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Role of Biomarkers in the Evaluation of Pharmacotherapy and Complementary and Alternative Medicine in Patients with Major Depressive Disorders

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ABSTRACT

Background information: Major depressive disorders (MDD) are characterized by mood, cognitive, and even psychotic features that cause substantial impairment in quality of life. In 2015, 216 million people were affected by MDD worldwide. According to the World Health Organization, MDD will be the leading cause of global disability by the year 2030. Depressive patients have higher health care utilization, impairment in psychosocial functioning and are at greater risk for suicide. In MDD, neurohistological changes are seen in the hippocampus and other areas of brain. The resultant neuroplasticity is reversed by antidepressant drugs as evidenced by analysis of biomarkers in various body fluids. However, these drugs do not produce complete remission. This review is aimed at understanding the pathogenesis of MDD and the role of complementary alternative therapy in addition to pharmacotherapy especially in MDD.

Discussion: Articles were collected using various search engines like Pubmed, Google scholar, Cochrane library etc. for the last 20 years. Neuroplasticity is the ability to exhibit structural and functional changes in the brain resulting in synaptic strengthening, dendritic growth and new synapse formation in the hippocampus and the prefrontal cortex. These are mediated by brain-derived neurotrophic factor (BDNF). There have been vast developments in handling depression patients, from identifying the exact cause for depression and suggesting the most appropriate pharmacotherapy. Biomarkers are essential in advancing this strategy and have the potential to aid diagnosis, prognosis and predict response to different therapeutic strategies. Complementary therapies in the form yoga, exercise etc. have been tried but not much research has been done in these areas.

Conclusion: The diagnosis of MDD relies on the subjective clinical judgment with potential variability. Biomarker panels specific to subtypes if developed will assist in diagnosis, progrnosis and treatment of depression. This can enhance utility of alternative therapies in MDD.

Keywords: Major depressive disorders, Neuroplasticity, Treatment-resistant depression, Complementary and alternative medicine, Gut microbiota, Biomarkers in depression, Exercise in depression, Yoga and meditation in depression

Abbreviations

MDD: Major Depressive Disorder; WHO: The World Health Organization; TRD: Treatment-Resistant Depression, BDNF: Brain-Derived Neurotrophic Factor; WMH: World Mental Health; AOO: Age Of Onset; DSM: Diagnostic and Statistical Manual of Mental Disorders; ECT: Electro Convulsive Therapy; CSF: Cerebrospinal Fluid; HPA axis: Hypothalamo-Pituitary-Adrenal axis; LCSPT circuit: Limbic-Cortisol-Striatal-Pallidal-Thalamic circuit; ACC: Anterior Cingular Circuit; PET: Positron Emission Tomography; SPECT: Single-Photon Emission Computed Tomography ; MRI: Magnetic Resonance Imaging; fMRI: Functional MRI; sMRI: Structural MRI; EEG: Electroencephalogram; 5HTT: 5-hydroxy tryptamine transporter; 5HT2: 5-hydroxy tryptamine receptor 2 subfamily; MAOA: Monoamine Oxidase A; ACTH: Adrenocortic Trophic Hormone; CRH:Corticotrophin Releasing Hormone; GR: Glucocorticoid Receptor; IL-1: Interleukin-1, sICAM: Soluble Intercellular Ahesion Molecule; CRP: C-Reactive Protein; COX2: cyclooxygenase2; IFNγ: Interferon gamma; TNFα: Tumor Necrosis Factor alpha; MDA: Malondialdehyde; SOD:Superoxide dismutase; MPO: Myeloperoxidase; PLA2G2A: Phospholipase A2 Group IIA ; 8OHdG: 8 hydroxy deoxy guanidine, iNOX: inducibe nitric oxide synthase; SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin and Norepinephrine Reuptake Inhibitor; DALYS: Disability adjusted for life years; GSH: Glutathione; NGF:Nerve Growth Factor; NT: Neurotrophin; Trk: Tropomyosin receptor kinase; DNA: Deoxy ribonucleic acid; IGF-1: Insulin-like Growth Factor-1; VEGF: Vascular Endothelial Growth Factor; VGF: Neurotrophin-inducible gene(non-acronymic); FGF:Fibroblast Growth Factor; serotonin transporter-linked promoter region; SLC6A4: DNA methylation of the serotonin transporter gene; NR3C1: Nuclear Receptor subfamily 3 group C member1; α1AT: Alpha 1 antitrypsin; HTR2A: The serotonin 2A receptor; TPH: Tryptophan Hydroxylase; COMT: Catechol-O-Methyl Transferase; TL: Telomere; TEL: Telomerase; miR: microRNA; FKB5: FK506 binding protein 5; NMDA: N-Methyl D-Aspartate; CAM: Complementary and Alternative Medicine; FDA: Food and Drug Administration; TMS: Transcranial Magnetic Stimulation; CDT: Comprehensive Decongestive Therapy; rTMS: Repetitive TMS; VNS: Vagus Nerve Stimulation; tDCS: transcranial Direct Current Stimulation; PUFA: Polyunsaturated fatty acid; SCFA:Short-chain fatty acids; SIBO: Small Intestinal Bacterial Overgrowth; APA: American Psychiatric Association; GHSR1: Ghrelin Receptor1; GWAS: Genome-Wide association Study; NGS:Next Generation Sequencing

