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A REVIEW ARTICLE ON DEPRESSION

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INTRODUCTION

Depression is one of the most popular psychological constructs given the related generated studies and the usage that the general community has made of it. However, confusions about what is really conceived as depression can be seen, often observing interchanges in the conceptions of emotion, state, disorder and disease, and also, being used as a synonym with other alterations such as “melancholy”. Derived from the above, the present study intends to make an analysis of the term “depression”, starting from its de nition and generating later reactions of what is found in the area.

Definition and delimitation

The word depression comes from the Latin “depression” which means sinking. The person feels sunk with a weight on their existence. It is a mood disorder that varies from: normal transient low mood in daily life itself, to clinical syndrome, with severe and f duration and associated signs and symptoms, markedly different from normality.[104] Depression consists of a disease with decayed mood as its main symptomatology. There are also painful feelings, bad humour, anguish and panic attacks, performance decay of various psychic and cognitive functions, tendency to isolation, demotivation, apathy, abulia, difficulty to enjoy, hopelessness, motor inhibition, hypotonia and negative thoughts, including possible delusions in cases of serious severity. On the other hand, it can present a very diverse associated somatic symptomatology, some organic alterations often corresponding to larval or encapsulated ways of going through a depression.(105)It is considered a mental disease consisting of a mood disorder, being its

usual symptom a state of dejection and unhappiness that may be transient or permanent.[106] In this sense, it is de ned as a mental disorder characterized by the presence of sadness, loss of pleasure, feelings of guilt and low self-esteem, accompanied with alterations in the sleep pattern and the appetite, lack of concentration, and feelings of being tired, which can become chronic and recurrent, making the person dysfunctional in their daily activities; when it is mild it can be treated with psychotherapy, but when it is moderate or severe, pharmacological treatment may be needed.[107]

Major depressive disorder (MDD), a main cause of disability worldwide, is characterized by physical changes such as tiredness, weight loss, and appetite loss. Anhedonia is a classic feature of MDD, and MDD is also accompanied by a lack of drive, sleep issues, cognitive challenges, and emotional symptoms such as guilt.[108] The prevalence of depression is increasing yearly. About 300 million people in the world are affected by MDD, which has become one of the main causes of disability.[109] In 2018, MDD ranked third in terms of disease burden according to the WHO, and it is predicted to rank first by 2030.[110] Pregnant women, elderly people, children, and others have a higher incidence rate of MDD, which may be related to genetic, psychological, and social factors.[111] Depression can be accompanied by recurrent seizures, which may occur even during remission or persist for longer than the disease itself.[112] Pharmacological therapies for MDD can effectively control symptoms; thus, patients may experience recurrence within a short time after discontinuing medication.[113] During recurrence, the patient experiences symptoms of low mood, loss of interest in life, fatigue, delayed thinking, and repeated fluctuations in mental state.[114]

There is a certain correlation between the occurrence of MDD and social development.[115] A survey reported that with the development of the economy and increased life pressure, MDD has begun to emerge at a younger age, and the incidence of MDD in women is approximately twice that in men.[116] Specifically, women are more likely to develop depressive symptoms when they encounter social emergencies or are under significant stress.8 Additionally, autumn and winter have been reported to be associated with a high incidence of MDD, namely, seasonal depression.[117]

Moreover, people aged 50 years and more have a 1.5 times higher risk for developing depression than younger people.[118] Modern lifestyle promotes independence of the environmental light/dark cycle, which leads to shifting in sleep-wake patterns. Circadian rhythm disruption is affected by the increase in nocturnal activity, decrease of sleep, and

extended exposure to artificial light during the nighttime.[119] Limbic brain regions, monoamine neurotransmitters, and the hypothalamic-pituitary-adrenal (HPA) axis are under circadian regulation. It is thought that the perturbation of circadian rhythms contributes to the prevalence of depression and other mood disorders.[120]

Factors Associated with the Development of Depression

1. Environmental Factors

Environmental conditions play an important role in the onset of depression, with evidence suggesting that the connection between the cerebellum and depression may be influenced by these factors. It can then be postulated that some environmental factors alter cerebellar functionality and lead to vulnerability to depression.[121]

- Environmental factors related to xenobiotics, such as agricultural pesticides,[122,123,124,125,126,127]
- Exposure to these pesticides disrupts dopaminergic, serotonergic, and neurological functions.[128]

