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DEPRESSION AS A DYSFUNCTION OF IMMUNE SYSTEM: A REVIEW

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Abstract: Researchers worldwide, in the recent years have expanded our understanding of how, and the degree to which, the immune system interacts with the nervous system, and vice versa. The immune system is important for the protection of the body against injury and disease. In the past several decades, the association between stress and immune function has received considerable attention. By initiating changes in the hypothalamic-pituitary-adrenal axis and the immune system, chronic stress acts as a trigger for anxiety and depression. Both experimental and clinical evidence shows that a rise in the concentrations of proinflammatory cytokines and glucocorticoids, as occurs in chronically stressful situations and in depression, contribute to the behavioural changes associated with depression.

Defects in serotonergic function are associated with hypercortisolemia and increased pro-inflammatory cytokines associated with depression. Glucocorticoids and proinflammatory cytokines promote the conversion of tryptophan to kynurenine. In addition to the resulting reduction in brain serotonin synthesis, this leads to the formation of neurotoxins such as the glutamate agonist quinolinic acid, which contributes to increased astrocyte, oligodendroglial, and neuronal apoptosis. The importance of the inflammatory hypothesis of depression is that it raises the possibility that psychotropic drugs with central anti-inflammatory activity will become a new generation of antidepressants.

Chronic stress-induced neuroendocrine and immune system dysregulation is associated with psychological and physiological disorders, including depression. Several recent clinical and preclinical evidences suggest that neuroinflammation is a key factor interacting with three neurobiological correlates of major depressive disorder: brain serotonin Deficiency, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, and alterations in the continued production of adult neurons generated in the dentate gyrus of the hippocampus.

We are pleased to introduce a new overview series in this month's issue. Depression and their interaction as immune system dysfunction. An overview of how depression affects immune function is provided, and the literature evidence on various intrapersonal and interpersonal factors that may exacerbate or mitigate the health effects of depression is reviewed. Also, we have introduced new medications for depression and improvements in brain stimulation as a future treatment.

Keywords: Glucocorticoids, Pro-inflammatory cytokines Hypercortisolemia, Hypothalamic-pituitary-adrenal (HPA), Chronic stress-induced neuroendocrine.

Introduction

The immune system is essential to protect the body from injury and disease. However, the immune system does not work alone. It works in concert with another highly complex system designed to maximize survival: peripheral neurons, spinal cord, and brain.

Major depression is a common and sometimes fatal condition identified by the World Health Organization as the leading cause of disability worldwide. Antidepressants are undoubtedly an effective treatment in about 70% of cases, but a significant proportion of patients are partially or completely non-responsive to treatment. There is no simple explanation for treatment resistance, but current antidepressants may not be effective in targeting all of the pathological processes responsible for the main symptoms of depression.

In today's world, depression has become one of the most common and difficult social disorders, affecting approximately 4.4% to 25% of the population worldwide. Depression has a variety of symptoms, including behavioral changes, loss of interest and enjoyment in daily activities, fatigue, insomnia, and constant weight gain and loss. [1]

The relationship between activation of the immune system's inflammatory response and depression has long been known. Depressive symptoms and associated stress were initially associated with a decrease in learned immune system natural killer (NK) and T cells, suggesting that decreased NK activity is a reliable predictor of depression. I was. These effects are due to elevated levels of corticotropin-releasing hormone (CRH) in the CNS, which reduces immune responses, particularly NK cell numbers, and regulates the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis. is activated. Cortisol suppresses the immune response. It was later found that depression is directly related to the secretion of inflammatory cytokines such as IL-1, IL-6 and TNF-α secreted by the innate immune system. cell. These cytokines increase both the CRH and HPA axes, disrupt glucocorticoid receptor function, and create a self-reinforcing inflammatory cascade. Other molecular mechanisms triggered by cytokines such as IL-2, IFN-α lead to the degradation of tryptophan, a precursor of serotonin and thus known to cause depression.[2]

Therefore, there is an urgent need to expand the targets that antidepressants are designed to act on. All currently available antidepressants have been developed based on the monoamine hypothesis of depression. This hypothesis suggests disruption of biogenic amines in the limbic and cortical circuits as the cause of the main symptoms of depression.

