A Review on Prevalence of Depression Among Bangladeshi Youths: Current Antidepressant Therapies, Emerging Drug Developments and Synthetic Approaches

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (B. Pharm.)

School of Pharmacy
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

The thesis titled "A Review on Prevalence of Depression Among Bangladeshi Youths: Current Antidepressant Therapies, Emerging Drug Developments and Synthetic Approaches" submitted by MD Zonayed Hasan (21146024), of Spring 2021 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This project does not involve any kind of animal or human trial.

Abstract

Depression among Bangladeshi adolescents is a fast-growing public health problem driven by academic pressure, economic stress, and lifestyle changes. This review article examines the prevalence of depression among Bangladeshi adolescents with a focus on university students and reviews traditional and new antidepressant treatments. Traditional treatments like selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressant (TCAs) are effective but are often plagued by side effects and delayed onset of action. Recent developments such as ketamine-based treatments, psilocybin, and neurosteroid modulators offer faster-acting alternatives. The study also examines the chemical structures, mechanisms of action, and synthetic approaches to access these compounds, emphasizing the need for sustainable and effective synthetic routes. This review article aims to guide future pharmacological interventions and policy-making in Bangladesh to improve the availability and effectiveness of mental health treatment for youth.

Keywords: Antidepressants; Youth mental health; Novel therapies; Drug synthesis; SSRIs; Ketamine

Dedication

This work is dedicated to my wonderful family whose unwavering encouragement, motivation and sacrifices have been a source of inspiration in the course of my academic advancement. I also dedicate this success to myself, appreciation for the perseverance and dedication that have seen me reach this milestone.

Acknowledgement

First and foremost, I would like to thank the Almighty for His innumerable blessings, wisdom, and grace, which have incessantly strengthened and guided me throughout this academic pursuit.

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List of Acronyms

SSRI – Selective Serotonin Reuptake Inhibitor

SNRI – Serotonin-Norepinephrine Reuptake Inhibitor

TCA – Tricyclic Antidepressant

MAOI – Monoamine Oxidase Inhibitor

NMDA – N-Methyl-D-Aspartate

TRD – Treatment-Resistant Depression

FDA – Food and Drug Administration

GABA – Gamma-Aminobutyric Acid

ADHD – Attention Deficit Hyperactivity Disorder

PIU – Problematic Internet Use

MTDL – Multi-Target Directed Ligand

NRI – Norepinephrine Reuptake Inhibitor

DAT – Dopamine Transporter

SERT – Serotonin Transporter

NET – Norepinephrine Transporter

Chapter 1

Introduction

Depression is a serious global public health issue that affects around 264 million people globally, with a substantial proportion of cases occurring among adolescents and young adults (Arusha & Biswas, 2020). In Bangladesh, the rate of mental health issues, especially depression and anxiety, has reached critical levels, with about 7 million affected individuals (Arusha & Biswas, 2020).

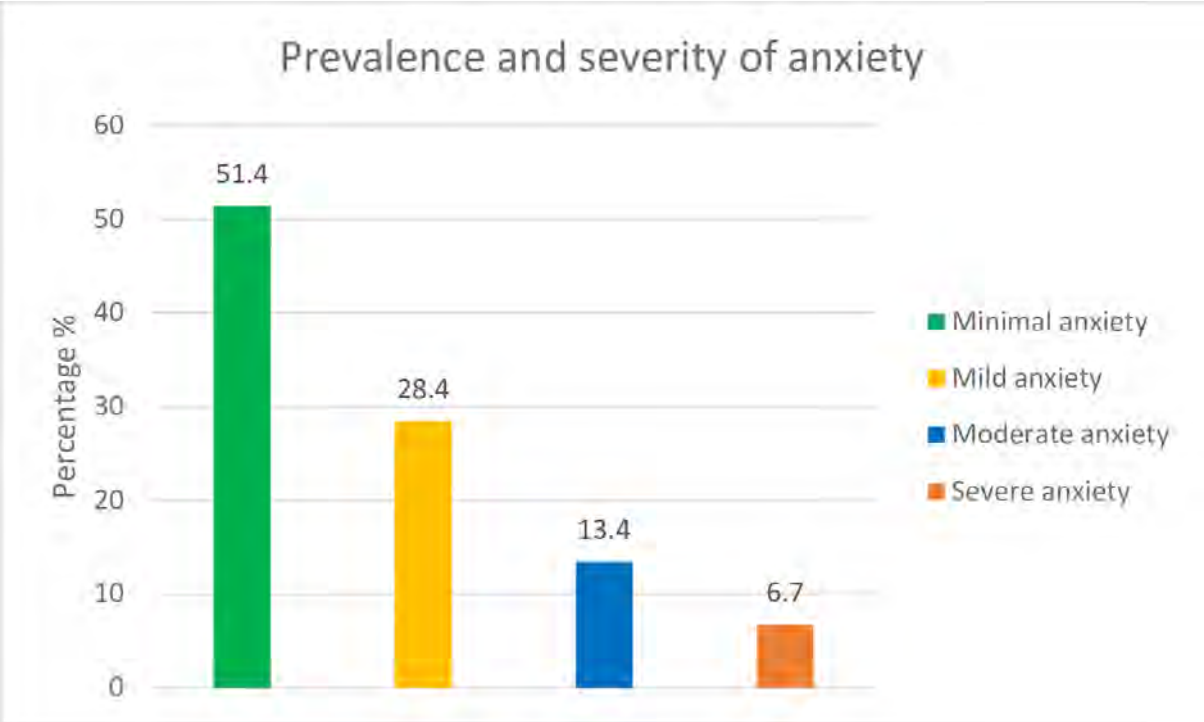

Figure 1: Prevalence and severity of anxiety among the population (Anjum, Hossain, Hasan, et al., 2022).

Figure 1 illustrates the distribution of anxiety levels, indicating that while over half experience minimal anxiety, a substantial portion suffers from mild to severe symptoms, underscoring the urgency of intervention.

The prevalence of depressive symptoms is specifically alarming as previous studies reported that 47.7% to 54.3% of university students (Sakib et al., 2021) and 24.5% to 36.6% of school-going adolescents (Anjum, Hossain, Sikder, et al., 2022; Mridha et al., 2021) in Bangladesh have depressive symptoms. This study confirms that there is an urgent need to prevent and manage mental and physical health challenges through effective means, such as medications and novel drugs.

There are various factors behind the high prevalence of depression amongst youth in Bangladesh. The main culprit being academic stress where students experience extreme pressure due to examinations, unfriendly learning environments and, subject selection is made based on career prospects instead of preference (Arusha & Biswas, 2020; Sakib et al., 2021). Socioeconomic factors are important as well, as students from low-socioeconomic backgrounds are at increased risk for depression from financial instability, contaminated living environments and food insecurity (Kundu et al., 2021) (Mridha et al., 2021). Moreover, un-scheduled sleeping patterns, dietary in-activity, over usage of social media and lack of physical movement increases the symptoms of depressions (Sayeed et al., 2021) (Anjum, Hossain, Sikder, et al., 2022) (Anjum, Hossain, Hasan, et al., 2022).

The state of mental health has worsened because of the ongoing COVID-19 pandemic, where reported rates of depression prevalence increased due to the number of students quarantining at home, suggesting that depressive symptoms were noted in up to 62.9% of students (Khan et al., 2020).

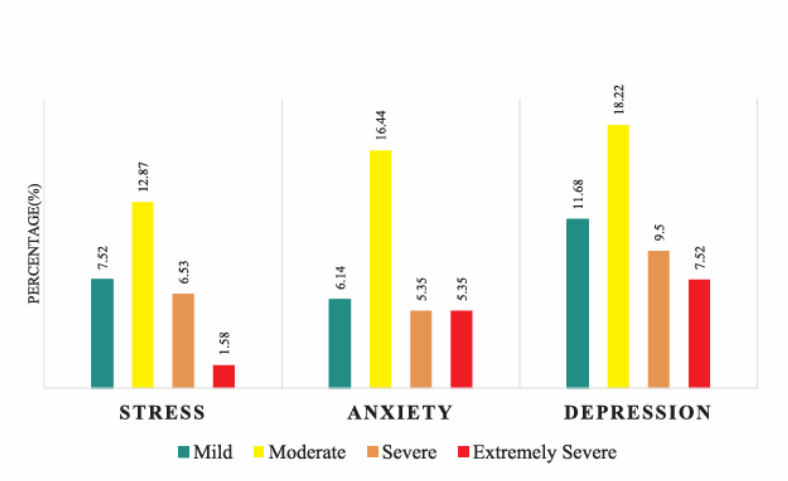

Figure 2: Prevalence of stress, anxiety, and depression related to COVID-19 among home-quarantined students in Bangladesh (Khan et al., 2020).

This figure highlights the high rates of moderate to extremely severe symptoms in all three domains of mental distress, reinforcing the urgency of targeted mental health support during pandemic conditions. The extended time without contact, not knowing what life looks like academically or professionally, and its bad effect on social and interpersonal lives were significant factors in this rise. Moreover, problematic internet use (PIU) (such as engaging in heavy online gaming, social media fanaticism, and passive content consumption) has also been associated with higher prevalence rates of depression among college students (Sayeed et al., 2021).

