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Navigating Depression: Traditional and Emerging Therapies

Karuna Zambare[1]*, Sandesh Lodha[2], Chandana Ravula[3]
[1]*Texila American University, Guyana*
[2]*Uka Tarsadia University, Gujarat, India*
[3]*SASTRA University, Tamil Nadu, India*

Abstract

Major depressive disorder (MDD) is a severe illness marked by a minimum of one distinct episode of depression lasting for a minimum of 2 weeks. This period is defined by clear shifts in mood, interests, and pleasure, as well as alterations in cognitive function and vegetative symptoms. On a global scale, it is considered one of the primary causes of illness burden, especially in North America. The treatment landscape for major depressive disorder (MDD) heavily relies on serotonergic drugs, despite their limited efficacy, prompting the search for new mechanisms and targets. This has led to the exploration of other processes and targets in search of novel treatment approaches. Recent endeavors in drug discovery have produced some innovative candidates, although a significant number of them have proven unsuccessful in clinical testing. The pressing want for safer and more efficacious antidepressants highlights the significance of continuous research endeavors. A full discussion is provided on the development of clinical research on potential medications and recent advancements in the discovery of small-molecule therapeutics. The primary objective of the study is to offer a comprehensive assessment of the existing status of antidepressant therapy, with the goal of guiding future research endeavors. The review contributes to the collective effort to improve outcomes for individuals with Major Depressive Disorder (MDD) by explaining the intricacies of depression and the ongoing progress in drug research.

Keywords: *Major Depressive Disorder, Novel Molecules.*

Introduction

Major depressive disorder (MDD) is characterized by a persistently depressed state of mind. Low self-esteem is associated with anhedonia, the loss of interest or pleasure in typically pleasurable activities. Psychotic, atypical, seasonal, postpartum, melancholia, and catatonic subtypes of major depression are among examples [1, 2]. MDD is a debilitating illness characterized by the presence of at least one distinct depressive episode lasting a minimum of 2 weeks. This period is marked by noticeable alterations in mood, interests, and pleasure, as well as impairments in cognitive function and vegetative symptoms [6].

MDD, a significant health condition, impacts more than 15 million American adults annually, representing 6.7% of individuals aged 18 and above in the country. Depression is the primary cause of disability in the United States for individuals aged 15 to 44. MDD typically starts in individuals aged 20 to 30 and reaches its highest point between the ages of 30 and 40. It is more common in women than in men. According to the World Health Organization (WHO), major depression is currently ranked as the fourth largest contributor to the worldwide burden of illness, and the leading cause in North America [3, 4, 5].

This article majorly focuses on the treatment available for depression and

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****Corresponding Author: karunatalpate@gmail.com***

summarizes novel research that is ongoing to enhance the treatment of depression.

Materials and Methods

A literature search was carried out to understand on the current development and research ongoing in the depression therapy area. The details of these molecules were searched on electronic database (Embase, clinicaltrial.gov, molecule originator's company sites, abstracts in various conferences).

Results

Traditional Treatment and Management of MDD

Antidepressant medicines are commonly prescribed for those suffering from depression, however in exceptional cases they may also get psychotherapy or counselling. The primary objective of treatment is achieving remission. All antidepressants have equivalent efficacy in this regard (Table 1). Antidepressants have an impact on the general equilibrium of the three neurotransmitters in the brain that regulate emotions, stress responses, and the physiological needs for sleep, food, and sexual desire. Advocates of the monoamine theory argue that the selection of the most efficacious antidepressant should be based on careful consideration. Individuals who exhibit symptoms of anxiety, irritability, reduced energy levels, and diminished enjoyment of life can benefit from the administration of selective serotonin reuptake inhibitors (SSRIs) or serotonin noradrenaline reuptake inhibitors (SNRIs) [6, 7, 8].

These medications are important breakthroughs in MDD pharmacotherapy, but their limits show the need for safer, mechanistically innovative treatments.

