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Decoding Depression: A Narrative Review of Its Molecular Mechanism and Emerging Treatments

Tamonan, Ian Clark
Villanueva, Charlyn
Brodit, Demosthenes John

I. Background

Depression refers to a range of mental problems characterized by loss of interest and enjoyment in ordinary experiences, low mood and associated emotional, cognitive, physical and behavioral symptoms (Penninx et al., 2013). It is currently one of the most important causes of mortality and morbidity, which occurs in all genders, ages, and social backgrounds. Serious problems, such as suicidal behavior, are frequently occurring in the patients with depression (Jeon & Kim, 2016). The World Health Organization (WHO) recently reported that about 154 million people are suffering depression and 877, 000 are dying by suicide every year (World Health Organization, 2020). These figures show how serious the problem of depression is. Everybody experiences stressful events but sometimes the stress gets so unbearable that some would fall into depression. This problem is often explained through psychiatric inquiries which incorporates physiological facts. Researchers are now looking into different lenses to better understand the problem. Among these lenses is the molecular mechanism of depression. Molecular events in the synapse determine whether appropriate neuronal connections will form and be maintained (Varidaki et al., 2016). Several hormones, enzymes and other proteins regulate these molecular mechanisms. However, dysregulation of these proteins may lead to maladaptive response whenever someone experiences stressful events. Recent studies combining behavioral, molecular and electrophysiological techniques reveal that certain aspects of depression result from maladaptive stress-induced neuroplastic changes in specific neural circuits (Krishnan & Nestler, 2009). Aside from neurological aspects of depression, researchers are also looking into genetics to be able to explain which genes are responsible for its occurrence and how depression among pregnant mothers affect their off springs. Evidences coming largely from animal and cellular studies revealed that activation of the main hormonal stress-response system, the HPA (hypothalamic–pituitary–adrenal) axis, in mothers who are depressed during pregnancy may affect maternal care as well as offspring's behavior and future psychopathology (Pariante, 2014). Specific genes were also found by researchers to be common among patients with depression. They were also able to note some genes that can effectively be targeted with antidepressant drugs. Depression is not only a neurological and a genetic problem. It is also a metabolic problem which disrupts the way our body utilizes energy. Research on health outcomes associated with obesity and diabetes has traditionally focused on cardiovascular disease. However, metabolic dysregulation influences brain function and disturbances in peripheral glucose regulation might be associated with cognitive impairment and depressed mood (Hendrickx et al., 2005). These evidences constitute the molecular mechanism of depression. Treatments and interventions for this problem are now designed based on these information. Currently available antidepressant drugs are notoriously problematic, with suboptimal remission rates and troubling side-effect profiles (Ch´avez-Castillo et al., 2019). However, a myriad of neuropsychopharmacological approaches is being produced each year. Thus, it is important for us to take note of these innovations for us to be able to monitor where we are now in the context of psychiatric care for depression. A multi-dimensional overview of the molecular mechanisms and treatments for depression might be a major help for future psychiatric care and research. In this paper, a systematic review of the different published literatures discussing the molecular mechanisms of depression and the interventions used to treat the said problem was established. This paper specifically attempts to describe the molecular mechanism of depression in terms of its genetic and physiological (metabolic, cardiovascular and neurological aspects) dimensions based on published literatures. This paper also attempts to examine the different treatments initiated so far for depression based on published literatures for the past two decades.

II. Genetics of Depression

Depression can run in families, but family history alone does not mean a person will get depression. Understanding of the biological basis for depression has been one of the more recent and significant findings regarding the etiology and risk factors for this disorder. Researchers look at patterns of illness in families to estimate their "heritability," or roughly what percentage of their cause is due to genes. Family, twin, and adoption studies from Bertelsen, et al. (1977) and McGuffin, et al. (1996) have provided evidences of the genetic contribution to the etiology of depressive disorders and clearly shown the transmission of increased risk through heredity. Twin studies, in particular, also point to a strong role of the nonshared (i.e., individually experienced) environment in the causation of depression (Kendler, et al., 1999). However, understanding of the genetics of behavioral variation and of mental illness has proven enormously complex and has been constrained by small sample populations with sometimes unclear or limited ranges of environmental variation. The segregation of environment and gene effects into separate bodies is inaccurate, because the effect of the environment on depression can be influenced by genetic factors. Researchers have come up with two types of models to explain this occurrence: gene-environment correlations and gene-environment interactions (Lau & Eley, 2004). Gene-environment correlations have been described as genetic control of exposure to the environment, such that genes can contribute to the psychiatric illness by predisposing individuals to select themselves into high risk environments. Gene-environment interactions can be described as the impact that a stressful life event may have on genetic factors on an individuals' sensitivity to depression.

