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Alternative Therapeutic Strategies for the Treatment of Depressive Disorders- A Review

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Abstract

Depression like many diseases is pleiotropic but unlike Alzheimer's disease and cancer it is still largely marked out and falls into the dark shadesfor human illness. Depression is a social stigma which causes failure in the treatment of the disease despite the use of various conventional anti-depressants. The patient undergoes different symptoms such as Sadness, tearfulness, emptiness, or hopelessness. The various depressive disorders mentioned in the review highlight the role of biological differences, Neurotransmitters, Hormones in pathophysiology of depression. The review mentions several anti-depressants used as conventional treatment like SSRIs, TCAs, MAOIs. This review addresses the definition, causes, evaluation, treatment, and the prevalence of repurposing the drug for the treatment of depression. Finally, the review briefly sparks emerging targets for antidepressant drug discovery and the novel effects of rapidly acting antidepressants, without any side effects.

Keywords: Ascorbic acid, Depression, Major Depression, Noradrenaline

Introduction

Depression is one of the major mental disorders and involves a triad of symptoms with low or depressed mood, anhedonia, and low energy or fatigue [1]. It affects up to 25% of women and 12% of men and is a highly chronic disorder [2]. Antidepressant drugs used in the treatment of major depressive disorders are believed to act on the central monoaminergic systems mainly 5-HT and nor-adrenergic synaptic neurotransmissions. Selective serotonin reuptake inhibitors (e.g., fluoxetine) and nor-adrenaline reuptake inhibitors (e.g., reboxetine) are the most prescribed antidepressant drugs [3]. Since about one-third of the depressed patients show only partial or no response to these drugs [4], so there is a great need for the discovery of more effective and better-tolerated antidepressants.

Mental illnesses are one of the primary causes of worldwide health problems. Depressive and anxiety disorders were the two most damaging mental disorders, according to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019, both ranking among the top 25 main causes of burden worldwide in 2019. [5, 6] This burden was substantial across the lifespan, for both sexes, and in a variety of settings. 2 Perhaps more crucially, despite clear evidence of therapies that minimize their impact, there has been no reduction in global prevalence or burden for either illness since 1990. [7]

The COVID-19 pandemic has resulted in a significant increase in the prevalence and burden of major depressive disorder and anxiety disorders. Increases in the incidence of major depressive disorder and anxiety disorders were linked to rising SARS-CoV-2 infection rates and reduced human mobility in 2020. The combined consequences of the virus's transmission, lockdowns, stay-at-home orders, reduced public transportation, school and company closures, and fewer social interactions

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were all factored into these two COVID-19 impact indicators. The nations severely hit by the pandemic in 2020 would have the highest rise in the prevalence of these illnesses [8].

Symptoms

Although depression might strike only once in a lifetime, most people have several episodes. Symptoms can last for most of the day, almost every day, and include [9,10]Sadness, tearfulness, emptiness, or hopelessness, Loss of pleasure or interest in most or all typical activities, such as sex, hobbies, or sports, Sleep problems, such as insomnia or sleeping too much, Tiredness and a lack of energy, making even simple chores more difficult.A decrease in appetite and weight reduction, or a rise in food desires and weight gain, Trouble thinking, concentrating, making decisions, and remembering things

Pathophysiology of Depression:

Depletion of NE, 5-HT, and DA presynaptic reserves resulted in a depression-like state. In contrast to the effects of reserpine, some patients receiving iproniazid, a tuberculosis drug that boosted brain concentrations of NE and 5-HT by blocking the metabolic enzyme MAO, experienced euphoria, and hyperactive behavior. Monoamine oxidase is a flavin-containing enzyme found in nerve terminals, the liver, intestinal mucosa, platelets, and other organs. It is found in mitochondrial membranes and is widely dispersed throughout the body in nerve terminals, liver, intestinal mucosa, platelets, and other organs. MAO-A preferentially deaminates epinephrine, norepinephrine, and serotonin, and is selectively inhibited by clorgyline of the two primary molecular forms of MAO [11]. MAO inhibitors suppress this enzyme system, resulting in a decrease in metabolism and an increase in the quantities of certain chemicals. In FST, therapy with CGP56433A, a selective GABAB receptor antagonist, reduced immobility both acutely and chronically. As a result, GABAB receptor antagonism could be used to develop new antidepressants [12]. The neurological basis of depression has been linked to an imbalance in glutamate function. In a variety of experimental paradigms in laboratory animals, NMDA receptor antagonists have an antidepressant-like effect [13]. The major regulator of the stress response, the hypothalamic-pituitary-adrenal (HPA) system, is now thought to play a role in the pathophysiology of depression. When the HPA axis is activated, the paraventricular nucleus of the hypothalamus produces corticotropin-releasing factor (CRF), which stimulates the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland, which stimulates the release of glucocorticoids from the adrenal gland (primarily cortisol in humans and corticosterone in rodents). Hypothyroidism and major depression symptoms overlapped, indicating a link between the hypothalamic-pituitary-thyroid (HPT) axis and mood disorders. In depressive patients, the levels of thyrotropin-releasing hormone in the CSF were shown to be higher, but not in all cases [14]. Somatostatin levels in the CSF (which limit the production of growth hormones, CRH, and ACTH) are also lowered in depression. Stress, whether acute or chronic, is known to raise Substance P levels in numerous parts of the brain. New antidepressant medications based on substance P antagonists of neurokinin 1 (NK1) receptors are gaining popularity [15]. In FST, neuropeptide Y was shown to have an antidepressant-like effect [16]. In depressing illness, there was an increase in the synthesis of interleukin (IL-1, IL-2, IL-6, and IL-8), interferon, and tumor necrosis factor-alpha (TNF-) [17]. Clinical research suggests that depressed patients have higher amounts of prostaglandin E2 (PGE2) in their plasma. Antidepressants such as tricyclics and MAO inhibitors restored central neurotransmission by lowering cytokine and PGE2 levels in the brain [18]. Nitric

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oxide appears to play a role in both stress susceptibility and adaptability, according to neurobehavioral and molecular studies [19]. There is compelling evidence that the BDNF has a role in both the etiology of depression and the mechanisms of antidepressant activity [20]. Several medications enhanced BDNF expression in the rat brain as well as in depressed patients. Stress reduces CREB (Cyclic AMP response element-binding protein) expression in the hippocampal formation [21]. SSRIs, NRIs, MAOIs, and ECS (electroconvulsive seizure therapy) are among the antidepressants that increase CREB expression in the hippocampus and cerebral cortex. As a result, CREB has emerged as an intriguing, shared target for many antidepressant classes [22].

Depression symptoms in children and teens

The signs and symptoms of depression in adolescents and teenagers are like those in adults, with notable exceptions.Sadness, irritability, feelings of worthlessness, anger, poor performance or poor attendance at school, feeling misunderstood and extremely sensitive, using recreational drugs or alcohol, eating, or sleeping too much, self-harm, loss of interest in normal activities, and avoidance of social interaction are some of the symptoms that teens may experience [23].

Depression symptoms in older adults

Depression is not a natural aspect of aging, and it should never be dismissed. Unfortunately, depression in older individuals is frequently undiagnosed and untreated, and they may be hesitant to seek help. In older persons, depression symptoms may be different or less noticeable, such asMemory difficulties or personality changes**,** Physical aches or pain**,** Fatigue, loss of appetite, sleep problems or loss of interest in sex — not caused by a medical condition or medication**,** often wanting to stay at home, rather than going out to socialize or doing new things andSuicidal thinking or feelings, especially in older men [24].

