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Effects of Antidepressants on Neurotransmitter Systems and Their Mechanisms of Action in the Treatment of Depression

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Abstract:

Antidepressants are widely used for treating anxiety and depression, conditions affecting nearly 20% of the global population. The objective of this study is to investigate how antidepressants affect neurotransmitter systems understanding both their therapeutic and side effects. The main objective of this study is to identify the adaptive changes that are induced in brain structures by these drugs as well as describe their function in increasing synaptic levels of neurotransmitters like catecholamines and indoleamines. These functions are essentially exerted either by inhibiting the reuptake of neurotransmitters by neurons or by the metabolic deamination exerted by monoamine oxidase. However, the study concerns the nonappearance of a straightforward relationship between an action of antidepressants upon specific postsynaptic receptor sites and their therapeutic strength as well as adverse effects associated with adrenergic, muscarinic, and histaminergic receptors. The study focuses deeper into comprehension of long-term changes in neurotransmitter transmission as it could open up avenues that shed light upon issues related to the efficacy and optimization of antidepressant treatments for millions of people worldwide.

1. Introduction

Depression and anxiety are severe mental illnesses [1] requiring medical intervention, with contrasting yet shared symptoms. Depression is typically characterized by persistent sadness accompanied by emotional and physical withdrawal, whereas anxiety is a state of fear for no apparent reason. The two disorders constitute one of the highest burdens on global health. Medical treatment generally includes antidepressants in combination with counselling. However, they present challenges like therapeutic effects taking weeks to appear, the variable responses to treatment, and debilitating side effects [2]. These limitations highlight the need to understand the mechanisms of these disorders in order to develop faster-acting and better-targeted treatments.

Animal behavioural studies [3], using tools such as the elevated plus maze for anxiety and forced swim tests for depression [4], have thus been instrumental in identifying deregulated systems associated with these conditions. These include the HPA axis (hypothalamic pituitary adrenal), controlling stress responses; the monoaminergic system, with neurotransmitters including serotonin as well as norepinephrine; the GABA (γ-aminobutyric acid) system, crucial for inhibitory signalling; and adult hippocampal neurogenesis, influencing mood and cognitive functions [5]. Research into the mechanisms of antidepressant action has revealed how these systems are altered in depression or anxiety states and how interventions reverse these alterations to re-equilibrate them. It includes the search for new antidepressive drug targets and mechanisms with the help of findings from behavioural studies and transgenic mouse models. This research is the basis to advance our understanding of depression and anxiety, improve the range of possible treatments, and address the unmet needs of patients suffering from treatment-resistant forms.

1.1 Antidepressant therapy

For years, the pharmacological treatment of MDD (major depressive disorder) has been built on antidepressants that target serotonin, noradrenaline, and dopamine- the monoaminergic neurotransmitter systems [6]. Their mechanisms of action are through inhibiting the reuptake of these neurotransmitters or blocking monoamine oxidases, which degrade these neurotransmitters. While the therapeutic and side effects of these drugs have been extensively studied, their delayed onset of action and limited efficacy in some patients have prompted exploration into alternative approaches. The table includes the therapeutic uses of antidepressants in treating various symptoms and diseases such as depression, anxiety disorders, PTSD, OCD, and other related conditions.

Table 1: Types of Antidepressants and their use

Antidepressant	Uses
Bupropion	Depression, Smoking Cessation, ADHD, Anxiety (off-label)
Venlafaxine	Depression, Anxiety, Panic Disorder, Social Anxiety Disorder
Fluvoxamine	OCD, Anxiety, Depression

Citalopram	Depression, Anxiety, Panic Disorder
Sertraline	Depression, Anxiety, Panic Disorder, PTSD, OCD
Fluoxetine	Depression, Anxiety, OCD, Bulimia, Panic Disorder
Trazodone	Depression, Insomnia, Anxiety
Nefazodone	Depression, Anxiety
Paroxetine	Depression, Anxiety, PTSD, Panic Disorder, OCD
Mirtazapine	Depression, Anxiety, Insomnia, Appetite Stimulation
Tricyclic Antidepressant	Depression, Anxiety, Panic Disorder, Insomnia

One such breakthrough in antidepressant therapy involves the use of a dissociative anesthetic ketamine that mainly acts on the glutamatergic system. Unlike conventional antidepressants, ketamine's rapid-acting antidepressant properties were first demonstrated in pioneering studies by Berman et al [7]. This research renewed interest in unconventional treatments for depression. The succeeding endorsement of a derivative of ketamine- intranasal esketamine, for action resilient depression marks a significant advancement in this field. Esketamine, along with the intravenous administration of ketamine, has also shown promise in addressing acute suicidality [8], offering new hope for patients with severe depressive symptoms who do not respond to traditional medications.

