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A Review Article: Antidepressants Drugs Action on Bipolar Disorder

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Abstract: ***Bipolar disorder (BD) is a chronic psychiatric illness marked by alternating episodes of mania and depression. The management of depressive episodes in BD poses significant clinical challenges, particularly due to the potential for treatment-emergent mood switching and other complications. Antidepressant (AD) medications, including Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), and Tricyclic Antidepressants (TCAs), are frequently employed to alleviate depressive symptoms. However, their efficacy and safety in the context of BD remain subjects of ongoing debate.This review critically evaluates the mechanisms of action, pharmacodynamic pathways, and pharmaceutical considerations related to the use of antidepressants in BD. Special attention is given to bioequivalence challenges and the role of personalized treatment strategies, offering comprehensive insights for clinicians and researchers. The goal is to support informed, evidence-based decision-making in the nuanced and often controversial application of antidepressants in bipolar disorder.***

Keywords: Bipolar disorder, Antidepressants, SSRIs, SNRIs, TCAs, depression.

I. INTRODUCTION

Bipolar disorders are long-lasting psychiatric illnesses marked by cyclical episodes of elevated (manic) and low (depressive) mood.[1] They often lead to disability and premature death, primarily due to suicide and heart-related conditions .These disorders come from a mix of genetic factors, mental changes, and environmental factors. Additionally, they frequently coexist with other mental and physical health issues, making accurate diagnosis and effective treatment more challenging.[1] average onset age of bipolar disorder is between 20 and 40 years, while the lifetime prevalence ranges from 0.5% to 1.5%, with equal occurrence in women and men. It is a common condition affecting an estimated 40 to 50 million people worldwide[2]Clinically, BD is classified into two main subtypes: bipolar I disorder, in which manic episodes typically alternate with depressive episodes, and bipolar II disorder, characterized by the occurrence of at least one hypomanic and one depressive episode. [3] Over the last half-century, the management of bipolar disorder has been largely focused on manic phase treatment, and a great deal of research attention has been received regarding bipolar disorder treatment during this period[4]. Antidepressants are prescribed for unipolar depression and mood stabilizers for bipolar depression [5].Antidepressants are used to treat variety of conditions. They include, but are not limited to: depression, anxiety disorder agitation, obsessive compulsive disorders (OCD), manic depressive disorders, childhood enuresis (bedwetting), major depressive disorder, diabetic peripheral , neuropathic pain, social anxiety disorder, posttraumatic stress disorder (PTSD) etc. the efficacy and safety of antidepressant drug treatment in bipolar disorder is the subject of long-standing debate based on a scientific literature that is limited and inconsistent [6]

II. BIPOLAR DISORDER

Bipolar disorder (BD) is a long lasting mood condition marked by repeated episodes of mania or hypomania followed by depressive episodes. It is often misdiagnosed in the early stages. [7] **Bipolar disorder**, also known as manic-depressive illness, is a prevalent and severe psychiatric condition characterized by recurrent mood episodes. Although primarily classified as a mood disorder, it also affects cognitive functions and behavior. In some cases, it may be accompanied by psychotic features, including delusions, hallucinations, and disorganized thought processes, which further complicate diagnosis and management.[8]

Individuals diagnosed with bipolar disorder often experience more psychiatric conditions and chronic medical illnesses. The disorder usually appears in adolescence or early adulthood, though symptoms may go unrecognized for several years before a diagnosis is made. Those affected experience episodes of elevated mood, such as mania or hypomania, as well as depressive episodes and sometimes psychosis, alternating with times of relative emotional stability..[9]

The criteria for bipolar I disorder show what we currently know about the classic manic-depressive disorder or affective psychosis that was described in the nineteenth century. They differ from that earlier description mainly in that neither psychosis nor the lifetime experience of a major depressive episode is necessary. However, most people whose symptoms fit the criteria for a complete manic episode will also go through major depressive episodes at some point in their lives. [10]