In the context of gene-environment correlation model of depression, several studies were examined. In order to examine nature gene-environment correlation model, Schnittker (2010) explored several facets of this model such as sources of stress, depressive symptoms and depressive disorders for these facets may vary from people to people and may have specific relations to genes. It was then found that most, but not all, measures of stress have moderate heritability, suggesting that genes influence exposure to the environment in a broad fashion. Yet, despite this, the relationship between stress and depression is generally robust to gene-environment correlations. It was also found that there are some notable exceptions. For example, allowing for gene- environment correlations, marital conflict is generally unrelated to depression. Moreover, gene-environment correlations are generally stronger for major depression than depressive symptoms, encouraging further elaboration of the distinction between the onset of depression and its recurrence, especially in the context of genes. In the study of Wilkinson et al. (2013), quantitative genetic modeling was used to explore common and unique genetic and environmental influences on both family environment and later depressive symptoms. They found that depressive symptoms at age 12 were significantly heritable. Moderate genetic effects influenced parenting style and family chaos at the age of 9, indicating gene–environment correlation. There were significant genetic correlations between family environment and depressive symptoms.

In terms of gene-environment interactions model, different or partially overlapping gene sets play a major role in the development of personality traits including also affective temperaments, in the mediation of the effects of environmental factors, and in the interaction of these elements in the development of depression. Certain genes are associated with personality traits and temperaments including e.g., neuroticism, impulsivity, openness, rumination and extroversion (Bagdy et al., 2012). Environmental factors consist of external (early and provoking life events, seasonal changes, social support etc.) and internal factors (hormones, biological rhythm generators, comorbid disorders etc). Some of these environmental factors, such as early life events and some prenatal events directly influence the development of personality traits and temperaments. Depression in pregnancy (also called 'antenatal depression') is being increasingly recognized as a clinically relevant condition that affects obstetric outcome, maternal behavior and children's future mental health (Pariante, 2014). Some studies also suggest that there are some notable association between sleep deprivation and depression. Bunney and Potkin (2008), somehow, concluded in their study that certain body clock genes responsible in regulating the circadian rhythm were closely associated with the onset of depression in an individual. They described that the activities of peripheral and central nervous system clock genes are coordinated by a small area of the brain known as the SCN which is located in the anterior hypothalamus. These clock genes in the SCN maintain rhythmicity throughout the body and that abnormal function in clock genes that are specific to entrainment to day and night cycle may lead to depressive disorders following diurnal or seasonal changes (e.g. SAD) in light. In the study conducted by Bozorgmehr et

al. (2018), specific genes and resulting pathway deficiencies were described to be common among individuals undergoing depression and at risk of suicide. The results demonstrated that BDNF, SLC6A4, CREB1, and TNF are the most fundamental shared genes; and generally, disordered dopaminergic, serotonergic, and immunologic pathways in neuronal projections are the main shared deficient pathways. In addition, they also found two genes, SLC6A4 and SLC6A2, to be the main therapeutic targets, and Serotonin-Norepinephrine Reuptake Inhibitors (SNRI) and Tricyclic Antidepressants (TCA) to be the most effective drugs for individuals with depression at risk for suicide. BDNF encodes a nerve growth factor which promotes neuronal survival in the adult brain and encourages the neural differentiation and synaptogenesis (Felmingham et al., 2017). CREB1 encodes a leucine zipper transcription factor which binds as a homodimer to the cAMP-responsive element (Antonescu et al., 2006). SLC6A4 encodes a membranous integral protein which transports serotonin from synaptic spaces into presynaptic zones in a sodium-dependent manner (Gelernter et al., 1997). Tumor necrosis factor (TNF) encodes a proinflammatory cytokine which is involved in the regulation of cell proliferation, differentiation, and apoptosis (Chu, 2013).