These developments underscore the importance of expanding beyond monoaminergic targets to understand and innovate treatment options for depression, ultimately aiming to provide faster, more effective relief for a broader range of individuals.

1.2 Mechanism of Action

Antidepressants have been largely prescribed to children and adolescents for treating mood disorders such as depression, anxiety, and obsessive-compulsive disorder (OCD) which include selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) [9]. While many studies on tolerability and discontinuation rates of antidepressants have been conducted [10], only two meta-analyses specifically addressed the risks of adverse effects in younger populations [11]. In these studies, the risks of discontinuation due to adverse effects were an equivalency with the relative risks emerging from broader network meta-analyses, which additionally compare other drug classes such as TCAs, benzodiazepines, and α2 agonists.

With children and adolescents, SSRIs result in activation symptoms such as agitation or restlessness, as well as gastrointestinal issues like abdominal pain [11]. They are also associated with sedation or drowsiness, and the risk of discontinuation because of side effects is more significant than with placebo therapies. The interesting thing here is that the tolerability of SSRIs, despite their differences, is the same for various child and adolescent psychiatric disorders, including anxiety disorders, OCD, and depression. However, despite these findings, there is a lack of comprehensive, recent guidance synthesizing the risks of antidepressants in younger patients [12]. This gap in information places clinicians in a difficult position, as they are ethically and medicolegally obligated to discuss potential side effects and risks with both patients and their families before initiating treatment. It remains crucial to further investigate the safety profile of antidepressants in this age group to ensure that treatment decisions are made with a full understanding of both therapeutic benefits and potential harms.

2. Effects of Antidepressants

Antidepressants induce adaptive changes in brain structures by promoting neuroplasticity and altering the functioning of neurotransmitter systems, particularly those involving catecholamines (such as serotonin, norepinephrine, and dopamine) and indoleamines (primarily serotonin) [13]. These adaptive changes are essential for the therapeutic effects of antidepressants, as they help restore the balance of neurotransmitter activity that is often dysregulated in individuals with mood disorders like depression and anxiety.

One of the main mechanisms by which antidepressants enhance neurotransmitter activity is through the inhibition of neuronal reuptake [14]. Under normal conditions, neurotransmitters like serotonin and norepinephrine are released into the synaptic cleft and bind to receptors on the postsynaptic neuron to transmit signals. These neurotransmitters are normally reabsorbed back into the presynaptic neuron through transporters. The reuptake inhibitors are particularly SSRIs and SNRIs, which block these transporters [15], causing a higher concentration of neurotransmitters in the synaptic cleft. This prolonged exposure to neurotransmitters actually makes the postsynaptic receptors extensively excited to mitigate symptoms of depression and anxiety.

Besides reuptake inhibition, another mechanism of action is through the inhibition of metabolic deamination, which an effect mediated by an enzyme is called monoamine oxidase (MAO). MAO helps break down neurotransmitters in the brain, such as serotonin, norepinephrine, and dopamine [16]. The inhibition of MAO blocks the breakdown of these neurotransmitters, thus raising their synaptic concentrations. This allows for sustained neurotransmitter signalling, which is believed to improve mood and reduce the symptoms of depression.

Through these mechanisms-both the inhibition of reuptake and the prevention of metabolic breakdown-antidepressants help restore the normal functioning of a neurotransmitter system that usually is impaired in people suffering from mood disorders. These changes are slow, but they can result in lasting improvements in brain function and structure, promoting neuroplasticity and increasing the brain's ability to adapt to stress and emotional challenges. The outcome, therefore, was better mood, better cognitive function, and the regulation of emotions in the patients undergoing treatment for depression and anxiety.

The figure illustrates the bidirectional effects of chronic serotonin (5-HT) [17] reuptake inhibitors, such as SSRIs, on developmental stages of granule cells within the dentate gyrus, which can be distinguished by stage-specific marker expression as well as by specific neural function, indicating that chronic SSRI treatment may have opposite effects on differentiating immature neurons and mature neurons depending on the maturity/differentiation stage.