Causes

It's not known exactly what causes depression. As with many mental disorders, a variety of factors may be involved, such as:

- Biological differences—Depressed people seem to have physical changes in their brains. The importance of these changes is still unknown, although they may eventually aid in the identification of causes.
- Neurotransmitters are naturally occurring brain chemicals that are thought to play a function in depression. Changes in the function and action of these neurotransmitters, as well as how they interact with neurocircuits important in maintaining mood stability, have recently been discovered to play a role in depression and its therapy.
- Hormones-Changes in the body's hormone balance may play a role in the development or onset of depression. Hormone shifts can occur during pregnancy and in the weeks and months following birth (postpartum), as well as because of thyroid disorders, menopause, and a variety of other diseases.
- Inherited traits- People with depression are more likely to have blood relatives who also suffer from it. Researchers are looking for genes that may play a role in the development of depression

It's natural to feel down now and then, but if you're sad all the time and it's affecting your daily life, you might be suffering from clinical depression. It's a condition that can be treated with medication,

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talking to a therapist, and making lifestyle changes.Depression comes in a variety of forms. Some are caused by events in your life, while others are caused by chemical changes in your brain [25].

Types of Depression

1. **Major Depression**

This may be referred to as "major depressive disorder". If you're depressed most of the time, most days of the week, you probably have this type.Other symptoms you may have had toinclude Loss of enjoyment or interest in your hobbies, Weight increase or loss, having trouble sleeping or feeling sleepy throughout the day,feeling restless and agitated, or otherwise very sluggish and slowed down physically or mentally, beingexhausted, and lacking energy,feeling worthless or guilty, having trouble concentrating or making decisions. You may diagnose with major depression if you have five or more of these symptoms on most days for two weeks or longer. At least one of the symptoms must be a depressed mood or a loss of interest in activities. Major depression manifests itself in various ways in different people. Melancholy is characterized by profound sadness and a loss of interest in previously enjoyed activities. Even when nice things happen, you feel horrible. You might also: You've lost weight, you've been sleeping poorly,you've had suicidalthoughts, if you have melancholic depression, your symptoms may be worse first thing in the morning. Consider enlisting assistance with your first tasks of the day. Even if you don't feel hungry, make sure to eat regularly, Agitated Most of the time, you are uneasy [26].

When therapy and medication aren't working, other options are

- Electroconvulsive therapy (ECT) [27].
- Transcranial magnetic stimulation (TMS) [28].
- Vagus Nerve Stimulation (VNS) [29]

ECT uses electrical pulses, TMS uses a special kind of magnet, and VNS uses an implanted device. All are designed to stimulate certain areas of brain activity. This helps the parts of your brain that control your mood work better.

2. **Persistent Depressive Disorder** [30]

Persistent depressive disorder is defined as depression that lasts for at least two years. Previously known as dysthymia (low-grade persistent depression) and chronic severe depression, this word is now used to designate two illnesses.Symptoms may include changes in appetite (not eating enough or overeating), Sleeping too much or too little, Lack of energy or weariness, Low self-esteem, Trouble concentrating or making decisions,feeling hopeless. Psychotherapy, medicine, or a combination of the two may be used to treat you.

3. **Bipolar Disorder** [31].

Bipolar illness, sometimes known as "manic depression," is characterized by mood swings that vary from high energy and an "up" mood to low energy and a "depressive" mood.When you're in a low phase, you'll have strong depressive symptoms.Medication can help bring your mood swings under control.

The FDA has approved three medicines to treat the depressed phase:

- Seroquel
- Latuda

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- Olanzapine-fluoxetine combination

  Other medicines, such as the anticonvulsant lamotrigine or the atypical antipsychotic Vraylar, are often prescribed "off-label" for bipolar depression.

  Traditional antidepressants aren't always advised as first-line therapies for bipolar depression since studies show that they're no better than a placebo (a sugar pill) at treating depression in persons with the disease. In addition, several standard antidepressants may raise the risk of inducing a "high" phase of illness or increasing the frequency of having additional episodes over time in a small number of persons with bipolar disorder.Psychotherapy can also assist you and your family in coping.

4. **Seasonal Affective Disorder (SAD)** [32].

   Seasonal affective disorder (SAD) is a type of serious depression that occurs most frequently during the winter months, when the days grow shorter and the amount of sunlight available decreases. In the spring and summer, it usually goes away. Antidepressants can aid people with SAD. Light therapy can also help. You'll need to spend 15-30 minutes each day in front of a very bright lightbox.

5. **Psychotic Depression** [33].

   Hallucinations (seeing or hearing things that aren't there) People with psychotic depression have both profound depression and "psychotic" symptoms, such asFantasies (false beliefs), Anxiety (wrongly believing that others are trying to harm you). Psychotic depression can be treated with a combination of antidepressant and antipsychotic medications. ECT is also a possibility.

6. **Peripartum (Postpartum) Depression** [34].

   Peripartum depression is defined as serious depression in the weeks and months following childbirth. In the peripartum period, about one out of every ten men suffers from depression. Antidepressantmedications can aid in the same way that they can in the treatment of serious depression that is unrelated to childbirth.

7. **Premenstrual Dysphoric Disorder (PMDD)**At the start of their period, women with PMDD experience depression and other symptoms.You may also have the following symptoms in addition to depression: Mood fluctuations,Irritability,Anxiety, Difficulty Concentrating,Fatigue, Changes in eating or sleep patterns, Feelings of being overwhelmed. PMDD can be treated with antidepressants or, in certain cases, oral contraceptives [35].

8. **'Situational' Depression: -**This isn't a technical term in psychiatry. However, if you're having trouble coping with a major life tragedy, such as a family death, divorce, or job loss, you may be depressed. This is "stress response syndrome."A stressful situation can often trigger a depressive episode, and psychotherapy can help you overcome it. [36].

9. **Atypical Depression: -**This is not the same as the constant sadness that comes with depression. It's a "specifier" that describes a particular pattern of depressive symptoms. If you suffer atypical depression, a pleasurable experience can temporarily lift your spirits. Symptoms include Increased hunger,sleeping more than normal,feeling of heaviness in your arms and legs, Oversensitivity to criticism are some of the other signs of atypical depression.Antidepressants might be helpful. An

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SSRI is a first-line treatment (selective serotonin reuptake inhibitor).They may also suggest an older form of antidepressant known as an MAOI (monoamine oxidase inhibitor), which is a well-studied class of antidepressants for treating atypical depression[37].

10. **Treatment-Resistant Depression:** - About a third of individuals who are treated for depression fail to respond to several treatments. If this sounds like you, you might have treatment-resistant depression. Your depression could be resistant to therapy for a variety of reasons. Other medical concerns, for example, could make treating your depression difficult.If you've been diagnosed with depression that hasn't responded to treatment, Electroconvulsive therapy (ECT) may be helpful in this situation. [38].

Anti-depressants along with their limitations: Serotonin and noradrenaline reuptake inhibitors are used to treat major depression, mood disorders, and possibly, but less commonly, attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety disorders, menopausal symptoms, fibromyalgia, and chronic neuropathic pain (SNRIs). SNRIs raise brain levels of serotonin and norepinephrine, two neurotransmitters that play a key role in mood regulation.

CATEGORIES OF ANTI-DEPRESSANTS:

Selective serotonin reuptake inhibitors (SSRIs)are the most often prescribed antidepressants (SSRIs). They are less harmful than other antidepressants and are effective in the treatment of depression.Serotonin reuptake inhibitors (SSRIs) block serotonin from being reabsorbed in the brain. This makes it easier for brain cells to receive and deliver messages, resulting in happier, more stable moods.They're called "selective" because they only seem to affect serotonin, not other neurotransmitters.The following are possible adverse effects of SSRIs and SNRIs hypoglycemia(lowblood sugar), hyponatremia (low sodium),nausea,rash, dry mouth, constipation or diarrhea, weight loss, sweating,tremor drowsiness, sexual dysfunction, sleeplessness,headache,dizziness,anxiety, and agitation. Examples include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline [39].

There have been reports that people who use SSRIs and SNRIs, and especially those under the age of 18 years, may experience thoughts of suicide, especially when they first start using the drugs.

Tricyclic antidepressants (TCAs): - Tricyclic antidepressants (TCAs) acquire their name from the fact that they have three rings in their chemical structure. They are used to treat depression, fibromyalgia, and some types of anxiety and can help manage chronic pain.Tricyclics may have the following side effectsepilepsy,sleeplessness,anxiety, arrhythmia (irregular heartbeat), hypertension,rash, nausea and vomiting, stomach cramps, weight loss, constipation, urine retention,increased pressure on the eye [40].Examples include amitriptyline,amoxapine-clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and trimipramine.

Monoamine oxidase inhibitors (MAOIs): - This type of antidepressant was commonly prescribed before the development of SSRIs and SNRIs.It inhibits monoamine oxidase, a brain enzyme. Monoamine oxidase is a protein that aids in the breakdown of neurotransmitters such as serotonin.If less serotonin is broken down, there will be more circulating serotonin. In theory, this should lead to more stable moods and less anxiety.If SSRIs haven't worked, therapy is increasingly turning to MAOIs. Because MAOIs interact with a variety of different drugs and foods, they are often reserved

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for cases where other antidepressants have failed. Side effects include blurred vision,rash,seizures,edema, weight loss or gain, sexual dysfunction,diarrhea, nausea, and constipation,anxiety, insomnia and drowsiness,headache,dizziness, arrhythmia, or irregular heart rhythm, fainting, or feeling faint when standing up, arrhythmia, or irregular heart rhythm [41].

Noradrenaline and specific serotoninergic antidepressants (NASSAs): -Anxiety disorders several personality disorders, and depression are all treated with these.Constipation, dry mouth, and weight gain are all possible adverse effects, as are tiredness and sedation, impaired vision, and dizziness.Seizures, white blood cell decrease, fainting, and allergic responses are among the more significant side effects.Examples include Mianserin and Mirtazapine. [42].

Withdrawal symptoms

Unlike some other drugs, antidepressants do not require ongoing dose increases to get the same effect. In that sense, they aren't addictive.When you stop taking an antidepressant, you won't have the same withdrawal symptoms as you would if you stopped smoking.However, when people stop using SSRIs and SNRIs, more than a third of them develop withdrawal symptoms.Symptoms lasted from 2 weeks to 2 months and included anxiety, dizziness, nightmares or intense dreams, bodily sensations like electric shocks, flu-like symptoms, discomfort in the abdomen, in most cases, symptoms were mild. [43].

Potential antidepressants: -The following are the vitamins and anti-viral agents which have the potential to be used as anti-depressants

1. **Pyridoxine**: Pyridoxine also known as vitamin B6 exists in three isoforms: pyridoxine, pyridoxal, and pyridoxamine and has been used in the pharmacotherapy of Alzheimer's disease, hyperactivity, autism, anxiety disorder, etc. [44]. The deficiency of pyridoxine is responsible for the emergence of depression [45].and the level of PLP is suggested to be inversely associated with depressive symptoms [46].Further, the higher intake of vitamin B6 is known to lower the incidence of depression [47].It has been reported that the lower level of 5-HT increases the risk of the development of depression [48). Pyridoxine has been shown to increase the level of 5-HT [49].by promoting the uptake of tryptophan in the brain [50]. and by increasing its conversion into 5-HT [51]. Pyridoxine also reduces the level of nitrite in the brain and the latter has been implicated in the pathogenesis of depression and is known to modulate the level of 5-HT. These lines of evidence suggested that pyridoxine may play a key role in the treatment of depression and should be explored for its antidepressant-like effect.
2. **Ascorbic acid**: - Ascorbic acid (AA) (reduced form of vitamin C) is an important antioxidant responsible for the maintenance of synaptic activity [40] and homeostatic mechanisms inside the neurons [52]. AA recycles tetrahydrobiopterin [53] and the latter acts as a cofactor for the enzyme tryptophan hydroxylase involved in the synthesis of 5HT [54]. AA thus promotes the synthesis of 5-HT implicated in the pathogenesis of depression [55]. Depression itself is accompanied by a reduced level of AA in the brain [56]. Thus, the reduced level of AA is responsible for the 5-HT deficit and contributes to the emergence of depression and related symptoms [57]. AA also confers antagonism at NMDA receptors [58], alters the redox state of NMDA receptors [59], and inhibits the glutamate mediate excitotoxicity [60]. Further NMDA receptor stimulation is responsible for the increased expression of enzyme neuronal nitric oxide synthase (nNOS) further responsible for the increased production of NO [61]. Further, the inhibition of NMDA receptor and NO confer antidepressant-like effects in various animal models [62]. AA through its antagonistic action at NMDA receptor

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suppresses the synthesis, production, and bioavailability of NO [63]. These lines of evidence suggested that the AA deficiency is responsible for the emergence of depression and AA supplementation may improve the outcomes in depression. AA also promotes the synthesis of 5-HT and counteracts the production of NO.

3. **Amantadine: -**In the 1960s, amantadine hydrochloride, a synthetic tricyclic amine, was first used as a preventative antiviral drug to treat influenza A virus infection [64]. Amantadine is now approved for the treatment of Parkinson's disease as a monotherapy or in combination with levodopa or dopaminergic agonists [65]. Amantadine appears to act via several pharmacological mechanisms, none of which has been identified as the primary mode of action. It is a dopaminergic, noradrenergic, and serotonergic substance that inhibits monoaminoxidase A and NMDA receptors and appears to increase beta-endorphin and beta-lipotropin levels [66]. However, which of these actions is relevant in therapeutic doses is still unknown. One novel aspect is amantadine's antiviral effect on the Borna disease virus, which is thought to play a role in affective disorders. All these actions could be considered antidepressant properties, and it has been proposed that amantadine may act as an antidepressant not through a single mechanism, but through several mechanisms thought to be related to the antidepressant activity [67]. This ‘‘wonder" molecule has been discovered to play a ‘‘dual role" in a variety of neurological disorders. There is evidence that it plays a significant role in the pathophysiology of major depression. Norepinephrine, serotonin, dopamine, and glutamate, the key neurotransmitters involved in the neurobiology of major depression, are all modulated by nitric oxide. Various new generations of antidepressants have been shown to have nitric oxide modulatory action. Amantadine is an uncompetitive NMDA receptor inhibitor that enters the open state of the channel (associated with NMDA receptors), binds to its blocking site, and stays there for a prolonged amount of time [68]. Aside from inhibiting NMDA receptors, amantadine also stabilizes the glutamatergic system and protects neurons against NMDA toxicity [69]. Because NMDA receptors are linked to nNOS, NMDA receptor activation is responsible for the production of NO [70]. Treatment with amantadine has been demonstrated to lower NO production as a result, amantadine affects NO levels, which are known to have a role in the development of depression.
4. **Lithium: -**Lithium is exclusively used to treat depression caused by bipolar illness. When combined with an antidepressant, it may be useful for other types of depression, but further research is needed Lithium is one of the most studied agents used to augment the pharmacologic effect of antidepressant drugs, particularly in refractory depression [71]. Continued work to decipher lithium’s molecular actions will likely lead to the development of not only improved therapeutics for BD, but to neurotrophic enhancers that could prove useful in the treatment of many other illnesses [72]. The anti-suicidal effect of lithium during its long-term administration has been demonstrated and should also be considered as the element of personalized medicine for the pharmacological prophylaxis of patients with mood disorders [73]. As a result, lithium may be useful as a short-term treatment for those suffering from manic episodes.

Conclusion: Although there are a lot of varieties of the anti-depressants used in various neurological disorders, they come along with certainmerits and limitations which affect the overall development of the patient.

Henceforth, it can be concluded that Amantadine, Vitamin C, Vitamin B6, and Lithiumcan serve as the best treatment alternatives in depression due to their negligible sideeffects.

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