Young Bangladeshi are mostly handled by pharmacological and psychological approach to treat depression. Conventional antidepressants like Selective Serotonin Reuptake Inhibitors (SSRI) like fluoxetine, sertraline, etc., and also Serotonin-Norepinephrine Reuptake Inhibitors (SNRI), for example, venlafaxine, duloxetine, etc., are still in the first line of treatment (Islam et al., 2021). These medications work by boosting serotonin and norepinephrine levels in the brain, which can help stabilize mood and emotions. Nevertheless, they have several restrictions, including delayed onset of action, side effects such as weight gain, insomnia, sexual dysfunction, and risk of treatment resistance in some patients (Islam et al., 2021).

Other pharmacological treatments include Atypical Antidepressants (e.g., bupropion, mirtazapine), Tricyclic Antidepressants (TCAs) (e.g., amitriptyline), and Monoamine Oxidase Inhibitors (MAOIs) (e.g., phenelzine). Although these medications may provide alternative mechanisms of action, they are known to have harsher side effects and are therefore employed less commonly with the younger populations (Islam et al., 2021).

As traditional antidepressants come with limitations, researchers are investigating innovative drugs to serve as more potent and fast-acting treatments for depression. One notable discovery in recent times is the emergence of Ketamine-based therapies, including Esketamine, which display rapid antidepressant effects, even in treatment-resistant populations (Islam et al., 2021). Whereas it can take weeks for traditional antidepressants, including SSRIs and SNRIs, to take effect, ketamine acts on the glutamate system, leading to rapid relief of depressive symptoms within hours. Esketamine is a N-methylated derivative of ketamine, which is produced through selective chiral synthesis to produce S-enantiomer with greater antidepressant potency than its R-enantiomer counterpart.

The other promising emerging antidepressants are Psychedelic-assisted therapies; psilocybin (in magic mushrooms) and MDMA-assisted psychotherapy. Health and wellness enthusiasts may find this topic of great interest though the substances have been shown to be effective in treating major depression and PTSD through their neuroplastic and affect processing properties (Islam et al., 2021). The synthetic pathways toward these compounds are often multi-step chemical syntheses, including, but not limited to, precursor modifications, catalytic hydrogenation and crystallization techniques used to isolate pure active compounds.

Neurosteroid Modulators, like Brexanolone, have been introduced as antidepressants, mainly for postpartum depression. This medication acts on the gamma-aminobutyric acid (GABA) receptors to foster relaxation and stabilize mood. Brexanolone is synthesized via a multi-step organic synthesis approach including steps associated with steroidal modification and

hydrogenation reactions for improving bioavailability and receptor selectivity (Islam et al., 2021).

The increasing prevalence of depression in Bangladeshi youth is an emerging concern of academic stress, socioeconomic factors, and lifestyle factors (Sakib et al., 2021) (Anjum, Hossain, Sikder et al., 2022; Mridha et al., 2021) Although standard treatment for MDD continues to be traditional antidepressant therapies (SSRIs, SNRIs, and TCAs), limitations of current therapies have led to a search for alternative pharmacological options (Islam et al., 2021). New drugs such as ketamine, psychedelics, and neurosteroid modulators provide rapid-acting options believed to be of great potential, for which new synthetic methods have been employed to enhance efficacy and minimize adverse reactions (Islam et al., 2021). These advances are critical to improve mental health interventions in Bangladesh by providing youth better access to innovative treatment models.

This article focuses to found out the burden of depression in young population in Bangladesh, overview on antidepressants therapies, current state of affairs and future of drugs with research on synthetic route. This study attempts to shed light on the perspective of patient-centered pharmacotherapy in mental health care, by reviewing both conventional and novel pharmacological agents, from a context-sensitive point of view for practice in Bangladesh.

Chapter 2

Methodology

A systematic search was conducted in databases such as PubMed, Google Scholar, and Scopus using keywords related to depression and antidepressant treatments. Studies published between 2010 and 2024 that focused on depression in adolescents and young adults in Bangladesh or similar regions were included. Articles were screened for relevance, and key data regarding antidepressant drugs, including their mechanisms of action, chemical structures, clinical efficacy, and limitations, were extracted and analyzed. The findings were synthesized thematically to provide an overview of current treatments and emerging therapies.

Chapter 3

Causes of depression and its cost to the individual, family and Bangladeshi society

Depression is one of the major public health problems among Bangladeshi youth due to various social, economic, academic and familial factors. The rate of depression symptoms had increased, and research had cited several underlying causes and terrible impacts on individuals, families, and systems.

3.1 Causes of Depression

Some of the factors contributing to depression among Bangladeshi youth is social, economic and psychological. Financial pressures, academic stress and family dynamics all have profound effects on mental health outcomes. Moreover, the COVID-19 pandemic has worsened prevailing mental health issues, and lifestyle choices and gender disparities have increased susceptibility to depression. Identifying these causes is necessary to help create prevention and addressing strategies.

3.1.1 Socio Economic and Financial Strain

According to research, financial difficulties are among the top predictors for depression for youth in Bangladesh. Financial stress has also been found to be a significant factor in heightened levels of anxiety, stress, and depression, particularly for unemployed individuals, as reported through a study (Mamun et al., 2020). There are no jobs and people feel hopeless, and this leads to mental health problems. To make matters worse, many families are facing economic instability which exacerbates emotional distress and further contributes to their uncertainty towards the future (Mamun et al., 2020).

The distribution of depression severity among Bangladeshi adolescents underscores the urgency of addressing its root causes. Figure 1 illustrates the prevalence of various levels of depressive symptoms reported in a recent study.

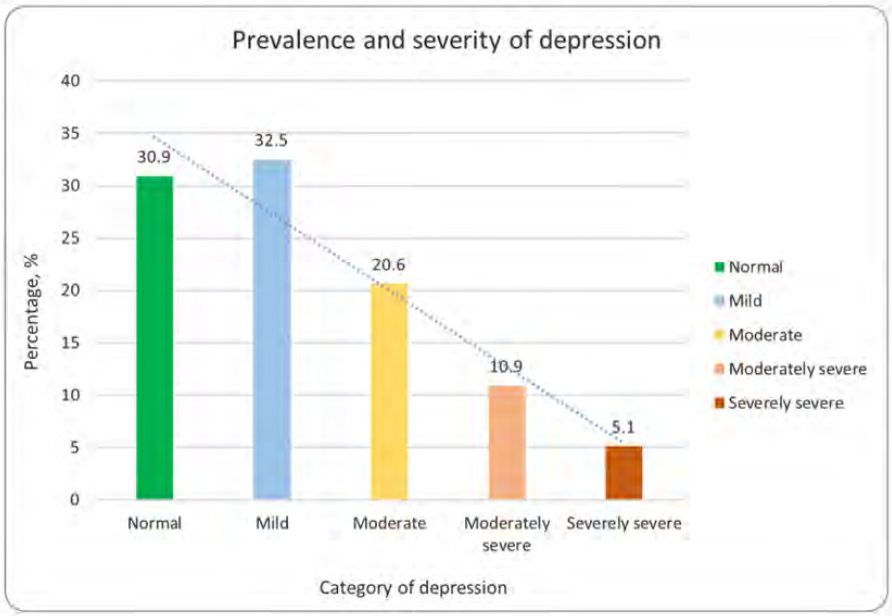

Figure 3: Prevalence and severity of depression among adolescents in Dhaka, Bangladesh (Anjum et al., 2022).

3.1.2 Academic Pressure and Stress Related to School

The need to perform academically is yet another reason leading students towards depression. Previous studies have shown that depressive symptoms correlate with low academic motivation, school failure and dissatisfaction with university culture (Elmelid et al., 2015); (Islam et al., 2020). The pressure for top grades, competitive job prospects, and the promise of seemingly secure careers puts tremendous pressure on students with you. Public university students are at a heightened risk of experiencing mental distress owing to greater socioeconomic stress compared to private university students (Shovo et al., 2021).

3.1.3 How the Pandemic Is Affecting Mental Health

With fear, social isolation, and uncertainty accompanying the COVID-19 pandemic, depression was found to be heightened amongst students (Shovo et al., 2021). Almost half

(45.9%) of university students suffered from depression during the pandemic, struggling with online education, financial distress, and worries about their future careers (Shovo et al., 2021).

3.1.4 Dysfunctional Families and Parenting Styles

Family processes are critical factors in adolescent mental health. Low family emotional expressiveness, poor family communication and high conflict (poor family functioning) has been linked to extensive depressive symptoms (Freed et al., 2016). Parenting styles were also found to play a role in risk for depression, with authoritarian parenting (high control and low warmth) associated with increased tendencies towards depression, while authoritative parenting (balance of warmth and control) associated with greater emotional well-being (Prativa & Deeba, 2019).

3.1.5 History of Gender Differences in Rates of Depression

Numerous studies demonstrate that adolescent females are more likely to experience depression than males (Elmelid et al., 2015), (Shovo et al., 2021), (Hossain et al., 2019), (Anjum, Hossain, Sikder, et al., 2022) Biological, social, and cultural factors have been implicated, including gendered societal and familial expectations and interpersonal stress. Academic dissatisfaction and financial concerns have also been found to have a more significant impact on female students (Hossain et al., 2019).

3.1.6 Lifestyle and Behavioral Patterns

These include the trends of physical inactivity, sedentary behavior, poor sleep quality and substance use, which are all played a significant role in causing depression of Bangladeshi youth (Islam et al., 2020), (Hossain et al., 2019), (Anjum, Hossain, Sikder et al., 2022). Exposure to extended SBSB and irregular sleeping hours can put students at risk of developing depressive symptoms (Anjum, Hossain, Sikder, et al., 2022).

