REVIEW ARTICLE

Modern Approaches to Depression: From Monoamines to Medicinal Plants and Neuromodulation

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Abstract

One of the most common mental health conditions in the world, depression severely reduces social functioning, productivity, and personal well-being. Over 300 million people are impacted globally, and by 2040, it is expected to overtake all other causes of disability. A thorough discussion of major depression, also known as major depressive disorder, is given here, along with an examination of its complex etiology, which includes genetic, neurochemical, and sociocultural factors. Its pathogenesis is primarily characterized by the dysregulation of the hypothalamic-pituitary-adrenal axis, glutamatergic signaling, and monoaminergic transmitters including dopamine, serotonin, and norepinephrine. Due to their delayed onset, adverse effects, and resistance to therapy, conventional antidepressant therapies such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors remain first-line treatments. In addition, this review covers new approaches to treatment, including psychedelic-assisted therapy, brain stimulation techniques such as electroconvulsive therapy, transcranial magnetic stimulation, deep brain stimulation, and vagus nerve stimulation and rapid-acting pharmaceuticals such as ketamine and esketamine. The use of medicinal plants such as *Withania somnifera*, *Curcuma longa*, *Hypericum perforatum*, and others demonstrates promise due to their multi-targeted action, safety, and accessibility. These phytochemicals modulate neurotransmitter activity, reduce oxidative stress, and support neurotrophic factors. A holistic and personalized treatment approach, integrating pharmacotherapy, neurostimulation, and complementary herbal medicine, may optimize outcomes in depression management. Addressing stigma, increasing early diagnosis, and ensuring mental health-care accessibility remain imperative. Future research should focus on novel drug targets, patient-tailored therapies, and bridging the gap between traditional and modern practices.

Key words: Antidepressants, major depressive disorder, medicinal plants, neuromodulation, treatment-resistant depression

INTRODUCTION

Globally, around 450 million individuals struggle with mental or behavioral disorders, and in many places, access to care is restricted.[1] In 2022, the World Health Organization reinterpreted mental health as "a state of mental well-being that enables people to cope with the stresses of life.and contribute to their communities."[2] The idea that "mental disorders are like any other health illness" highlights both its biological foundation and the necessity of treating it fairly. Emotion, perceptions, ideas, and behavior essential components of the self are impacted by mental illnesses.[3] Despite increased understanding, people with mental illness are frequently underappreciated in all societies.[4] The WHO emphasizes that "mental health is essential to overall health,"[5] and it stated in 1948 that the combination of social, mental, and physical well-being was the definition of health. Nonetheless, the word "complete" has come under fire for being unattainable.[6] An estimated 1.8 billion people between the ages of 5 and 19 lived in the world in 2014. Research from 27 different

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nations reveals varying perspectives on mental disease.[7] In 2002, the prevalence of mental illness among industrial workers in India varied from 14% and 37%, while in Western countries it was over 75%. This disparity may have been caused by methodological discrepancies or protective aspects of culture.[8] According to the GBD research (2017), there are 45.7 million cases of depressive illness and 44.9 million cases of anxiety worldwide,[9] with depression being recognized as a serious health issue.[10]

DEPRESSION

Around 350 million individuals worldwide suffer from depression, which the WHO predicts will overtake all other causes of disability by 2040.[11,12] Although it may be treated, stigma and lack of availability frequently keep people from getting treatment.[12] Over the course of their lives, around 17% of Americans suffer from severe depression, and in some other countries, the prevalence is higher.[13] It is the leading cause of disability,[14] affecting over 300 million people globally and prevalent in both developed and developing nations.[15] The name "depression" comes from the Latin word depressio, indicating "to press down," reflecting its harsh emotional toll. Unlike normal melancholy, depression is a persistent, incapacitating condition.[16] Even when there is no overtly depressed mood, it can start after stressful circumstances in life and frequently manifests as physical symptoms.[17] It significantly impairs quality of life and productivity, ranking as the third leading cause of disability-adjusted life years and the second leading cause of years lived with impairment.[18]

Depression often manifests as a variety of physical and cognitive symptoms, including poor mood and loss of interest. In addition to being prevalent among young people, it disproportionately affects women.[13,19] The Foundation for Mental Health states that depression can strike anyone at any stage of life[20] and that mental health is a reflection of how people handle life's obstacles.[21] Persistent melancholy, emptiness, or irritation, together with considerable functional impairment, are the DSM-5's definitions of the term, which originated in the latter part of the century to describe intense sadness.[12,22]

SIGNS AND SYMPTOMS

According to the DSM-IV, a persistently depressed mood or a notable lack of enjoyment or enthusiasm are prerequisites for diagnosing depression. Sleep difficulties, psychomotor abnormalities, changes in appetite or weight, exhaustion, low self-worth, guilt or worthlessness, difficulty concentrating, and thoughts or acts of suicide are examples of supporting symptoms.[23]

