression.

4.4 NEUROINFLAMMATION

Rises in evidence from many fronts have led to the realization that some sort of immune or inflammatory activity is probably also involved in depression. In a proportion of cases, blood inflammatory markers are higher and the effects of inflammatory agents (the 'signals') can be quite wide-ranged. These could involve: the brain chemistry of neurotransmitters, neuroendocrine functions and synaptic changes.

These may include ways of getting to neuroinflammation.

- Higher levels of pro-inflammatory cytokines (cell signaling molecules)
- Microglial (immune cells in the brain) activation is either too much or not enough
- Altering the ratio of tryptophan to kynurenine (two amino acids)
- Producing reactive oxygen species leading to damage (oxidative stress)
- Neurotransmitter metabolism is modified
- Neuroplasticity is affected
- Still, one ought not to look at neuroinflammation as a catch-all explanation for depression. Instead, the data are in favor of the idea of a subset of patients in which inflammatory pathways can account for depression.

5. GUT-BRAIN AXIS

The research into the microbiotas-gut-brain axis as a mechanism in depression has gained interest.
The Gut and Brain communicate with each other through.

- Neural pathways
- Vagus nerved signaling
- Endocrine pathways
- Immune pathways
- Microbial metabolites

We are finding out that psychological stresses not only result into physical alterations like a change in the composition of microbiome of the gut but also the intestinal function is affected by it and changes in microbiome may result into immune signaling or the metabolism of neurotransmitter or may even affect the activity of HPA-axis.

How does it work? Stress situation HPA-axis activation
Changes in microflora of the gut
Altered microbial metabolites / Intestinal permeability
Signaling through immune and inflammatory means
Dual pathway of signaling: vagal and neuroendocrine
Different functions of brain and depression symptoms.

The research so far seems hopeful, but microbioma-based treatment should be seen as a developing area and not as a substitute for the established depression treatment methods.

6. METABOLIC AND BIOMARKER RESEARCH

Metabolomic profiling has shown that the metabolites involved in neurotransmission, inflammation, signaling pathways inside the cell and metabolizing energy have been disturbed.

The compounds Kynurenine and acylcarnitine have come up for special study, but the current evidence is insufficient to make a diagnostic metabolomic biomarker a standard laboratory test for the identification or the selection of treatment.

Simultaneously, the genetic and inflammatory biomarkers are under study for predicting who are going to respond to which treatment. Nevertheless, depression is at present mostly considered as a disease that can be diagnosed based only on symptoms of the case history, rather than a laboratory-defined disease.

7. CLINICAL SIGNS

Some of the clinical features are.

Features of depressed emotions

- Depression all the time and sad feeling.
- Not finding pleasure in life or lack of interest in it.
- Cheerless view on future situations or life in general.
- Feelings of low self-worth and no value to society.

- Shame of past deeds leading to the feeling of excessive guilt,

Mental features

- Becoming a bit scatter-minded and being unable to concentrate.
- Indecision and hesitation.
- Constantly thinking oneself to be a failure or not capable of doing the work.
- The drive and desire to do what one used to like have been reduced.

Features of depressed physical functioning

- A state of fatigue or tiredness which does not disappear with rest.
- Sleep-related problems: either sleeping much more or not getting enough sleep at all.
- Changes in eating habits or weight loss or gain.
- In cases of psychomotor retardation or psychomotor agitation.
- Lack of energy and feeling of tiredness despite sleep and rest.

Symptoms of the highest danger

- The loss of one's normal functions of working and interacting with other people and even going outside or being in the society.
- Death wishes being the only thing to look for and to talk about.
- The idea and plan to commit suicide or the behavior that is associated with it.
  The number of symptoms, the kinds of symptoms, and symptoms being combined are significantly varying between persons.

8. ASSESSMENT AND DIAGNOSIS

It is still a fact that most diagnosis are based on the patient's history and the clinician's assessment of symptoms through interviews etc. that match the recognized diagnostic criteria.

The examination is usually based on:

- Elaboration of the medical condition of the patient Psycho-moral assessment as a test of consciousness or mind A check for signs and symptoms that help to differentiate depression from other disorders The length of time that the symptoms have been present as well as the degree of their severity are important aspects of assessment An assessment of functional disability such as being unable to take care of oneself, etc. Critical assessment for the presence of bipolar disorder or other mental illness Screening for drug, medicine, or other substance abuses. Finding out other medical issues that may have contributed to depression An appraisal of suicide risk is carried out where a clinical condition warrants it.

The PHQ-9

The PHQ-8 or PHQ-9 questionnaire is an extensively used depression symptom inventory and is also useful for screening. The largest meta-analysis which examined pooled data from individuals used PHQ-9 as one of the main measures with many different kinds of psychiatric diagnosis interviews as the others.

Questionnaires like such assist the process of diagnosis, but are a part of the diagnostic assessment which is comprehensive in nature.

9. MEDICINAL TREATMENTS

Drugs that treat depression are still one of the important parts of the therapy especially when depression is moderate to severe.

Broad categories of depression drugs

Drug Groups Example Drugs

A network-wide meta-analysis of major drug trials comparing different drugs and involving nearly 1.6 million people (21 antidepressant drug studies) concluded that when compared with placebo antidepressants were effective in acute adult MDD, but there were considerable differences in effectiveness and acceptability among individual drugs.

Previous reviews have confirmed that antidepressant-placebo differences are influenced by factors like study characteristics, patient characteristics and severity, besides others.

That’s why it is necessary to take all relevant factors like the patient's history of symptoms, risk of side effects, co-morbidities, history of drug response and patient preferences into consideration when choosing antidepressants.

10. PSYCHOTHERAPY

Psychologically oriented therapies play a fundamental role in the comprehensive treatment of depression.

Cognitive Behavioral Therapy

The basic mechanism of CBT is targeting the interrelation among three aspects: Thinking → feeling → acting.

In practice, the goal is to help the patient become aware of their distorted thinking and then change it by employing more suitable thinking and behaving.

According to a meta-analytical review, CBT is considered as an effective treatment for recurrent depression.

Psychologically-based interventions that could be used are.

- Behavioral activation
- Interpersonal
- Psychotherapy Problem-solvingtherapy
- Based psychotherapy
- Mindfulness

- supportive

Treatment options include drug, psychology or the two combined depending on the specific clinical presentation.

11. EXERCISE AND LIFESTYLE INTERVENTIONS

Exercise is among the non-drug treatments that have shown to help the persons suffering from depressions.
The paper included in the 2024 BMJ is essentially the biggest ever review of the role of exercise in the treatment of depression in a network meta-analysis framework.

Some of the mechanisms that explain why it is helpful are.

- Brain plasticity enhancement
- Enhancers of healthy sleep
- Better regulation of stress hormones
- Heart health promotion
- Sociability increase
- Positive effects on body inflammation and metabolism

Exercise, although an essential part of mental health improvement, should not be considered only as an alternative to drug treatment. It is rather meant to complement the latter when appropriate, and at the same time enhance the overall recovery.

12. DIGITAL INTERVENTIONS

Websites, mobile apps, and virtual reality-based interventions are among the many forms that digital mental health interventions can take.

- The ones offering
- You will find a wide
- range of
- Internet-based cognitive behavioral therapy
- Smartphone interventions
- Digital self-help
- Telepsychotherapy
- Guided
- Online
- Therapy
- Digital
- Exercise
- Interventions

The Bayesian network meta-analysis, conducted in 2023, involved a number of 72 randomized trials, with the sample of the participants of 13100. According to the results of this analysis, CBT and psychological interventions via digitized mode were highly recommended based on strong evidence.

The research on digital psychotherapies in humans that published a 2024 systematic review comprises 160 studies. The approximate number of people participating in such studies amounted to 70720, illustrating the growing support for the digital therapies.

Incorporating technology into mental healthcare can open the door to a lot of people who might not otherwise have access to the traditional therapies.

13. TREATMENT AND RESISTANT DEPRESSION

Treatment-resistant depression (TRD) continues to be a big obstacle in terms of patient management.

This has resulted in a major source of confusion since definitions of TRD can be quite varied, even within research communities. However, a general agreement of a regulatory framework has been an inadequate response to at lest two sufficient antidepressANTs.

There are a series of things clinicians should be aware of before making a decision of true treatment resistance.

- Proper Diagnosis
- Correct Antidepressant Dosage
- Sufficient Treatment Duration
- Adherence to Medication
- Medication Reactions
- Other Psychiatric Problems
- Chemical Substance Abuse
- Medical Illness
- Bipolar Psychiatric Disorder

It is very important to be able to identify which of the two: genuine biological resistance or simply inadequate treatment is the cause of treatment resistance, since the former may lead to totally different treatment strategies.

14. KETAMINE AND ESKETAMINE

Ketamine plus esketamine are a breakthrough in the treatment of depression as they primarily target the glutamatergic system whereas traditional antidepressants influence the monoamine system.

The action of ketamine involves inhibition of NMDA receptors and this can affect a range of neurochemical changes which will lead to a restoration of synaptic connectivity in the brain.

Clinical studies have confirmed a quick and strong effect against depression in cases where previous treatment attempts failed, but patient selection, the site for administration, observation period and safety over the long term are essential factors.

Another line of functional assessment is gaining momentum. A review in 2026 reported functional improvements with the use of intranasal esketamine for depression but further data are awaited that would show the same with ketamine, so the conclusion cannot yet be drawn with certainty.

15. NEUROMODULATION

The methods of Neuromodulation include.

- Electroconvulsive therapy (ECT)

- Repetitive Transcranial Magnetic Stimulation (rTMS)
- Theta-Burst Stimulation
- TranScranial-DirEcT-CurrEnt- (tDCS-)
- Vagus nerve stimulation is an option but very few people would be eligible

These methods have the purpose of modulating or influencing the activities of the abnormal neural circuits. As opposed to classical approaches that primarily operate through the changes in the neurotransmitter levels, these methods target the level of activity of the neural networks themselves.

A systematic literature review has found that there were several clinical trials that documented the emergence of structural or functional brain changes in patients as a result of therapy, nevertheless, the relationship between such changes in the brain and the relief of the symptoms still needs to be verified in studies.

16. NEW THERAPIES

Some of the latest research topics include.

- New drugs targeting neurotransmitter glutamate
- Ketamine and esketamine
- Psychiatry combined with psychedelic therapy
- Methods aimed to reduce inflammation
- Treatments intended to support neural plasticity
- Neuromodulation
- Digital therapeutic agents
- Interventions based on microbiome alterations
- Custom drug prescriptions
- Treatment strategies based on biomarkers

Lancet's overview of new and current treatments calls for the development of more effective, tolerable and fast acting therapies.

17. INTEGRATED MODEL OF DEPRESSION

Broad scientific support exists for a comprehensive picture where: Genetically based susceptibility.
Environmental pressure / trauma / social influence Rhythm of HPA axis disruption
Cascade of inflammatory and immune disorders Microbiome and gut alteration + metabolic shifts
Neurotransmitter imbalance and excessive glutamatergic activity Neuroplastic deficiency and changed synaptic function Abnormalities in neural networks
The triad of cognitive, emotional and behavioral changes Depression
This picture aligns better with what we know than just a one-way explanation for depressive disorders.

18. CHALLENGES IN DEPRESSION

Problems in the Study of Depression There are a lot of issues and there is an ongoing dialogue: Clinical differences, although they might carry the same label, different people exhibit a wide range of symptoms. Biological differences different biochemical processes may be central for different patients. Patients Treatment Variability patients vary greatly in the kind of treatment they respond to. A few useful biomarkers are scarce at present, there is no clinical practice of using a biomarker to replace clinicial assessment. Resistance to treatment the traditional form of treatment may not be enough for certain group of people. Relapse depression is often an intermittent illness that reoccur. Comorbidity depression is often seen together with various psychiatric and physical conditions. Limited provision of mental health care psychological and specialist treatments may not be available universally. Research methods diversity due to differences of diagnosing criteria, outcome instruments, and the study group of participants, it becomes difficult to make proper comparisons.

19. FUTURE PERSPECTIVES

The Vision of a Bright Future Depression studies will probably shift towards precision psychiatry wherein apart from considering the presenting symptoms, doctors will also be able to determine an effective regimen based on other factors like biology and behavior. Some possible upcoming trends include the following.

Antidepressant prescription based on a person's biomarkers Genes-related drug selection (Pharmacogenetics) Brain imaging as a tool for choosing treatments Classification by a person's immune response using a set of measurable traits of a disease (Inflammatory biomarkers) The application of gut microbiome to treat depression Medications which have fast effects (rapid-onset antidepressant)Treatment of the brain which adapts to the patient (personalized brain neurostimulation) Tracking of mental and physical health parameters in real time (Digital health monitoring)Use of machines which provide help to clinicians to assess patients quickly (AI-driven healthcare assistance) Medications & Psychological therapies put together.

There is, however, much of what have been proposed in terms of biological markers and newly- discovered treatments are still being trialed and need clinical studies which are extensive and scientifically rigorously designed to verify them.

CONCLUSION

Depression is a very complicated disorder with multiple causes, including genetics, environment, psychological, neurobiological, immune, metabolic, and sociological components. While the basic concept of depression as being a monoamine disorder is one way to interpret a couple of the treatments which are well established, it is not the whole story as far as depression is concerned. Recent findings are supporting the idea of a model of biological dysfunction that includes connectivity between different brain areas, inability to grow neurons properly (neuroplasticity impairment) and also the gut-brain-microbiota axis. Diagnosis is done mainly by doctors based on physical and emotional observations supported by standard questionnaires like PHQ-9. Treatments continue to be medication and talks with a

mental health professional. In addition, there are some well-founded suggestions that using the right kind of physical movement and computerized tools can benefit people. Those who cannot improve with existing medicines are referred to as treatment-resistant patients. The problem has encouraged the search for ketamine, esketamine and other forms of neuromodulation as alternatives. Research efforts in the future are recommended to be centered on identifying clinically significant subgroup populations and designing interventions that meet the needs of each individual, thereby ensuring that people not only get symptoms-free, but also lead a functional life and are kept safe from another episode.

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