3.2 Depression: The cost to individuals, families and society

The impact of depression is devastating, not only to the individual but also to families and society. It results in academic failures, emotional struggles and lifelong mental health issues. Anguish with financial and emotional, social output reductions, healthcare expenditure escalation and social turbulence as all stakeholders of the system go haywire. Overcome depression and secure the well-being of individuals and in a society that is more productive.

3.2.1 Impact on Individuals

Depression has been shown to have a significant impact on personal and academic life: poor performance, loss of interest in academic work, and a heightened risk of dropping out of school (Elmelid et al., 2015). Depression in its severe form is linked to substance abuse, suicidal ideation and self-harm (Mamun et al., 2020). Moreover, students with depression are also more likely to develop long-term mental health disorders, which can last until adulthood (Anjum, Hossain, Sikder, et al., 2022).

3.2.2 Burden on Families

Family members of depressed individuals suffer emotional and financial burden. Parents feeling unreceptive to their child's issue because of hazy understanding and societal stigma (Prativa & Deeba, 2019), (Freed et al., 2016) may struggle to ameliorate mental health of their child; Communication breakdown and emotional distress can also emerge due to dysfunctional family relationships that are exacerbated by depressive symptoms (Freed et al., 2016).

3.2.3 Cost to Bangladeshi Society

Youth depression has wide impacts on the country's economy and social structure. High depression rates cause reduced productivity, increased burden on healthcare systems and high rates of unemployment (Mamun et al., 2020). Untreated depression has been shown to be a measure of illicit drug consumption, alcohol dependence, and criminality, all of which

increases overall societal resource usage (Mamun et al., 2020). Moreover, Bangladesh suffers from inadequate mental health facilities, with few specialized institutions to attend to the growing mental health crisis in the country (Hady). Many people do not seek treatment due to the stigma associated with mental illness, which worsens the overall situation and affects society at large (Hady).

Chapter 4

Standard Antidepressant Drugs Currently in the Market: Chemical Structure, Mechanisms of Action, and Limitations

Depression is one of the most common mental health disorders, globally and among Bangladeshi youth, and requires an effective pharmacological therapy. Antidepressant medications are classified by mechanism, chemical structure, or neurotransmitter target. Standard antidepressants primarily consist of SSRIs (Selective Serotonin Reuptake Inhibitors), SNRIs (Serotonin-Norepinephrine Reuptake Inhibitors), TCAs (Tricyclic Antidepressants), MAOIs (Monoamine Oxidase Inhibitors) and novel agents like NMDA receptor antagonists. Though these drugs exhibit similar therapeutic effects, they also exhibit severe limitations, preventing their efficacy in select individuals. The core structures of major antidepressant classes illustrate how their chemical makeup informs both their mechanism and side-effect profiles. Figure 5 presents representative structures of fluoxetine (SSRI), venlafaxine (SNRI), and imipramine (TCA).

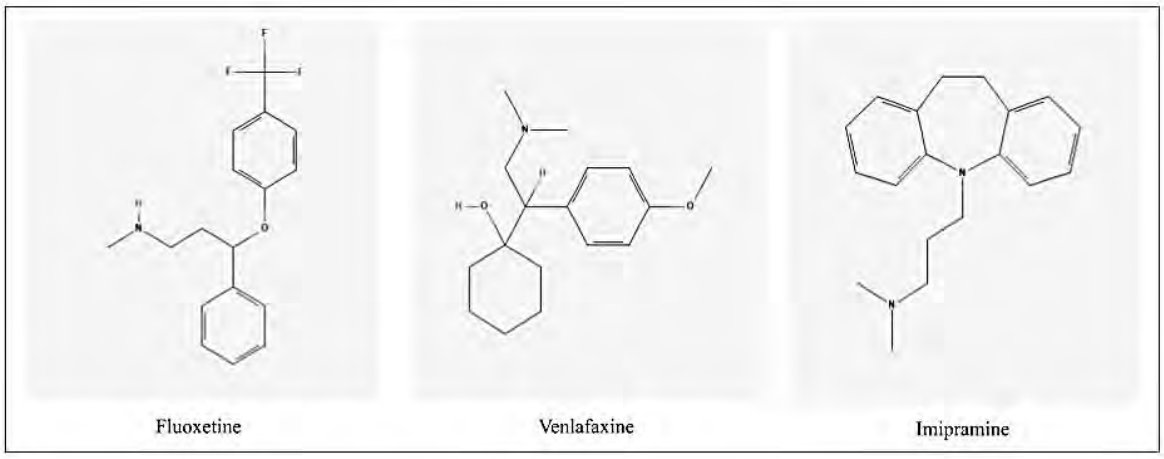

Figure 4. Chemical structures of fluoxetine (SSRI), venlafaxine (SNRI), and imipramine (TCA), annotated to highlight key pharmacophores. Source: PubChem (Fluoxetine: CID 3386; Venlafaxine: CID 5656; Imipramine: CID 3696).

4.1 Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective Serotonin Reuptake Inhibitors (SSRIs) are among the most commonly prescribed antidepressants, favored for their relatively favorable side effect profile and selectivity in targeting serotonin reuptake. Common SSRIs include fluoxetine, sertraline, paroxetine, escitalopram, and citalopram (Mahmoudian Dehkordi et al., 2021). Chemically, these drugs typically have an aromatic ring system that is substituted with halogen-substituted amine groups appended to it, which enhance their ability to enter the blood-brain barrier and target central nervous system targets (Xue et al., 2020).

The primary mechanism of action for SSRIs involves the inhibition of the serotonin transporter (SERT), resulting in increased synaptic concentrations of serotonin. Notably, escitalopram has been shown to bind uniquely to both the S1 and S2 binding sites on SERT, which may explain its prolonged efficacy compared to citalopram (Xue et al., 2022). Despite their effectiveness, SSRIs are associated with several limitations. A major drawback is their delayed onset of action, often requiring several weeks before noticeable improvement in depressive symptoms occurs (Mahmoudian Dehkordi et al., 2021). Additionally, they can produce side effects such as nausea, insomnia, weight gain, emotional blunting, and sexual dysfunction (Xue et al., 2022). Another concern is the relatively high non-response rate, with approximately 40% of patients not gaining any significant therapeutic benefit (Mahmoudian Dehkordi et al., 2021). Furthermore, abrupt discontinuation of SSRIs can lead to withdrawal symptoms, making careful dose tapering necessary (Xue et al., 2020).

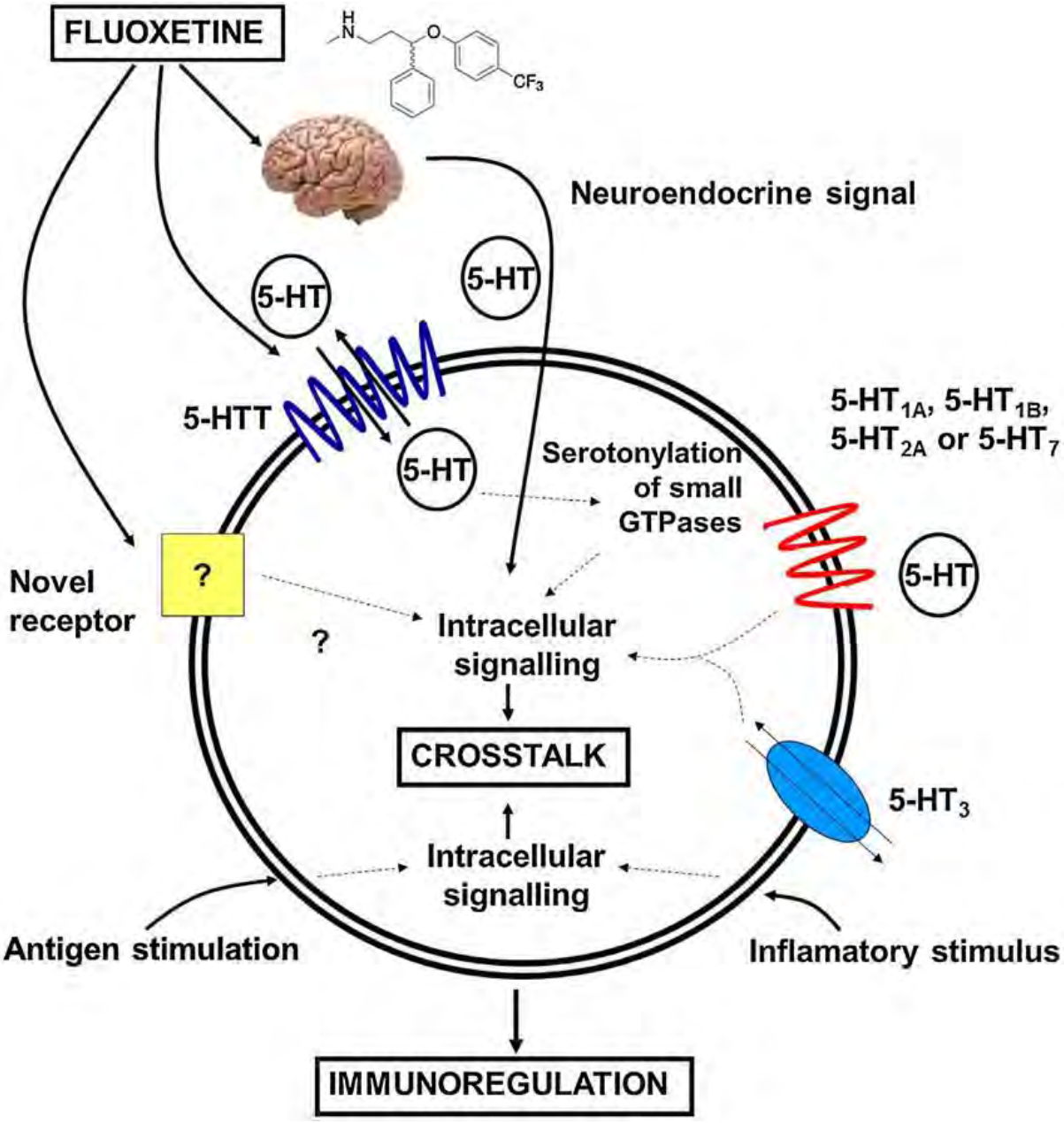

Figure 5. Mechanism of action of SSRIs: SSRIs block the serotonin reuptake transporter (SERT), increasing serotonin levels in the synaptic cleft and enhancing serotonergic neurotransmission (Di Rosso, Palumbo, & Genaro, 2016).

