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A REVIEW OF BIPOLAR DISORDER

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ABSTRACT:-

Bipolar disorder is a chronic, recurrent mood disorder characterized by oscillations between depressive and manic or hypomanic episodes, affecting approximately 1-3% of the global population. Over the past two decades, substantial advances have been made in understanding its genetic, neurobiological, and psychosocial underpinnings. This review synthesizes current evidence on the epidemiology, Etiology, clinical presentation, diagnostic challenges, and treatment approaches for bipolar disorder. Findings highlight the disorders multifactorial nature, involving complex interactions among genetic vulnerability, neurotransmitter dysregulation, circadian rhythm disturbances, and environmental stressors. Despite the availability of mood stabilizers, atypical antipsychotics, and psychosocial interventions, delayed diagnosis and treatment resistance remain major clinical concerns. Emerging therapies-including neuromodulation, biomarker-based prediction models, and personalized medicine strategies-show promise but require further validation. Continued research is essential to refine early detection, improve long-term outcomes, and reduce the global burden associated with bipolar disorder.

KEYWORDS: Bipolar Disorder, Mania, Depression, Genetic predisposition, Neurotransmitter dysregulation, Psychodynamic theory.

INTRODUCTION:-

Life is full of mood swings, especially when confronted with difficult situations. However, if mood swings are strong, persistent, and result in obvious pain or disability, there may be an underlying affective disease. Recurrent bouts of sadness and high mood, followed by changes in energy or activity and linked to distinctive behavioral, somatic, and cognitive symptoms, are hallmarks of bipolar disorders. When a substantial and prolonged increase in mood is accompanied with psychotic symptoms and causes a noticeable disruption in behavior and function, it is referred to be mania. The term “Hypomania" refers to milder mood fluctuations that frequently don't need medical attention and might be comparatively brief and disruptive. But mania can arise from hypomania (1).

Approximately 2% of people worldwide suffer from bipolar disorder, a chronic mental condition. It can cause anything from dysphoria, low energy, and hopelessness during depressive episodes to extremely high and excitable mood states (mania). The condition is a major contributor to disability and early death, and it typically first appears in young adults (2).

It causes a person's energy and mood to fluctuate suddenly and hinders their capacity for logical thought. Bipolar disorder is caused by a neurotransmitter imbalance in addition to environmental and genetic elements heart disease, diabetes, and metabolic syndrome are more common in those with bipolar disorder (3). Bipolar illnesses seriously impair psychosocial functioning and are associated with a loss of around 10–20 potential years of life. The primary causes of the mortality gap between populations with bipolar disorders and the general population

are excess fatalities from cardiovascular disease and suicide. About 70% of cases of bipolar disorder are inherited. Genetic risk alleles are shared by bipolar disorders and other mental and physical disorders (4).

Approximately 25% of individuals with bipolar disorder make an attempt at suicide. The main issue for patients with bipolar illness is inadequate therapy, since depression is still being treated. Bipolar disorder can be divided into the following classes according to its severity.

1.TYPES OF BIPOLAR DISOREDR

There are three main types of bipolar disorder in humans, and they are distinguished by observable changes in mood, energy, and activity levels. Among these moods are manic and depressive episodes (5).

Bipolar I :-

When someone has a manic episode, Bipolar I disorder is the diagnosis made for them. Bipolar I disorder sufferers have extreme mood swings, such as experiencing intense happiness or excruciating agitation, and a marked increase in energy during a manic episode. In addition to periods of neutral mood Most individuals with bipolar I illness also go through periods of depression or hypomania. Bipolar I disorder, which is typified by the occurrence of a syndromal, manic episode, has an estimated lifetime prevalence of between 0.6% and 1.0%.

The majority of patients Some people with bipolar I illness may only experience manic or mostly manic periods, but others are affected differently by depression symptoms and episodes. The illness's early onset—more than 70% of people show clinical symptoms before the age of 25—is a commonly repeated result in research on bipolar disorders (4).

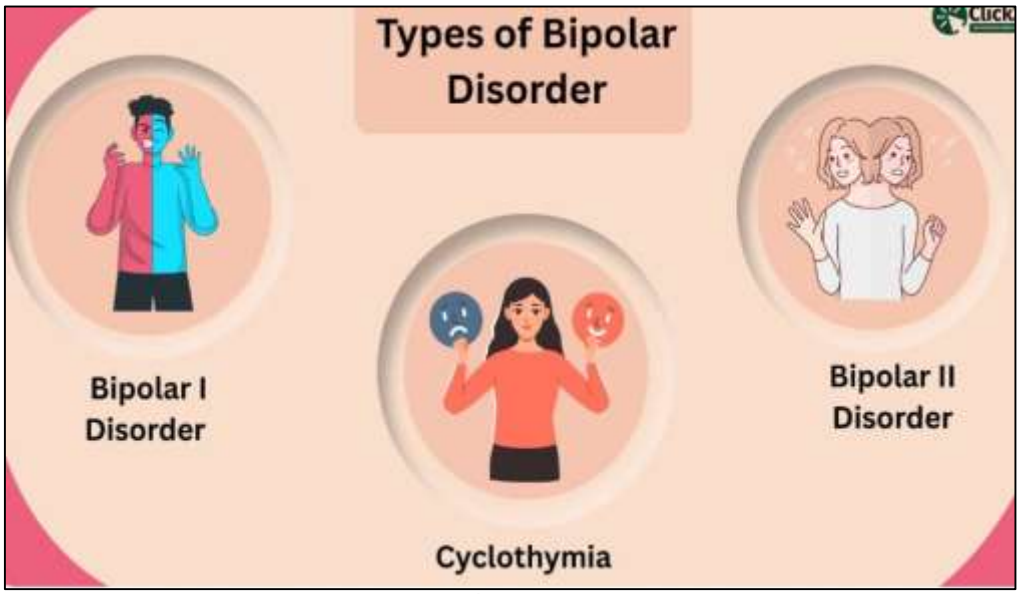
Bipolar II:-

Although the episodes are not as severe as those of bipolar I disease, syndromal, hypomanic, and major depressive episodes are the hallmarks of bipolar II disorder, which is thought to affect 0.4–1% of people worldwide during their lifetime. Individuals with bipolar II disorder were more likely to be female, older, married, or widowed. More episodes before starting lithium therapy, fewer referrals after a single episode, a later "bipolar" presentation, and a higher age at initial (hypo) mania and treatment were all associated with bipolar II disorder.

Bipolar II disorder requires a minimum of for a diagnosis to be made, one major depressive episode and one hypomanic episode are required. People with bipolar II frequently resume their usual routines in between episodes. Bipolar II patients frequently seek treatment for their depression. Episodes first because hypomanic times can be fun and even boost performance at work or school (6).

Cyclothymic disorder:-

In cyclothymic disorder, hypomania and depressed symptoms are common, and there are numerous "mood swings," a milder version of bipolar illness. Cyclothymia although their symptoms are not as severe as those of bipolar I or II condition, sufferers experience emotional ups and downs (7).



2. EPIDEMIOLOGY

It has been shown that around 1% of a population has bipolar I disorder throughout their lives. Bipolar disorder I often manifests at age 18, whereas bipolar disorder II typically manifests around age 22. Roughly 2-3% of people have bipolar spectrum illness throughout their lifetime, and 0.4% has bipolar disorder II, according to a survey conducted in roughly 11 different nations. According to an MDQ survey, the prevalence is roughly 3.7%. According to a survey conducted by DBSA members, it took an average of eight years to acquire an accurate diagnosis after seeking proper care, and for nearly five years, over half of the patients did not seek medical care. Bipolar I disorder affects both men and women equally; however bipolar II disorder is more common in women. Suicide is also more common among patients with mood problems. Additionally, bipolar disorder is more prevalent among solitary people. A patient may experience significant losses and receive the incorrect therapy if they socioeconomic level or social or demographic structural elements. It is observed that about one in three patients make an attempt at suicide, with 15–20% of these attempts being successful (8).

Twin studies and adoption studies are two methods that do permit genetic impacts to be distinguished from environmental ones. There has been little and contradictory research on BPD adoption. Twin studies, however, have unequivocally demonstrated that hereditary most cases of BPD in families are caused by causes. These studies show that dizygotic or DZ twin pairs, which share, on average, half of their genes, have a far lower concordance rate for BPD than monozygotic or MZ twin pairs, who are genetically identical. The three best recent twin studies (Kendler et al., 1995; McGuffin et al., 2003; Kieseppa et al., 2004) show that the concordance rate for MZ twins is 38.5–43%, while the concordance rate for DZ twins is 4.5–5.6%. The heritability of BPD, or the percentage of the population's disease risk attributed to genetic variation, was estimated by these studies to be between 79 and 93%.

3. ETIOLOGY

Although the exact origin of BD is yet unknown, environmental, neurochemical, genetic, and epigenetic variables seem to be involved.

3.1. Genetic predisposition :-

If one of the parents has a mood condition, the likelihood of having bipolar depression or another issue is around 10–25%. However, there isn't a single theory that can reconcile the anatomical, genetic, pharmacological, and biochemical information on bipolar disease (10). According to According to estimations, a kid has a 27% probability of acquiring a mood disorder if only one parent has bipolar disorder, and a 50–70% chance if both parents have the condition. This is because it has been demonstrated that certain families have a higher prevalence of mood disorders (11).

3.2. Biogenic Amines :-

We found that those three systems are hypoactive in depressed individuals, whereas their receptors are hypersensitive. In people with depression, decreased serotonin levels in certain brain regions are linked to pessimism, disturbed sleep, and a loss of pleasure and happiness. Physical symptoms of depression, such as anorexia, loss of energy and libido, as well as a decline in concentration and neurovegetative system activity, are brought on by a decrease in noradrenaline concentration in the hypothalamus and hippocampal regions. Dopamine levels in the basal ganglia are reduced, which results in psychomotor slowness. Autonomic system dysfunction is indicated by the up-regulation of α and β receptors. Additionally, glutamate and gamma-aminobutyric acid (GABA) dysfunctions were discovered. Endogenous catecholamines and opioids are more active in manic patients (12).

3.3. Neurodegenerative theory :-

The patients' magnetic resonance imaging Images showed a decrease in the prefrontal lobe's volume and the overall brain, as well as an increase in the globus pallidus and lateral cerebral ventricles. The age and length of the illness itself determine how severe these alterations are (13). The hippocampus, amygdala, prefrontal cortex, and anterior cingulated cortex are key regions for emotional regulation, response, and stimuli conditions. Furthermore, it has been proven that anomalies in the frontal and temporal lobes are commonly connected to bipolar disease. Additionally, mania was linked to lesions on the right side, whereas sorrow was linked to lesions on the left (3).

3.4. Psychodynamic theory :-

Depression, according to Freud, is caused by the unresolved grieving process that followed the loss. Instead than focusing on the misplaced item, the patient focuses his unpleasant emotions on himself. Depression is essentially a desperate cry for affection and a reversion to the oral stage of psychosexual development, during which the patient craves love and care (14).

3.5. Cognitive theory :-

Beck claims that negative thinking and conceptualizing lead to depression because it causes a person to feel inadequate, abandoned, and immoral sentiments of regret, loneliness, and grief. Depressive symptoms are brought on by a distinct cognitive triad: negative ideas about oneself, the future, and the world (15).

3.6. Stressful event theory :-

In the six months before a manic or depressive episode, more than 60% of adult BD patients said that at least one "stressful life event" had occurred. Stressful circumstances have been linked to the beginning of the first depressive episode. The life events hypothesis, which maintains that the condition develops in people who are unable to adjust to changing situations in their lives, also explains this. The illness may appear right away or later (16).

4.PATHOPHYSIOLOY

Although the exact pathophysiology of bipolar illness is unknown, research indicates that it is a heritable condition. However, a variety of factors, such as the environment and circadian rhythm, contribute to bipolar illness. There is over 85% heritability. BDNF and other neurotrophic chemicals function as signaling molecules for brain plasticity and dendritic sprouting. A recent review paper on neurobiology goes into great detail about the topic of "genetic components, signaling pathways, biochemical changes, and neuroimaging findings" within BD (17). Both a significant hereditary component and an epigenetic influence are supported by data. Neurotrophic signaling is a biological mechanism linked to reduced neuroplasticity, according to human studies that have revealed alterations in brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) in BD patients. Other possibilities include oxidative stress, hypothalamic-pituitary-adrenal axis dysfunction, immune-inflammatory imbalance, and mitochondrial dysfunction (3). As

mentioned earlier, problems with intracellular signaling systems that control mood and systems connected to monoaminergic neurotransmitters like dopamine and serotonin are believed to be the cause. Nonetheless, no singular neurotransmitter system dysfunction has been identified (18).

Pathophysiology of the Inflammatory-Mood Pathway

The reciprocal relationship between BD and immunological dysfunction may be mediated by a variety of ways. Animal models have been used to establish several of these processes. These preclinical results appear to be valid in humans as well, according to more recent clinical research. Here, we enumerate a few of the primary biological processes that could be involved in the inflammatory-mood pathway. The capacity of peripherally circulating cytokines to cross the blood-brain barrier (BBB) is essential for the inflammatory-mood pathway. The body's circulating cytokines can pass through the BBB through leaky areas and active transport pathways.

These alterations ultimately result in neurodegeneration and reduced neuroplasticity in important brain areas, which might cause the phenotypic alterations seen in BD and other brain illnesses (19).

4.1. Cytokine-Induced Neurotransmitter Changes:-

Research on mood disorders has long focused on alterations in monoamines. Furthermore, changes in monoamine levels are the main mechanism of action for most psychiatric drugs. Through a variety of routes, pro-inflammatory cytokines can change monoamine levels both directly and indirectly in the central nervous system. More specifically, it has been demonstrated that TNF-α, IL-2, and IL-6 directly affect monoamine levels.

4.2. Pathological Microglial Over-Activation:-

The central nervous system contains macrophages called microglia, which are crucial for neuroplasticity. To make more room and energy available for neuronal circuits that are used more frequently, microglia help prune out useless neural circuits. Microglia may efficiently select the most crucial neuronal pathways under physiological circumstances, resulting in the best possible brain shape and function.

4.3. Inflammation and Increased Oxidative Stress:-

Since inflammation amplifies oxidative damage, which in turn increases inflammation .Oxidative stress is intimately associated with immunological dysregulation and has been connected to mood problems. An imbalance between antioxidants and ROS generation that counteract those leads to oxidative stress. Repeated research has shown that BD causes elevated ROS and reduced antioxidants, which results in pathologic neurodegeneration in important brain areas that support mood and cognition.

4.4. Over-Activation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis: -

Pro-inflammatory cytokines include TNF-α, IL-6, and IFN.that dramatically increase HPA activity, which raises systemic cortisol levels. HPA activation is beneficial in physiological settings to support the stress response needed in the event of an acute illness or damage. Chronic inflammation, on the other hand, may extend HPA activation and have negative consequences linked to chronic hypercortisolemia.

4.5. The Gut-Brain-Microbiota Axis:-

There has been a lot of interest in the link between neuropsychiatric disorders and the gut-brain-microbiota axis in recent years. The parasympathetic nervous system (primarily the vagus nerve), the gut neuroendocrine system, the circulatory system (which transports neuroactive metabolites and neurotransmitters generated in the gut), and—above all—the immune system all contribute to bidirectional communication between the gut and the brain.

4.6. Inflammation and Sleep Dysfunction:-

One of the main signs of BD is trouble sleeping. Changes in sleep patterns are common at all stages of illness Manic or hypomanic episodes are characterized by a noticeable decrease in the need for sleep. People may have hypersomnia, which means they sleep a lot more than the average person, or they may have trouble getting enough sleep when they're sad, either in terms of how much sleep they get or how well they sleep. Sleep issues are still common in BD, even when the person is feeling good.

5. CLINICAL FEATURES

Severe sadness, mania, hypomania, and mixed features—mood swings with opposing polarity symptoms—are some of the manifestations of bipolar disorder. The severity of these syndromes varies greatly between patients and even within the same person. Subsyndromal symptoms are prevalent. Furthermore, some symptomatic people go into remission and reach a condition of euthymia Some people, however, do not attain a condition of euthymia and instead move directly from one type of illness to another (for instance, from severe depression to mania).

5.1. Mania episodes :-

Clinically substantial alterations in mood, behavior, energy, sleep, and cognition are all part of manic episodes [20]. It is unknown if a patient's manic symptom profile remains constant over several episodes. Patients differ greatly in the severity of their manic episodes. One of the main indicators of mania is an abnormally high, agitated, and unpredictable mood (21). Classic mania, which is marked by an abnormally positive, euphoric, or high mood, is characterized by disinhibition (e.g., wearing gaudy clothes or undressing in public), disregard for social boundaries, expansiveness, and an unrelenting quest for stimulation and social activities (e.g., acting flirtatious, renewing old friendships, or making long phone calls with strangers) (22).

Patients might initially interact with others because their enhanced mood is contagious. But their insensitivity to other people's needs usually makes them annoying. Additionally, mania differs from insomnia, which is the inability to fall asleep even when feeling weary, in that it frequently manifests as a decreased desire for sleep (21). Manic people may feel calm after Even after going days without sleep, they can still feel "wired" and aroused after only three hours of sleep [22Common cognitive signs of mania include increased mental activity, racing ideas, distractibility, and trouble distinguishing between pertinent and irrelevant thoughts. Sudden changes in focus from one subject to another are referred to as “flight of ideas.” Based on comprehensible linkages, are caused by these symptoms (21).

Furthermore, individuals could not remember things that happen during manic episodes. Jokes, singing, clanging (the selection of words based on sound rather than meaning), and theatrical gestures can all accompany manic speech, which is typically loud, rapid, or rushed, and hard to stop. Patients who are irritable frequently say hurtful things, curse more frequently, or go on furious outbursts (22).

Mania frequently presents as a sudden onset of illness with episodes that develop rapidly over several days. In a prospective observational study while recovery from 50% and 75% of the episodes took seven to fifteen weeks, recovery from 25% of the 246 manic episodes occurred within four weeks of the onset. Weeks to months may pass during a manic episode (23).

5.2. Hypomania Episodes :-

Similar to mania, but less severe, mood, behavior, energy, sleeps, and cognitive abnormalities are hallmarks of hypomanic episodes. Here are a few **examples:**
Thought form is more structured in hypomania, although mania and hypomania can cause mental hyperactivity and flight of thoughts.

While mania is characterized by rushing, disjointed thoughts that result in aimless overactivity, hypomania is characterized by fast, creative thinking that leads to positive increases in goal-directed activities.

Though it might be loud and fast, hypomanic speech is usually simpler to interrupt than manic speech.

In contrast to mania, which significantly degrades functioning, hypomania either improves or slightly impairs psychosocial functioning.

By definition, mania typically necessitates hospitalization, whereas hypomania does not.

Usually Over the course of one to two days, hypomania develops rapidly after starting abruptly. Recovery from 25% of the episodes occurred two weeks after they started, whereas recovery from 50% and 75% of the episodes occurred three and six weeks later, according to a prospective observational study of 126 hypomanic episodes (23). Typically, episodes conclude in a few weeks.

5.3. Major depression:-

Clinically severe alterations in mood, behavior, energy, sleep, and cognition are all part of major depressive episodes. Episodes vary greatly in severity.

Energy is poor, memory and attention are compromised, and there is less interest in enjoyable activities (such as sex). Although most people have decreased hunger and weight reduction, some may experience increased appetite and weight gain. Despite their relatively sluggish demeanor, some patients exhibit signs of agitation, such as wringing their hands or difficulty sitting still. Bipolar depression is frequently accompanied by suicide thoughts and actions, feelings of worthlessness and excessive guilt, and sleep difficulties (hypersomnia or sleeplessness) (20).

Additional clinical features of severe depression include decreased psychosocial performance, somatic symptoms (such pain), gloomy and pessimistic thinking, and poor eye contact [20]. Particularly in bipolar II patients, