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Review Article

Depression: A Widespread Mental Illness

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Abstract:

Depression is a widespread mental illness, mental health which affects million people globally with a significant prevalence in India. The condition's multifaceted nature and unpredictable course underscore the need for tailored interventions and support systems. Depression manifests in emotional and physical symptoms, including unhappiness, cognitive deficits, and suicidal tendencies. Its impact is significant, with 264 million sufferers globally. In India, 15% of adults require mental health intervention, with women at higher risk. Moreover, it is important to emphasize that, despite all these clinical manifestations, this review also highlights the severe negative effects of depression on various functions: both cognitive impairments and social isolation and the tendency to develop comorbid conditions, including anxiety and addiction, are assumed. Based on this background, evidence-based interventions including pharmacotherapy; psychotherapy and new modalities such as TMS and ketamine infusion are considered. Particular focus is paid to the new personalized medicine field that offers the possible treatment for every specific case.

Keywords: Depression, Mental Health, Globally, Health Intervention.

Introduction

Depression is defined as a mental illness with that affects the emotional and physical state of an individual. It is characterized by unhappiness, loss of appetite, agitation, fatigue, loss of interest in day today activities, cognitive deficits, and sense of worthlessness, sleep pattern changes, anxiety, restlessness and suicidal inclination.

Worldwide 264 million individuals suffer from depression [1]. The National Mental Health survey conducted in 2015-2016 delineated that one in 20 Indian suffers from depression and 15% Indian adults need intervention related to mental health [2].

The suicide cases reported in India by 2012 are 258,000 with most cases ranging from age group 15-49years [2]. Women have a 2 times higher prevalence for encountering depressive events when compared to men [3].

Depression develops gradually but in some cases it may be an abrupt event. Depression is an episodic and unpredictable illness. Therefore, the duration, number and pattern of depression are variable in the patients.

Diagnosis of Depression

There are two classification systems for the diagnosis of depression i.e. i) Diagnostic and Statistical Manual of Mental disorders (DSM) ii) International Classification of Diseases (ICD) [4]. Above mentioned systems is dependent on the presence of the key symptoms which are – depressed mood, anhedonia, feeling of worthlessness, suicide attempt, fatigue and sleep pattern changes (Figure 1). Both the classification systems are used for characterizing depression but DSM system is most preferred for the research purpose.

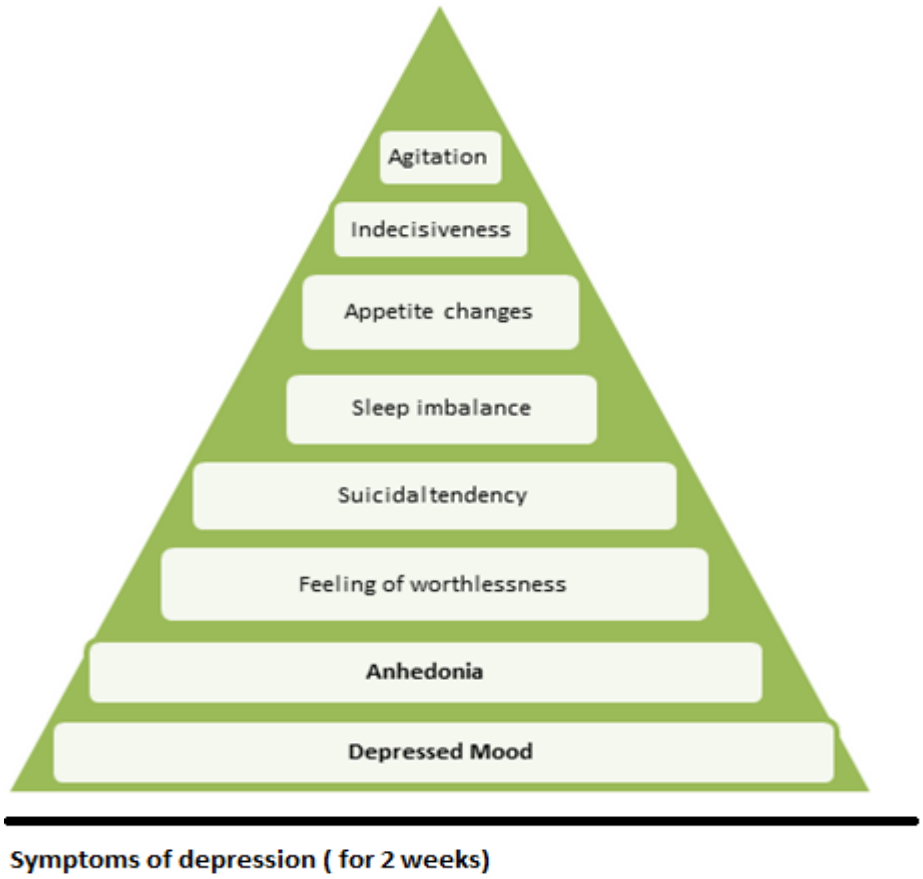

Figure 1: Key symptoms of depression as per DSM classification

Anhedonia and continuous depressed mood are fundamental symptoms. Symptoms must last for more than 2 weeks for an individual to be claimed as sufferer of depression

For an individual to be stated as depressed, it is important that individual possesses five or more symptoms as mentioned in DSM classification for more than 2 week span at regular basis. Presence of the depression symptoms mentioned by DSM in lower severity or lesser in number are known as sub threshold symptoms. They act as early predictor of severe depression syndrome.

Types of Depression

Depression affects the emotional and physical state of an individual. It can be classified into following subtypes:

1. Major Depressive disorder(MDD)
2. Persistent Depressive disorder(PDD)
3. Bipolar Disorder (BD)
4. Post-Partum disorder (PPD)
5. Premenstrual Dysphoric Disorder (PMDD)
6. Seasonal Affective Disorder (SAD)
7. Atypical Depression

1. Major Depressive Disorder: It is also known as clinical depression. It includes all the symptoms as mentioned in the Figure 1.

2. Persistent Depressive Disorder (PDD): Also known as dysthymia. It is a type of chronic depression where the symptoms resides for more than 2 years but the severity of depression is less than that in Major Depressive Disorder.

Patient with PDD experiences recurrent periods of depression with relief lasting for less than a month or two [5].

3. Bipolar Disorder (BD): It is mood disorder with severe mood swings known as mania. Depending on the severity, it can be hypo or hyper Bipolar disorder. Patients with bipolar disorder experiences severe depression [6]

4. Post-Partum disorder (PPD): Depression can occur during or after the pregnancy due to the hormonal changes that occur throughout the gestation period. Along with the other symptoms of depression, individual with PPD have trouble connecting with the newborn. They also have thoughts of harming themselves and the newborn.

5. Premenstrual Dysphoric Disorder (PMDD): Symptoms includes fatigue, anxiety, bloating, and craving for food. Symptoms related to mood swings are more prominent.

6. Seasonal Affective Disorder (SAD): It is also known as Major Depressive Disorder with seasonal

pattern. The episodes of depression occur with the onset of winter season which may be due to fluctuations in the circadian rhythm.

7. Atypical Depression: Its symptoms include hypersomnia, increased appetite, fatigue, feeling low over rejections.

The distinctive feature of patients with atypical depression is that emotional state of these patients gets better with positive events that happen whereas no such episodes occur with typical depression.

Pathology of Depression

Despite the advancement in the field of neurophysiology and neuropsychiatry, the pathophysiology of depression is still not known. Depression being a complex disease may account for this. For understanding the pathophysiology of depression, animal model-based studies have been done. But the data cannot be directly correlated for further clinical use [7]. This also explains less utility of antidepressants for some patients as antidepressants does not work for approximately 80% of the patients [8, 9].

For the better understanding of pathophysiology of the depression, interrogating the mechanism is very crucial. By far known mechanisms explaining the pathology of depression are-

A. Monoamine Hypothesis: Hypertensive patients on Reserpine treatment showed positive correlation between drug use and inclination towards depression. Such patients show decrease in amount of monoamines, suggesting the role of monoamine neurotransmitters in pathology of disease. Antidepressants like-monoamine oxidase inhibitors increased the activity of monoamine transmitters and subsided the depression in some patients [10]. This later concluded the fact that antidepressants work by modulating monoamine neurotransmitters. This model is unable to explain the inability of same antidepressants to work for some patients [11].