4.2 Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) is a class of antidepressants which also targets the systems of serotonin and norepinephrine neurotransmitters, thereby being extremely effective in managing major depressive disorder, especially for patients with linked pain syndromes. Examples include venlafaxine, duloxetine, desvenlafaxine, and levomilnacipran. (Xue et al., 2020). Structurally, SNRIs are characterized by the presence of two aromatic rings bridged by alkyl chains or heteroatoms, contributing to their affinity for neurotransmitter transporters (Xue et al., 2020).

Mechanistically, SNRIs inhibit both the serotonin transporter (SERT) and the norepinephrine transporter (NET), thereby increasing the synaptic concentrations of these neurotransmitters. The dual mechanism is theorized to be responsible for their effectiveness in the treatment of depression with somatic symptoms. However, SNRIs also have their limitations. Cardiovascular side effects, such as increased heart rate and increased blood pressure, are common and can at times be clinically significant, particularly in patients who already have cardiovascular illnesses (Xue et al., 2020). Additional adverse effects include dizziness, nausea, dry mouth, and insomnia. Furthermore, like SSRIs, SNRIs can lead to discontinuation syndrome if stopped abruptly, manifesting as flu-like symptoms, irritability, and sensory disturbances (Xue et al., 2020). These limitations must be carefully weighed against therapeutic benefits during treatment planning.

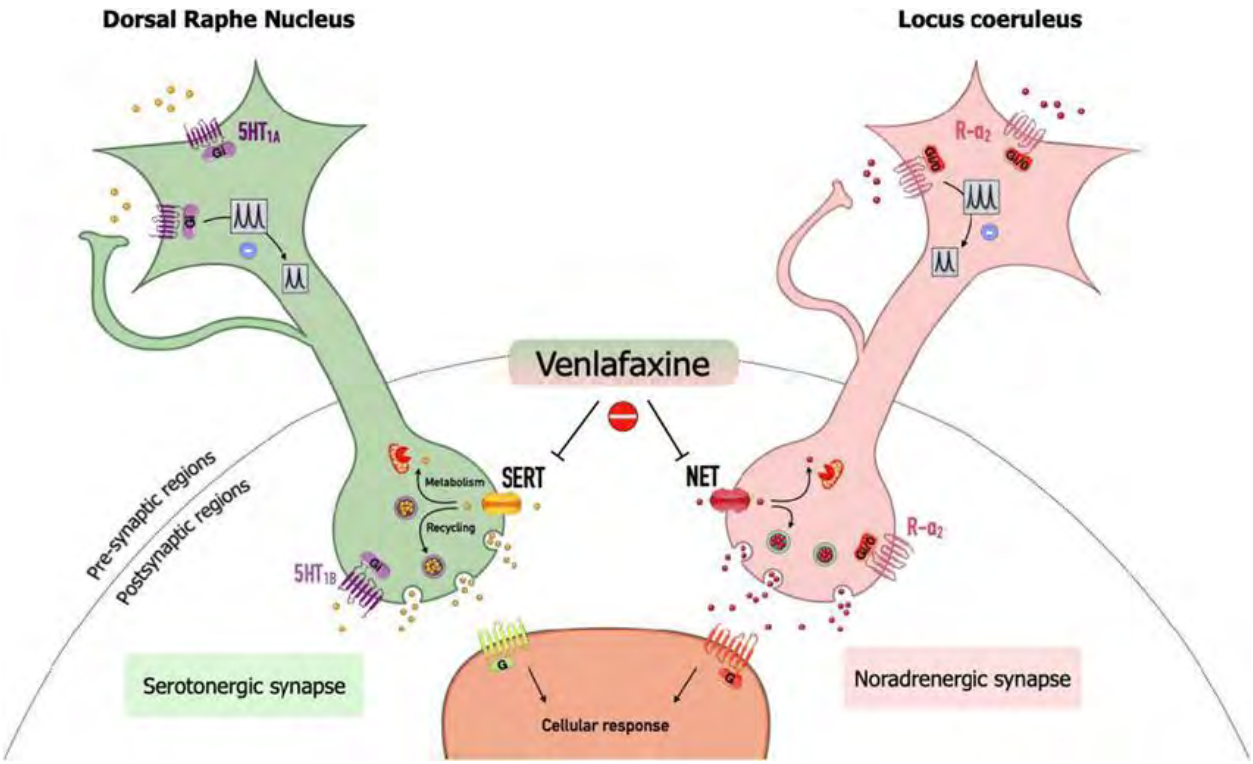

Figure 6. Mechanism of action of SNRIs: SNRIs inhibit both serotonin (SERT) and norepinephrine (NET) reuptake transporters, enhancing the concentration of these neurotransmitters in the synaptic cleft to improve mood and alertness (Coutens, Yrondi, Rampon, & Guiard, 2022).

4.3 Tricyclic Antidepressants (TCAs)

Tricyclic Antidepressants (TCAs) are among the most ancient antidepressant medication classes and have proven broad efficacy for major depressive disorder as well as several anxiety and pain disorders. TCAs such as imipramine and amitriptyline have as their main mechanisms blockade of SERT and NET transporters as well as serotonin and norepinephrine reuptake inhibition, elevating the level of these neurotransmitters in the synaptic cleft (Riggs & Gould, 2021). While effective, TCAs are distinguished from newer antidepressants by their broader receptor binding profiles, which contribute to their extensive side effect profile.

One of the primary limitations of TCAs is their pronounced anticholinergic effects, which include dry mouth, constipation, blurred vision, urinary retention, and cognitive impairment. These side effects often limit tolerability, particularly in elderly populations (Riggs & Gould, 2021). Besides, TCAs have significant cardiotoxicity in overdose and have a high potential for

causing lethal arrhythmias, making them a dangerous option for suicidal risk patients. Also, their effect as an antagonist at histaminergic receptors causes severe sedation, which is beneficial to some but detrimental to others (Riggs & Gould, 2021). Despite these drawbacks, TCAs remain a valuable therapeutic option in certain clinical scenarios, especially where newer antidepressants have failed.

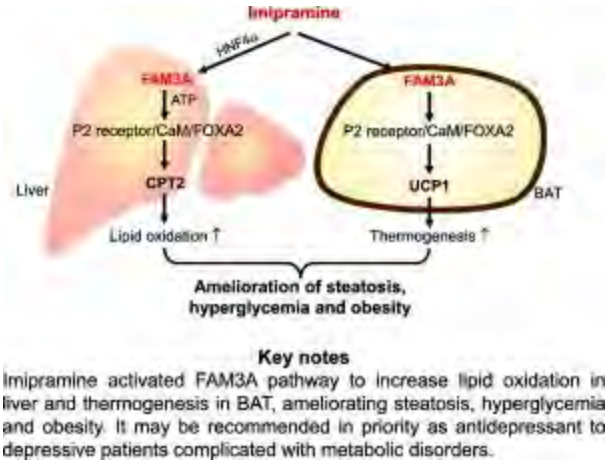

Figure 7. Mechanism of action of TCAs: Tricyclic antidepressants inhibit SERT and NET, while also interacting with histaminergic, cholinergic, and adrenergic receptors, resulting in antidepressant effects along with characteristic side effects (Riggs & Gould, 2021).

4.4 Monoamine Oxidase Inhibitors (MAOIs)

Monoamine Oxidase Inhibitors (MAOIs) are an older generation of antidepressants that act by inhibiting the activity of monoamine oxidase enzymes, which metabolize important neurotransmitters such as serotonin, norepinephrine, and dopamine. Inhibition of this breakdown reaction by MAOIs increases the concentration of these neurotransmitters in the brain, thereby mitigating depression symptoms (Riggs & Gould, 2021). Notable examples of MAOIs include iproniazid and phenelzine.

While pharmacologically useful, MAOIs use has fallen significantly due to their side effect profile and dietary restrictions. One of the most critical concerns is the risk of hypertensive

crisis when patients consume tyramine-containing foods such as aged cheeses, cured meats, and certain alcoholic beverages. This is due to the fact that blocking the metabolism of monoamines within the gastrointestinal tract results in the tyramine being made available to enter circulation and induce deadly surges in blood pressure (Riggs & Gould, 2021). In addition to dietary restriction, MAOIs are also accompanied by hepatotoxicity, hemorrhage risk, and complex drug interactions, making them less favorable nowadays. However, in treatment-resistant depression where other modalities have been unsuccessful, MAOIs remain capable of providing therapeutic benefits with close medical surveillance.

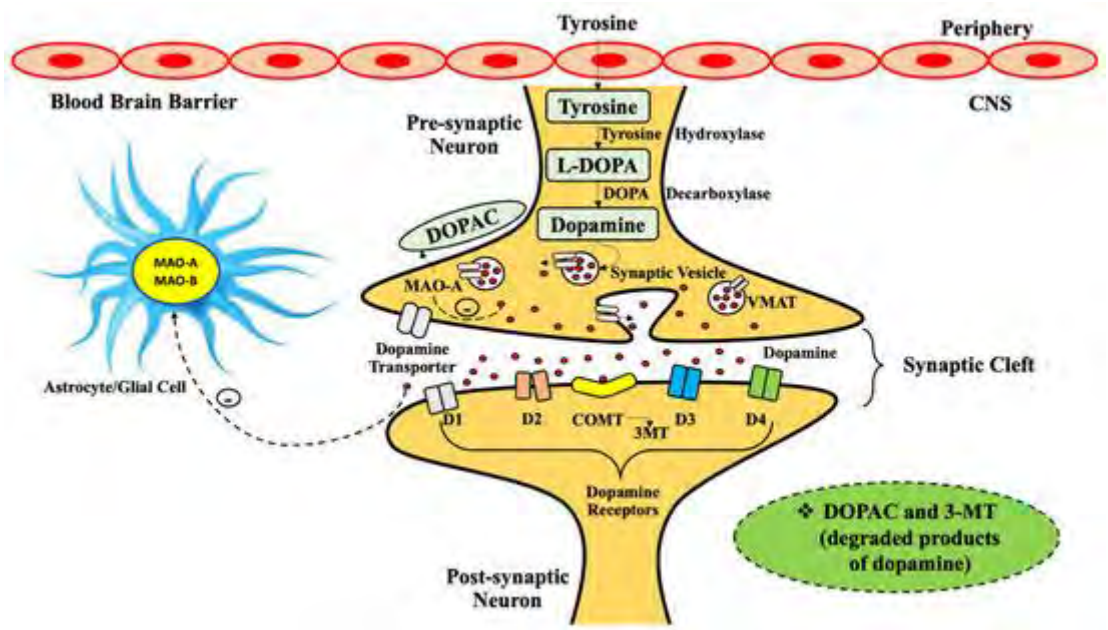

Figure 8. Mechanism of action of MAOIs: MAOIs irreversibly inhibit monoamine oxidase enzymes (MAO-A and MAO-B), preventing the breakdown of serotonin, norepinephrine, and dopamine, thus elevating their levels in the brain (Asadi, Shahin, & Miremadi, 2023).

4.5 Novel NMDA Receptor Antagonists

Recently, novel antidepressant medications targeting the glutamatergic system have been suggested as potential alternatives, particularly in treatment-resistant depression (TRD).

Among them, NMDA (N-methyl-D-aspartate) receptor antagonists have been of particular interest due to their rapid onset compared to traditional monoaminergic antidepressants. Ketamine and its S-enantiomer esketamine are the most studied drugs of this category. Chemically derived from phencyclidine, ketamine is a non-competitive antagonist of NMDA receptors, resulting in enhanced glutamatergic transmission and synaptogenesis stimulation via brain-derived neurotrophic factor (BDNF) pathways (Riggs & Gould, 2021; Kalmoe et al., 2020).

Despite their rapid antidepressant effects—often observable within hours to days—NMDA receptor antagonists have several notable limitations. Their therapeutic benefits are typically short-lived, often lasting only days to weeks, necessitating repeated administration (Riggs & Gould, 2021). Moreover, ketamine and esketamine are associated with side effects such as dissociation, hallucinations, nausea, and a potential for abuse, which has raised concerns about long-term use and safety (Kalmoe et al., 2020).

Nitrous oxide, another NMDA receptor antagonist, also exhibits antidepressant properties. In addition to NMDA receptor blockade, it interacts with kappa-opioid receptors, contributing to its mood-elevating effects (Kalmoe et al., 2020). However, its value is decreased by its short duration of action and potential neurologic toxicity on long-term exposure, e.g., spinal cord degeneration. Though NMDA antagonists are a leap in the art of rapid-onset antidepressants, their shortfalls underscore the need for future innovation and aggressive safety evaluation.

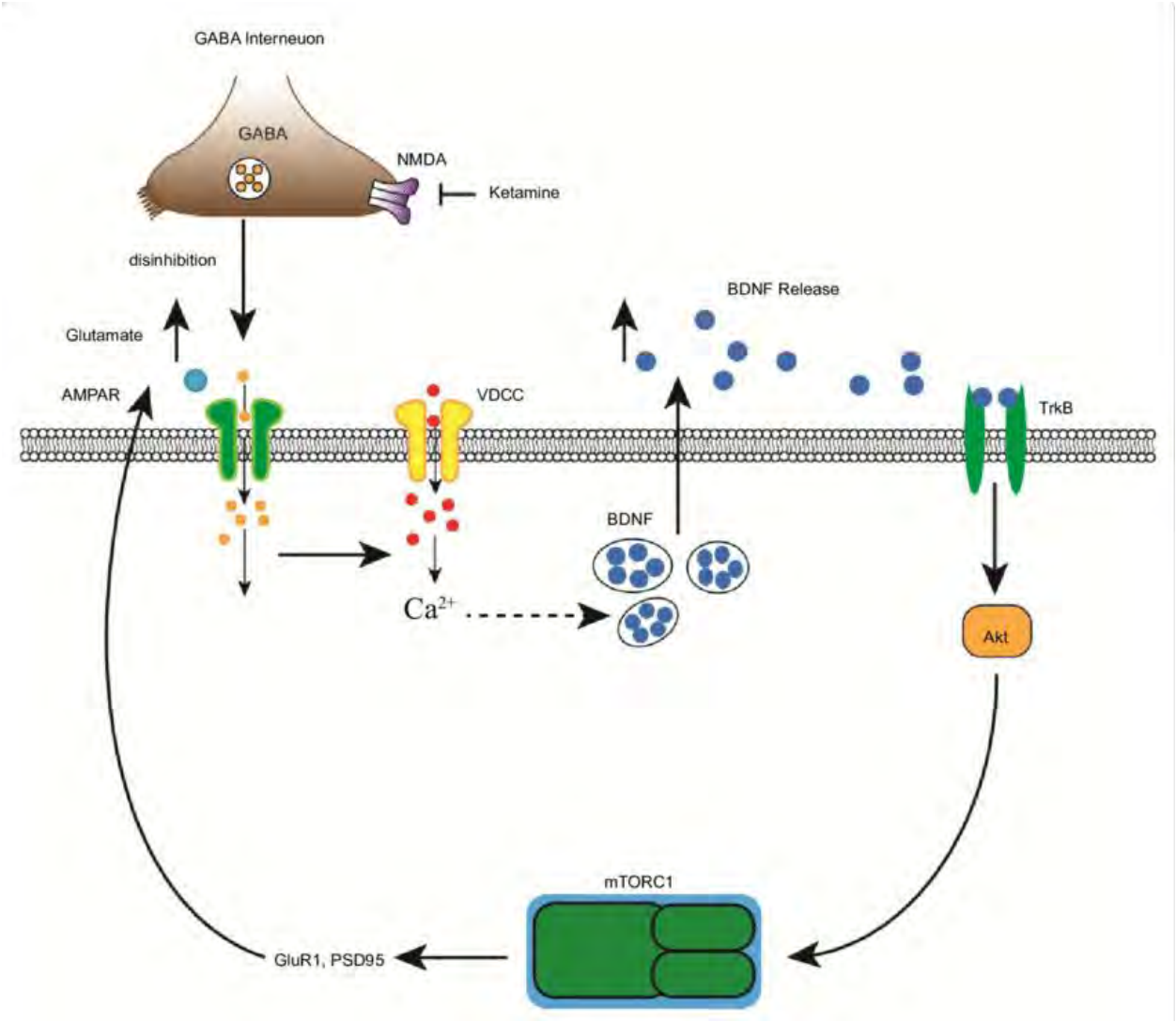

Figure 9. Mechanism of action of ketamine: Ketamine acts as a noncompetitive NMDA receptor antagonist, modulating glutamatergic transmission and enhancing synaptic plasticity, resulting in rapid antidepressant effects (Adu-Nti, Ghartey-Kwansah, & Aboagye, 2019).

4.6 Piperazine-Based Antidepressants

Piperazine antidepressants are a heterogeneous class of compounds that all share a common structural feature—a piperazine ring—that enhances their blood-brain barrier penetration and central nervous system receptor binding ability. By virtue of this structural motif, these compounds can bind at multiple neurotransmitter systems, offering new pharmacodynamic profiles. Trazodone, vilazodone, and vortioxetine are examples, with each compound's antidepressant action mediated by different mechanisms (Kumar et al., 2021).

These drugs have multiple mechanisms of action: vortioxetine is a mainly selective serotonin reuptake inhibitor (SSRI), vilazodone is an SSRI and an agonist at the 5-HT1A receptor (only partial), and trazodone is a 5-HT2A receptor antagonist with weak inhibition of serotonin reuptake. This multimodal activity is the basis for their antidepressant efficacy and theoretically broader symptom targeting. Some of these similar agents include befuraline, an SNRI, and buspirone, a 5-HT1A agonist whose primary application is for its anxiolytic properties (Kumar et al., 2021).

However, in spite of their pharmacological flexibility, piperazine-type antidepressants are not flawless. Their patients tend to develop such side effects as sedation, nausea, sexual dysfunction, and weight gain. In addition, they carry a significant risk of relapse, as the majority of the patients are found to develop recurrence of depressive symptoms following cessation or dose reduction (Kumar et al., 2021). While their complex mechanisms may offer benefits in specific clinical contexts, the potential for adverse effects and relapse necessitates careful patient selection and monitoring during treatment.

4.7 Viloxazine: A Norepinephrine Reuptake Inhibitor (NRI)

Viloxazine is a bicyclic antidepressant which has gained recent interest once more, particularly for its repurification for treating Attention Deficit Hyperactivity Disorder (ADHD). Created and marketed originally as an antidepressant, the mechanism of action of viloxazine is selective norepinephrine reuptake blockade, thereby increasing the concentration of norepinephrine in the synaptic cleft and enhancing the mood regulation (Findling et al., 2021). In addition to its primary action as a norepinephrine reuptake inhibitor (NRI), viloxazine also exhibits antagonistic activity at α2-adrenergic receptors and has been shown to modulate serotonin receptors indirectly, further contributing to its antidepressant and cognitive-enhancing effects (Findling et al., 2021). In terms of structure, viloxazine consists of a bicyclic oxazine backbone and an ethoxyphenoxy group, which aids in penetration to the central nervous system as well as receptor selectivity. Though it shows promise as a next-generation antidepressant, viloxazine is not free of side effects. It can affect patients with gastrointestinal side effects such as nausea and vomiting, as well as insomnia (Findling et al., 2021). These side effects are generally dose-dependent and may be titrated or treated symptomatically. Even with the limitations, viloxazine's multimodal activity and tolerability profile offer a second option for nonresponsive patients to conventional antidepressants.

Chapter 5

Emergence of New Antidepressant Drugs Currently in the Market or Being Investigated in Clinical Trials

Antidepressant therapies have evolved over time, resulting in the emergence of new drug candidates that act on different biochemical pathways beyond just the typical serotonin and norepinephrine systems. Despite the variety of existing anti-depressants, depression, and especially treatment-resistant depression (TRD) are serious public health problems requiring new mechanisms of action with a rapid onset of action, greater efficacy and improved tolerability. Recent clinical trials using novel pharmacological agents, including glutamate modulators and neurosteroids, have been conducted to overcome the limitations of existing antidepressants. These innovative methods are especially important in the case of Bangladeshi young people, where there are currently serious issues with both limited access to mental health services and ineffective reactions to traditional therapies.

5.1 Glutamate Modulators: Ketamine and Esketamine

The rapid antidepressant effects of ketamine have been a game-changer for psychiatric treatment. In contrast, the SSRIs (selective serotonin reuptake inhibitors) and SNRIs (serotonin-norepinephrine reuptake inhibitors) can take weeks to months to see therapeutic effects, whereas ketamine provides rapid relief of symptoms through NMDA receptor antagonism and subsequent synaptic plasticity (Marwaha et al., 2023). Esketamine, its derivative, has received US FDA approval for TRD and is delivered as a nasal spray, providing a novel drug delivery route with a fast onset of action (Marwaha et al., 2023). Since treatment resistant depression is quite common in this youngs including Bangladesh population, esketamine may represent an exciting therapeutic opportunity in the clinical arena.

5.2 Emerging Role of Psilocybin as a Rapid-Acting Antidepressant

Psilocybin, a naturally occurring psychedelic compound, has shown rapid and lasting antidepressant effects in clinical studies. Psilocybin enhances neuroplasticity through a strong 5-HT2A receptor agonism, and encourages profound psychological experiences, thought to mediate its reported antidepressant actions (Marwaha et al., 2023). Previous research well supports the potential clinical relevance of psilocybin, and emerging evidence indicates its promise in TRD patients, including those unresponsive to SSRIs (Goodwin et al., 2023). The increasing popularity of psychedelic-based therapy is becoming a place of treatment as patients realize, especially in populations that may have been mentioned to have a poor response with the common therapies.

5.3 Orexin Receptor Antagonists in the Treatment of Depression

Orexin receptor antagonists (e.g. almorexant, seltorexant) are in development for the regulation of mood, stress, and sleep patterns (Fagan et al., 2023). Background The orexin system is increasingly recognized as a critical modulatory system of sleep-wake regulation, with evidence also implicating its involvement in major depressive disorder (MDD). Such factors are prevalent in this population, as sleep disorders often accompany depression, and orexin receptor modulators would improve sleep disruption symptoms, as well as depressive symptoms. Preclinical and early clinical studies have shown depression-like effects of these drugs as stress modulating pathways, serving as new innovations for individuals with depression (despite not being one of the classical indications for treatment) (Fagan et al., 2023)

5.4 Pharmacogenetic Perspectives in Antidepressant Therapy

The current era of personalized medicine has resulted in greater interest in pharmacogenetic-guided antidepressant therapy. Polymorphisms in drug-metabolizing enzymes, especially CYP2D6 and CYP2C19, produce inter-individual differences in response to tricyclic antidepressants (TCAs) and other psychotropic medications (Vos et al., 2023). Ratios for Median Genotype PhenotypesSet of hand for studies have also found for dosing genotypotypes that target antidepressants to increase the effect of these drugs and reduce negative effects. The advantages of pharmacogenetic-guided treatment are still under study but may transform the treatment of depression by customizing drug regimens to an individual's genetic makeup (Vos et al., 2023).

5.5 The discovery of Triple Reuptake Inhibitors

An emerging class of antidepressants, the so-called triple reuptake inhibitors (TRIs),[1] like ansofaxine simultaneously inhibit the reuptake of serotonin, norepinephrine, and dopamine (Vasiliu, 2022). These compounds work through a more complex mechanism of actions by acting on several different neurotransmitter pathways, potentially yielding a greater and broader therapeutic action than that of conventional treatment with SSRIs and SNRIs. TRIs seem to have the potential to be more effective in the treatment of patients suffering from severe or treatment-resistant depression (Vasiliu, 2022).

5.6 Brexanolone and Zuranolone: Neurosteroids and GABAergic Modulators

Neurosteroids (brexanolone, and zuranolone) are a new class of antidepressant treatments that act on GABAergic system. An example of a novel pharmacological treatment is brexanolone which is a positive allosteric modulator of GABA-A receptors that is approved for postpartum depression but being investigated for use in TRD (Vasiliu, 2022). Zuranolone, like ketamine,

has shown rapid and sustained antidepressant effects in clinical studies, with some reports of symptom relief in as little as days (Clayton et al., 2023).