2. Changes in Neurotransmitters

Changes in neurotransmitters are believed to play a significant role in the development of psychiatric disorders. In depression, there is a decrease in the number of neurotransmitters released, but the reuptake pump and enzyme continue to function normally. Thus, a receptor neuron captures fewer neurotransmitters, and the nervous system operates with fewer neurotransmitters than is normally needed.[129] There is a relationship between the three main monoamine neurotransmitters in the brain (dopamine, norepinephrine, and serotonin) and the specific symptoms of MDD. The increase or decrease in these neurotransmitters is linked to specific symptoms, highlighting that specific neurochemical mechanisms are responsible for certain symptoms of depression. Thus, antidepressants can be targeted at specific neurotransmitters to treat these symptoms.[130]

3. Prolonged Stress Situations and Traumatic Experiences

Since the beginning of humanity, people have suffered from stress. Stress is a well-known factor significantly involved in the onset of nearly all major depressive disorders.[131]

4. Medical Conditions

The presence of adverse emotional conditions, such as depression, can trigger or exacerbate chronic health problems. These emotional changes are intrinsically related to eating

behaviors, influencing individuals to seek emotional relief and gratification through food consumption to address possible affective deficiencies. An individual's eating behavior encompasses a range of actions related to food, from choice to consumption. This behavior can be influenced by the interaction of biological, psychological, and social factors in which the individual is embedded. Any alteration in these aspects will directly influence their eating behavior.[132]

5. Changes in Hormone Levels

Changes in hormone levels are a significant factor in the development of depression, reflecting the intricate interplay between the endocrine system and the nervous system. Hormones and neurotransmitters share common pathways and receptor sites in areas of the brain linked to mood, particularly through the hypothalamic–pituitary–gonadal axis.[133] Disruptions in this axis can contribute to the onset of depression. For example, the HPA axis, which responds to stress, has been extensively studied for its role in the pathophysiology of anxiety and depression, and its influence on cognitive functioning.[134]

6. Substance Abuse

Substance use involves the consumption of various substances, including alcohol, tobacco products, drugs, inhalants, and other substances that can be ingested, inhaled, injected, or otherwise absorbed by the body. This usage can potentially lead to dependence and other adverse effects.[135] When dependence develops, it results in substance abuse, which has significant negative repercussions for the individual. This behavior can compromise both physical and mental health and negatively impact social, professional, and family life.[136]

7. Socioeconomic Factors

Socioeconomic conditions play a crucial role in the prevalence and severity of depression and other mental disorders. Research indicates that individuals from poorer socioeconomic backgrounds have fewer opportunities and resources, which can significantly influence the occurrence of depressive episodes.[137]

8. Psychological Disorders

Depression is frequently linked with a range of other mental disorders, creating a complex and challenging clinical picture.[138]

9. Food Preferences

Individuals with depression often have a preference for fast food, snacks, and foods of low nutritional quality, characterized by high energy content. Those experiencing severe depression tend to follow an unhealthy diet, marked by reduced consumption of fruits and vegetables (FV), fish, chicken, milk, and grains.[139,140]

10. Sedentary Lifestyle

Studies indicate that individuals who are less physically active and engage in minimal exercise have a higher likelihood of developing depression later in life.[141,142]

11. Genetic and Epigenetic Factors

Genetic predisposition plays an important role in the development of depression. A family history of depression significantly increases the likelihood of developing the condition. Studies have demonstrated that genetic factors contribute substantially to the risk of depressive disorders.[143]

12. Inflammation

Depression is intricately connected to a systemic immune response, characterized by the activation of inflammatory substances and the migration and regulation of peripheral cells to the central nervous system, facilitated by the permeability of the blood–brain barrier (BBB). Given the multifaceted nature of depression, investigating and monitoring the inflammatory process through the quantification of biomarkers is essential for identifying the disease and its unique characteristics, as well as providing insights into the efficacy of treatments.[144,145]

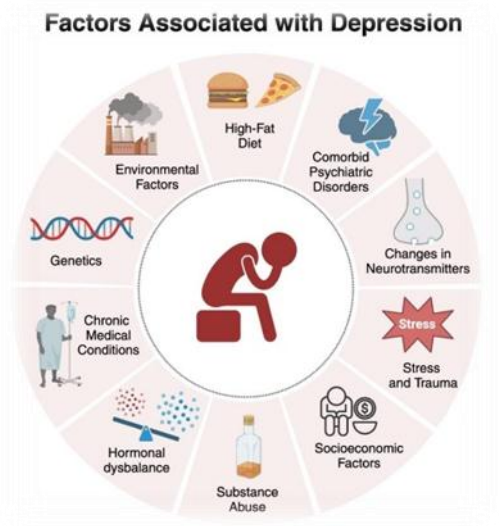

Figure 10: Factors associated with depression.