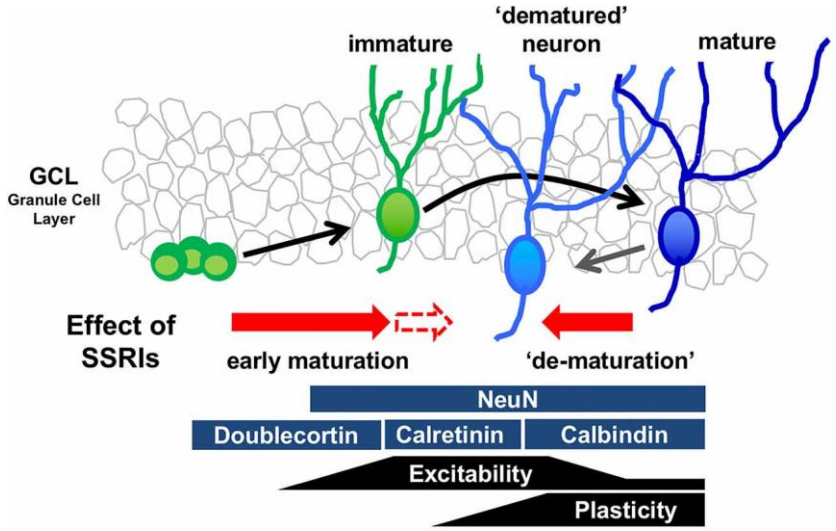

Figure 1: Bidirectional effects of chronic 5-HT serotonin [17]

Most antidepressants that target monoaminergic neurotransmission initially exert their effects within the synapse, where they influence neurotransmitter levels. These actions subsequently lead to alterations in intracellular signalling and the activation of second messenger pathways. This process enhances the synaptic concentrations of key neurotransmitters such as serotonin, norepinephrine, and dopamine, contributing to mood regulation and symptom relief in conditions like depression and anxiety. However, the impact of antidepressants goes beyond modulating monoamine systems. Recent research highlights that these medications also influence the glutamatergic system and other neurochemical pathways, further expanding their therapeutic potential.

In addition to modifying neurotransmission, antidepressants promote neuroplasticity [13], which is essential for long-term recovery in the brain. They can stimulate the differentiation, proliferation, and survival of neurons, aiding in the repair of damaged neural circuits and improving brain functions. Furthermore, antidepressants have been shown to inhibit the activation of neuroimmune cells, reducing the release of inflammatory mediators and lowering oxidative stress and apoptosis (cell death) of neurons [18]. These effects contribute to the restoration of brain health and function, which are often impaired in individuals with mood disorders.

Moreover, antidepressants can enhance synaptic density and function, fostering synaptic plasticity—the ability of synapses to strengthen or weaken over time in response to activity. This leads to improvements in learning, memory, and overall cognitive function. These changes are mediated by the regulation of gene expression, epigenetic modifications [19], and signal transduction pathways, all of which play crucial roles in synaptic remodelling and brain adaptation.

While it may be an oversimplification to categorize antidepressants into distinct classes based solely on their major pharmacological actions, such classification remains useful in clinical practice due to the broad and overlapping effects these

medications have. By promoting neurogenesis [20], altering gene expression, and enhancing synaptic plasticity, antidepressants provide a multifaceted approach to treating depression and related disorders, ultimately leading to significant therapeutic benefits.

2.1 Antidepressants and Their Mechanisms of Action

Antidepressants exert their therapeutic effects through a variety of mechanisms that primarily target neurotransmitter systems in the brain. The most commonly prescribed antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), work by inhibiting the reuptake of key neurotransmitters like serotonin and norepinephrine. This increases their concentration in the synaptic cleft, enhancing neurotransmission and alleviating symptoms of depression and anxiety. Another class, monoamine oxidase inhibitors (MAOIs), works by inhibiting the enzyme monoamine oxidase, which breaks down neurotransmitters such as serotonin, norepinephrine, and dopamine, leading to prolonged activity of these molecules. In addition to these well-known actions, emerging evidence suggests that antidepressants also influence other systems, such as the glutamatergic system, which is involved in synaptic plasticity and cognitive functions. These medications can promote neuroplasticity by enhancing neuronal growth, survival, and differentiation, which helps repair the neural circuits impaired by depression. Furthermore, antidepressants have been shown to reduce inflammation and oxidative stress in the brain, creating a more conducive environment for neural repair and function. Ultimately, the combined effects of neurotransmitter modulation, neuroplasticity enhancement, and cellular protection contribute to the therapeutic efficacy of antidepressants, making them a cornerstone in the treatment of mood disorders.

3. Literature survey

The role and contribution of existing studies in understanding adherence to antidepressant medications and associated challenges are crucial for improving treatment outcomes. Research indicates that adherence to antidepressants is often lower compared to medications for chronic conditions like diabetes or hypertension, emphasizing the need to identify and address factors affecting adherence [21]. These factors span multiple domains, including patient-related, medication-related, illness-related, and clinical setting-related characteristics. Patient-related factors, such as beliefs about medication, literacy levels, economic constraints, and social support, significantly influence adherence. Medication-related issues, including adverse side effects and perceived efficacy, also play a pivotal role [22]. For instance, SSRIs and SNRIs are associated with side effects like agitation, sexual dysfunction, and digestive issues, while TCAs can cause drowsiness, dry mouth, and weight gain [15]. These adverse reactions, particularly in the early stages of treatment, often lead to discomfort, requiring effective communication and patient education to ensure continued adherence.