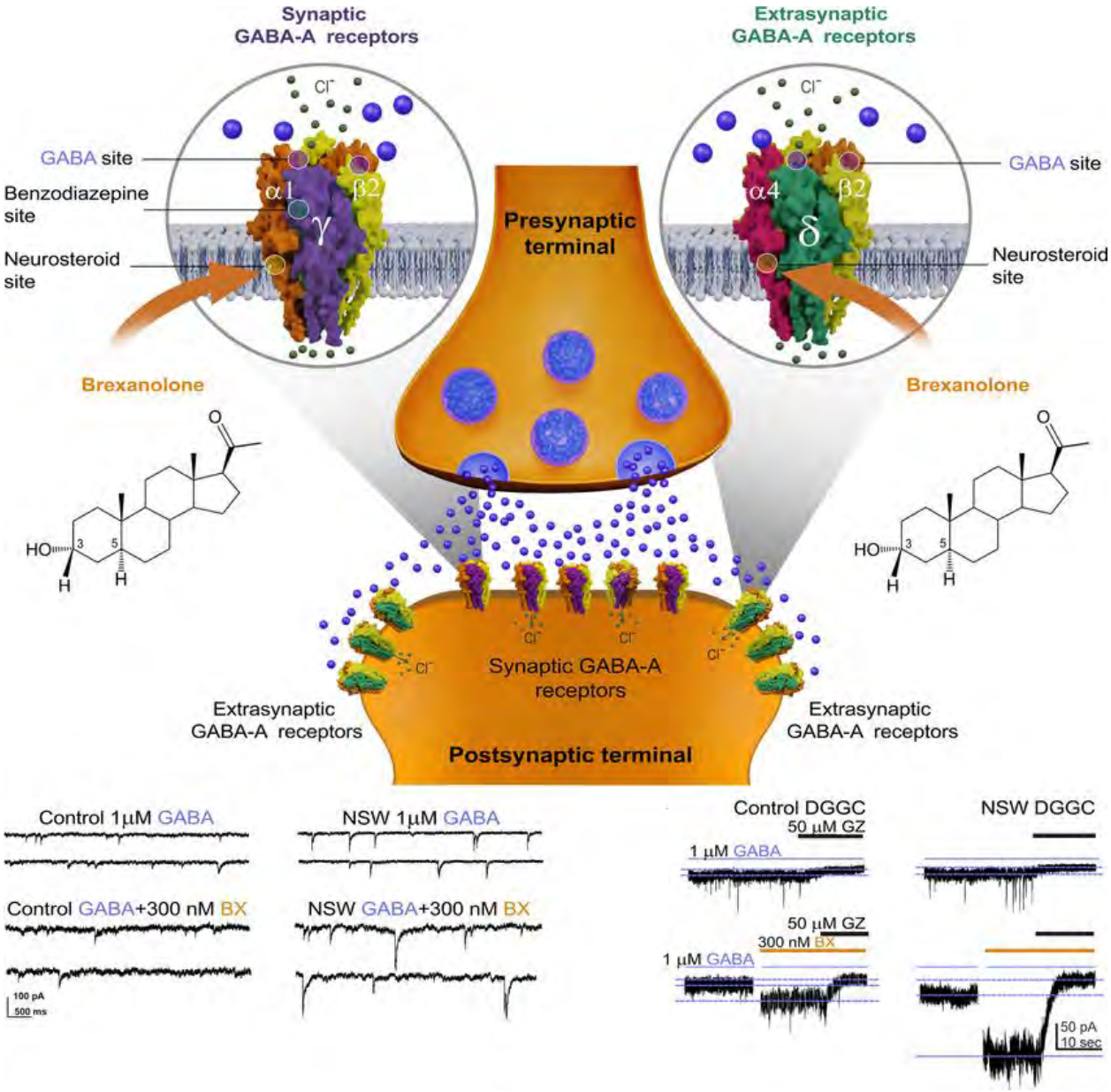

Figure 10. Mechanism of action of brexanolone: Brexanolone is a positive allosteric modulator of GABA-A receptors, enhancing inhibitory neurotransmission and producing rapid mood-stabilizing effects in postpartum and treatment-resistant depression (Reddy, Mbilinyi, & Estes, 2023).

5.7 The Role of Atypical Antipsychotics in Augmenting Antidepressants

Novel therapies such as atypical antipsychotics (i.e., aripiprazole, brexpiprazole, cariprazine) are increasingly used as adjunctive agents in TRD (Jha & Mathew, 2023). These medications work by modifying dopaminergic and serotonergic activity and thus potentiate the action of classical antidepressants. Antipsychotic augmentation is also gaining interest in non-remitting patients treated with gold-standard antidepressant therapies, supporting their role against resistant depression (Jha & Mathew, 2023).

5.8 Non-Traditional Drugs in treating Depression

Some non-conventional pharmaceuticals, including simvastatin, have been studied for antidepressant effect, based on anti-inflammatory and neuroprotective mechanisms (Husain et al, 2023). However, clinical trials have shown no consistent or significant improvement in depressive symptoms, suggesting that drug repurposing for psychiatric disorders can be problematic. However, despite the data contributing to the attrition of new antidepressants in clinical testing, there is critical importance in pursuing repurposing efforts for youth with depression through the combination of translation & reproducibility of effects (Husain et al., 2023) given the lack of response from current antidepressants.

Chapter 6

Different synthetic procedures of standard and emergent antidepressant drugs; their advantages in the process of synthesis, challenges and future direction

This has led to advances in antidepressant synthesis to improve efficacy and reduce side effects and to improve sustainability. It focuses on different synthetic approaches, such as sulphonamides, phytopharmacotherapy, multitarget ligand, green chemistry, and metal-catalyzed reaction. Although these approaches have advantages such as structural diversity and eco-friendliness, it also faces limitations of interacting bioavailability and construction scale. Look ahead to AI-enabled design and biocatalysis of newer, safer, and more potent drugs.

6.1 Sulphonamides and Sulphonyl-Hydrazones as Antidepressant Scaffolds

Sulphonyl-hydrazones and sulphonamides are a class of synthetic drugs that have shown promising antidepressant activity in recent preclinical studies. These compounds are synthesized by Diels–Alder reaction between sulphonyl chlorides and diene like furan or 2-methylfuran. Sulphonyl–hydrazones can also be synthesized through condensation of hydrazine hydrate with cyclic imides or benzaldehydes and amines under controlled conditions, allowing chemical modifications with varying range (de Oliveira et al., 2011). These approaches enable the synthesis of structurally sophisticated compounds, some of which have higher activity than reference antidepressants like imipramine. Their pharmacological activity is established by in vivo models with reproducible improvement in depression behaviors. Solubility issues with certain derivatives limit their therapeutic utility, requiring novel

formulation techniques or prodrug strategies. In addition, some molecules exhibit less monoamine target inhibition than fluoxetine, suggesting further optimization.

Figure 11. Chemical structure of a representative sulphonamide derivative synthesized via Diels–Alder reaction pathways. Source: PubChem (Sulfamethoxazole: CID 5329).

Looking forward, the continued exploration of multi-target pharmacodynamics and extended toxicological profiling of sulphonamide derivatives may help position these compounds as viable candidates for next-generation antidepressants.

6.2 Phytopharmacotherapeutics and Herbal-Derived Antidepressants

Natural compounds have been studied for their therapeutic benefits for many years, and a number of herbal extracts—such as St. John's Wort, saffron, and ginseng—exhibit antidepressant action through various mechanisms. These include blocking monoamine reuptake, anti-inflammatory mechanisms, and neurotrophic modulation (Berg et al., 2021; Dobrek & Glowacka, 2023). One of the key advantages of herbal-based antidepressants is their multimodal mechanism, which might have broader coverage of symptoms. Additionally, these molecules are less likely to cause side effects than conventional antidepressants, and therefore they are interesting for long-term therapy. Nevertheless, there are challenges in standardizing plant extracts and ensuring consistent bioavailability. Phytochemical content variability and

lack of large-scale clinical confirmation also complicate regulatory approval and clinical adoption.

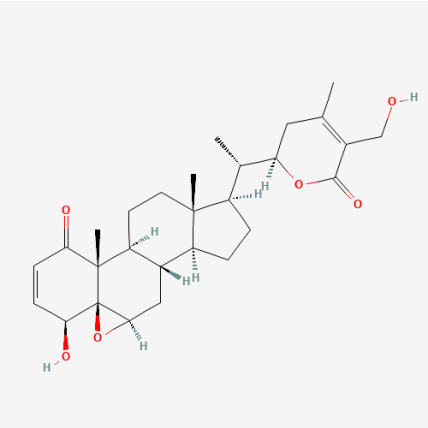

Figure 12. Chemical structure of Withaferin A, a representative herbal-derived compound with demonstrated antidepressant effects via multi-target neurochemical mechanisms.

Source: PubChem (Withaferin A: CID 265237).

Future advancements may focus on hybrid drug design, integrating synthetic pharmacophores with phytochemical cores to create potent, bioavailable, and standardized therapies. Improved delivery systems and controlled clinical trials will be essential to realize their therapeutic potential.

6.3 Multi-Target Directed Ligands (MTDLs) and Hybrid Antidepressants

Multi-target directed ligands (MTDLs) are a strategic evolution from the conventional single-target antidepressants. MTDLs are designed by molecular hybridization and fragment-based drug design to interact with multiple biological pathways of depression, including serotonergic, dopaminergic, and GABAergic systems (Singh et al., 2022). MTDLs have also been shown to enhance antidepressant activity but reduce side effects, due to their structural versatility and potency for strong receptor binding. The molecules possess a number of shortcomings, such as being poorly permeable into the blood-brain barrier, and some display risks of cytotoxicity due

to the general activity of their receptors. This highlights the need for rigorous molecular optimization and selectivity profiling.

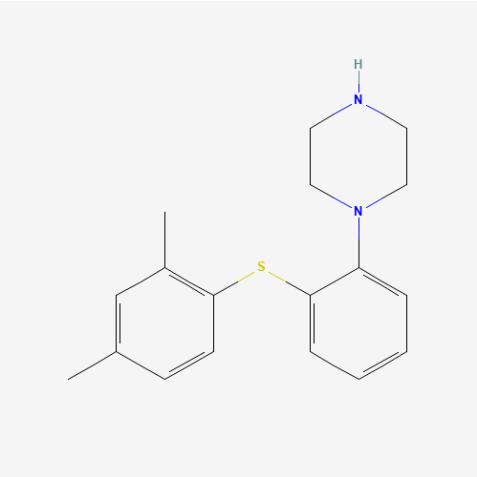

Figure 13. Chemical structure of Vortioxetine, exemplifying multi-target directed ligand design in antidepressant therapy. Source: PubChem (Vortioxetine: CID 9966051).

The future of MTDLs most likely resides in the use of artificial intelligence and machine learning to forecast safety profiles and optimize ligand-receptor interactions. Treating cognitive impairments and treatment-resistant phenotypes through polypharmacology is a future direction for next-generation antidepressant drug development.

6.4 Green Chemistry in Antidepressant Synthesis

Green drug synthesis has become a paradigm in drug development, and green chemistry methods—such as microwave-assisted organic synthesis (MAOS) and solvent-free reactions—are increasingly being utilized in antidepressant drug development (Banik et al., 2024). These techniques reduce toxic waste and improve process efficiency while maintaining high yields.

The advantages are staggering: green processes, reduced long-term expense, and improved environmental and worker safety profiles. Nevertheless, scalability to bulk industrial production is unknown, and the economic feasibility of producing green catalysts is still under evaluation. Complete commercialization by large pharmaceutical manufacturers will also be contingent on regulation-based incentives and proof of comparable therapeutic efficacy. Going

forward, the integration of computational chemistry with green synthesis—especially biocatalytic approaches—could revolutionize how antidepressants are manufactured, aligning clinical efficacy with environmental responsibility.