Table 1. Antidepressants Commonly used in the Treatment of MDD

Antidepressants in used today for treatment of depression (the list is not exhaustive)		
Classes	**Pharmacological Targets**	**Mechanism of action**
Monoamino oxidase inhibitors (MAOi): Selegiline, Phenelzine	Monoamino oxidase enzymes (MAO-A and MAO-B)	Prevent 5-hydroxytryptamine (5-HT) degradation; increase 5-HT availability at the synapses
Tricyclic antidepressants (TCA): Amitriptyline, Imipramine, Nortriptyline	5-HT reuptake transporters; norepinephrine (NE) reuptake transporters	Inhibit NE and 5-HT reuptake transporters; increase 5-HT and NE availability at the synapses; bind to postsynaptic receptors for noradrenaline, histamine and acetylcholine
Selective serotonin reuptake inhibitors (SSRI): Fluoxetine, Paroxetine, Sertraline, Escitalopram	5-HT reuptake transporters	Specifically inhibit 5-HT reuptake, increasing 5-HT availability at the synapses
Noradrenaline and specific serotonergic antidepressants (NaSSA): Mianserin, Mirtazapine	a2 NE receptors 5-HT receptors	a-2 NE receptor antagonists that induce an increase in 5-HT and NE release; act as antagonists/agonists of several specific 5-HT receptors
Serotonin noradrenaline reuptake inhibitor (SNRI): Duloxetine Venlafaxine	5-HT receptors and NE reuptake transporters	Inhibit the reuptake of both 5-HT and NE, and increase their availability at the synapses

Atypical (multimodal) antidepressants: Bupropion, Vortioxetine, Agomelatine	5-HT receptors NE receptors Melatonin receptors *others	Bupropion acts as a DA and NE reuptake inhibitor; vortioxetine acts as an agonist/ antagonist of several 5-HT and NE receptors; agomelatine activates melatonergic receptors and antagonizes some 5-HT receptors

Table is adapted from - Tsugiyama LE. Drug Discovery Today. 2023 Dec 1;28(12):103804.

Emerging Treatment Options in MDD

Current treatments have low responsiveness and efficacy. Thus, stronger and safer antidepressants are urgently needed. We reviewed the literature on small molecules being developed to treat depression. Table 2 shows innovators' most promising depression drug targets.

Table 2. Small- Molecules being Investigated for their Potential to Treat Depression

Molecule code[13]	**Mechanism**	**Current stage of development[16]**	**Formulation**	**Chemical name**	**WHO ATC code**	**Company or Institute**
NV-5138	mTORC1 activator	Phase II Study (NCT05066672) Ongoing	Capsule, Liquid	(2S)-2-Amino-5,5-difluoro-4,4-dimethylpentanoic acid	N06A (Antidepressants)	Navitor Pharmaceuticals, Inc.
BTRX-335140 (also known as **NMRA-335140)**	KOR antagonist	Phase III study (NCT06058039, NCT06058013, NCT06029439, NCT06029426) ongoing	unspecified	1-[6-ethyl-8-fluoro-4-methyl-3-(3-methyl-1,2,4-oxadiazol-5-yl)quinolin-2-yl]-N-(oxan-4-yl)piperidin-4-amine	N07X (Other Nervous System Drugs)	Originator-BlackThorn Therapeutics Developer-Neumora Therapeutics
JNJ-54175446	brain-penetrant antagonist of the adenosine triphosphate (ATP)-gated P2X7 channel	Phase II study (NCT04116606) ongoing	Capsule, Suspension	Methanone, (2-chloro-3-(trifluoromethyl)phenyl)((4R)-1-(5-fluoro-2-pyrimidinyl)-1,4,6,7-tetrahydro-4-methyl-5H-1,2,3-triazolo(4,5-C)pyridin-5-yl)-	N06A (Antidepressants)	Janssen Pharmaceuticals