The literature also underscores the persistence of antidepressant-related side effects in over half of the patients even after 75–105 days of treatment, often overlooked by healthcare providers, leading to poor communication regarding prescriptions [23]. This communication gap contributes to early treatment dropout, typically within 6.5–7 weeks due to side effects, underscoring the need for proactive patient support during this period. Furthermore, the clinical setting plays a vital role, with factors such as follow-up rates and doctor-patient interactions being instrumental in improving adherence. These findings highlight the importance of tailoring interventions to address multifaceted barriers, ultimately improving adherence and treatment efficacy in managing depression.

Existing studies conducted from 2013 to 2020 in Europe, Africa, and Asia [24] provide valuable insights into the treatment and prevalence of depression as shown in the table. These studies primarily involved adult participants over 18 years of age diagnosed with depression as their primary psychiatric condition. A notable trend across these studies was the overrepresentation of female participants, highlighting the gender disparity often observed in depression prevalence. The sample sizes in these studies varied widely, ranging from small cohorts of 53 participants to large-scale investigations involving 50,824 individuals. This range demonstrates the diversity in study designs, from targeted clinical trials to population-based analyses. The geographic distribution of these studies highlights the global nature of depression research, addressing its impact across various cultural, social, and healthcare contexts. The data gathered from these studies play a crucial role in understanding depression's demographic patterns, treatment responses, and the influence of cultural and regional differences on mental health outcomes. Additionally, the studies underscore the importance of tailoring treatment approaches to account for varying participant demographics, such as gender and age distribution.

Table 2: Existing Studies on Treatment and Prevalence of Depression

Disease	Ref.	Setting	Country	Age (Years)	N
MDD	Abegaz et al. [25]	Prospective cross-sectional study at Gondar University Hospital	Ethiopia	30.94 ± 8.85	217
Depression	Marasine et al. [26]	Prospective cross-sectional study at Outpatient Department of B.G. Hospital	Nepal	18-65	174
MDD	Yau et al. [27]	Retrospective cohort study at Prince of Wales Hospital	Hong Kong	20–88	189
Mood disorders	De las Cuevas et al. [28]	Cohort study at 2 Community Mental Health Centres	Canary Islands, Spain	>30	145
MDD	Kostev et al. [29]	Cross-sectional study at 1192 General Practices	Germany	>18	50,824
	Deniz et al. [30]	Cross-sectional study at Haydarpasa Numune Training and Research Hospital	Turkey	33.25 ± 11.29	53
Major depressive episode	Baeza-Velasco et al. [31]	Cross-sectional study at the Department of Emergency Psychiatry, University Hospital	France	18–77	360

Antidepressants, primarily those targeting monoaminergic systems, induce significant long-term changes in neurotransmitter systems that extend beyond their immediate pharmacological actions. These prolonged effects play a crucial role in their therapeutic efficacy, particularly in addressing the complex neurobiological underpinnings of depression and anxiety disorders as shown in Table.

Table 3: Long-Term Effects of Antidepressants on Neurotransmitter Systems

Effect	Description	System/Pathway
Monoaminergic System Modulation [6]	Sustained increases in synaptic serotonin, norepinephrine, and dopamine concentrations; receptor desensitization and sensitivity changes.	Monoaminergic system (5-HT, NE, DA)
Neuroplasticity and Synaptic Changes [13]	Increased synaptic density, upregulation of brain-derived neurotrophic factor (BDNF), improved communication between neurons.	Prefrontal cortex, hippocampus
Regulation of HPA Axis [5]	Normalizes dysregulated HPA axis; reduces cortisol overproduction and modulates glucocorticoid receptor sensitivity.	Hypothalamic-pituitary-adrenal (HPA) axis
Impact on Glutamatergic System [32]	Modulation of NMDA receptors, promoting synaptic remodeling and neuroplasticity.	Glutamatergic neurotransmission
Impact on GABAergic System [5]	Stabilizes GABAergic pathways, reducing excitotoxicity and hyperactivity in neural circuits.	GABAergic neurotransmission
Neurogenesis in the Hippocampus [20]	Stimulates proliferation and differentiation of neural progenitor cells, reversing hippocampal atrophy.	Hippocampus
Reduction of Inflammatory and Oxidative Stress [18]	Decreases activation of neuroimmune cells, reduces pro-inflammatory cytokines, lowers oxidative stress and neuronal apoptosis.	Neuroimmune pathways
Epigenetic and Gene Expression Changes [19]	Alters gene expression through histone acetylation and DNA methylation, normalizing disrupted neural circuits.	Gene regulation and epigenetics
Tolerance and Dependency Risks [10]	Prolonged use may lead to tolerance, reduced efficacy, withdrawal symptoms upon discontinuation.	Neuroadaptive responses

In summary, the long-term effects of antidepressants on neurotransmitter systems are multifaceted, encompassing enhancements in monoaminergic transmission, neuroplasticity, and neuroprotection. These adaptations underlie the delayed therapeutic benefits

of these drugs and their ability to mitigate chronic symptoms of depression. However, understanding the nuanced balance between therapeutic efficacy and potential risks remains essential for optimizing long-term treatment strategies.

4. Challenges in Antidepressant Therapy

Antidepressant therapy faces several challenges due to adverse effects and the underlying mechanisms of action, often complicating the treatment of depression. A significant issue is the prevalence of side effects, which range from mild to severe.

Adverse Effects: In the short term, patients frequently experience symptoms such as agitation, anxiety, nausea, insomnia, dizziness, and headaches. These can discourage adherence, especially during the critical initial weeks of treatment. Over the long term, persistent side effects like sexual dysfunction, weight gain, and fatigue negatively impact the quality of life and often lead to discontinuation. More severe reactions, including serotonin syndrome, cardiovascular complications (notably with tricyclic antidepressants), and heightened suicidal ideation (particularly in younger populations), further underscore the risks involved. These adverse effects frequently result in early treatment dropout, making sustained recovery more challenging.

Mechanism of Action: The mechanisms of action of antidepressants also contribute to the difficulties in therapy. Many medications have a delayed onset of therapeutic effects, requiring weeks to induce the neuroplastic changes necessary for symptom relief. This delay can prolong patient distress and diminish adherence. Moreover, while most antidepressants target monoaminergic pathways (serotonin, norepinephrine, dopamine), their non-specificity often leads to off-target effects, such as sedation (via antihistaminergic action) or dry mouth (via anticholinergic action). Furthermore, the monoamine hypothesis of depression does not fully capture the disorder's complexity, leaving gaps in treatment efficacy. Current antidepressants rarely address alternative pathways, such as glutamatergic signaling, which may play a critical role in depression pathophysiology.

Individual variability: Individual variability in response to antidepressant therapy further complicates treatment. Genetic polymorphisms affecting drug metabolism (e.g., CYP450 enzyme variations) and patient-specific factors such as age, comorbidities, and concurrent medications lead to differing tolerability and efficacy across populations. These variations underscore the need for more personalized approaches to therapy.

Balancing Efficacy and Safety: Ultimately, it remains a critical challenge. Efforts to enhance therapeutic outcomes often increase the risk of adverse effects, limiting the development of universally effective and well-tolerated treatments. The lack of novel antidepressants with entirely new mechanisms of action further restricts options for patients who cannot tolerate existing drugs. Addressing these challenges requires a deeper understanding of depression's complex mechanisms, innovative drug design, and personalized treatment strategies to improve patient outcomes.

Delayed Onset of Action: One of the significant challenges in antidepressant therapy is the delayed onset of therapeutic effects, which typically takes several weeks. This delay can prolong the patient's distress, particularly for individuals seeking immediate relief from depressive symptoms. As a result, the waiting period often increases the risk of treatment discontinuation and non-adherence, especially for patients who are unaware of the time required for these medications to take effect. During this critical period, there is also a heightened risk of suicide or worsening of symptoms, necessitating vigilant monitoring by healthcare providers to ensure safety and support.

Treatment-Resistant Depression and Emerging Alternatives: A substantial proportion of patients—estimated at 20–30%—do not respond to standard antidepressant therapies, a condition referred to as treatment-resistant depression (TRD). This lack of efficacy necessitates the exploration of alternative treatment strategies. Augmentation approaches, such as combining antidepressants with mood stabilizers, atypical antipsychotics, or incorporating psychotherapy, have shown promise in managing TRD. Additionally, novel therapies like ketamine, transcranial magnetic stimulation (TMS), and electroconvulsive therapy (ECT) are being actively investigated for their potential to provide rapid and effective relief in resistant cases. The emergence of personalized medicine, particularly pharmacogenetics, offers hope for tailoring treatments to the unique genetic and biochemical profiles of TRD patients, potentially improving outcomes.

Individual Variability in Response: The response to antidepressants varies significantly among individuals due to differences in genetic makeup, age, gender, comorbidities, and psychosocial factors. Genetic polymorphisms, such as those in serotonin transporter genes (SLC6A4) and cytochrome P450 enzymes, play a crucial role in determining drug metabolism and efficacy. These variations can lead to diverse therapeutic outcomes and side effect profiles, with some patients experiencing severe adverse effects that contribute to early discontinuation of therapy. Additionally, differences in psychosocial factors and coexisting conditions further complicate treatment effectiveness. Efforts to identify biomarkers and conduct pharmacogenetic testing are underway to predict individual responses more accurately and reduce reliance on trial-and-error prescribing practices.