III. Physiological Dimension of Depression

Depression is a medical disorder that can affect anyone. It presents with a sad mood, loss of interest, feelings of guilt, powerlessness, poor concentration, low self-confidence, sleep disturbances and changes in appetite and weight. These can lead to compromised daily activities and individual responsibilities. And as mentioned previously, depression can also lead to intentionally taking one's own life-suicide. With all these manifestations of depression, researchers tend to investigate not only the genetic aspects of depression, but also its physiological manifestations. Physiological aspects of depression give us a glimpse of how depression is influenced by multiple molecular and environmental factors.

a. Neurological Aspects of Depression

Our knowledge about the manifestation of depression in our nervous system is still limited even though we've already described specific neural circuitry associated with normal mood and psychiatric abnormalities. This lack of knowledge is underscored by the fact that even if it were possible to biopsy the brains of patients with depression, there is no consensus in the field as to the site of the pathology, and hence the best brain region to biopsy (Nestler et al., 2002). Researchers are now contemplating on data from different brain imaging techniques which show the alterations of blood flow in the brain of individuals undergoing depression. In the review of Lang & Borgwardt (2013), it was noted that decreased hippocampal volumes have been found in a series of studies in humans exposed to chronic stress leading to the hypothesis that chronic stress can inhibit neurogenesis, retract dendritic processes lead to neuronal loss in the hippocampus. The structural-anatomical data indicate that there may be a relationship between decreased gray matter volume (in the hippocampus, the prefrontal cortex, the orbitofrontal cortex, the subgenual anterior cingulate cortex, and basal ganglia structures) and depressed mood, but the reasons for this remain unclear according to Kaltenboek & Harmer (2018) as cited by Jansson (2020). It is not known whether these reduced hippocampal volumes are a result of depression or an antecedent cause (Nestler et al., 2002). Current brain imaging techniques could not exactly point out the stress response of the brain in relation to depression. Thus, researchers have to look into other means of investigating how depression affects our nervous system. Some have resorted to investigating the activities of neurotransmitters and other neurochemicals. Research suggests a link between depressed mood and monoamine depletion, elevated cortisol, and inflammation, but existing laboratory evidence is inconclusive. The neurochemical framework centers on the three monoamine neurotransmitters: serotonin, dopamine, and norepinephrine, with existing data indicating a link between abnormal monoamine regulation and depressed mood. Depressive disorders appear to be associated with altered brain serotonin and norepinephrine systems. Both of these neurochemicals may be lower in depressed people (Bhowmick et al., 2012). Depression is "associated with" instead of "caused by" abnormalities of these neurochemicals because we really cannot discern if low levels of neurochemicals in the brain can cause depression or whether depression results to low levels of neurochemicals in the brain. What we do know is certain medications that affect the levels of norepinephrine or serotonin can improve the symptoms of depression.

The core hypothesis of depression as a stress-related disorder is that chronic stress elicits corticosteroids impair corticosteroid-receptor signaling, which is a key risk factor in rendering an individual

prone to stress-related disorders from the study of Holsboer & Ising (2010). Corticotrophin-releasing hormone and arginine vasopressin are the central drivers of the stress hormone system. These hormones also act as neuromodulators in the brain, affecting higher mental functions including emotion, cognition, and behavior. If these stress hormones are persistently hypersecreted, they can lead to severe clinical conditions and can also hinder an adequate reaction or adaptation to stress. It is clear that more advance tools and techniques must be utilized to further enhance our capacity understand the neurological dimension of depression. We are trying to describe it neurologically but, somehow, data coming from different studies often describe the mechanism of depression in terms of hormones, enzymes, and other neurochemicals.