Daily life is severely hampered by major depressive disorder (MDD), frequently more so than by many long-term physical ailments. Sadness, worry, hopelessness, impatience, guilt, exhaustion, trouble concentrating, change in appetite, sleep problems, and unexplained physical concerns are typical symptoms.[24] These symptoms have a significant negative influence on functioning and can last for months or years. Anhedonia, exhaustion, disturbed sleep and appetite, suicidal thoughts, guilt, and poor mood are the usual clinical manifestations of depression.[25-27]

PATHOPHYSIOLOGY OF DEPRESSION

There are significant clinical ramifications to comprehending the biochemical underpinnings of severe depressive disorder. One important early idea postulated that mania is caused by the overactivity of monoamine neurotransmitters, including dopamine (DA), serotonin (5-HT), and norepinephrine (NE), whereas depression is caused by a lack of these neurotransmitters. Although less well-defined than in bipolar illness, genetic variables may nonetheless be important in an unipolar depressive condition.[28,29]

Arousing curiosity about the function of the hypothalamic-pituitary-adrenal (HPA) axis was the dexamethasone suppression test. Despite not always being the case, many sad people exhibit elevated HPA activity.[30,31]

AVAILABLE PHARMACOLOGICAL TREATMENT

Early antidepressants, such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), were developed in 1960s as a result of the monoamine insufficiency theory. Subsequent understanding of the function of serotonin resulted in the usage of serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs), which are currently first-line treatments.[32]

MAOIs, SSRIs, SNRIs, TCAs, and atypical antidepressants are the four primary types of antidepressants in Table 1.[33]

In the 1980s, research on serotonin replaced NE, which led to the widespread usage of SSRIs. Their limited impact in severe circumstances and delayed effect, however, continue to be issues.

Antidepressants primarily function by blocking receptors, inhibiting monoamine-degrading enzymes, and preventing monoamine reuptake.[34] It is only one aspect of treating depression. Comorbidities, psychosocial variables, and suicide risk should all be taken into account during a clinical evaluation before beginning medication.[35]

The majority of studies originate from wealthy nations. The prevalence of primary care depression in India varies

between 21% and 83%.[36] There is a significant disparity between the age group most frequently treated (over 45) and the highest prevalence age (14–25 years), indicating that therapy in young people is delayed. Potential contributing variables include stigma and underdiagnosis, underscoring the necessity of youth-focused education and anti-stigma initiatives.[37] Although SSRIs represent a significant development in treatment, the exact processes underlying antidepressants' use are still unknown.[38]

INVESTIGATING INNOVATIVE DEPRESSION TREATMENT APPROACHES

About 4.4% of people worldwide suffer from severe depression (MDD), which contributes significantly to behavioral health-related disability that is linked to detrimental outcomes such as obesity, committing suicide, and cardiovascular disease. These adverse effects highlight the necessity of more potent, quicker-acting, and more palatable drugs, especially when the current ones are not working.[43]

NOVEL TARGETS FOR RAPID-ACTING ANTIDEPRESSANTS

Potential as a quick-acting antidepressant is demonstrated by ketamine, a non-selective N-methyl-D-aspartate (NMDA) receptor blocker. It may be more effective and cause fewer negative effects to target particular NMDA subtypes or use modulators. Muscarinic receptor antagonists like scopolamine have also demonstrated quick antidepressant effects. According to these results, the glutamate synapse is a prime target for the creation of short-acting depression medications.[44,45]

EXPERIMENTAL PHARMACOLOGICAL TREATMENT: THE ROLE OF KETAMINE

An anesthetic at first, ketamine has become a viable treatment for patients who are not responding to electroconvulsive therapy (ECT). Its antidepressant effects, which have been observed since 2000, are associated with glutamatergic system antagonism of NMDA receptors. Ketamine, when administered IV at a dose of 0.5 mg/kg for 40 min, has shown benefit in animal and clinical models of depression.[46-48]

ADVANCES IN ANTIDEPRESSANT RESEARCH: FOCUS ON KETAMINE

Conventional antidepressants that alter monoamine neurotransmission usually take 2–3 weeks to start working and do not work for 30–40% of patients. Due to these restrictions, new treatments with quicker onset have been created, like ketamine, a well-known anesthetic that acts on the NMDA receptor instead of the monoaminergic system.[49]

Intranasal, intramuscular, intravenous, sublingual, and oral delivery methods have all been examined for ketamine, a racemic mixture of (S)-ketamine and (R)-ketamine. The intravenous injection offers constant dose and 100% bioavailability.[50] Single doses administered intravenously or intranasally can have positive effects on depression that last for a maximum of 7 days. At anesthetic dosages of 1–3 mg/kg, ketamine is stable and has been utilized to treat depression and pain at 0.1–1 mg/kg.[51]