B. Dysregulation of hypothalamus- pituitary adrenal axis: A positive correlation between increased level of cortisol, corticotrophin releasing factor, unregulated glucocorticoid feedback mechanism and depression is observed [12-18]. HPA hyperactivity was also demonstrated by inability of depression patients to reduce cortisol levels when administered exogenously [19-21]. Antiglucocorticoids have proven useful against depression in animal and human studies [22].

C. Genetic: Genes involved in depression has been determined including apolipoprotein E (APOE), methylenetetrahydrofolate reductase (MTHFR), guanine nucleotide binding protein (GDN3) and serotonin transporter (SLC6A) [23, 24]. Genome-wide association (GWA) studies have also shown association of these genes with depression [25].

D. Environmental factors: studies have demonstrated that stressful life events like death of a family member, loss of job, sexual harassment, rape, child abuse, social isolation, make an individual more prone to depression. Encounter with any traumatic event in life may leads to depression [26].

E. Neurogenesis: The process of Generation of new neurons is known as neurogenesis. Neurogenesis is dependent on brain derived neurotrophic factor (BDNF) and this factor is found to be low in patients with depression. The levels of BDNF can be increased by use of antidepressants [27]. Therefore, increasing the level of BDNF can be useful way of treating depression.

F. Inflammation: Cytokine levels are known to affect the astrocytes and microglia via varied ways. This explains the higher propensity of individuals with autoimmune disease and individuals with high infection encounters towards depression [28]. This suggests the use of anti-inflammatory drugs for depression treatment

Antidepressants

Major antidepressants for the treatment of depression target the monoaminogenic transmission pathways. Some of the drugs are listed in table 1.

Table 1: List of available antidepressants showing the receptor targets of the antidepressants

Antidepressant	Target transporter			Target receptor (pre-synaptic)		Target receptor (post- synaptic)			
	5HT	NA	DA	5HT	alpha2	5-HT	alpha1 alpha2	H1	M1
Agomelatine		+				+			
Amitriptyline	+	+					+	+	+
Clomipramine	+	+							+
Doxepin						+	+	+	+
Fluoxetine	+	+							
Milnacipran	+								

Trazodone	+	+				+	+	+	
Venlafaxine	+								
Vilazodone	+			+	+	+			
Vortioxetine	+			+	+	+			

5HT=serotonin, NA – noradrenalin, DA-dopamine

New Therapeutic Targets for Depression

New therapeutic target for depression is Galanin, a neuropeptide molecule that is found endogenously in the brain. Carmello Millon et al have shown that the 1-15 mer peptide sequence at the N- terminal of the Galanin can induce depression in rat model. This small fragment of Galanin can be used as analogous target for developing drugs against depression [33]. A study has shown that gut microbiota plays an important role in depression. The gut microbiota of the healthy individuals differs from the individual suffering from depression. Therefore, understanding the gut microbiota of an individual and improving the gut microbiota with probiotics can improve the depression.

Animal Models for Screening Drugs for Depression

Animal models for depression can be used for screening of antidepressants, for finding the mechanism of action of antidepressants and for studying the neurobiology behind the disease.

- Reserpine induced system: Reserpine is derived from Rouwolfia and is known to decrease the monoamine levels which are reported in patients suffering from depression. So, reserpine-based mice model can be used for screening for antidepressants and for finding the biology behind it [29].
- Olfactory bulbectomy: In this method, rats are bulbectomized and parameters like activity of the brain in different regions and corticosteroid levels in the blood plasma are analysed after drug treatment [30].
- Apomorphine based model: Apomorphine acts as dopamine agonist and play role in inducing depression. Therefore, apomorphine induced mice model can be used for drug screening for depression [31].
- Isolation induced hyperactivity in mice: In this model mice are kept in isolation for 15 days. Drugs are tested by measuring the locomotor activity of the mice after administration of the drug in comparison with control mice [32].

Drug Delivery System for Depression

Oral drug delivery system has been used for the administration of the drugs for depression. But these drugs delivery system has side effects and does not sustain for longer duration. Passive diffusion based drug delivery system are efficient for transdermal antidepressant delivery [34]. Depot based drug delivery system has an advantage of controlled release of drug hence more sustainable release of drugs. Lactide/glycolide polymers are commonly used biodegradable polymers for the drug delivery of antidepressants. These polymers are metabolized and removed from the body continuously [35].

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