b. Metabolic Aspects of Depression

Often clinical metabolic dysregulations are assessed in the context of the metabolic syndrome: a cluster of general metabolic risk factors including abdominal obesity, increased blood glucose (hyperglycemia), elevated blood pressure, increased triglycerides and decreased HDL cholesterol (Penninx et al., 2013). These metabolic risks factors are associated with several somatic conditions like diabetes, cardiovascular diseases, obesity and even cancer. These risks factors indicate the heterogeneity of the associations of depression into various somatic metabolic processes. Researchers are now trying to consolidate as much data as possible to better understand the relationship between metabolic syndrome and depression. In their review article, Breznoščáková and Nagyová (2013) found out that complications caused by diabetes are considered as the most serious, and treatment of diabetes is significantly more complicated and worse if depression is present at the same time. Gonzales et al., (2008) emphasized that patients with depression and diabetes were physically less active, smoked more, had fewer healthy dietary habits and were less inclined to diabetic treatment. Thus, most of these patients who are diabetic and depressed are undiagnosed properly. The risk of having complications or fluctuations within the endocrine system of the body increases, worsening the condition being suffered by the patient. But the relationship between metabolic syndrome and depression seems a lot more complicated than expected. Penninx and Lange (2018) reviewed several research articles about metabolic syndrome among psychiatric patients and found the bi-directional relationship between these two conditions. Prospective evidence is scarce but does confirm a bidirectional relationship, with depression predicting the onset of metabolic syndrome, and metabolic syndrome predicting the onset of depression over time. However, Penninx and Lange (2018) also found out that the most consistent evidence of a bidirectional relationship exists between depression and obesity-related components (abdominal obesity, low HDL-C, hypertriglyceridemia). It is important to note that obesity is one of the major risk factors for diabetes. Thus, data from studies concerning the relationship between obesity and depression are often used as bases in explaining the relationship between depression and diabetes.

Nutrient activated gut to brain signaling pathways play a major role in the control of digestive function, appetite and energy intake. These include the modulation of gastric emptying and gastrointestinal transit and are regulated by the release of a number of signaling peptides from nutrient sensing enteroendocrine cells, glucagone-like peptide-1 and cholezystokinin (Chaudhri et al. 2008 as cited by Lang & Borgwardt 2013). Hormones like ghrelin and leptin were also noted to have a great influence in in the regulation of mood and the treatment of depressive symptoms. In the review article of Lang & Borgwardt (2013), it was discussed that leptin influences how we intake food. Its secretion signals the brain that we have enough energy and consequently inhibits our intake of food. However, when a person is experiencing stressful events such as repeated social defeat, scenarios may happen depending on how his/ her body response to stress. Normally, when we experience stress, our glands fire hormones such as cortisol, norepinephrine, vasopressin and aldosterone into our blood. This initial response action of the body leads to increased levels of leptin and insulin levels. Since more carbohydrate is being taken up by the cells, ghrelin becomes suppressed. Since ghrelin manifests antidepressant effects on the body, its suppression often leads depressive symptoms.

Aside from leptin and ghrelin, some other factors like insulin-like growth factor (IGF), cholecystokinin, galanin, neuropeptide Y and brain-derived neurotrophic factor (BDNF) were also noted by researchers to affect the way our body utilizes energy (see Wang et al. 2016; Levada & Troyan 2017; Santi et al. 2018; Beck 2006; Sah & Geracioti 2013; Lang et al. 2015). The main function of IGF-1 in the brain is to control cell growth, differentiation, maturation (through mitosis stimulation and DNA synthesis), and

metabolic processes (i.e., glucose uptake and protein production) (Szczęsny et al., 2013). In their review article, Levada & Troyan (2017) noted that IGF-1 can influence many cerebral processes such as synaptic plasticity, adult neurogenesis, and differentiation, it has been assumed that impairments in the IGF-1 system might be responsible for clinical abnormalities observed over the course of major depressive disorder, including cognitive dysfunction. Cholecystokinin is a classical gut hormone released in the small intestine when fats and proteins are ingested (Lang et al. 2015). It is also a transmitter in the intestinal neurons which is, as well, consider as a powerful experimental panic inductor (Becker et al. 2008). Galanin is a regulatory 29-30-amino acid peptide, widely distributed in the nervous system and gut (Gentleman et al., 1989). In the study of Wang et al. (2016), they explored the possible role of galanin and its receptors in a rat model of depression based on chronic mild stress using quantitative real-time PCR combined with viral-mediated delivery of galanin receptor 1 (Galr1) siRNA. Their results indicated that GALR1 receptor subtype has an involvement in the ventral periaqueductal gray in depression-like behavior could possibly represent a novel target for antidepressant therapy. Neuropeptide Y (NPY) is one the most potent orexigenic peptides found in the brain. It stimulates food intake with a preferential effect on carbohydrate intake (Beck, 2006). In the review article of Sah and Geracioti (2013), they concluded that suboptimal NPY concentrations in various brain regions, particularly in the amygdala, hippocampus, prefrontal cortex, hypothalamus and brain stem, may subserve the clinical manifestations of PTSD and that individuals with low levels of NPY expression or who are less capable of recruiting the NPY system in response to trauma would be more vulnerable to trauma-evoked disorders such as PTSD. Lastly, Brain-derived neurotrophic factor (BDNF) is a neurotrophin that is vital to the survival, growth, and maintenance of neurons in key brain circuits involved in emotional and cognitive function (Phillips, 2017). In the review article of Lang et al. (2015), they also noted that BDNF is a mediator of food intake control via reward-related behavior, modulates vagal afferent gastrointestinal impulses and thereby drives overeating and weight gain associated with increased meal size and frequency. Low expression of BNDF was observed from patients undergoing depression. As a consequence of its low expression, patients who are having depression are more likely to gain weight. The evidences from different literatures suggest that individuals undergoing depression are more likely to suffer metabolic syndrome at the same time. The risk of having diabetes, cardiovascular diseases and even cancer increases as an individual continues to be exposed to stressful events. However, we must also take note that the onset of metabolic syndrome is still dependent on how an individual respond to stress.

c. Cardiovascular Aspects of Depression

A close, bidirectional relationship exists between depression and cardiovascular disease. Major depression is associated with an increased risk of coronary artery disease, myocardial infarction, congestive heart failure, and isolated systolic hypertension leading to increased mortality and morbidity in patients (Nemeroff & Goldschmidt, 2012). Elevation in systemic arterial pressure, increased circulating levels of norepinephrine, higher sympathetic tone, increased systemic vascular resistance, elevations in blood viscosity, decreased plasma volume and extra coronary atherosclerosis are associated with a higher prevalence of depressive disorders (Lippi, et al., & Tiemeier, et al.) Additionally in depressed patients an increased blood coagulation and fibrinolysis, D-dimer, plasminogen activator inhibitor-1 protein and platelet activation can be observed (Geiser, et al., 2008 and Nemeroff & Musselman, 2000). In conclusion, various pathophysiological mechanisms may underlie the risk of cardiovascular disease in patients with depression: increased inflammation, susceptibility to blood clotting, oxidative stress, hypothyroidism, hyperactivity of the sympathoadrenomedullary system and the hypothalamic-pituitary-adrenal axis, reductions in endothelial progenitor cells and arterial repair processes and decreased heart rate variability. (Lang & Borgwardt, 2013).

IV. Treatments

Traditional treatments for depression typically feature tricyclic anti-depressants, selective serotonin reuptake inhibitors (SSRIs), and, more recently, selective norepinephrine reuptake inhibitors (SNRIs) (Prytkova & Barnes, 2015). However, the exact mechanisms of these treatments are not fully deciphered by

researchers. Thus, these treatments are the subject to intense research. Conventional treatment of depression with antidepressant medications and cognitive behavioral therapy can be effective in 60-80% of patients. However, the efficacy of treatment with antidepressants has been called into question for some years now (Bernaras et al., 2019). Most antidepressant therapy has a variety of undesirable side effects such as sedation, decrease of blood pressure, increase of weight, indigestion or sexual dysfunction (Lang & Borgwardt, 2013). These side effects often discourage patients to comply with the necessary regimens. Thus, researchers are now in the quest of finding or formulating an effective pharmacological approach which has a minimal side effects on the patient.

Recent increase in understanding of the molecular mechanisms of depression and anxiety has provided alternative molecular targets for these disorders. In particular, receptors within the glutamate, g-aminobutyric acid and neuropeptide systems provide a diversity of drug targets, and molecular biological and behavioral studies of these receptors have revealed the important roles they play in depression and anxiety (Chaki et al., 2019). In the review conducted by Krishnan and Nestler (2008), they took note of some neurobiological systems that were previously unexplored in depression. Particularly, they were able to highlight from the study of Zarate et al. (2006) that sub-anaesthetic doses of intravenously infused ketamine (a non-competitive NMDA (N-methyl-D-aspartate) glutamate receptor antagonist and psychotomimetic) produce a rapid but transient antidepressant effect on individuals with treatment-resistant depression. This effect suggests that depressive symptoms can be improved by altering the actions of glutamate, the major excitatory neurotransmitter in the brain.

GABA is the principal neurotransmitter mediating neural inhibition in the brain (Luscher et al., 2011). GABA is the major inhibitory neurotransmitter in the brain—it acts as the "brakes" of neural activity—and its dysfunction is implicated in a wide range of neuropsychiatric disorders. Currently used antidepressants are designed to enhance the function of serotonin, or less often, norepinephrine. These drugs are ineffective for about 40 percent of patients and they suffer from a characteristically slow therapeutic onset, taking weeks before patients notice any significant improvement. This slow mode of therapeutic action indicates that the mechanism of these drugs is only distantly related to their direct targets. Instead, the current work suggests that these drugs ultimately act by enhancing the function of GABA-releasing interneurons. Indeed, earlier research in the Lüscher lab has shown that these drugs can alleviate a depressive-like brain state in mice that was induced by genetic defects in GABA transmission. Thus, antidepressants that act through serotonin or norepinephrine ultimately appear to normalize defects in GABA transmission, suggesting that new drugs that target GABA signaling may be effective antidepressants (Sholtis, 2016).

In the review article of Madaan and Wilson (2009), they emphasized that there is increasing evidence that some neuropeptides, including substance P, corticotropin-releasing factor, neuropeptide Y, vasopressin and galanin, may have relevance in both depression and anxiety. As mentioned in the previous section of this paper, galanin is a regulatory 29-30-amino acid peptide, widely distributed in the nervous system and gut. The pathways of these neuropeptides are perceived to be possible targets for novel approaches in depression treatment. Integration of anatomical, physiological and clinical evidence suggests that modulation monoaminergic transmission is the most likely mechanism by which neuropeptides may work in this disorder. An example of these evidences is the study of Steinberg et al. (2001) about selective blockade of neurokinin-2(NK_2) receptors which revealed that NK_2 receptor blockade may constitute a novel mechanism in the treatment of depression and CRF (Corticotropin-Releasing Factor)-related disorders.

Researchers are also considering the potential antidepressant effect of chromium in our system. Chromium plays a crucial role in glucose and fat metabolism and improves insulin sensitivity in the hypothalamus, which enhances hypothalamic function by increasing glucose use, leading secondarily to an

increased synthesis of serotonin, norepinephrine and melatonin (Horacek et al.,1999 & McCarty 1994 as cited by Lang & Borgwardt, 2013). Lang & Borgwardt, 2013 three pilot trials of chromium from the studies of McLeod et al. (1999); McLeod et al. (2000); and Davidson et al. (2003) which indicate an antidepressant effect in patients with unipolar depression when used as adjunctive or monotherapy.

With the emerging antidepressant approaches presented above, we could say that the main problem with our current available antidepressant drugs have a profound side effects on the patients. Specific targeting solutions are needed to alleviate the depression that is prevailing in our modern society.

V. Summary

Depression is a mental condition regarded as having loss of interest or pleasure, low mood and accompanying emotional, cognitive, physical and behavioral changes. Depression can affect people from all walks of life. Suicidal behavior often manifested by most depressed people leads to mortality and morbidity. The problem of depression is a serious concern that needs to be properly addressed. Looking into the different lenses help us to better understand and offer solutions to the problem.

Molecular mechanisms of depression are described in this paper in terms of its genetic and physiological-metabolic, neurological and cardiovascular- aspects. Evidences show that there is genetic contribution and increased risk of heredity for depression. Family history alone does not mean a person will develop depression. Two types of models are used to explain the effect of the environment on depression which can be influenced by genetic factors. The gene-environment correlations describe the genetic control of exposure to the environment. Several features of this model such as sources of stress, depressive symptoms and disorders vary from every person and may have specific relations to genes. Most measures of stress have moderate heritability. In gene-environment interactions, different or partially overlapping gene play a major role in the development of personality traits including affective temperaments in the involvement of environmental factors and its interaction on these elements in the development of depression. Depression during pregnancy is a relevant condition that affects maternal behavior and child's future mental health. BDNF, SLC6A4, CREB1, and TNF are the major shared genes of persons experiencing depression and at risk of suicide. The main shared deficient pathways are generally disordered dopaminergic, serotonergic, and immunologic pathways in neuronal projections. SLC6A4 and SLC6A2 are the main therapeutic targets of the treatments for depression. Depression can be also associated with abnormalities in the neurochemicals of the brain. Medications that affect the level of norepinephrine and serotonin improves the symptoms of depression. The core hypothesis of depression as a stress-related disorder is that chronic stress yields corticosteroids which impair the corticosteroid-receptor signaling and is a key risk factor for an individual to be prone to stress-related disorders. General metabolic risk factors indicate the heterogeneity of the associations of depression into various somatic metabolic processes. Hormones like ghrelin and leptin to have great influence in mood regulation and treatment of depressive symptoms. Impairments in the IGF-1 system might be responsible for clinical abnormalities observed in major depressive disorder and cognitive dysfunction. A close and bidirectional relationship exists between depression and cardiovascular disease. Major depression is associated with an increased risk for cardiovascular diseases, such as coronary artery disease and myocardial infarction. Various pathophysiological mechanisms underlie the risk of cardiovascular disease in patients with depression.

Tricyclic anti-depressants, selective serotonin reuptake inhibitors (SSRIs) and norepinephrine reuptake inhibitors (SNRIs) are the common and traditional treatments for depression. Most antidepressant therapy have undesirable side effects and often discourages the patients to comply with the therapeutic regimen. Understanding the molecular mechanisms of depression has provided alternative molecular targets. Depressive symptoms can be improved by altering the actions of glutamate in the brain, enhancing the

function of GABA-releasing interneurons, selective blocking of neurokinin-2 (NK2) and considering the potential effects of chromium, based on various studies.

VI. Conclusion

The enormous quantity of studies conducted to explore depression is a proof that we have plenty of information about this disorder. Despite of numerous advances made in the context of psychiatric care for depression, only few of these ideas are being deciphered by people. This causes people to underestimate the profound consequences that this disorder could inflict to its sufferer. Molecular and physiological information collected and analyzed in this paper have described that depression is more than just a psychological disorder. Its genetic aspects indicated that the mental health of parents, particularly mothers, could affect the mental health of their offspring later in life. This implies that health care providers and families should also boost not only the physiological health of the pregnant mother but also her mental health. Several genes were also noted to be common among individuals experiencing depression. These genes could provide possible avenue for future treatments and medications for depression. Metabolic, neurological and cardiovascular consequences of depression have given us an idea that depression can both lead to and be caused by some somatic and environmental variables. Its complex mechanism in the body demands a broad-spectrum solution or treatment. Most of the available medications target the mechanisms of neurotransmitters and hormones. However, this characteristic of available medications and interventions for depression poses problems to patients. These medications often have undesirable side effects on the body of the patient and thus, risking the health of patients in general. The challenge right now for our scientists is to develop medications or interventions for depression which are safe and effective in alleviating depression among its sufferers. Based on the studies that were analyzed, our knowledge about the genetic aspects of depression offers promising starting points in developing safe and more specific treatments for depression. Indeed, the molecular mechanism of depression is so complex to decipher that we could not totally exterminate its occurrence in the society even with our current medical advances. However, with continuous review and innovation in the field psychiatric care, this disorder could become more manageable in the future.

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