Table 1: Overview of major antidepressant drug classes -mechanism, side effects, and examples

Class of drug	MOA	Side effect	Example	References
Selective Serotonin Reuptake Inhibitors	Increases serotonin by limiting its reabsorption or reuptake of serotonin.	Vomiting, nausea, diarrhea, pain, thirst, sleeplessness, anxiety, lightheadedness	Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, and Sertraline.	[39]
Serotonin-Norepinephrine Reuptake Inhibitors	reuptake inhibition of monoamines, serotonin, and noradrenaline.	Perspiration, bloating, nervousness, sleeplessness, vomiting, thirst, and trouble in urination	Duloxetine, venlafaxine, Desvenlafaxine, and milnacipran.	[40]
Tricyclic Antidepressants	Inhibition of neurotransmitter reuptake, increase of 5-HT and NE levels	Dry mouth, Unsteady vision Constipation suffering issues with peeing, putting on weight	Nortriptyline, clomipramine, imipramine, and amitriptyline.	[41]
Monoamine Oxidase Inhibitors	Inhibit both enzymes (MAO A and B) which metabolize monoamines such as serotonin, dopamine, and norepinephrine.	Headache vomiting High bp Blurred vision Insomnia	Isocarboxazid, Nialamide, Phenelzine, and Hydracarbazine selegiline.	[42]

Ketamine's S-enantiomer, esketamine, is an antagonist of the noncompetitive NMDA receptor. In 2019, the FDA approved it for use as a spray for the nose to treat depression that is resistant to treatment in combination with conventional antidepressants.[52]

DEPRESSION THAT IS UNRESPONSIVE TO TREATMENT: DEEP BRAIN STIMULATION (DBS)

One novel treatment for depression that is resistant to treatment (TRD) is deep neural stimulation (DBS), which involves surgically placing electrodes in particular brain regions.[53] These electrodes are attached to a rhythm generator, which is placed under the skin, usually in the chest, and offers continuous electrical stimulation.[54] DBS may work by depolarization blockade, neurotransmitter depletion, synaptic inhibition, or functional lesions, while the precise processes are still unknown. In areas that have been activated, both excitatory and inhibitory neuronal responses have been noted.[55,56]

ECT

When standard therapies fail to alleviate severe or treatment-resistant depression, ECT can be a useful alternative. It is usually given 2–3 times a week for 6–12 sessions under general anesthesia, using electrical stimulation to cause controlled seizures.[57] Though its exact processes are unknown, evidence indicates that ECT may have an impact on immunological response, neuroplasticity, neuroendocrine function, and monoaminergic transmission. ECT has demonstrated strong antidepressant effects in clinical settings, frequently surpassing conventional medicines in circumstances where treatment is not working.[58] ECT is still the most successful treatment for TRD, with remission rates of about 60%; nevertheless, other brain stimulation methods have been investigated due to concerns about stigma and neurological side effects.[59,60]

TRANSCRANIAL MAGNETIC STIMULATION (TMS)

TMS is a new approach for depression, especially for those who have depression that is intolerant to or resistant to treatment. Similar to conventional antidepressants, it has demonstrated efficacy by stimulating particular brain areas with short magnetic pulses.[61,62] The FDA has approved TMS for MDD since 2008; it targets specific cortical areas by using a pulsed magnetic field to cause neuronal depolarization.[63,64] Rare adverse effects like seizures have been documented, despite the medication's general safety and well-tolerated nature. TMS is a potentially effective non-invasive treatment for TRD in addition to vagus nerve stimulation (VNS).[65,66]

VNS

VNS stimulates the vagus nerve manually or electrically and was first used to treat epilepsy. In 2005, VNS was approved by the FDA to treat chronic depression that is resistant to therapy (TRD). Pregnancy-related concerns are unknown; it is safe, and it can be used in conjunction with ECT and medicines.[67] The treatment entails implanting a pulse generator surgically in the chest. This device sends electrical impulses to the left vagus nerves, which then affects different parts of the brain through the nucleus tractus solitarius. VNS was first approved for epilepsy in 1997 and then for TRD in adults who were not responding to many medications.[68] Cost, invasiveness, and limited coverage are the main obstacles to its use. Serotonin and NE are important neurotransmitters implicated in depression, and research indicates that VNS raises their levels in the brain.[69,70]

PSYCHEDELIC THERAPY

Substances known as psychedelics function as agonists of the serotonin 5-HT receptor, changing sensory perception and causing effects such as visual hallucinations. Lysergamides, DMT, psilocybin, and mescaline are examples of common psychedelics. Increased sensory awareness brought on by these medications is sometimes characterized as a spiritual experience that promotes harmony with the cosmos. The release of glutamate after 5-HT2A receptor stimulation may be the cause of their antidepressant effects.[71] Psycholytic therapy, which was used to relax the mind or spirit, was the precursor to psychedelic therapy in Europe in the 1950s.[72,73]

ROLE OF MEDICINAL PLANTS AS ANTIDEPRESSANTS

Through methods other than monoamine modulation, such as HPA axis regulation, antioxidant and anti-inflammatory actions, and neurotrophic factor support like brain-derived neurotrophic factor, medicinal plants have been investigated for their potential as antidepressants. *Withania somnifera* (ashwagandha), *Curcuma longa* (turmeric), and *Hypericum perforatum* (St. John's wort) are plants that contain phytochemicals such flavonoids, alkaloids, saponins, and terpenoids that have been proven to be effective in reducing the symptoms of depression. These substances may improve mood and resilience to strain by enhancing GABAergic, dopaminergic, and serotonergic transmission. Particularly for mild to severe depression or cases that are resistant to therapy, medicinal plants offer a promising alternative or supplemental treatment because of their safety and multi-target effects in Table 2.[74-76]

Table 2: Medicinal plants with antidepressant properties and their mechanisms of action

S. No.	Name of plant (Botanical name)	Chemical constituents	Uses in depression	Mechanism of action
1	*Hypericum perforatum* (St. John's Wort)	Hypericin, Hyperforin, Flavonoids, Hypericum[74]	Mild to moderate depression and anxiety[75]	Inhibition of monoamine re-uptake (5-HT, NA and DA)[76]
2	*Withania somnifera* (Ashwagandha)	Withanolides, Sitoindosides Alkaloids[77]	Antioxidant, anxiolytic, antidepressant, anti-inflammatory[78]	Modulates HPA axis, GABAergic, and serotonergic activity[79]
3	*Curcuma longa* (Turmeric)	Curcumin, diferuloylmethane Demethoxycurcumin[80]	Antidepressant, anti-inflammatory, antioxidant, neuroprotective[81]	Inhibits pro-inflammatory increases brain-derived neurotrophic factor (BDNF), modulates serotonin[82]
4	*Bacopa monnieri* (Brahmi)	Bacosides A & B, Alkaloids[83]	Enhance memory, reduce anxiety and depression[84]	Modulates serotonin (5HT1 and 5HT2) increase BDNF[85]
5	*Crocus sativus* (Saffron)	Crocins, Safranal, Crocetin, Picrocrocin[86]	Antidepressant, anxiolytic, antioxidative[87]	Antioxidant, anti-inflammatory, serotonergic, hypothalamus-pituitary-adrenal (HPA) axis-modulating and neuroprotective effects[88]
6	*Rhodiola rosea*	Rosavin, Salidroside rosin, Rosarin[89]	Antidepressant property[90]	Stimulates norepinephrine (NE), dopamine (DA), serotonin (5-HT)[86-91]
7	*Lavandula angustifolia* (Lavender)	linalool, linalyl acetate[92]	Anxiety, stress, and depression[93]	Modulates NMDA and GABA receptors, increases serotonin[94]
8	*Zingiber officinale* (Ginger)	Gingerols, Shogaols, Zingerone[95]	Antioxidant, tyrosinase inhibitory, anti-inflammatory, antidepressant[96]	Modulates serotonin (5HT1A)[97]
9	*Ocimum sanctum* (Tulsi)	Eugenol, Rosmarinic acid, Ursolic acid[98]	Antidepressant, antiepileptic, anti-inflammatory, antioxidant, hepatoprotective[99]	Increase the level of noradrenaline, 5HT, and dopamine[100]
10	*Panax ginseng*	Ginsenosides, Ginseng Polypeptides, Polysaccharides[101]	Insomnia, depression, anxiety[102]	Modulating the monoamine neurotransmitter system, regulating the function of the HPA axis[103]

CONCLUSION

Depression remains a complex, multifactorial disorder with profound global public health implications due to its high prevalence, chronicity, and impact on individual functioning and socioeconomic development. While traditional antidepressants such as SSRIs, SNRIs, TCAs, and MAOIs have formed the treatment backbone, their limitations such as delayed onset, side effects, and treatment resistance underscore the urgent need for more effective and rapid therapies. This review highlights advances including rapid-acting agents such as ketamine, neuromodulation techniques (TMS, ECT, DBS, and VNS), psychedelic-assisted therapy, and phytomedicine, which offer promising multi-target effects and improved safety. A deeper understanding of depression's neurobiology, involving monoaminergic, HPA axis, and glutamatergic dysregulation, supports more precise, personalized treatment strategies. Addressing stigma, enhancing mental healthcare access, and integrating pharmacological with psychosocial approaches are essential for lasting recovery. Future research should optimize these novel interventions, particularly through personalized medicine and expanded access in resource-limited settings, fostering innovation toward more effective, holistic depression management worldwide.

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