Bipolar II Disorder is diagnosed when an individual has experienced at least one major depressive episode and at least one hypomanic episode, without ever having a full manic or mixed episode.[11] It is no longer considered a "milder" form of bipolar I, mainly because people with bipolar II often spend more time in depression and deal with significant mood instability. This can seriously affect their ability to function at work and in social situations.[10] Bipolar depression accounts for the largest part of morbidity and mortality of bipolar disorder [12]

People living with bipolar disorder frequently experience other psychiatric conditions alongside their mood-related symptoms. Among the most common co-occurring issues are anxiety disorders, impulse-control difficulties, attention-deficit/hyperactivity disorder (ADHD), and substance use disorders. The presence of these additional conditions tends to worsen overall health outcomes Physical health risks are also elevated in bipolar individuals. Conditions such as obesity, type 2 diabetes, and cardiovascular disease occur at higher rates than in age-matched peers without the disorder. In particular, people with bipolar disorder face a notably greater risk of heart and vascular disease—even compared to individuals with other mental illnesses Suicidal behavior is alarmingly prevalent in bipolar disorder. Compared with the general population, suicide rates are estimated to be 10 to 30 times higher among those affected. Around one-third of individuals with bipolar disorder will make a suicide attempt during their lifetime—placing it among the psychiatric conditions with the highest risk for self-harm or death.[9] More severe types of bipolar disorder—including those with psychotic features—can be clinically indistinguishable from schizophrenia in terms of symptoms. [13]

Antidepressants drugs on bipolar disorder. The efficacy of antidepressants in treating bipolar depression has been investigated across different pharmacological classes, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), other antidepressants, and novel agents such as esketamine [14] Selective Serotonin Reuptake Inhibitors (SSRIs) are the most frequently prescribed antidepressants worldwide. They work by inhibiting the serotonin transporter (SERT), which increases the amount of serotonin in the synapse and enhances signaling in the brainntidepressants are recommended only as second-line treatment and then always with a mood stabilizer to stop switching to mania. [15] Because SSRIs are highly selective and have fewer effects on other neurotransmitter receptors, they tend to have a more favorable tolerability profile compared to older antidepressants like tricyclics or MAOIs[16]

Antidepressant medications are the treatment option for managing depression. They are often prescribed alongside brief supportive psychotherapy to enhance their effectiveness.[17]

Bipolar disorder is mainly marked by depression. While it's diagnosed based on manic or hypomanic episodes, most people with bipolar disorder experience more depressive episodes. These symptoms often begin around age 15, and many may only have depression for years before any signs of mania appear. In some cases, depression can be an early sign of bipolar disorder, but a full diagnosis usually isn't made until later, during late teens or early adulthood, when mania or hypomania shows up.

During this time, if treatment is given, it's often just with antidepressants. [18]

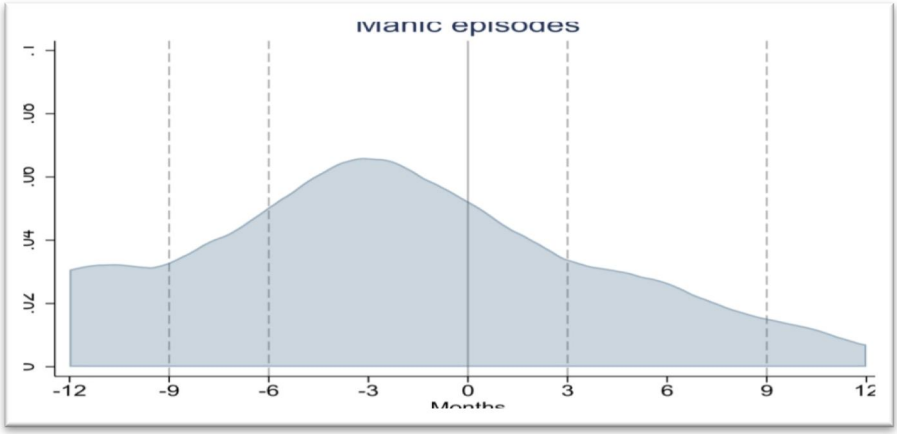

Fig 1 The occurrence of manic episodes relative to the initiation of antidepressant treatment in patients with bipolar disorder who had a depressive episode within the 12 months preceding the initiation of antidepressant treatment.[19]

Factor which influence to choice for antidepressant in bipolar disorder[20]

1) presence of a specific symptoms
2) concern about suicidality
3) medical illness
4) patient had a prior good response
5) patient age
6) history of disorder to patient
7) side effect of medication

III. TYPES OF ANTIDEPRESSANT

Types of antidepressant is shown by following flow chart fig 2

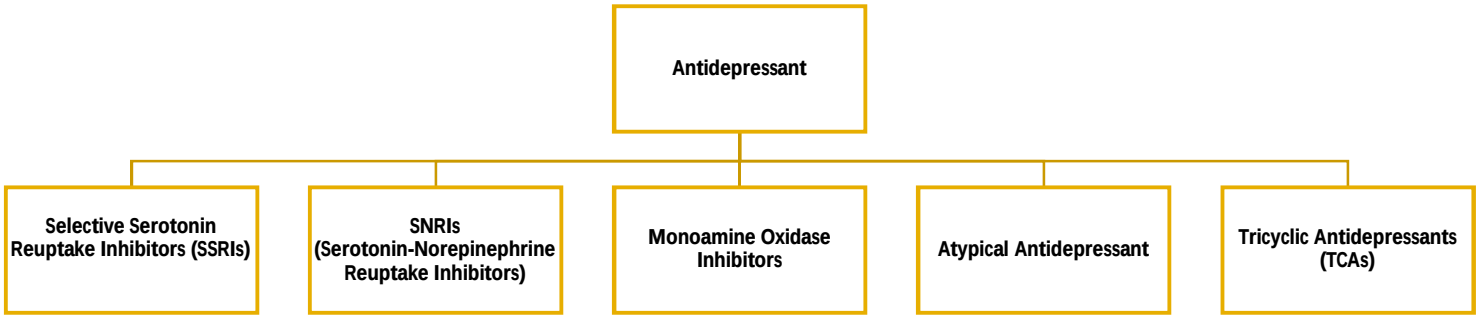

Fig 2: TYPES OF ANTIDEPRESSANT

A. Selective Serotonin Reuptake Inhibitors (SSRIs)

The selective serotonin reuptake inhibitors (SSRIs) have been accepted as effective antidepressant agents[21].Selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed for the treatment of depressive disorder in children and adolescents.[22]

SSRIs are commonly prescribed antidepressants used not only for depression but also for bipolar disorder, anxiety disorders, and various other mental health conditions. Their broad therapeutic effects—spanning disorders like panic attacks, OCD, bulimia, PTSD, and premenstrual dysphoric disorder have sparked debate.[23]This wide applicability raises important questions about the accuracy and relevance of the diagnostic classifications found in the DSM-IV.

1) Mechanism of action

SSRIs block the serotonin transporter (SERT), causing serotonin to accumulate in the synaptic cleft, which elevates cAMP and activates PKA→CREB signaling over weeks—a cascade that boosts BDNF and TrkB expression, stimulates hippocampal neurogenesis, enhances synaptic plasticity, and induces epigenetic remodeling—additionally, SSRIs may directly bind to and activate TrkB independently of serotonin, reawakening juvenile-like brain plasticity; these molecular and cellular adaptations unfold gradually, explaining the typical 4–6 week delay before clinical mood improvement.[24]

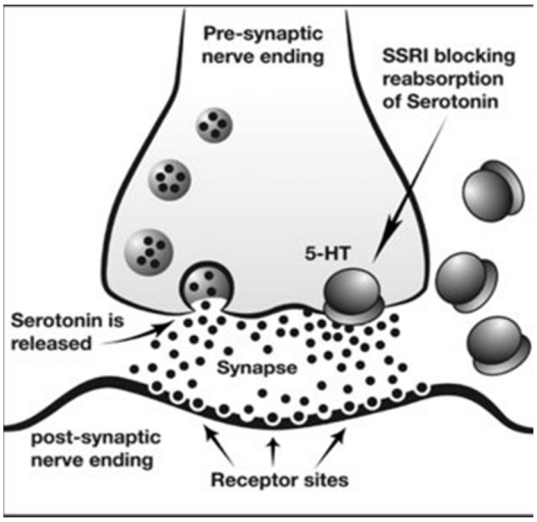

Fig no 3 : MECHANISM OF ACTION OF Selective Serotonin Reuptake Inhibitors(SSRIs)

2) Side effects of SSRIs [25]

SSRIs are popular because they work well and usually have fewer side effects than other types of antidepressants.. The most common side effects include:

- Difficulty sleeping
- Headaches
- Weightchanges
- Worseninganxiety
- Dizziness
- Nauseaandvomiting
- Drymouth
- Sexual dysfunction

3) Example of SSRIs to treat depression There are several types f SSRIs that your doctor can prescribe[26]

- Citalopram (Celexa)
- Escitalopram(Lexapro)
- Fluoxetine(Prozac)
- Fluvoxamine(Luvox)
- Sertraline

Citalopram, sold under the brand name *Celexa*, was approved for clinical use in the United States in 1998.[26]

–Indications and Therapeutic Range:

The U.S. Food and Drug Administration (FDA) has approved citalopram to treat major depressive disorder (MDD). The typical therapeutic dosage ranges from 10 to 60 mg daily.[26]

– Receptor Profile:

Citalopram shows little to no binding affinity for several receptor types, including serotonin (5-HT)1A and 5-HT2A, dopamine D1 and D2, alpha-1, alpha-2, and beta-adrenergic receptors, histamine H1, GABA, muscarinic cholinergic, and benzodiazepine receptors. This receptor selectivity contributes to its profile as a highly targeted selective serotonin reuptake inhibitor (SSRI).[26]

B. Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are a type of antidepressant. They block the reabsorption of both serotonin and norepinephrine in the brain.SSRIs are more effective than TCAs for treating depression with anxiety. SSRIs have shown to be effective for obsessive-compulsive disorder, panic disorder, and social phobia..[27]

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1) Mechanism Of Action

SNRIs are medicines that help your brain by keeping two important mood chemicals—serotonin (which makes you feel good) and norepinephrine (which boosts energy and focus)—in the space between nerve cells for longer. Different SNRIs stick to these chemicals in different ways: for example, venlafaxine mostly works on serotonin, duloxetine targets both fairly equally, and milnacipran affects both about the same. This means some are better for lifting mood and others can help with energy, attention, or nerve pain. [28]

2) Side Effect of SNRI are as follows[26]

- dizziness
- nausea
- dry mouth
- fatigue
- sleeping
- Anxiety
- Constipation
- Headaches

3) Example of drug used in snri [26]

- Duloxetine
- Venlafaxine (Effexor)
- Desvenlafaxine (Pristiq)
- LevomilnacipraN
- Milnacipran
- Venlafaxine

Duloxetine, marketed under the brand name *Cymbalta*, received FDA approval for medical use in the United States in 2004.

– Indications:

The FDA has approved duloxetine for treating major depressive disorder (MDD), generalized anxiety disorder (GAD), diabetic nerve pain, fibromyalgia, and chronic musculoskeletal pain.

–Therapeutic Range:

For both MDD and GAD, the effective daily dosage typically ranges from 60 to 120 mg.

– Receptor Profile: Duloxetine prevents the reabsorption of serotonin and norepinephrine in the central nervous system.. It also enhances dopamine activity in the prefrontal cortex, a region where dopamine transporters are relatively sparse. The drug shows little to no binding activity at receptors or transporters related to dopamine, acetylcholine, histamine, opioids, glutamate, or GABA. Therefore, duloxetine is considered a selective reuptake inhibitor targeting the serotonin (5-HT) and norepinephrine (NE) systems.

As classified by the Neuroscience-based Nomenclature (NbN), duloxetine falls under the SmF-RI category, indicating it is a serotonin multifunctional reuptake inhibitor. [26]

C. Tricyclic Antidepressants (TCAs)

Tricyclic antidepressants were developed from antihistamine compounds, which also served as a foundation for the creation of phenothiazines—a significant milestone in biological psychiatry. In 1948, scientists Häflinger and Schindler at Geigy synthesized 42 compounds derived from iminodibenzyl. One of these compounds, labeled G-22150, became the focus of research led by Roland Kuhn.

Tricyclic antidepressants (TCAs), named for their characteristic three-ring molecular structure, were the earliest antidepressants to reach the market.

While they played a foundational role in treating depression, they are no longer the preferred first-line option. Over time, newer classes of antidepressants have largely supplanted TCAs due to their more favorable side-effect profiles and significantly lower toxicity risks, especially in overdose situations. [26]

1) Mechanism of Action

TCAs, like amitriptyline, work by blocking the reabsorption of neurotransmitters such as serotonin and norepinephrine in the brain.. This increases their availability in the synaptic cleft, enhancing mood and emotional balance. In addition to this, amitriptyline interacts with other receptors, including muscarinic M1 (involved in functions like saliva production) and histamine H1 (linked to wakefulness).

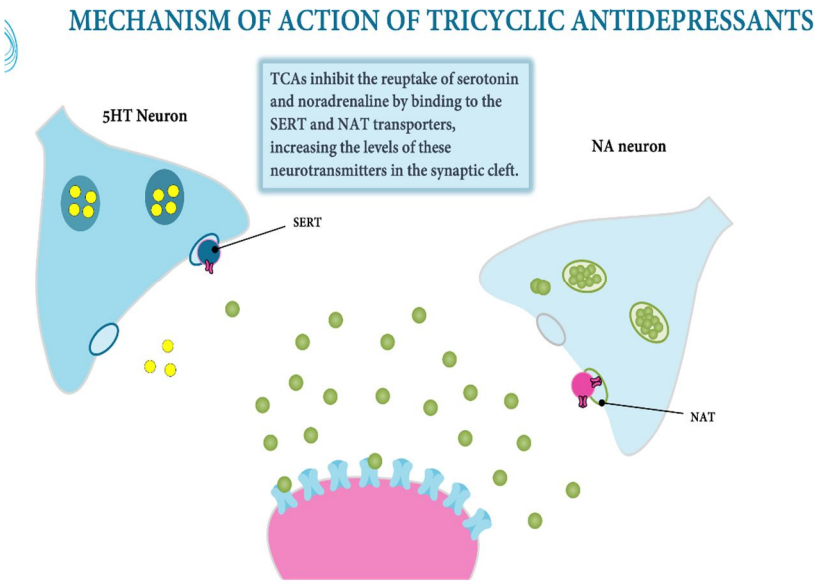

Fig no 4 mechanism of action of tricyclic antidepressants

2) Side effect of Tricyclic antidepressants are as follow[26]

- Dry mouth
- Urinary Retention
- QRS prolongation
- Seizures
- Dry Orthostatic Hypotension

3) Examples of drugs used are as follow

- Clomipramine
- Imipramine
- Amitriptyline [26]

Clomipramine is a tertiary-amine tricyclic antidepressant in the dibenzazepine family. It exhibits exceptionally strong affinity for the serotonin transporter (SERT)—approximately 100 to 200 times higher than for the norepinephrine transporter (NET)

Through its potent SERT inhibition, clomipramine elevates serotonin levels in the synaptic cleft. Additionally, its active metabolite, desmethylclomipramine, is a potent NET inhibitor (with $K_i \approx 0.32$ nM) and typically circulates at higher levels than the parent drug. Consequently, clomipramine produces a balanced increase in both serotonin and norepinephrine, akin to the actions of an SNRI [29]

D. Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) have been used for many years to treat depression.. Their therapeutic effect stems from selective inhibition of the MAO-A enzyme in the central nervous system, which reduces the breakdown of serotonin, norepinephrine, and dopamine, thereby increasing their levels in the brain[30]

There are two types of MAO in the body:

- MAO-A mainly breaks down serotonin and adrenaline.
- MAO-B helps break down dopamine.

MAOIs are usually only used when other antidepressants haven't worked because they can cause serious side effects if taken with certain foods (like cheese, wine, and cured meats) or. other medications. These reactions can lead to very high blood pressure..

The first MAOI, Iproniazid, was actually made in 1952 to treat tuberculosis. Doctors noticed it also improved mood in depressed patients. Later, scientists found out it worked by blocking the MAO enzyme, which led to the "monoamine theory"—the idea that low levels of certain brain chemicals cause depression.[26]

In the 1950s to 1970s, MAOIs like Phenelzine, Isocarboxazid, and Nialamide were commonly used. But because they blocked MAO permanently (irreversibly), they caused risky side effects and became less popular.

Once scientists discovered there are two types of MAO (A and B), they developed selective MAOIs that target just one type These newer drugs are safer and have less side effects.

MAOIs inhibit the monoamine oxidase enzyme responsible for catabolizing serotonin, norepinephrine, and dopamine. Monoamine oxidase inhibitors were the first antidepressants to be found. MAOIs are not recognized as the first-line treatment for depression because of the adverse effects and drug-drug interactions. [31]

Mechanism of action of monoamine oxidase inhibitors (MAOIs)

Monoamine oxidase inhibitors (MAOIs) block the enzyme monoamine oxidase, which normally breaks down several key neurotransmitters in the brain—including serotonin, norepinephrine, dopamine, and tyramine.

. By inhibiting this enzyme, MAOIs prevent the degradation of these chemicals, thereby raising their levels and enabling them to remain active longer in neural circuits linked to mood and depression

. In doing so, they amplify neural communication and can lift depressive symptoms by enhancing mood-regulating neurotransmission[32]

1) Monoamine Oxidase Inhibitors (MAOIs)

- Selegiline
- Moclobemide
- Tranylcypromine
- Isocarboxazid
- Phenelzine

2) Side effect of Monoamine oxidase inhibitors (MAOIs)

- Potential for serotonin syndrome
- Sexual dysfunction

E. Atypical Antidepressant

The term "atypical depression" (AD) was first clearly defined in 1959 by West and Dally. They described it as a type of depression that responded particularly well to monoamine oxidase inhibitors (MAOIs).However, the term had already been used earlier—in 1948—to describe patients with depression who showed symptoms like agitation, paranoia, and confusion, and who responded well to electroconvulsive therapy (ECT).Later, in the DSM-III (Diagnostic and Statistical Manual of Mental Disorders, 3rd edition), "atypical depression" was used more broadly to include cases such as : Depression that occurred alongside schizophreniaDysthymic disorder with long symptom-free periodsShort-term depressive episodes that didn't fit the criteria for adjustment disorder .[33]

Atypical antidepressants have various mechanisms of action**.**

Bupropion, for example, works by inhibiting the reuptake of dopamine and norepinephrine at the presynaptic cleft

Agomelatine acts as an agonist at melatonin receptors MT1 and MT2. It also blocks serotonergic 5-HT2C receptors, which increases the release of dopamine and norepinephrine.[34]

Examples of atypical antidepressant

Bupropion

Mirtazapine

Side effect of atypical Antidepressants are as follow[34]

- Agomelatine- hepatotoxicity
- Mirtazapine-Sedation, Weight gain
- Bupropion- Seizures

Selection criteria of antidepressant in bipolar disorder

When choosing an antidepressant, prescribers can benefit from systematically evaluating five key aspects:[35]

1) Effectiveness – How well the medication works in clinical trials.
2) Safety – The risk profile and possible negative effects..
3) Tolerability – How manageable the side effects are for patients in everyday life.
4) Real-world performance – How effective the drug is when used outside clinical trials.
5) Cost-effectiveness – How the medication's price fits with the patient's financial circumstances and broader economic considerations.

While efficacy, safety, and tolerability have long been standard in treatment selection, factoring in real-world outcomes and economic impact reflects real behaviors and rising concerns about affordability.

IV. CONCLUSIONS

Antidepressants may offer short-term benefit for bipolar depression—especially when combined with SGAs—yet their long-term effectiveness is limited by increased risk of affective switch. Treatment should be personalized, weighing patient subtype (e.g., BD-I vs BD-II), prior history of switching, and antidepressant class. The central clinical challenge is identifying which subsets of patients derive benefit versus harm from AD therapy. Future high-quality trials are needed to refine treatment algorithms and optimize risk stratification.

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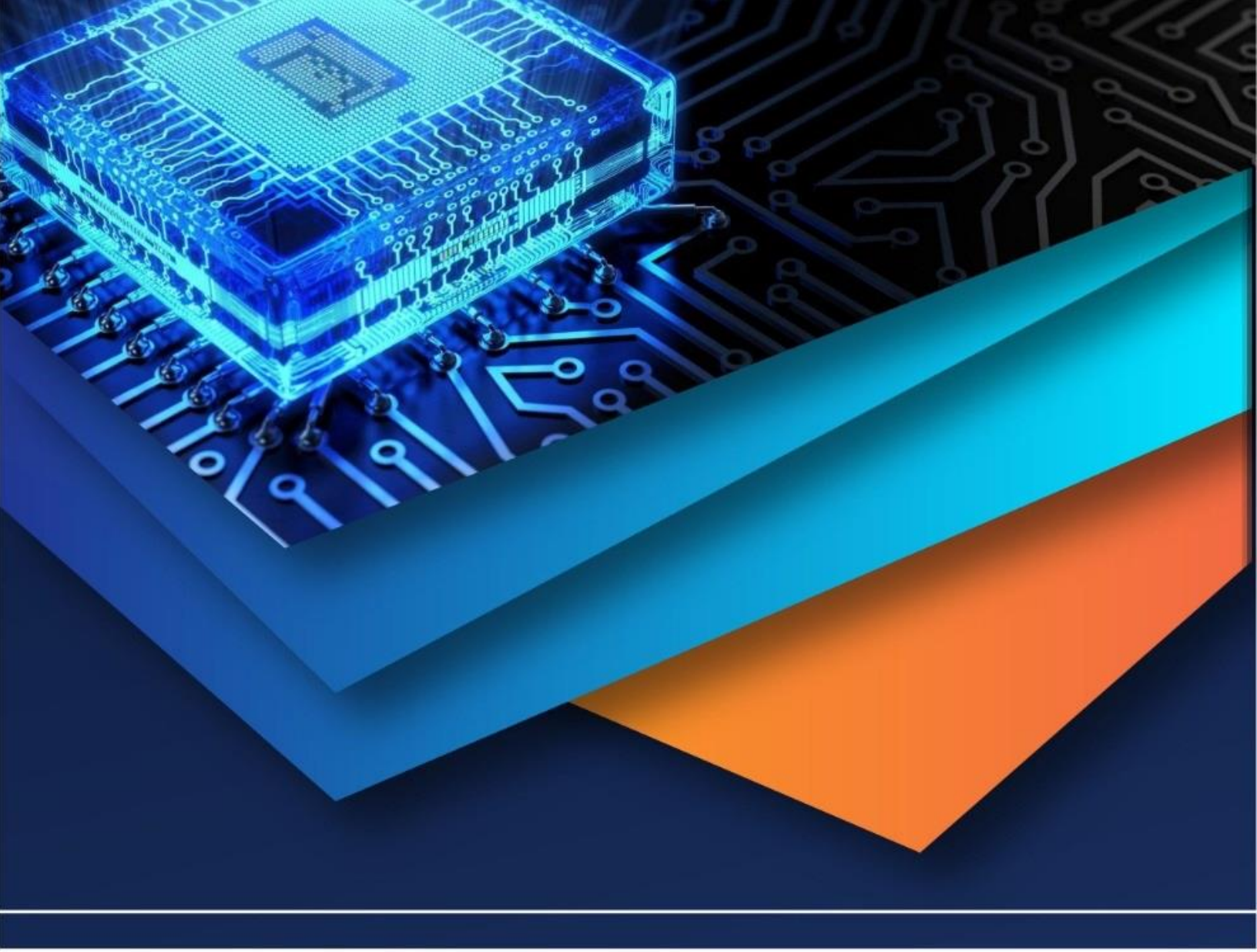

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