This figure illustrates various factors associated with depression, including genetic and epigenetic factors (inherited traits and gene expression changes), environmental factors (pollution and living conditions), prolonged stress and traumatic experiences, comorbid psychiatric disorders (such as anxiety and bipolar disorder), a high-fat diet, chronic medical conditions (such as hypertension and diabetes), hormonal dysbalance (imbalances in thyroid and sex hormones, cortisol overproduction, etc.), substance abuse, socioeconomic factors (financial stress and low socioeconomic status), and changes in neurotransmitters (alterations in serotonin and dopamine levels).[146]

Risk factors

Depressive disorder is a result of the interplay of many different factors: Environmental, genetic, neurobiological, and cultural.[147] Known environmental risk factors for developing depressive disorder are poverty, negative experiences in the family (bad relationship, violence, divorce, child maltreatment), or other stressful life events. In the time after a stressful life event, the risk for depressive disorder is elevated but the effects of adversity can persist over time.[148] In depressive symptoms that persist over time, especially at the level of epigenetics, might be involved.[149]

Genetic heritability for depressive disorder, estimated from twin studies, is around 35%–40%.[147,150] Genome-wide association studies have discovered multiple loci with small effects that contribute to MDD.[151] Pandya et al.[152] collected results from neuroimaging, neuropsychiatric, and brain stimulation studies and showed similar results. In recent years, more and more studies are oriented towards epigenetics to understand new mechanisms and the way epigenetics is linked to a depressive state. The nervous system is susceptible to shifts in the activity of epigenetic modifiers, which allow for significant plasticity and response to rapid changes in the environment.[153] They are very important for early development of the organism as well as later in life, as a response to external factors.[154]

From a biological perspective, there are four theories of depressive disorder: Monoamine theory, stress induced theory, neurotrophic theory, and cytokine theory (Figure 11)

Theories of depressive disorder

1. The monoamine theory of depressive disorder

Monoamine neurotransmitters (serotonin, nore-pinephrine, and dopamine) are chemical messengers involved in the regulation of emotion, arousal, and certain types of memory. The

monoamine hypothesis of depressive disorder proposes development of depressive disorder by signal dysfunction between neurons: A decreased level of neurotransmitters leads to the depressive state.[155,156]

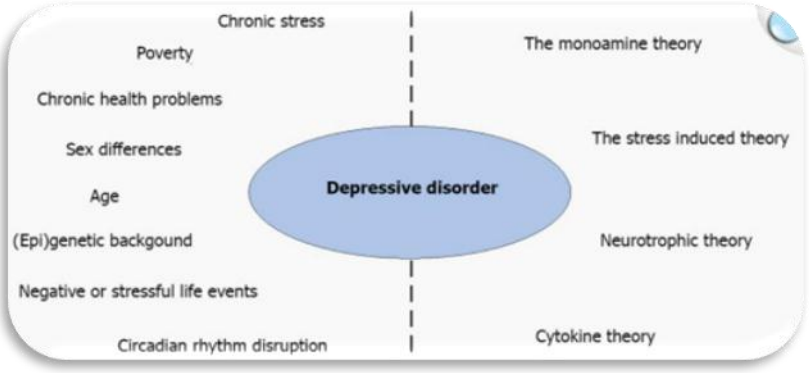

Fig. 11: Depressive disorder risk factors. Depressive disorders are influenced by various and often overlapping risk factors that form theories of depressive disorders.

2. The stress induced theory of depressive disorder

Prenatal stress, early-life adversities, chronic stress, and stressful life events are all strong predictors of the onset of depressive disorder. The HPA axis, a neuroendocrine system, is responsible for adaptation to changing environments. Response to stress begins in the hypothalamus, with the secretion of corticotropin-releasing hormone, which affects the pituitary gland to release adrenocorticotropic hormone. Adrenocorticotropic hormone circulates in the blood and stimulates the release of glucocorticoid hormones (cortisol) in the adrenal cortex. Cortisol binds to glucocorticoid receptors in the brain, which are key regulators of the stress response. Cortisol with a negative loop inhibits the HPA axis. Dysregulation of the negative loop is associated with depressive disorder.[155,156]

3. Neurotrophic theory of depressive disorder

Neurotrophic factors are peptides or small proteins that support the growth, survival, and differentiation of developing and mature neurons. Decreased neurotrophic support affects the development of depressive symptoms. Brain-derived neurotrophic factor (BDNF) is a very well examined neurotrophic factor. Many studies made on brain and blood showed decreased expression of BDNF in patients with depressive disorder. Also, decreased BDNF expression has been associated with epigenetic modifications of the BDNF gene.[156]

4. Cytokine theory of depressive disorder

Cytokines are small secreting proteins important in cell signaling. Cytokines include chemokines, interferons, interleukins (IL), lymphokines, and tumor necrosis factors (TNF).[157] The cytokine (or inflammation) theory of depressive disorder suggests that inflammation has a significant role in its pathophysiology. Patients with depressive disorder have increased inflammatory markers, IL-1β, IL-6, TNF-α, and C-reactive protein.[158] Depressive disorder is not a typical autoimmune disease, so the elevation of cytokines in patients with depressive disorder is lower than in autoimmune or infectious diseases.[155]

There are several proposed theories by which the immune system (cytokines and immune cells) could affect depressive-like behavior.[159] For example, inflammation in peripheral tissue can signal the brain via the vagus nerve, cytokine transport systems, and a leaky blood-brain barrier caused by rising TNF-α, which leads to brain accessibility for other peripheral signals.[158]

Signs and symptoms

If you experience one of the first two symptoms (and at least four of the remaining symptoms) for most of the day for at least two weeks, you may be experiencing some form of depression, per the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).

You feel persistently sad, hopeless, or empty
You're no longer interested in your passions
And your sleep schedule isn't helping:
You can't focus:
Your appetite changes are really significant
You're dealing with unexplained pain.
You feel super restless or really lethargic
You're having thoughts about self-harm.[160]

Depression can occur in kids as young as three years old—but children don't always show the typical signs of depression. For example, young kids (between ages three and eight) may complain more about sickness or pain, be more irritable, show signs of anxiety, or misbehave. As kids get older, they may start to develop more classic symptoms of major depressive

disorder. According to the Centers for Disease Control and Prevention and the Mayo Clinic, this includes the following:

- They are frequently sad or irritable.
- They don't want to do fun activities, like go out for ice cream.
- They eat more or less than they normally do.
- They have self-destructive behavior and get in trouble at school.
- They have a hard time focusing.
- They talk about feeling bad about themselves.
- They become frustrated or angry over small things, like spilling their water.
- They stop hanging out with their friends.
- They have trouble making decisions.
- They begin drinking or using

For example, maybe they're suddenly not hanging out with friends, getting homework done, or going to sports practices. "These are all things that would start to perk up my sense that the person may be struggling,".[161]

Depressive illness comes in different forms, just as many other illnesses:

i. Major depression

ii. Dysthymia

iii. Manic-depressive or bipolar[162-163]

Pathological Mechanism

Due to the complexity of the pathological mechanism of MDD, accurate diagnostic approaches and pharmacological therapeutic strategies are relatively limited. Several hypothesis were developed to explain MDD pathogenesis pathogenic including

(i) The hypothalamic–pituitary–adrenal (HPA) axis dysfunction hypothesis,

(ii) The monoamine hypothesis,

(iii)The inflammatory hypothesis,

(iv)The genetic and epigenetic anomaly hypothesis,

(v) The structural and functional brain remodeling hypothesis, and

(vi)The social psychological hypothesis.[164,165,166]

(Fig. 12). However, none of these hypotheses alone can fully explain the pathological basis of MDD, while many mechanisms proposed by these hypotheses interact with each other. Specifically, increasing evidence suggests that astrocytic dysfunction plays a substantial role in MDD.[167] Pharmacological ablation of astrocytes in the medial prefrontal cortex (mPFC) causes depressive-like symptoms in experimental animals,[168] and postmortem studies of patients with MDD have shown reduced densities of glial cells in the prefrontal cortex (PFC), hippocampus and amygdala.[169] In addition, glial fibrillary acidic protein (GFAP), one of the markers of astrocytes, is expressed at various levels,[170] and the levels of connexins,[171] glutamine synthase (GS), glutamate transporter-1 (GLT-1),[171,172] and aquaporin-4 (AQP4)[173] are reduced in patients with MDD

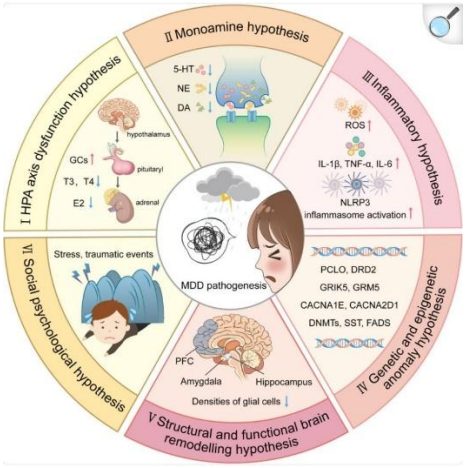

Figure 12: An outline map of the hypotheses to explain MDD pathogenesis.

(I) HPA axis dysfunction hypothesis: high levels of glucocorticoids (GCs) play a core role in the pathogenesis of MDD, and thyroid hormone (TH) and estrogen are also involved in functions of the HPA axis; (II) the monoamine hypothesis: the functional deficiency of serotonin (5-HT), dopamine (DA) and norepinephrine (NE) are the main pathogenesis of MDD; (III) the inflammatory hypothesis: the neuro-inflammation induced by reactive oxygen species (ROS), inflammatory cytokines and inflammasomes activation is suggested to promote the occurrence of MDD; (IV) the genetic and epigenetic anomaly hypothesis: some genes are susceptible in the patients with MDD, including presynaptic vesicle trafficking (PCLO), D2 subtype of the dopamine receptor (DRD2), glutamate ionotropic receptor kainate type subunit 5 (GRIK5), metabotropic glutamate receptor 5 (GRM5), calcium voltage-gated channel subunit alpha1 E (CACNA1E), calcium voltage-gated channel auxiliary subunit alpha2 delta1(CACNA2D1), DNA methyltransferases (DNMTs), transcription levels of

somatostatin (SST), fatty acid desaturase (FADS); (V) the structural and functional brain remodeling hypothesis: the postmortem results of patients with MDD are mostly associated with the reduced densities of glial cells in the prefrontal cortex (PFC), hippocampus, and amygdala; (VI) the social psychological hypothesis: the traumatic or stressful life events are the high risks of the occurrence of MDD. Adobe Illustrator was used to generate this figure

Diagnosis and assessment

Diagnosis in individuals young and old is difficult given that depressive symptoms can mimic other disorders and often, coexisting conditions can confound an accurate diagnosis. Many individuals are diagnosed based on treatment response to one or several antidepressant medications.

1. Nonlaboratory methods to diagnose MDD

The long-standing approach to depression diagnosis is often subject to great variation in the methods for information gathering and processing. For clinical study conduct, a structured or semistructured interview method (SDI) is standard; however, in routine practice, clinical diagnosis is used. A recent Psychiatric Times article described a meta-analysis of 38 studies, and nearly 16 000 patients showing these 2 approaches often result in different rather than comparable diagnoses.[174] A K statistic for each study ranged from 0.6 to 0.8 (interpreted as “acceptable” to “good”), and the statistic from the meta-analysis across all diagnoses was 0.27.[175] This demonstrates a “gap” in the real world vs study-based methods to achieve accurate diagnoses. Another study reported clinical diagnosis for MDD relative to SDI to be poor.[176]

2. Laboratory methods to diagnose MDD

The dexamethasone suppression test (DST) was developed to differentiate various types of Cushing syndrome and other conditions mediated by hypercorticism and also has been used for depression diagnosis.[177,178] The DST assesses the negative feedback of dexamethasone, a cortisol-like synthetic hormone on pituitary corticotropin release. Dexamethasone administration, typically at a low dose (1–2 mg), should reduce corticotropin levels and lead to decreased cortisol levels in healthy individuals, but in many depressed patients, cortisol levels remain elevated.[177] Despite being a pioneering laboratory method, the DST has proven inconvenient for patients and lacked good clinical performance for depression assessment.[179] The test may differentiate severe melancholic depression, mania, or acute psychosis from chronic psychosis (87% specificity) or dysthymia (77% specificity).[180]

3. Future directions

More advanced technology is emerging to assess depression, and although these newer techniques have not yet found full adoption in psychiatry, the practicing psychiatrist should be made aware given that similar methods have found use in other therapeutic areas. These are discussed below.

4. Genomic methods

With the sequencing of the human genome in the 1990s and development of new techniques for rapid sequencing, genomic applications in many medical areas, including psychiatry, are emerging. Measuring gene expression profiles in blood cells holds promise for identifying disease classifiers and risk markers in psychiatric disorders, and one recent study describes such a profile for MDD.[181,182] An estimate of the gene panel's clinical performance showed good sensitivity but poor specificity.[182]

5. Proteomic and metabolomic methods

Proteomic techniques facilitate the study of multiple protein and modified protein products of disease-relevant genes. This can lead to the study of differentially expressed protein profiles in diseased vs non-diseased populations.[183– 185] Few systematic studies have been done on either brain tissue or with biological fluids from depressed patients. Most work have been done in animal models with a focus on biomarker changes due to antidepressant treatment rather than to identify biomarkers to diagnose depression.[186] Proteomic analysis identified glyoxalase-I as a protein marker down- regulated in various areas of the brain in 1 study and a modified enolase phosphatase isoform in HAB mice in another.[187,188]

Mass spectrometry analysis of plasma metabolites yielded an expression pattern that was most similar between the remitted group and the never depressed control group, and both differed from the currently depressed group.[189] The study suggests that changes in lipid and neurotransmitter metabolism associated with depression may alter these metabolic pathways. These metabolites then might serve as a "signature" to identify depressed patients, pending additional study to validate these findings.

6. Systematic biological pathway analysis

Components of several biological pathways undergo changes in various psychiatricconditions or in response to antipsychiatric therapy.[190,191] Pathways such as the inflammatory, neurotrophic express and respond to many regulatory biochemicals that include steroids,

neuropeptides,cytokines, and neurotransmitters.[192–194] These systematic interactions provide the molecular basis for integrated neuroendocrine-immune responses to homeostatic perturbations induced by stress, inflammation, or infection. Many components of these pathways have been implicated in depression.[195] Severe depressive illness has been associated with elevations of cytokines or their soluble receptors, including interleukin (IL)-2, soluble IL-2 receptors (sIL-2R), IL-1b, IL-1 receptor antagonist (IL-1Ra), IL-6, soluble IL-6 receptor (sIL-6R), and γ-interferon.[192,196] A case control study found that serum resistin (a cytokine and metabolic marker) levels correlate with symptoms of atypical depression.[197]

Brain-derived neurotrophic factor alone may, however, lack some specificity for depression diagnosis, and the mechanism of BDNF release is not clearly understood [198]. Serum BDNF may serve as a biomarker to discriminate between unipolar and bipolar depression.[199] Hypercortisolism in depression is described by elevated mean 24-hour serum cortisol concentrations and increased 24-hour urinary excretion of cortisol.[200] In endocrine testing, using the DST, serum cortisol, and adrenocorticotrophin concentrations are not suppressed in some 20% to 50% of patients.[201]

Recently, a new blood test has been described for MDD diagnosis that is composed of representative components of the neurotrophic, metabolic, inflammatory, and HPA axis pathways.[202,203] Patients with endogenous depression often have lower levels of basal serum TSH and lower TSH changes from baseline to peak.[204] Depression may be associated with subclinical hypothyroidism or mild thyroid failure.[205]

7. Retrospective study

A retrospective case control study was conducted with a heterogeneous population of MDD patient samples to rigorously test the discriminatory capability of the candidate biomarkers to differentiate MDD from healthy subjects. A training set of 50 serum samples from patients with MDD and 20 healthy volunteers was obtained from a biobank (PrecisionMed, San Diego, CA) and were maintained frozen at −80°C until testing. In the MDD, 48 of 50 and 20 of 20 in the healthy subject groups were evaluable. disorder, or alcohol abuse. Blood draws were performed while the patients were in the depressed state.

8. Validation study

A prospective case-controlled validation study was conducted in 2 community-based psychiatric practices under an institutional review board–approved protocol. Subjects were

MDD psychiatric outpatients with a clinical diagnosis of MDD or clinical symptoms consistent with depression and were age- and sex-matched to healthy controls who were healthy volunteers. After completing informed consent, 28 MDD (10 men and 18 women) and 28 healthy subjects were prospectively enrolled. Subjects with MDD on antidepressants remained on those treatments.

Table 3

Comparison of methods outside primary care to diagnose MDD

Diagnostic method	Clinical performance in MDD
Structured Diagnostic Interview	
SDI vs clinical evaluation	$\kappa = 0.45$ [9]
SDI vs PHQ	Sensitivity, 40%; specificity, 87% [10]
DST	
DST vs clinical evaluation	Sensitivity, 60%–70%; specificity, 70%–90% [11]
	Confounders: patient use of barbiturates, anticonvulsants, or corticosteroids; use of alcohol; bioavailability of dexamethasone; acute "stress"; severe weight loss
Genomics	
Genomic signature vs CIDI (v. 2.1)	Sensitivity, 87.5% (n = 42); 76.9% (n = 26)
	Specificity, 61.5% (n = 42); 71.4% (n = 26) [16]
	No reports on clinical performance or effect of medication or comorbidities
Proteomics	No reports on clinical performance or effects of medication or comorbidities
Metabolomics	$P > .05$ for depressed vs remitted and never depressed groups [23]
	No reports on clinical performance or effect of medication or comorbidities
Biological pathway biomarker panel	
Biomarkers panel vs SDI	Sensitivity, 95%, specificity, 87.5% [36,37]
	No reports on effect of medication or comorbidities

POSSIBLE TREATMENTS OF DEPRESSIVE DISORDER

There are pharmacological and nonpharmacological (psychotherapy, lifestyle interventions, and neuromodulatory treatment) ways of treating depressive disorder.[206]

	Class	Commonly prescribed	Mechanism of Action (MOA)	Ocular adverse effects
1.	Selective Serotonin Reuptake Inhibitors (SSRIs)	Fluoxetine, Paroxetine, Escitalopram, Sertraline Citalopram Fluvoxamine	Inhibit reuptake specifically of Serotonin by binding to SERT	Dry eye Decreased accommodation and visual blurring (mainly with Paroxetine) Mydriasis Precipitation of AACG Ocular dystonia *(rare)* Optic neuropathy *(rare)* Maculopathy (Sertraline)
2.	Serotonin Noradrenalin Reuptake Inhibitors (SNRIs)	Duloxetine, Venlafexine, Desvenlafexine, Milnacipran, Levomilnacipran	Inhibit reuptake of both Serotonin (5 HT) and Noradrenalin (NA) by acting on SERT and NAT	Mydriasis, Precipitation of AACG (*lesser than SSRIs and TCAs*)
3.	Tricyclic Antidepressants (TCA)	Amitriptyline Nortriptyline Imipramine, Desipramine Clomipramine Nortriptyline Doxepin	Inhibit reuptake of both 5HT and NA by acting on SERT and NAT. Anti H1, H2 histaminic receptors; Anticholinergic	Dry eye Decreased accommodation and visual blurring *(1/3rd patients)* Mydriasis, precipitation of AACG
4.	Mono Amine Oxidase Inhibitors (MAOI)	Phenelzine Selegiline Moclobemide	Conventional *(rarely used)* New Reversible	Mydriasis and AACG precipitation
5.	Atypical Antidepressants	Bupropion	Dopamine reuptake inhibitor	
		Nefazodone Vortioxetine	Serotonin receptor modulators and reuptake inhibitors	Retinopathy *(rare)*
		Trazodone Mirtazapine	Above action with added anti α_1 adrenergic and anti H1 histaminic receptor action	Mydriasis and AACG precipitation *(rare)*

SERT (Serotonin transporter), NAT (Noradrenalin transporter), AACG (Acute Angle Closure Glaucoma), 5-HT (5 Hydroxytryptamine or Serotonin), NA (Noradrenalin)

Table 4: Classification of anti depressants based on MOA and ocular side effects.[207-223]

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