Antidepressants are therefore believed to work by correcting these abnormalities. However, in recent years, changes in the endocrine system and immune system have attracted attention for the interrelationship between the brain and peripheral organs (connection between the "mind and body"), and changes in the endocrine system and immune system have led to pathological changes in the brain. plays a big role in depression. Inflammation is thus beginning to emerge as a major factor contributing not only to depression and other major psychiatric disorders, but also to the medical disorders often associated with mental illness.

Major depressive disorder (MDD) is one of the most common and devastating psychiatric disorders, with an estimated prevalence of 15% in the general population (Andrade et al., 2003). MDD is twice as common in women as it is in men. MDD is known to dramatically increase the risk of premature death from common conditions such as suicide and vascular disease. Our understanding of the neurobiology of depression stems from the serendipitous discovery of the antidepressant properties of drugs that increase monoamine neurotransmission in the brain. This knowledge was reinforced by his findings of two other important mechanisms of depression: alterations in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis and changes in adult neurons in the dentate gyrus of the hippocampus. Possible role of continuous production. [3]

The concept of a dysfunctional immune system, which plays a major role in mental health, can be traced back to ancient times. Over the last 30 years, clinical and experimental evidence for

Over the past two decades, much attention has been focused on the role of immunomodulators and immunotransmitters, especially pro- and anti-inflammatory cytokines. Maes et al. reported that interleukin-6 (IL-6), an important pro-inflammatory cytokine, is elevated in the blood of depressed patients. They also found that about 45% of patients treated with the pro-inflammatory cytokine interferon-alpha (IFN) developed major depressive symptoms that ended when the cytokine was discontinued. Recently, a meta-analysis of nine cytokines in major depression evaluated 24 studies and concluded that only basal levels of IL-6 and TNF were significantly elevated. Such clinical observations suggest that proinflammatory cytokines contribute to the major symptoms of depression and now form the basis of the inflammation, cytokine, or inflammatory response hypothesis of depression.[4]

History

What was once known as melancholy and is now known as clinical depression or major depressive disorder or simply depression and is commonly referred to by many medical professionals as major depressive disorder has a long It has a history, and similar disorders date back at least to classical times.

The term depression comes from the Latin verb deprimere, to become depressed. From the 14th century, to be depressed meant to submit or to feel better. and was used in a similar sense by the English writer Samuel Johnson in 1753. The term is also used in physiology and economics.

In the 20th century, German psychiatrist Emil Kraepelin was the first to distinguish between manic depression. The influential system proposed by Kraepelin integrated almost all types of mood disorders into manic depression. Kraepelin began with the assumption of underlying brain pathology, but also promoted the distinction between intrinsic (intrinsic) and extrinsic (extrinsic) types. We have defined the term known as manic depression. This mental health condition results in mood swings such as: B. Emotional ups and downs. Manic depression and bipolar disorder are considered the same because of these mood swings.[5]

Glossary of Depression Terms

Anxiety Disorders: Chronic disorders that cause anxiety. Some people with depression also have an anxiety disorder.

Bipolar disorder: A form of depression that can cause extreme mood swings between depression and mania (or hypomania). This condition was previously called manic depression.

Hypomania: Mild manic state.

Mania: A stage of bipolar disorder. Mania is periods of intense energy, euphoria or irritability, insomnia or light-headedness.

Dysphoric Mood: Depressed mood including dissatisfaction, restlessness, or depression.

Dysthymia Persistent Depressive Disorder A type of chronic low-grade depression milder than major depression. It can take years. Dysthymia does not disable a person, but it prevents them from functioning normally or feeling better. In the modern diagnostic system, dysthymia with chronic major depressive disorder (major depressive episodes lasting more than 2 years in adults and more than 1 year in children and adolescents) is referred to by the general term "persistent depressive disorder." ”.

Hypothyroidism: A condition in which the thyroid gland does not produce enough thyroid hormone. This can lead to symptoms of depression, fatigue, weight gain, and other health problems. Medical diagnosis of clinical depression. Causes symptoms such as low energy, fatigue and hopelessness. [6-10]

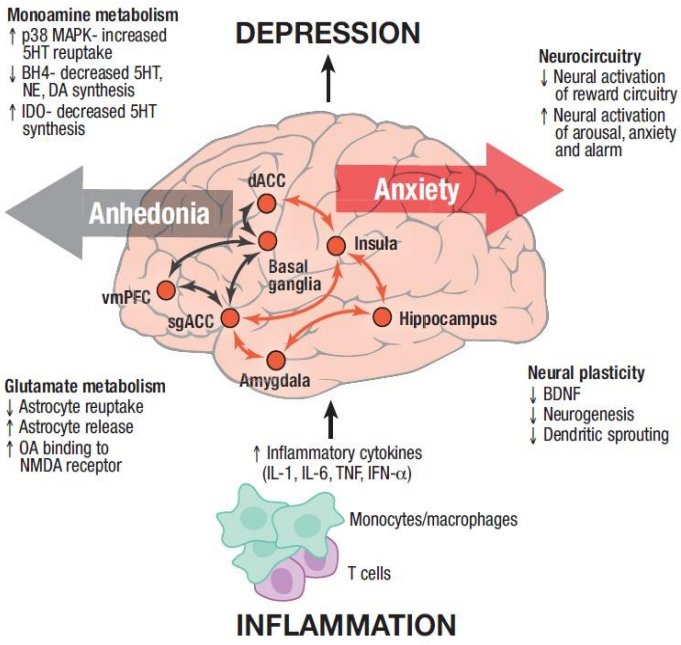

Fig: Impact of inflammation on brain and behaviour

Inter-relationship between cytokines and brain function: relevance to depression?

Until recently, the brain was considered to be an immunologically privileged organ that was protected from the peripheral immune system by the blood-brain-barrier. It is now apparent that this view is incorrect and that the brain is directly influenced by peripherally derived cytokines, chemokines, prostenoids and glucocorticoids, as well as some immune cells, that can access the brain and thereby influence those neuronal networks that appear to be malfunctioning in depression. The influence of large molecules from the periphery on the brain is somewhat surprising as specific transporters for peptides such as the interleukins do not appear to be present at the blood-brain-barrier. Nevertheless, there is now experimental evidence to indicate that such molecules could access the brain a) via a leaky blood-brain-barrier that occurs in major depression, b) by activation of endothelial cells that line the cerebral vasculature and produce inflammatory mediators inside the barrier c) by binding to cytokine receptors associated with the vagus nerve and thereby signalling inflammatory changes in the brain via the nucleus tractus solitarius and hypothalamus. Once in the brain, the proinflammatory cytokines activated both neuronal and non-neuronal (for example, the microglia, astrocytes and oligodendroglia) cells via the nuclear factor-kappa-beta (NF-kB) cascade in a similar manner to that occurring in the peripheral inflammatory response.[11]

There is also evidence from clinical studies that peripherally administered cytokines can enter the brain. Thus, therapeutic administration of IFN to patients with hepatitis results in cerebrospinal fluid (CSF) increases in IL-6 and monocyte chemoattractant protein (MCP-1) as well as IFN. Experimental studies have shown that MCP-1 activates microglia to release IL-1 and TNF. Inflammatory response in the brain. In addition, proinflammatory cytokines modulate the release of biogenic amine neurotransmitters. Recently, much attention has been paid to the activation of the tryptophan–kynurenine pathway by these cytokines, which redirect tryptophan from the synthesis of serotonin to the synthesis of kynurenine. We will discuss the importance of this signaling pathway in more detail later, but it is clear that it is an important mechanism by which serotonergic function declines in depression. It also reduces the activity of the dopaminergic system in response to inflammation. For example, IFN reduces the synthesis of dopamine by reducing the concentration of the cofactor tetrahydrobiopterin (BH4), thereby reducing the synthesis of dihydroxyphenylalanine (DOPA), the immediate precursor of dopamine from tyrosine. Since IFN increases nitric oxide synthesis by activating his BH-4 dependent enzyme, nitric oxide synthase, in microglia, decreased dopaminergic function is thought to be associated with increased nitric oxide. increase. This gaseous neurotransmitter is known to activate the glutamatergic system, promoting apoptosis and neurodegeneration when physiological limits are exceeded. [12]

Cytokines and their signaling pathways have been shown to promote the reuptake of monoamine neurotransmitters, thereby reducing functionally important intersynaptic concentrations in the brain. For example, IL-1 and TNF have been shown to activate the serotonin transporter on neurons by stimulating the p38 mitogen-activated protein kinase pathway.

In addition to regulating neurotransmitter function, proinflammatory cytokines contribute to key symptoms of depression by activating the HPA axis by increasing the release of CRF, thereby contributing to major depression. Contributes to the characteristic hypercortisolemia. The mechanism by which cytokines induce hypercortisolemia involves desensitization of glucocorticoid receptors, resulting in glucocorticoid resistance. Both brain and peripheral receptors become desensitized to glucocorticoid activation. Although the exact mechanism by which proinflammatory cytokines cause glucocorticoid receptor insensitivity is unknown, cytokines are known to activate the inflammatory cascade. This activates the NF-kB, p38MAPK, and 5-STATS (Signal Transducer and Activator of Transcription 5) pathways, inhibits translocation of the glucocorticoid receptor from the cytoplasm to the nucleus, and reduces the active form of the receptor. To do. Although glucocorticoid receptor resistance appears to be correlated with increased serum levels of proinflammatory cytokines, it is unlikely that glucocorticoid resistance is directly related to the psychopathology of depression. Even in those who do not, pro-inflammatory cytokines are increased, leading to glucocorticoid resistance even in the absence of significant changes in mood. reveals the fact that many aspects of cell-mediated and humoral immunity remain unsuppressed, despite elevated plasma glucocorticoid concentrations, a hallmark of the disease.[13]

The role of stress and proinflammatory cytokines.

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In addition to modulating neurotransmitter function, proinflammatory cytokines contribute to the core symptoms of depression by activating the HPA axis by increasing the release of CRF, thereby contributing to major depression. contribute. Contributes to characteristic hypercortisolemia. The mechanism by which cytokines induce hypercortisolemia involves desensitization of glucocorticoid receptors, resulting in glucocorticoid resistance. Both brain and peripheral receptors are desensitized to glucocorticoid activation. Although the exact mechanism by which proinflammatory cytokines cause glucocorticoid receptor insensitivity is unknown, cytokines are known to activate the inflammatory cascade. It activates the NF-kB, p38MAPK, and 5-STATS (Signal Transducer and Activator of Transcription) Signaling pathways, inhibits translocation of the glucocorticoid receptor from the cytoplasm to the nucleus, and releases the active form of the receptor. Decrease. make. Although glucocorticoid receptor resistance appears to be correlated with elevated serum levels of inflammatory cytokines, it is unlikely that glucocorticoid resistance is directly related to the psychopathology of depression. Even in those who do not, proinflammatory cytokines are elevated, leading to glucocorticoid resistance even in the absence of significant mood swings. It points to the fact that many aspects of humoral immunity are not suppressed. [14]

The mechanisms by which psychological stress influences both peripheral and central inflammatory cascades are coordinated by the autonomic nervous system. Thus, after activation of the sympathetic nervous system, release of norepinephrine and adrenaline leads to activation of both alpha- and beta-adrenergic receptors on immune cells, thereby leading to the NF-kB cascade, particularly in macrophages and the peripheral nervous system. The release of pro-inflammatory cytokines is initiated via activation of blood monocytes; antagonists of these adrenergic receptors block stress-induced increases in these cytokines. Conversely, stimulation of the parasympathetic nervous system has the opposite effect on stress-induced inflammatory responses. Thus, stimulation of the vagus nerve releases acetylcholine, which activates the α-7 subunit at nicotinic receptors and reduces NF-kB activation. The antidepressant effects of vagus nerve stimulation, which is sometimes used to treat resistant depression, may be associated with such anti-inflammatory effects.[15]

Why does inflammation occur in depressed patients despite the frequent observation of elevated glucocorticoids? A possible explanation is that stress-induced increases in the sympathetic nervous system, combined with steroid resistance, contribute to the fact that most types of immune cells are not suppressed. It is said that it leads to the activation of the globules, resulting in an inflammatory state.[16]

Serotonin, stress and depression

Among the numerous neurotransmitters hypothesized to be dysfunctional in major depression, serotonin is widely implicated in roles that contribute to the symptoms of the disorder (sleep disturbance, depressed mood, anorexia, decreased libido, and anxiety). Serotonin modulates the stress axis by activating the corticotropin-releasing factor pathway in the paraventricular nucleus, thereby increasing corticotropin release from the anterior pituitary. There is a close relationship between plasma cortisol concentrations and the serotonergic system. Thus, stress-induced increases in cortical concentrations are associated with increased serotonin turnover, a change associated with stimulation of the rate-limiting enzyme tryptophan hydroxylase in the pathway leading to the synthesis of serotonin from tryptophan. Chronic stress, which leads to a sustained increase in cortisol, has the opposite effect, decreasing the release of serotonin. This is associated with the glucocorticoid activation of tryptophan dioxygenase in the liver whereby tryptophan is diverted from serotonin synthesis down the tryptophan-kynurenine pathway.[17]

Increased anxiety and dysadjustment to chronic stress observed in both animals and humans are mediated by altered functional activity of 5HT1A somatodendritic receptors located in the median nucleus raphe and localized to the hippocampus. I can explain. Experimental studies have shown that rats housed in stressful and crowded environments exhibit increased anxiety that correlates with reduced functional activity of 5HT1A receptors. These receptors are affected by mineralocorticoid receptors that inhibit 5HT1A receptor activity under conditions of chronic stress. In contrast to 5HT1A receptors, 5HT2 receptors are activated by chronic stress, whereas 5HT1B receptors function as autoreceptors, thereby controlling transmitter release and are activated by chronic stress. Therefore, stress-induced changes in circulating glucocorticoids may help explain the reduced functional activity of serotonergic systems in depression.[18]

However, this evidence was mainly provided by experimental studies. What is the evidence from clinical trials? In some depressed patients in remission, administration of tryptophan-deficient amino acid drinks can induce acute depressive reactions. This change is associated with hypersecretion of cortisol. Plasma prolactin and cortisol elevations in depressed patients after acute administration of the serotonin-releasing agent fenfluramine are reduced in depressed patients, as is growth hormone secretion in response to tryptophan challenge. provide additional evidence for the importance of serotonin in disease. This is not only because of serotonin's mood-regulating role, but also because of its direct action on the endocrine axis. Results from experimental and clinical studies clearly demonstrate that chronic stress as a result of hypercortisolemia induces alterations in the serotonergic system and plays an important role in the development of anxiety and depression. [19]

Stress, depression and neurodegeneration.

The focus of this review is on the adverse effects of pro-inflammatory cytokines that likely cause cell damage at the pathological level in the brain and periphery. However, it should be remembered that these same cytokines at physiological concentrations provide trophic support for neurons, promote neurogenesis and contribute to normal cognitive function. When cytokines are present at pathological levels, such effects are severely impaired, with important changes for the psychopathology of depression. Thus, in major depression, prolonged activation of inflammatory networks in the brain results in decreased neurotrophins, decreased neuronal repair, decreased neurogenesis, and reduced activity of glutamatergic signaling pathways. catabolism is increased, leading to neuronal apoptosis, oxidative stress, and oxidative stress. Stress contributes to the induction of astrocyte and oligodendrocyte apoptosis. [20]

In addition to the proinflammatory cytokines, nitric oxide and the glucocorticoids, glutamate plays a crucial role in the pathological processes that are associated with depression. The proinflammatory cytokines, and inflammatory mediators such as nitric oxide, increase glutamate release and decrease the expression of glutamate transporters on astrocytes and oligodendroglia thereby decreasing glutamate reuptake and enhancing the inter-synaptic concentration.

Stimulation of the extra-synaptic N-methyl-D-aspartate (NMDA) glutamate receptor not only causes excitotoxic damage to the neurons and astrocytes but also results in a decrease in synthesis of brain derived neurotrophic factor (BDNF), a key neurotrophic factor governing neuronal repair. To add to the potential neurotoxic changes, IL-1 and TNF, that are generally raised in depression, trigger the release of reactive oxygen and nitrogen species from activated microglia and astrocytes; these are toxic to both neurons and oligodendroglia. The net result of these changes is a loss of astrocytes and oligodendroglia, and neuronal apoptosis particularly in the subgenual prefrontal cortex, the amygdala and the hippocampus, brain regions that are thought to be crucially involved in the genesis of the symptoms of depression. [21-25]