Addressing these challenges requires a multidisciplinary approach that integrates pharmacological advancements, personalized care, and emerging technologies. By understanding the complexities of antidepressant therapy, healthcare suppliers can improve patient support, and alleviate risks, with better treatment consequences.

4.1 Research Gaps

While antidepressants' immediate effects on neurotransmission are well-documented, the long-term impacts on brain plasticity, synaptic density, and cognitive function remain underexplored. Further research is needed to assess how prolonged antidepressant use influences neurogenesis, synaptic plasticity, and overall brain structure, especially in terms of therapeutic outcomes for depression.

- There is a lack of personalized treatment approaches for depression in Current treatment methods which often follow a trial-and-error approach due to the limited ability to predict individual patient's response to antidepressants. There is a need for deeper exploration into pharmacogenetics and the identification of biomarkers that can help predict treatment efficacy, side effects, and optimal dosages based on an individual's genetic profile, comorbidities, and personal factors.
- The inadequate exploration of non-pharmacological cures for treatment-resistant depression (TRD) needs more comprehensive studies to establish their long-term efficacy, optimal administration protocols, and potential integration with pharmacological treatments. Additionally, the impact of combining these novel therapies with antidepressants or other treatments has not been sufficiently investigated.
- The gaps in understanding the mechanisms behind delayed onset of action is a significant barrier to effective treatment. Research is needed to explore the underlying mechanisms contributing to this delay, such as changes in neural plasticity, gene expression, and neurotransmitter system adaptations.
- Due to insufficient exploration of gender and age-related differences in antidepressant efficacy and side effects, there is a lack of comprehensive studies examining how antidepressants affect different genders and age groups differently. While much research has focused on the general population though females and older adults often experience distinct side effect profiles and treatment responses, there is a clear need to explore these differences to optimize personalized treatment strategies.

Thus, the study adds value to depression treatment by addressing the existing gaps through the exploration of personalized approaches, and antidepressants' long-term effects, with innovative action policies. By focusing on individualized treatment plans informed by pharmacogenetics and biomarkers, the study provides new insights into optimizing antidepressant therapy. Furthermore, investigating alternative therapies such as ketamine and TMS in the context of TRD can offer valuable evidence of their effectiveness and safety. Finally, understanding the gender and age-related differences in antidepressant efficacy will ensure more equitable and tailored treatment options, ultimately improving patient adherence, satisfaction, and long-term outcomes in depression management.

5. Conclusion

In the modern era of advanced treatments, the study highlights the ongoing concerns surrounding the use of antidepressants in the management of depression. The effects of these medications, particularly their mechanisms of action on neurotransmitter systems, have been extensively studied, indicating that they primarily modulate serotonin, norepinephrine, and dopamine pathways to alleviate depressive symptoms. However, while these treatments have proven efficacy, their delayed onset of action, side effects, and limitations in treatment-resistant cases remain significant challenges. This overview also emphasizes the complexity of antidepressant therapy, as individual variability in response, influenced by genetic, environmental, and psychosocial factors, complicates optimal treatment. Furthermore, the study draws attention to emerging therapeutic strategies, such as pharmacogenetics, personalized medicine, and novel treatments like ketamine, that offer potential breakthroughs for patients who do not respond to conventional antidepressants. Ultimately, this study contributes to a deeper understanding of antidepressants' role in the treatment of depression, while calling for further research to address existing gaps, particularly in terms of long-term effects, treatment resistance, and individualized care. By advancing knowledge in these areas, the goal is to improve therapeutic outcomes and enhance the quality of life for individuals suffering from depression.

The study delivers valuable perceptions into the effects of antidepressants on neurotransmitter systems, but several limitations exist. The focus on general antidepressant classes limits understanding of specific medications or newer treatments like ketamine and TMS. Additionally, individual patient variability was not fully explored. Future research should prioritize pharmacogenetic

testing, the identification of biomarkers, and long-term safety studies to better personalize treatment. Exploring adjunctive therapies and improving patient adherence strategies will enhance depression treatment outcomes in clinical practice.

References

[1] E. I. Adesanya *et al.*, "Factors associated with depression, anxiety and severe mental illness among adults with atopic eczema or psoriasis: a systematic review and meta-analysis," *Br. J. Dermatol.*, vol. 188, no. 4, pp. 460–470, Mar. 2023, doi: 10.1093/bjd/ljac132.

[2] E. Niarchou, L. Roberts, and B. D. Naughton, "What is the impact of antidepressant side effects on medication adherence among adult patients diagnosed with depressive disorder: A systematic review," *J. Psychopharmacol.*, vol. 38, no. 2, pp. 127–136, Feb. 2024, doi: 10.1177/02698811231224171.

[3] A. S. Chitre *et al.*, "Genome-wide association study in a rat model of temperament identifies multiple loci for exploratory locomotion and anxiety-like traits," *Front. Genet.*, vol. 13, Jan. 2023, doi: 10.3389/fgene.2022.1003074.

[4] H. Çalışkan, F. Akat, A. D. Dursun, and N. Zaloğlu, "Chronic pregabalin treatment reduced anxiety, and acute pregabalin treatment increased depression-like behaviors in rats," *BMC Pharmacol. Toxicol.*, vol. 25, no. 1, p. 72, Oct. 2024, doi: 10.1186/s40360-024-00794-y.

[5] M. Nikbakhtzadeh *et al.*, "Cross-talk between the HPA axis and addiction-related regions in stressful situations," *Heliyon*, vol. 9, no. 4, p. e15525, Apr. 2023, doi: 10.1016/j.heliyon.2023.e15525.

[6] T. Zhao, T. Liu, L. Wang, K. Xie, H. Tang, and M. Tang, "Dysfunction of neurotransmitter metabolism is associated with the severity of depression in first-diagnosed, drug-naïve depressed patients," *J. Affect. Disord.*, vol. 349, pp. 332–341, Mar. 2024, doi: 10.1016/j.jad.2024.01.023.

[7] R. M. Berman *et al.*, "Antidepressant effects of ketamine in depressed patients," *Biol. Psychiatry*, vol. 47, no. 4, pp. 351–354, Feb. 2000, doi: 10.1016/S0006-3223(99)00230-9.

[8] F. Jollant *et al.*, "Ketamine and esketamine in suicidal thoughts and behaviors: a systematic review," *Ther. Adv. Psychopharmacol.*, vol. 13, Jan. 2023, doi: 10.1177/20451253231151327.

[9] C. M. Nicotra and J. R. Strawn, "Advances in Pharmacotherapy for Pediatric Anxiety Disorders," *Child Adolesc. Psychiatr. Clin. N. Am.*, vol. 32, no. 3, pp. 573–587, Jul. 2023, doi: 10.1016/j.chc.2023.02.006.

[10] L. M. Garcia-Marin *et al.*, "Discontinuation of antidepressant treatment: a retrospective cohort study on more than 20,000 participants," *Ann. Gen. Psychiatry*, vol. 22, no. 1, p. 49, Nov. 2023, doi: 10.1186/s12991-023-00480-z.

[11] J. R. Strawn, J. A. Mills, E. A. Poweleit, L. B. Ramsey, and P. E. Croarkin, "Adverse Effects of Antidepressant Medications and their Management in Children and Adolescents," *Pharmacother. J. Hum. Pharmacol. Drug Ther.*, vol. 43, no. 7, pp. 675–690, Jul. 2023, doi: 10.1002/phar.2767.

[12] P. Lampela, A. Tanskanen, M. Lähteenvuo, J. Tiihonen, and H. Taipale, "Effect of severity of depression on augmentation of antidepressant medication in young adults with depression," *Acta Psychiatr. Scand.*, vol. 149, no. 1, pp. 41–51, Jan. 2024, doi: 10.1111/acps.13633.

[13] C. E. Page, C. N. Epperson, A. M. Novick, K. A. Duffy, and S. M. Thompson, "Beyond the serotonin deficit hypothesis: communicating a neuroplasticity framework of major depressive disorder," *Mol. Psychiatry*, May 2024, doi: 10.1038/s41380-024-02625-2.

[14] G. Ilipilla and L. E. Arnold, "The role of adrenergic neurotransmitter reuptake inhibitors in the ADHD armamentarium," *Expert Opin. Pharmacother.*, vol. 25, no. 8, pp. 945–956, May 2024, doi: 10.1080/14656566.2024.2369197.

[15] G. H. Le *et al.*, "Electroencephalography (EEG) spectral signatures of selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs) and vortioxetine in major depressive disorder: A systematic review," *J. Affect. Disord.*, vol. 368, pp. 798–819, Jan. 2025, doi: 10.1016/j.jad.2024.09.081.

[16] A. Alunni *et al.*, "An Astyanax mexicanus mao knockout line uncovers the developmental roles of monoamine homeostasis in fish brain," *Dev. Growth Differ.*, vol. 65, no. 9, pp. 517–533, Dec. 2023, doi: 10.1111/dgd.12896.

[17] E. Segi-Nishida, "The Effect of Serotonin-Targeting Antidepressants on Neurogenesis and Neuronal Maturation of the Hippocampus Mediated via 5-HT1A and 5-HT4 Receptors," *Front. Cell. Neurosci.*, vol. 11, May 2017, doi: 10.3389/fncel.2017.00142.

[18] N. Ji, M. Lei, Y. Chen, S. Tian, C. Li, and B. Zhang, "How Oxidative Stress Induces Depression?," *ASN Neuro*, vol. 15, Jan. 2023, doi: 10.1177/17590914231181037.

[19] A. Inserra, A. Campanale, T. Rezai, P. Romualdi, and T. Rubino, "Epigenetic mechanisms of rapid-acting antidepressants," *Transl. Psychiatry*, vol. 14, no. 1, p. 359, Sep. 2024, doi: 10.1038/s41398-024-03055-y.

[20] S.-C. Park, "Neurogenesis and antidepressant action," *Cell Tissue Res.*, vol. 377, no. 1, pp. 95–106, Jul. 2019, doi:

10.1007/s00441-019-03043-5.

[21] M. Di Nicola *et al.*, "Adherence to, and Persistence of, Antidepressant Therapy in Patients with Major Depressive Disorder: Results from a Population-based Study in Italy," *Curr. Neuropharmacol.*, vol. 21, no. 3, pp. 727–739, Mar. 2023, doi: 10.2174/1570159X20666220411092813.

[22] A. H. Khalifeh and A. M. Hamdan-Mansour, "Prevalence, Barriers, and Interventions Related to Medication Adherence Among Patients With Major Depressive Disorder: A Scoping Review," *J. Psychosoc. Nurs. Ment. Health Serv.*, vol. 59, no. 1, pp. 39–51, Jan. 2021, doi: 10.3928/02793695-20201015-05.

[23] C. Fabbri and A. Serretti, "Clinical application of antidepressant pharmacogenetics: Considerations for the design of future studies," *Neurosci. Lett.*, vol. 726, p. 133651, May 2020, doi: 10.1016/j.neulet.2018.06.020.

[24] S. Shorey, E. D. Ng, and C. H. J. Wong, "Global prevalence of depression and elevated depressive symptoms among adolescents: A systematic review and meta-analysis," *Br. J. Clin. Psychol.*, vol. 61, no. 2, pp. 287–305, Jun. 2022, doi: 10.1111/bjc.12333.

[25] T. M. Abegaz, L. M. Sori, and H. N. Toleha, "Self-Reported Adverse Drug Reactions, Medication Adherence, and Clinical Outcomes among Major Depressive Disorder Patients in Ethiopia: A Prospective Hospital Based Study," *Psychiatry J.*, vol. 2017, pp. 1–8, 2017, doi: 10.1155/2017/5812817.

[26] N. R. Marasine, S. Sankhi, R. Lamichhane, N. R. Marasini, and N. B. Dangi, "Self-Reported Antidepressant Drug Side Effects, Medication Adherence, and Its Associated Factors among Patients Diagnosed with Depression at the Psychiatric Hospital of Nepal," *Depress. Res. Treat.*, vol. 2020, pp. 1–7, Oct. 2020, doi: 10.1155/2020/7024275.

[27] W. Yau *et al.*, "Noncontinuous use of antidepressant in adults with major depressive disorders – a retrospective cohort study," *Brain Behav.*, vol. 4, no. 3, pp. 390–397, May 2014, doi: 10.1002/brb3.224.

[28] C. De las Cuevas, W. Peñate, and E. J. Sanz, "Risk factors for non-adherence to antidepressant treatment in patients with mood disorders," *Eur. J. Clin. Pharmacol.*, vol. 70, no. 1, pp. 89–98, Jan. 2014, doi: 10.1007/s00228-013-1582-9.

[29] K. Kostev, J. Rex, T. Eith, and C. Heilmaier, "Which adverse effects influence the dropout rate in selective serotonin reuptake inhibitor (SSRI) treatment? Results for 50,824 patients," *GMS Ger. Med. Sci.*, vol. 12, 2014, doi: https://doi.org/10.3205/000200.

[30] S. Deniz *et al.*, "Determination of CYP2C19 Polymorphism, Side Effects, and Medication Adherence in Patients Who have Utilized Selective Serotonin Reuptake Inhibitors," *Klin. Psikofarmakol. Bülteni-Bulletin Clin. Psychopharmacol.*, vol. 26, no. 2, pp. 152–160, Jun. 2016, doi: 10.5455/bcp.20151003060610.

[31] C. Baeza-Velasco, E. Olié, S. Béziat, S. Guillaume, and P. Courtet, "Determinants of suboptimal medication adherence in patients with a major depressive episode," *Depress. Anxiety*, vol. 36, no. 3, pp. 244–251, Mar. 2019, doi: 10.1002/da.22852.

[32] B. Kadriu, L. Musazzi, I. D. Henter, M. Graves, M. Popoli, and C. A. Zarate, "Glutamatergic Neurotransmission: Pathway to Developing Novel Rapid-Acting Antidepressant Treatments," *Int. J. Neuropsychopharmacol.*, vol. 22, no. 2, pp. 119–135, Feb. 2019, doi: 10.1093/ijnp/pyy094.