NSI-189`	Neurogenesis stimulants	Phase II study completed; No active trial was registered on ClinicalTrials.gov.	unspecified	(2-(Piperazin-1-yl)pyridin-3-yl)(4-(pyridin-4-ylmethyl)piperazin-1-yl)methanone	A10X (Other Drugs Used in Diabetes), N05B (Anxiolytics)N06A (Antidepressants), N07X (Other Nervous System Drugs), N07X-X (Other nervous system drugs)	Neuralstem Inc
GW679769	Neurokinin 1 antagonists	Two Phase II trial completed, No active trial was registered on ClinicalTrials.gov.	Injection, Tablet	(2R,4S)-4-(4-acetylpiperazin-1-yl)-N-{(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-2-(4-fluoro-2-methylphenyl)-N-methylpiperidine-1-carboxamide	A04A (Antiemetics and Antinauseants), G04B-D (Drugs for urinary frequency and incontinence), N05B (Anxiolytics), N05C (Hypnotics and Sedatives),N06A (Antidepressants)	GlaxoSmithKline
CERC-301 (MK-0657)	NR2B N-Methyl-D-Aspartate antagonists	Phase II study completed (NCT01941043, NCT02459236), Phase III study planned, No active trial was registered on ClinicalTrials.gov.	Capsule, unspecified	(3S,4R)-4-Methylbenzyl 3-fluoro-4-[(pyrimidin-2-ylamino)methyl]piperidine-1-carboxylate	C01 (Cardiac Therapy), N04 (Anti-Parkinson Drugs), N06A (Antidepressants)	Avalo Therapeutics; Merck & Co
AV-101	Kynurenine modulators; NMDA receptor antagonists	Phase II study completed (NCT03078322, NCT02484456).	Capsule, Powder, unspecified	(2S)-2-Amino-4-(2-amino-4-chlorophenyl)-4-oxobutanoic acid	C02 (Antihypertensives), N02B (Other Analgesics and Antipyretics), N03A (Antiepileptics), N04 (Anti-Parkinson Drugs), N05A (Antipsychotics), N07X (Other Nervous System Drugs)	Aerovate Therapeutics; Baylor College of Medicine; National Institute of Mental Health; VistaGen Therapeutics

HR-071603	AMPA receptor agonists; NMDA receptor antagonists	Phase I study completed (NCT04108234)	Intranasal spray	(2R)-2-(2-chlorophenyl)-2-(methylamino) cyclohexan-1-one	N06A-X (Other antidepressants)	Jiangsu Hengrui Medicine Co.
SUVN-911	Alpha4beta2 nicotinic receptor antagonists	Phase II study ongoing (NCT06126497)	Tablet	(1R,3S,5R)-3-[(6-chloropyridin-3-yl)oxymethyl]-2-azabicyclo[3.1.0]hexane	N06A (Antidepressants)	Suven Life Sciences
NRX-1074	NMDA receptor agonists	Phase II study completed (NCT02067793), No active trial was registered on ClinicalTrials.gov.	unspecified	(2R)-1-[(2S)-1-[(2S,3R)-2-amino-3-hydroxybutanoyl]pyrrolidine-2-carbonyl]-N-[(2S,3R)-1-amino-3-hydroxy-1-oxobutan-2-yl]-2-benzylpyrrolidine-2-carboxamide	N06A-X (Other antidepressants)	AbbVie; Gate Neurosciences ; Naurex
REL-1017	NMDA receptor antagonists	Phase III study completed (NCT04855747, NCT06011577)	Tablet, unspecified	3-Heptanone, 6-(dimethylamino)-4,4-diphenyl-, (S)	N07B-C02 (Methadone)	Relmada Therapeutics

Discussion

MDD continues to be a disorder characterized by an enigmatic underlying mechanism. Currently, there are no recognized biomarkers for Major Depressive Disorder (MDD). Although certain causal elements and physiological processes have been established, there is still a lack of a comprehensive theory that fully explains the pathology of MDD. Therefore, identifying specific pharmaceutical targets for the treatment of MDD is challenging [9]. Although there have been significant breakthroughs in the treatment of depression, a considerable number of patients still exhibit poor response to currently available antidepressant medications. As a result, researchers have been motivated to investigate alternate ideas and mechanisms that cause sadness, with the goal of finding more efficient therapies [10].

Some areas of exploration include glutamate (Glu) and γ-aminobutyric acid (GABA) systems, crucial for mood and

cognition regulation, being investigated for potential imbalances contributing to depression. Additionally, dysregulation of stress response through the HPA axis is closely linked to depression [11, 12, 13, 14]. Researchers are studying how abnormalities in this system may contribute to depressive symptoms and whether interventions targeting it could be beneficial. Epigenetic mechanisms, changes in gene expression without altering DNA sequence, have also been implicated in depression. Research aims to understand how environmental factors influence these changes in the brain, potentially leading to novel treatment approaches. Moreover, increasing evidence suggests inflammation may play a role in depression. Immune dysregulation and chronic low-grade inflammation are observed in some depressed individuals, prompting investigation into anti-inflammatory treatments for depressive symptoms.