6.5 A Greener Route to Synthesizing Bupropion Hydrochloride

The NDRI bupropion has previously been synthesized through bromination and amination reactions with environmentally unsupportive solvents. Later publications have provided evidence for greener processes using bio-based solvents such as Cyrene and ethyl acetate, significantly reducing the environmental footprint of the synthesis (Andrew et al., 2022). The shift to benign solvents has achieved a substantial waste reduction of as much as 92 kg less per kilogram of end product while still maintaining good yields. These methods achieve sustainable development goals in the pharmaceutical industry. The disadvantage is to make sure that the greener processes are as efficient and cost-effective as the traditional processes at commercial scales. Future directions should involve applying similar green methodologies to other classes of antidepressants and validating these processes through life-cycle assessments and regulatory standards to encourage industry-wide adoption.

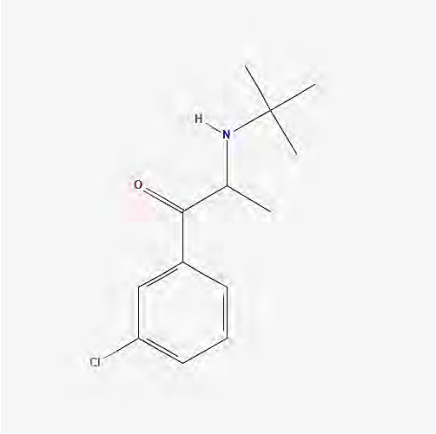

Figure 14. Chemical structure of Bupropion, highlighting eco-friendly synthesis approaches in antidepressant development. Source: PubChem (Bupropion: CID 444).

6.6 Benzimidazole Derivatives as Monoamine Oxidase Inhibitors

Benzimidazole derivatives have become potential candidates for treating depression due to their inhibitory action against the monoamine oxidase enzymes MAO-A and MAO-B. These derivatives are synthesized by condensation of cinnamic acid with o-phenylenediamine and produce both pharmacologically active and useful chemically intact structures (Sahariah et al., 2024). Their main advantages are improved pharmacological profiles, reduced toxicity, and selective inhibition of the MAO enzyme, all of which lead to beneficial antidepressant activity. Discrimination between MAO-A and MAO-B selectivity remains difficult, however, requiring more detailed biochemical characterization to avoid off-target effects and ensure therapeutic specificity.

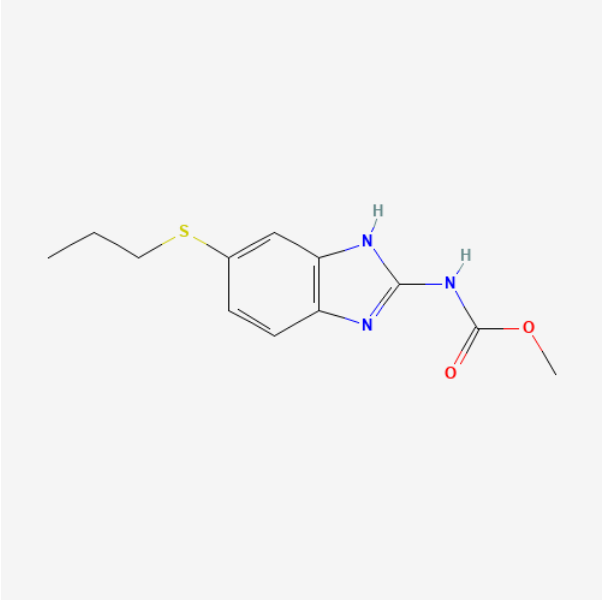

Figure 15. Chemical structure of a benzimidazole derivative, illustrating MAO inhibition potential in antidepressant therapy. Source: PubChem (Albendazole Oxide: CID 83969).

The next steps in benzimidazole research include comprehensive in vivo testing to confirm efficacy and safety, as well as potential modification of the core structure to enhance blood-brain barrier permeability and metabolic stability.

6.7 Metal-Catalyzed Reactions in Antidepressant Synthesis

Metal-catalyzed reactions have also been central to the streamlined synthesis of several classes of antidepressants, including SSRIs, MAOIs, TCAs, and ketamine analogs. By employing palladium, ruthenium, and nickel catalysts, these reactions improve the selectivity and yield of reactions, enabling the synthesis of pharmacologically active structures with accuracy (Kanwal et al., 2024). This approach offers various advantages: high selectivity, fewer reaction steps, and cleaner reaction profiles. Moreover, the majority of metal-catalyzed routes are green chemistry-compatible, offering environmentally friendly methods compared to conventional synthetic routes. However, the expense including precious metals and challenges in recycling or recovering the catalysts limit their widespread use. In addition, metal residue toxicity as well as industrial scalability need to be addressed.

Future innovation may come from the development of biobased or recyclable metal catalysts and renewable catalyst platforms, pushing forward both efficiency and sustainability in antidepressant production.

Table 1: Pharmacological and Clinical Overview of Novel Antidepressant Agents

Drug Name	Mechanism / Target Pathway	Delivery Method	Onset of Action	Common Side Effects	Clinical Status
Ketamine	NMDA receptor antagonist; enhances BDNF and synaptic plasticity	Intravenous (IV)	Hours	Dissociation, nausea, increased blood pressure	Approved for TRD in some countries
Esketamine	NMDA receptor antagonist (S-enantiomer of ketamine)	Intranasal	Hours	Dissociation, dizziness, sedation	FDA approved (nasal spray for TRD)
Psilocybin	5-HT2A receptor agonist; promotes neuroplasticity and insight	Oral (capsule)	1–3 hours	Hallucinations, nausea, emotional lability	Phase II–III clinical trials

Brexanolone	Positive GABA-A receptor modulator (neurosteroid)	IV infusion (60-hour)	24–48 hours	Sedation, dizziness, headache	FDA approved (for postpartum depression)
Zuranolone	GABA-A receptor modulator (oral neurosteroid analog)	Oral	Within days	Drowsiness, dizziness, fatigue	Phase III trials completed
Ansofaxine (TRI)	Triple reuptake inhibitor (SERT, NET, DAT)	Oral	1–2 weeks	Insomnia, nausea, dry mouth	Phase III trials in progress
Seltorexant	Orexin-2 receptor antagonist; modulates sleep and stress	Oral	1–2 weeks	Somnolence, fatigue, abnormal dreams	Phase II–III trials
Viloxazine	Norepinephrine reuptake inhibitor; modulates serotonin receptors	Oral	1–2 weeks	Nausea, irritability, insomnia	FDA approved for ADHD; off-label for MDD

Table 1 illustrates key features of novel antidepressant drugs currently approved or under investigation. Agents like ketamine and esketamine demonstrate rapid onset through NMDA receptor antagonism, while psilocybin and brexanolone offer alternative pathways via 5-HT2A and GABA-A receptor modulation, respectively. The table also includes drugs with unique mechanisms such as triple reuptake inhibition (e.g., ansofaxine), orexin antagonism (e.g., seltorexant), and repurposed agents like viloxazine, highlighting pharmacological diversity and the growing focus on personalizing therapy for resistant cases.

Chapter 7

Conclusion

The current state of depression in Bangladeshi youth life has become a crucial health problem because of academic stress pressures, socioeconomic challenges, and lifestyle factors. The impact of this review article is to provide a literature review to aid in addressing this pressing and urgent depression problem in Bangladesh. As discussed above, the increasing emergence of depressive symptoms in students and young adults highlights the demand for mental health interventions. Conventional backgrounds such as SSRIs, SNRIs, and TCAs are still the mainstay in pharmacological approaches. But these treatments come with limitations, including delayed onset, adverse side effects and treatment resistance, which emphasize the need for more effective alternatives.

Emerging classes of antidepressants with fast-acting and prolonged effects have recently been developed. Various novel agents—ketamine-based therapies, psychedelics such as psilocybin, and neurosteroid modulators such as brexanolone—have shown promise in treating treatment-resistant depression. These newer treatments range from ketamine and its derivatives to psychedelics, and they hold promise by targeting different neural pathways, providing faster relief, and causing less long-term harm than traditional antidepressants.

Tremendous developments have also been obtained in the synthesis of these new antidepressants through chiral synthesis and catalytic process and environmentally friendly methodologies. Antidepressant improvement is being driven by green chemistry, multi-target medicines, and bio-solvent alternatives to improve evaluation and use. Furthermore, these advances serve to enhance the treatment effect of the medicines and minimize the associated toxicity and waste, thus promoting a greener process within the pharmaceutical industry.

Moving forward, there is a need for a multi-dimensional overall strategy for the introduction of new therapy in the Bangladeshi healthcare system. These measures involve raising awareness of mental health, increasing access to psychiatric care, and introducing policies that facilitate affordable and innovative treatments. Additionally, there will need to be more studies in long-term effects and safety of novel antidepressants to know whether they could be viable mainstream treatments.

By integrating traditional pharmaceutical strategies with new-age therapeutic advancements, Bangladesh can successfully enhance mental health outcomes in youth as well. As the burden of depression continues to rise, a multifaceted approach combining medical progress, mental health awareness, and policy change will be critical in making sure the most effective solutions are available to those who need them.

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