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INTRODUCTION

Epidemiology

MDD was ranked fourth as a disease measured in disability adjusted for life years (DALYS) in 1990. Various search engines like Pubmed, Ovid, Google Scholar, Scopus, Web of Science, Science Direct, Cochrane Library etc. were used for looking for articles in the last 20 years. The World Mental Health (WMH) Survey found that on an average 1 in 20 people are reported to have an episode of depression in a year. Parallely, antidepressant use has also increased from 7.7% during 1999-2002 to 12.7% during 2011-2014. It has been estimated that the global prevalence of depression is 21.7% for females and 12.7% for males [1]. The World Health Organization (WHO) data (2014) has suggested MDD as the leading cause of global disease burden with global prevalence ranging from 3% - 17%, increasing to 9.3% - 23% in cases of depression with comorbid conditions [2]. In adolescents, prevalence is reported to be between 2.8% and 5.6% with females being more affected than males. In the geriatric population 12.3% individuals are affected by depression which can increase upto 37.9% in urban population [3]. In the United States 5%-9% of women and 2%-3% of men suffer from depression at any time. A Norwegian study showed that 24% of women suffer MDD and 13.3% from dysthymia; while 10% of men suffer from MDD and 6% from dysthymia [1]. As per WMH surveys in high-income countries, the age of onset (AOO) is 22.7years in the United States and 24.2years in New Zealand, whereas it is 30 years and 30.1 years in Spain and Japan respectively. The AOO is in low- to middle-income countries are, 22.3 years and 27.8 years in South Africa and Ukraine respectively whereas it is 31.9 years in Pondicherry, India. This infers that people in high-income countries would experience more stress than those in low- to middle-income countries. Thus, depression was considered to be an illness of affluence [4]. Depression is common in military personnel [5].

Clinical Presentation of MDD

On May 18, 2013, the American Psychiatric Association (APA), drafted Diagnostic and Statistical Manual of Mental Disorders (DSM-5) for classification and diagnosis of mental disorders. As per DSM-5 criteria, depression is characterized by significant impairment in everyday functioning (social, work, or other important areas of functioning), significant weight loss or gain, sleep disturbances, fatigue, loss of energy, feelings of worthlessness or excessive guilt, diminished ability to think or concentrate, and recurrent thoughts of death. All these symptoms must be present for atleast 2 weeks [6]. Clinically, diagnosis of MDD is subjective, based on patient interviews as well as supplemental information provided by family and friends [7]. Major depressive disorders may have depression alone or depression may be associated with anxiety [8]. With regard to personality, individuals with higher scores on the hardiness, correlates with lower scores on the depression scale suggesting that the person's ability to manage and respond to stressful life events with coping strategies that turn potentially unfortunate circumstances into learning opportunities [9]. Risk factors of major depression in late life include medical illnesses, such as cancer, heart diseases, infectious diseases or hip fractures which induce the feeling of advancing aging and a sense of mortality in the depressed patient [2]. Depression can be familial, while in most of the individuals it could be caused by environmental factors like stresses at home, work, or school or inablility to develop coping skills [1,10]. Presence of comorbid conditions could slow the recovery and increase the likelihood of its recurrence and chronicity of the disorder with frequent hospitalizations [11].

Structural and functional changes in the brain of MDD patients

In normally functioning brain the functional capacity of a neuron depends on its synaptic networks and connectivity. When dendrites and synapses are lost, this connectivity decreases with decreased neurogenesis subjecting to apoptosis. The hippocampus has projections to the dorsolateral prefrontal cortex, the ventral tegmental area and the hypothalamus. These areas are involved in learning, memory, coping behaviour, attention and concentration. Mesolimbic circuitry regulates the response to novelty and the experience of reward manifested as anhedonia. It also regulates higher mental functions such as motivation and judgment. On the contrary, histological changes in the amygdala include increased dendritic arborisation and increased synaptogenesis; with resultant increase in amygdalar volume and function. The amygdala is involved in social and emotional learning which manifest as anxiety and fear. Stress induced changes in the hippocampus gradually reverse with treatment, whereas stress-induced changes in the amygdala remain for weeks or longer. Thus, the depressed human overreacts to stress in a trait-dependent way. The physical and sexual abuse experienced by children manifest as depression in adult life [12]. Thus, depression could be a sum total of disturbances in the functioning of multiple parts of the brain [13, 14].

When individuals, who are vulnerable to depression, are exposed to stress, neurochemical, neuroendocrine, neurophysiological and neurohistological changes occur in the brain and these considered being the biological mediators of depression [8]. The neurohistological changes are the most important, since the cognitive, affective and behavioral impairments in depression could result from the neurohistological changes. Stress impairs neuroplasticity in certain parts of the brain and induces neuroplasticity in other parts of the brain. Antidepressant drugs reverse the neurohistological effects. Mild stress which is encountered in daily life is usually associated with successful adaptation to the environment as shown by the favorable neuroplasticity changes in the brain. During mild stress, cortisol acts at physiological level to stimulate hippocampal neurons, thus facilitating learning and memory. But at pathological levels as encountered in moderate or severe stress, cortisol overstimulates the hippocampal neurons and causes dendritic atrophy and loss of synapses resulting in neuronal apoptosis. The glucocorticoid receptor antagonist, mifepristone may decrease the cognitive impairments in MDD. Neurohistological changes in the hippocampus and prefrontal cortex can be seen as a reduction in hippocampal volume in the animal models; also seen in postmortem samples or MRI studies. The antidepressant-induced neurohistological effects are responsible for the initiation of clinical recovery. However, antidepressant drugs do not reverse the changes observed in the amygdala. The vulnerability to stress remains, thus requiring maintenance antidepressant therapy. Electroconvulsive therapy (ECT) can induce neuroplasticity in the brain [14]. All individuals have innate neuroplastic capability; hence some depressed individuals learn adaptive behaviours to recover from depression and antidepressant drugs may not be necessary. Children have an intrinsically plastic brain and may not need antidepressants. Different antidepressant drugs have different effects on the pathways that mediate the neuroplasticity response [14]. It is undisputed that suicidal behaviour is high in depressed adolescents before treatment and with each depressive episode there is an additional 10% risk of the disease becoming chronic [15]. The clinical heterogeneity observed in MDD makes it difficult to select the best treatment approach for an individual [16]. Antidepressants often take weeks to bring desired effect. Also, there are high rates of relapse and treatment resistance. Identification of biomarkers that could predict individual response is highly valued in clinical practice [9]. Many antidepressants are associated with cardiometabolic risk factors such as insulin resistance, obesity, and dyslipidemia [17]. 60% of patients with MDD experience some degree of non-responsiveness to these treatments. Therefore, identifying novel treatment approaches are of key importance [18].

Diagnostic modalities in Major Depressive Disorders

Various modalities are used to find the etiology and hence the treatment of MDD; they are postmortem brain research, measurements of biomarkers in body fluids, research in animal models, neuroimaging studies and genetic research.

Postmortem studies

Post-mortem studies of the brain have scientific merit, but the progressive character of many neuropsychiatric diseases and the fact that many patients have been treated with drugs for a substantial part of their lives limit the value of many postmortem data. In addition, it is difficult because of the inactivation of enzymes and immediate massive release of neurotransmitters after death [19].

Brain imaging studies

In MDD, structural and functional alterations are found in the amygdala, hippocampus, prefrontal cortex, ventromedial striatum, pallidum and thalamic nuclei forming the limbic–cortical–striatal–pallidal–thalamic (LCSPT) circuit involved in regulating emotional behavior. Areas involved in regulating emotional behavior are the cortical-limbic and ventral-dorsal circuits. Biochemical and biological targets in the brain are directly assessed by imaging techniques such as Positron Emission Tomography (PET), Single-Photon Emission Computed Tomography (SPECT) and Magnetic Resonance Imaging (MRI). These techniques are expensive, not well automated, time-consuming and only available in larger medical centers, limiting the potential use of these techniques in daily practice. Functional MRI (fMRI) can assess affective and cognitive processing; while structural MRI (sMRI) has demonstrated volume reductions in the grey matter of the involved brain regions in MDD patients [19]. Structural alterations correlated with changes in cerebral blood flow and metabolism in anterior cingulate cortex (ACC), amygdala and the ventral striatum. Negative emotions correlate with increased activation of the amygdala, para-hippocampal areas, dorsal anterior cingulate cortex and the left striatum and a decreased activation of the dorsolateral prefrontal cortex. In contrast, positive emotions correlated with an increased activity in the orbital frontal are cortex. Functional imaging may also indicate specific subtypes of depression [20]. Depression affects the structural brain as shown by alterations in electroencephalogram (EEG) findings. EEG measures different wavelengths directly that mirrors different brain activities. There are consistent changes in the EEG alpha and theta frequency ranges which change treatment outcomes. Another study has shown that in depression there are decreased delta power values and increased beta activity in frontal brain [21]. Advantages are non-invasive and are already used on a daily basis in clinical settings. Interestingly the effects of the BDNF val66met polymorphism, which is associated with the risk of developing depression, have low α wave activity [19].

Biomarkers have opened up various avenues in major depressive disorders

Subsequent to the publication of DSM 5, concerns were raised regarding validity of objective diagnostic modalities to assess

MDD and its specific correlation of the phenotypic presentation to the underlying mechanism [22]. MDD is a very heterogeneous disorder and also is the result of several biological mechanisms that influence each other in complex ways. Therefore, the use of a combination of several biomarkers reflecting changes in different biological mechanisms may be promising. There is no consensus on which biomarkers are sensitive and specific enough to be used in a clinical setting [21, 22]. Determination of the biomarkers, such as hormones, proteins and neurotransmitters in blood, urine or CSF is relatively cheap, non-invasive and widely available. But analysis of biomarkers remains as an indirect approach to extract information of brain. As the brain is protected by blood brain barrier, it selectively transports substances across its membrane and thus the correlation between central and peripheral concentration is questionable [20, 23].

Biomarkers of psychiatry disorders can be classified as diagnostic and treatment biomarkers. Based on the behaviour with disease process they can also be categorized into three groups as trait, state, and endophenotype markers. Trait biomarkers are persistent, irrespective of the onset-, during-, and after remission- of the disorder. Trait biomarkers decide which individuals are at risk for the disorder. State biomarkers are transient; present at the onset- and during-the disorder, but normalized with remission. Endophenotypic biomarkers are a subgroup of trait biomarkers, based on the association between genes and specific depressive phenotypes; they are persistent, and found to be higher in family members than in the normal population [3, 24, 25].

Various hypotheses have emerged regarding the etiology of MDD; all of them in general describe the dysfunction of many biological processes. Thus, multiple interacting biological systems are involved in the pathophysiology of MDD, with specific processes being more prominent in their respective subtypes. A biomarker representing the individual hypothesis may give a clarity in the presentation of different subtypes and their response to treatment [20, 26- 28]. Biomarkers could complement clinical assessment by analyzing the levels of biomarkers that occur ahead of changes in clinical symptoms, thus allowing to initiate therapy quickly [29, 30].

- **Monoamine hypothesis:** There is decreased level of monoamines (serotonin, norepinephrine and dopamine) in body fluids and postmortem brain tissue. Altered functions of 5-HTT and 5-HT2 receptor are found in the brain and platelets [20].
- **Stress hypothesis**: Deregulation of the hypothalamo-pituitary-adrenal (HPA) axis, is frequently implicated in the etiology of MDD. Due to impaired feedback patients have elevated levels of cortisol, ACTH and CRH in extracellular fluid and postmortem brain tissue. This is prominent in patients with melancholic features [3, 20] Normalization of dexamethasone (Dex)/CRH test was also used an objective measurement of clinical improvement [7].
- **Immune-inflammation hypothesis:** MDD is associated with increased levels of proinflammatory cytokines, such as IL-1, IL-6, TNF-α and IFN-γ and decreased levels of anti-inflammatory cytokines, such as IL-4 and IL-10 and activation of immune cells. Proinflammatory cytokines induce behavioral changes and chronicity of depression [20]. Patients with melancholic features had increased serum IL-1β, IL-1β/IL-10 ratio and neopterin [17, 22]. IL-6 and sICAM are associated with sleep disturbances; elevated IL-6 level is found in atypical depression. Increased CRP is found in patients with comorbid diabetes mellitus, predits response to Infliximab in treatment-resistant depression (TRD) and discriminates the differential treatment response to escitalopram versus nortriptyline. TNF-α and IL-1β are markers of treatment response and SSRIs reduce IL-6 levels. IL-8, TNF-α, CRP and IL-6 have trait characteristics [21, 31].
- Oxidative stress hypothesis: Low neuromembrane cholesterol content leads to failure of presynaptic serotonin reuptake manifested as increased violence and suicidal death [7]. Inflammation predisposes to oxidative stress with increased levels of COX-2, MDA, SOD, MPO, phospholipase A2 (PLA2G2A), 8-OHdG, F2-isoprostanes and iNOS [3]. Increased oxidative activity is reversed by SSRIs. Decreased GSH is found to correlate with severity of anhedonia and melancholic features in depressed patients [22].
- **Neurogenesis & neuroplasticity hypothesis:** Decreased hippocampal neurogenesis and levels of neurotrophic factors are causally related to MDD. BDNF is a neurotrophic factor that induces proliferation, survival and differentiation of existing neurons and the formation of new synapses. Antidepressant drugs increase neurogenesis, synaptogenesis and neurotrophic factors [20]. Neurotrophins [nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin (NT)-3, -4, and -5] interact with the tropomyosin receptor kinase (Trk) family of receptors and mediate neurogenesis and neural plasticity in both peripheral- and central nervous systems [17]. BDNF has the potential in evaluating therapy effects involving learning, memory, and executive functions. BDNF DNA methylation patterns have also been associated with depression severity, and the presence of suicidal ideation. BDNF has the potential to be a trait and state-like marker [22]. IGF-I is involved in neuroplasticity [17]. VEGF acts as a mediator of antidepressant effects. Studies have reported deregulated expression of several FGF transcripts in the dorsolateral prefrontal cortex, ACC and hippocampus, which was attenuated by SSRIs. VGF acts as a mediator of the effects of antidepressants. Its expression is induced by BDNF [3].

- **Deregulated metabolic products:** The proteins-histidine triad nucleotide-binding protein 1 (HINT1), glial fibrillary acidic protein, dihydropyrimidinase-related protein 2, ubiquinone cytochrome c reductase core protein 1, carbonic anhydrase 1 and fructose biphosphate aldolase C regulate axonal guidance, neuronal growth cone collapse, cell migration as well as energy metabolism; by altering cytoskeletal architecture and mitochondrial energy metabolism [7]. Metabolic markers like phenylalanine, tryptophan, purine, tocopherol and dihydroxyphenylacetic acid are helpful in assessing response to antidepressants. To distinguish MDD from early life stress (ELS), alanine, glycine, galactose, linoleic acid and cholesterol are analyzed. Malonate, formate, N-methyl nicotinamide, m-hydroxy phenylacetate, and alanine, found in urine of MDD patients [7, 12].

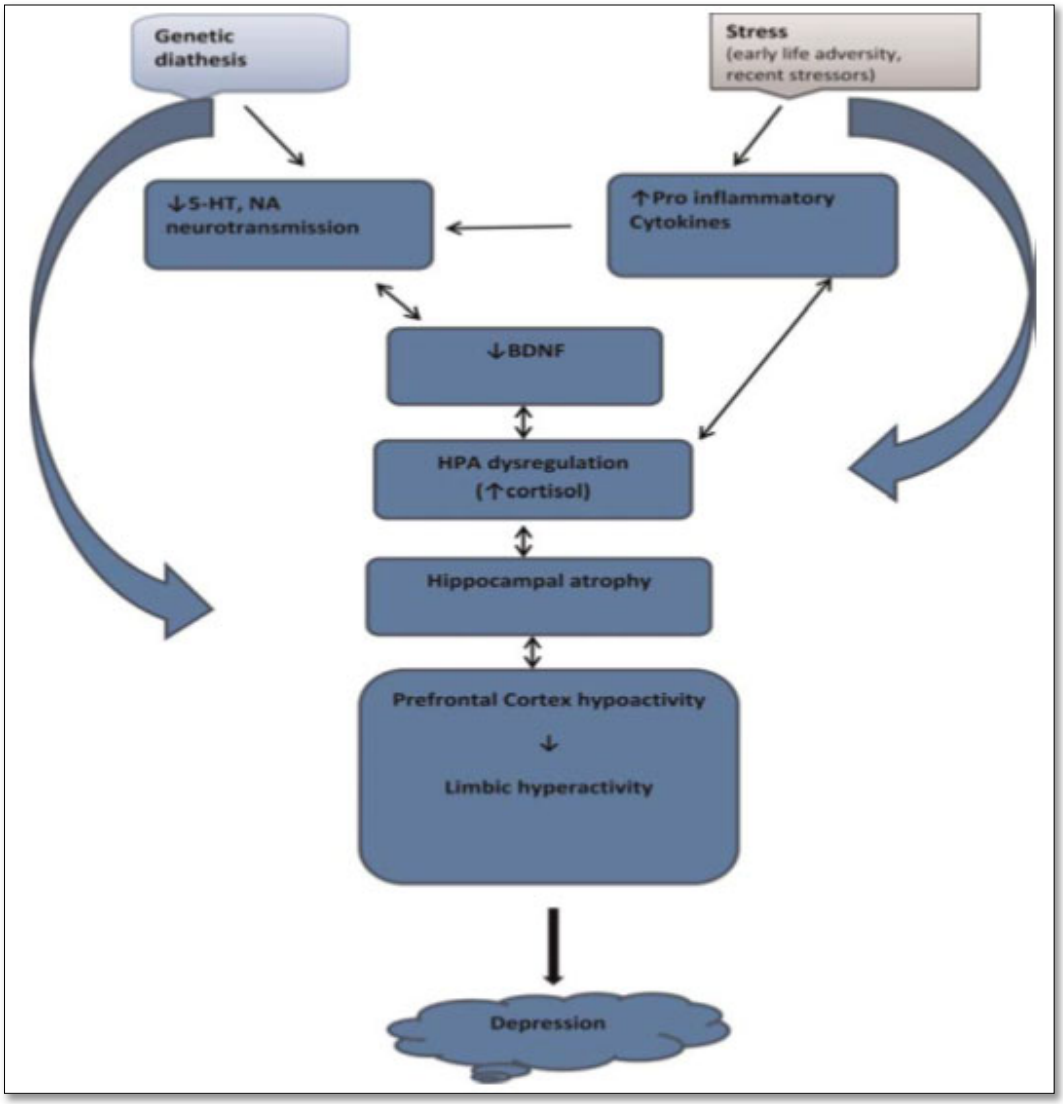

Figure 1. Schematic representation of the neurobiological mechanism involved in depressive disorder [8].

Genetic and epigenetic hypotheses

Genetic polymorphisms could possibly identify persons at risk for depression or predict response to antidepressant therapies. Novel techniques such as GWAS and NGS allow for the simultaneous identification of multiple single nucleotide polymorphisms (SNPs). The SNPs were related to the major hypotheses of MDD etiology: *SLC6A2* to monoamine hypothesis, *C5orf20* to the neurogenesis/neuroplasticity hypothesis, *TNF* to the neuro-inflammation hypothesis and *NPY* to both the monoamine and the stress hypotheses [20]. Several candidate genes involving DNA methylation, SLC6A4, BDNF, and NR3C1 have been studied [21]. 5-HTTLPR influences serotonin reuptake and

the serotonin receptor 2A (HTR2A) gene is downregulated by selective serotonin reuptake inhibitors (SSRIs). In humans, two distinct Tryptophan hydroxylase (TPH) genes, TPH1 and TPH2 have been studied. TPH1 A/A and A/C variants were associated with a poorer response to fluvoxamine, citalopram and paroxetine treatment in males. No study has shown the association of MDD with TPH2 SNPs. Long MAO-A alleles were associated with slower and less efficient overall response to mirtazapine in MDD females. COMT gene SNPs, Val/Val and Val/Met genotypes were associated with treatment response to mirtazapine, but not paroxetine. Met/Met genotype was associated with no remission of citalopram, but not fluvoxamine or paroxetine. The Met/Met variant of the COMT gene was the best genetic predictor of treatment outcome [7]. MicroRNAs like miR-132, miR-26b and miR-182 regulate expression of BDNF and thus prevent depression [3]. Patients with MDD had more mitochondrial DNA and there was a correlation between the amount of mtDNA and previous stress exposure [3]. Cortisol reduces the transcription of the telomerase (TEL) catalytic component as evidenced by reduced TEL activity in the hippocampus of animal models. During oxidative stress there was increased expression of FKBP5 which inhibits translocation of the GR to the nucleus and activation of GR is upstream of the production and release of CRF. Increased expression of FKBP5 would lead to a reduction in CRF in the hippocampus that could render it more susceptible to the effects of stress and consequently affect Telomere length (TL) [3].

In 2013, nine biomarker profile was accepted for the diagnosis of MDD; they are inflammatory and oxidative indices (α1AT, apo CIII, MPO, sTNFα Rtype II); the HPA axis (EGF, cortisol); neurogenesis (BDNF); and metabolism (prolactin, resistin). They were used for an objective diagnosis of MDD with a sensitivity of 91.7% and specificity of 81.3% [7, 21, 22].

Treatment of MDD: The present scenario

Diagnosis of MDD is made according to the subjective identification of symptom clusters. But this could not characterize the heterogeneity, which results in a considerable error rate [11]. Depressed individuals incur twice the medical expenses from consultations and antidepressant drugs. Approximately 30% of patients do not respond to typical antidepressants [1]. Three quarters of the patients experience more than one episode of depression and the risk of recurrence is higher if the first episode occurs at a younger age along with a family history of depression. Also the risk of recurrence increases further with each new episode. Thus maintenance treatment for several months during remission is essential after an acute episode of depression to prevent relapse. Unfortunately, many patients do not achieve full remission for various reasons like poor compliance, premature ending of treatment, the use of inadequate treatment etc.; all these factors predispose to the chronicity of the disease. Such patients are significantly subjected to social phobia, benzodiazepine abuse and impairment of both somatic and psychological well-being [8].

Treatment-Resistant Depression

Treatment Resistant Depression (TRD) or depressions with prominent somatic symptoms are found to be of inflammatory subtype. It is associated with increased functional impairment, mortality, morbidity and recurrent or chronic episodes in the long term. Psychotropic medications may be associated with weight gain and a higher BMI, this aggravates treatment resistance. Predictors of TRD include lack of full remission after previous episodes, comorbid anxiety, suicidality, early onset of depression, personality and genetic factors [24]. Patients may be prescribed a concomitant psychological and pharmacologic therapy or combination pharmacotherapy. Participants with no proinflammatory cytokine elevations might be indicated to receive psychological rather than pharmacologic therapy, while a subset of patients with high inflammation could receive an anti-inflammatory agent in augmentation to standard treatment. An individual having high TNFα levels, could benefit from short-term treatment with a TNFα antagonist. Targeting glutamate *NMDA* receptor antagonists, might represent efficacious treatment. Statins have antidepressant effects by altering neurobiological pathways. Lithium is shown to reduce inflammation through glycogen synthase kinase-3 pathways. People with a history of childhood trauma might respond better to psychological than pharmacologic therapies [24]. Currently, most pharmacological treatments have a delayed onset of action and can produce adverse side effects such as headaches, nausea, agitation, sedation, and sexual dysfunction [32]. Establishing a biomarker panel has implications for boosting diagnostic accuracy and prognosis, as well as for individualizing treatments at the earliest practicable stage of depressive illness and developing effective novel treatment targets [11, 24]. Similar to stratification, personalized treatment-selection strategies may be possible.

Complementary and Alternative Medicine (CAM)

During the 1990s, many alternative treatment strategies emerged which includes herbal medications, vitamins, nutritional supplements, magnetic and electroencephalographic synchronizing devices, energy treatments, and meditation-based therapies. These treatments may be provided by alternative medicine practitioners such as acupuncture, yoga, mindfulness meditation, homeopathy, Ayurvedic medicine, Reiki, and healing touch. Because of minimal FDA regulation and widespread over-the-counter availability, many of these treatments are self-selected and used by patients. Herbs are the most commonly used CAM products [33]. Alternative effective treatments for moderate-to-severe depression include a combination of somatic therapies. Antidepressants and cognitive-behavioral therapies show approximately comparable efficacy, but due to their differing mechanisms of action, it might be expected to have

different predictors of response [1, 11]. Non-pharmacological interventions include psychotherapy, ECT, transcranial magnetic stimulation (TMS), Comprehensive Decongestive Therapy (CDT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), transcranial direct current stimulation (tDCS), light therapy, sleep deprivation therapy and deep brain stimulation. Somatic treatments with antidepressant action seem to act by modifying neuroplasticity. While they are immediate, the antidepressant response is delayed [3, 14]. ECT is used for the treatment of the most severe, melancholic depressions, particularly in the elderly (who do not tolerate the adverse effects of antidepressants) and treatment resistant patients. However, patient accesses to alternative treatments are inadequate due to local availability and cost. Thus, it's clear that a combination of genetic, developmental, psychological, and environmental, socio-economic factors contributes to the optimal treatment of depressive disorders [1]. The cognitive model' predicts that when maladaptive thinking is corrected, both acute distress and the risk for recurrent symptoms will be reduced [34].

Mind–body interventions are commonly used to cope with depression and yoga is one of the most commonly used methods of treatment. One of the advantages lies in the fact that it is an easily accessible approach that has become widely accepted. In addition to the relatively low costs, yoga can be conducted as group activity, hardly any risks nor side effects are observed compared to pharmacological treatment. Yoga can be easily integrated into everyday life and therefore possibly contribute to preventing relapses. Further investigation of yoga as a therapeutic intervention in depressive disorders is needed and future studies should seek to identify which of the yoga-based interventions is most effective and what levels of severity of depression are more likely to respond to this approach [32, 35].

Physical exercise also induces neuroplasticity changes [20]. Exercise promotes hippocampal neurogenesis through activation of β-endorphins, VEGF, BDNF, and serotonin. This results in analgesia, anxiolysis, and a sense of well-being. Changes in HPA axis are associated with exercise. The APA and The National Guideline Clearing house state that exercise can be recommended as an adjuvant therapy to antidepressants or psychotherapy. Exercise can be a first-line treatment in mild to moderate depression as well as in older individuals who show delayed response to antidepressants. Both running and weight lifting were found to decrease depressive symptoms. Aerobic exercise may reduce generalized anxiety. Exercising at 70%–90% of maximum heart rate for 20 minutes three times a week has been shown to significantly reduce anxiety sensitivity [36].

Role of gut microbiota in depression

Recent studies have emerged with the concept of bidirectional communication between the central nervous system, enteric nervous system and the gastrointestinal tract, often referred to as the gut brain axis [6, 32]. The microbiome can influence the functioning of HPA axis and immune system; there are alterations in the levels of norepinephrine and serotonin in corticolimbic regions, as well as alterations in BDNF in the hippocampus. Endocrine-, neurocrine-, and inflammation-related signals originated from gut microbiota may influence brain functions. Also, the brain signals in the form of emotions can affect the microbial composition and functions in the gut. Bacterial species, *Bifidobacterium* and *Lactobacillus* have anti-anxiety effect [6]. Water-soluble vitamins such as ascorbate (vitamin C), biotin (B7), folate (B9), niacin (B3), pantothenic acid (B5) pyridoxine (B6), riboflavin (B2), and thiamine (B1) also can be generated by microbiota and absorbed in the colon and therefore are beneficial to the host [37]. Microbiota composition of gastrointestinal tract is influenced by genetics, age, sex, diet, stress, and psychiatric and metabolic disorders [16]. Even mild forms of stress or anxiety can cause intestinal dysfunctions, due to the predominance of *Bacteroides* and *Firmicutes* phyla in the intstine. Alterations in gut brain axis are associated with gut inflammation, irritable bowel syndrome, chronic abdominal pain and eating disorders, as well as overall behaviour [6]. This small intestinal bacterial overgrowth (SIBO) is likely to contribute to the limited nutrient absorption in MDD. Probiotic therapy is defined as using beneficial bacteria to improve the intestinal microbial balance of the humans. Probiotics have the potential to lower systemic inflammatory cytokines, decrease oxidative stress, improve nutritional status, and correct SIBO. Probiotics may be an adjuvant to standard care in MDD [23, 38, 39].

Leptin crosses the blood brain barrier and interacts with hypothalamus and hippocampus, thus regulating mood. There is association between atypical features of depression and elevated leptin levels. The secretion of leptin by adipocytes is regulated by microbial-derived metabolites independent of food intake, specifically short-chain fatty acids (SCFA). Lactobacillus and Bifidobacterium positively correlate with serum leptin levels. Acylated ghrelin circulates throughout the body and crosses the blood brain barrier, where it interacts with acylated ghrelin receptors (GHSR1) in the hypothalamus. Ghrelin gets elevated in acute stress, resulting in activation of the HPA axis. Ghrelin inhibits the release of serotonin, increases serotonin turnover, causing serotonin imbalance in MDD patients. Treatment with prebiotics has been found to alter ghrelin levels [16]. Omega 3 fatty acids rich in fish have been shown to decrease lipid peroxidation; and antioxidant supplementation can prevent the negative influence of saturated fat on BDNF levels and cognitive function [24, 40].

CONCLUSION

Major Depressive Disorder is a common debilitating disorder. Till date diagnosis is based on subjective evidence. MDD is highly heterogeneous in presentation; hence even though various diagnostic modalities are available, there is no

consensus among the researchers as well as clinicians in deciding the diagnostic panel. The same type or problem exists with treatment also. Hence it is mandatory to find out noninvasive, cost effective and easy techniques such as identification of biomarkers is the need of the hour which helps in diagnosing MDD cases before the onset of symptoms. Inclusion of nonpharmacological treatment along with pharmacotherapy may have a promising role in improving the quality of life.

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