Questions are currently being raised about the possible association of proinflammatory cytokines, excess glutamate, and the neurotoxic effects of the tryptophan-kynurenine pathway. Tryptophan is metabolized through her two main pathways. One leads to the synthesis of serotonin and the other leads to kynurenine and kynurenic acid. In the latter pathway, tryptophan is degraded by indoleamine-2,3-dioxygenase (IDO). This enzyme is fairly widespread in peripheral tissues and the brain. It is also degraded by tryptophan-2,3-dioxygenase (TDO), which is found primarily in the liver. Localized and metabolized. IDO is activated by inflammatory cytokines and TDO by glucocorticoids. Both cytokines and cortisol are elevated in major depression, so it is not surprising that tryptophan-kynurenine signaling is elevated. Anti-inflammatory cytokines reduce the activity of this pathway. After kynurenine formation, there are two main pathways leading to tryptophan metabolism. Kynurenine hydroxylase first metabolizes kynurenine to 3-hydroxykynurenine, then he to 3-hydroxyanthranilic acid and quinolinic acid. This signaling pathway is enhanced in depression and dementia. In glia and neurons, 3-hydroxykynurenine increases the formation of reactive oxygen species and quinolinic acid activates NMDA glutamate receptors, thereby promoting apoptosis. In contrast, kynurenine is metabolized by kynurenine aminotransferase to the neuroprotective end product kynurenic acid, which is an antagonist of the NMDA receptor. In the brain, tryptophan metabolism by IDO occurs in both microglia and astrocytes. Microglia synthesize both her 3-hydroxyanthranilic acid and quinolinic acid, whereas astrocytes mainly produce kynurenic acid. Astrocytes also metabolize quinolinic acid, which can reduce the effects of neurotoxins under physiological conditions. However, in chronic depression, activated microglia overproduce neurotoxins that are poorly metabolized by astrocytes. [26-28]

Depression and its negative effects on immune system

The brain isn't the only organ that reflects the negative effects of depression. The cardiovascular, digestive and reproductive systems are also affected. This is why depression is characterized by a wide variety of symptoms that affect every part of an individual's life. The immune system is also often affected by depression. Depression is also believed to affect the immune system. As you know, the immune system is responsible for keeping us healthy by fighting off common infections. A weakened immune system gradually reduces its ability to protect us from any potential threat, leaving our bodies at risk posed by common infections. leads to this. Left untreated, depression is thought to affect the immune system by reducing its ability and power to fight common infections. Patients diagnosed with depression would be expected to have a higher incidence of colds and infections than healthy individuals. Stress is often thought to trigger depression. Stress is also known to cause inflammation in the body, easily leading to heart disease, heart attack, stroke, and other potentially life-threatening conditions. The result is inflammation and a weakened immune system. Indeed, a scientific study published in the Archives of General Psychiatry has some pretty interesting results. [29-36]

Treatment

Antidepressant: A drug used to treat depression. Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressants that include drugs like citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), paroxetine (Paxil), and sertraline (Zoloft).

Monoamine oxidase inhibitors (MAOIs): A group of medicines sometime prescribed to treat severe depression. MAOIs increase the concentration of chemicals responsible for sending information for sending information between nerves in particular regions of the brain, which may lead to better mental functioning.

Electroconvulsive therapy (ECT): A treatment for depression performed under general anaesthesia that uses an electric current to create a brief, controlled seizure. It is safe and often effective for depression that hasn't responded to drugs or therapy or when symptoms are so severe that a rapid response is especially important.

Light therapy: (Also called phototherapy) Therapy consisting of exposure to light and mimics sunlight. It may help treat some forms of depression.

Mood Stabilizers: A class of drugs used to treat some types of depression, like bipolar disorder. They include lithium and some drugs originally used for seizures called anticonvulsants. These include carbamazepine (Tegretol), divalproex (Depakote), and Lamictal (lamotrigine).

Psychotherapy: A way of treating a mental or emotional disorder by talking with a therapist. It may be called 'talking therapy' or 'talk therapy'. **[37-40]**

Advances in the treatment for Major Depressive disorder

Major depressive disorder is the most widespread mood disorder in the world. Also called clinical depression, or just depression, it's when you have symptoms of low mood or hopelessness for at least 2 weeks. Scientists still don't know what causes it. But they know that treating it is complex and that people who have it need more ways to feel better faster.

For about half a century, scientists have put a lot of effort into improving medications that target a small set of neurotransmitters. Those are chemicals in the brain serotonin, norepinephrine, and dopamine in particular, that affect how your nerve cells talk to each other, which then affects your mood.

Most people respond to standard antidepressants. But at least 30% of people who try two different kinds of these drugs continue to have symptoms of depression. That's called treatment-resistant depression.

So, over the past 2 decades, scientists have changed how they think about treatment for major depressive disorder as their understanding of the brain biology behind depression has changed.

The biggest change is that medication research has gone past only targeting certain neurotransmitters. (e t al Gerard Sanacora).

New Medications and Faster Results

There's a long-held idea that depression takes weeks or months to resolve. But new fast-acting treatments have "changed what we think is possible in the field," (e t al Gerard Sanacora).

In 2019, the FDA approved **Brexanolone** (Zulresso). It's the first drug specifically for postpartum depression, which is a type of major depression. Experts aren't exactly sure how it works. But it's a human-made version of a steroid your body makes naturally. It affects your GABA receptors, which help regulate mood.

Brexanolone isn't as easy to take as other antidepressants. You get it through a vein in your arm at a health care facility over the course of 60 hours. But it can work quickly. Your depression symptoms might start to lift by the end of your treatment.

Esketamine is a prescription nasal spray. The low-dose psychedelic drug boosts the activity of glutamate in parts of your brain related to mood. Glutamate's job is to excite cells in the brain and nervous system. Esketamine can trigger new connections in your brain too. You may start to see improvements in your depression within hours or days of using it. (e t al Sanacora)

Esketamine offers lifesaving hope for people with suicidal thoughts and relief for people with treatment-resistant depression. But used alone, symptom relief may only last a couple of weeks. That's why experts agree you should take rapid-onset drugs alongside traditional treatments.

As for those with mild or moderate depression, study suggests cognitive behavioral therapy, followed by conventional antidepressants also known as selective serotonin reuptake inhibitors (SSRIs). Doctors need more information on the safety and long-term effects of newer treatments for depression.

"Over the past 20 years, we've had a transformative change in the way we treat depression," "But we still have to smooth it out to understand for which patients these treatments are best and when." (e t al Sanacora).

Improvements in Brain Stimulation as a Future Treatment

Medications aren't the only treatment for depression. Electroconvulsive therapy has been around for more than 70 years. It remains one of the most effective ways to manage major depressive disorder, especially if you don't respond to other treatments. While it isn't new, scientists have fine-tuned the procedure over the past decades.

Today, electroconvulsive therapy uses less energy than it did in the past. The goal is to give you the same benefits but with less negative impact on your memory and thinking skills. "That's been a huge improvement," (e t al Susan Conroy)

There is use of transcranial magnetic stimulation to treat depression, which has fewer side effects than electroconvulsive therapy. It works by sending magnetic pulses around your skull.

Brain tissue translates these signals into electrical energy, which changes the way areas of your brain talk to each other. "By changing that circuitry, we think that's how transcranial magnetic stimulation gets people better from depression." (e t al Conroy)

Lots of other promising treatments for depression are on the horizon. Deep brain stimulation is one. In this treatment, a surgeon implants electrodes in your brain. These nodes send painless zaps that alter the electrical activity that's causing your symptoms.

You can think of this treatment kind of like a pacemaker for your mood. While it's not approved for the general public, it might be soon.

Researchers are also studying a drug called SAGE-217 (Zuranolone). There's interest in how it might help prevent a serious relapse in people with a history of depression. The idea is that you'd take it as soon as your symptoms come back. "But you don't wait until the symptoms are full-blown." (e t al Sanacora). [41]

Conclusion

Living with depression is certainly not easy. Especially when we know that we are exposed to serious and life-threatening risks every day. Depression affects all aspects of a patient's life, robbing them of the opportunity to lead a normal life until effective treatment options completely eliminate depressive symptoms. And when we say depression puts people at life-threatening risk, we really mean it. There is also the risk of developing infections, autoimmune diseases, and even AIDS as a result of depression. In summary, depression also affects your immune system and puts your life at risk. Don't hesitate - get treatment for depression as soon as possible to prevent it from taking over your life further and putting you at risk!

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