Table 2 illustrates the diverse areas of focus beyond neurotransmitter systems currently under investigation by both the pharmaceutical industry and researchers. Specifically, attention is directed towards the Glu and GABA systems, with a primary focus on targeting the NMDA receptor, AMPA receptor, and GABA receptor. Promisingly, other agents, such as AV-101, which antagonize NMDA receptors, exhibit antidepressant-like actions in preclinical studies. Additionally, NV-5138 represents a groundbreaking agent designed for the mTOR pathway, a critical target for depression, acting as a downstream intracellular signal following direct activation of AMPA and neurotrophic factor receptors [14, 15].

SSRIs and SNRIs are frontline treatments for Major Depressive Disorder (MDD), yet a substantial number of patients do not respond adequately to these medications. Real-world studies indicate that despite multiple treatment trials, nearly 30% of MDD patients do not achieve remission. This suggests that current understanding of MDD pathogenesis is incomplete, necessitating further research into the pharmacological mechanisms of existing antidepressants. The persistence of treatment-resistant depression highlights the need for novel therapeutic targets and approaches. Continued investigation into how SSRIs and SNRIs interact with brain chemistry and neurotransmitter systems is crucial for developing more effective treatments. Addressing these gaps in knowledge could lead to improved outcomes and better quality of life for individuals struggling with MDD who do not benefit from current medication options [16, 17, 18].

Recent advancements in depression treatment include the discovery of new pharmacological targets and antidepressants that have gained clinical approval. Additionally, non-traditional therapies such as phototherapy and acupuncture have shown effectiveness in alleviating depressive symptoms. These developments highlight a growing interest in diversifying treatment options beyond conventional antidepressants like SSRIs and SNRIs. The exploration of novel targets and therapies represents a promising avenue for enhancing treatment outcomes and addressing the persistent challenge of treatment-resistant depression [18, 19, 20].

Moreover, a variety of small molecular candidates, including opioid receptor agonists, CRF1 receptor antagonists, NK1/2R antagonists, and partial agonists or antagonists, are in the experimental stage. These offer a spectrum of options for the treatment of depression, expanding the potential repertoire of therapeutic approaches under investigation.

Conclusion

The continuous development of the economy and society has brought about increasing pressures from various aspects of daily life and work. Consequently, there has been a progressive rise in the incidence of depression, with a concerning trend towards

younger age groups. This surge in depression cases has emerged as a significant social health issue that cannot be overlooked. Recent years have seen the identification of novel antidepressant targets, including opioid receptors, NMDAR, and mGluR (refer to Table 1) [14, 15]. Additionally, emerging research has highlighted the intricate relationships between depression and factors such as gut microbes, potassium ion channels, acid-sensing ion channels, and sigma receptors. These factors hold promise as potential antidepressant targets.

The development and adoption of immune-targeted therapeutics for depression could also revolutionize current treatment paradigms by challenging traditional syndromic categorizations like Major Depressive Disorder (MDD). Instead of solely relying on broad diagnostic labels, these therapies advocate for a shift towards targeting transdiagnostic symptom dimensions, such as anhedonia, which may be linked to identifiable immune mechanisms in specific subsets of patients. By focusing on these specific symptoms and underlying immune dysregulations, clinicians may be able to tailor treatments more effectively to individual patient profiles [17].

Moreover, targeting multiple receptors simultaneously has become a popular strategy in drug design, offering new avenues for the discovery and development of antidepressant medications. Recent advancements in drug design have leveraged machine learning, molecular dynamics, and protein docking techniques to elucidate the pharmacological mechanisms of antidepressants. These approaches not only optimize the pharmacological properties of antidepressants but also aid in the discovery of new antidepressant targets and scaffolds for lead compounds [10, 11, 12].

This paper presents a systematic, comprehensive, and instructive review of antidepressant research. It offers a wealth of research information, feasible ideas, and guidance, providing multidimensional support to drug researchers in related fields.

Conflict of Interest

There is no conflict of interest.

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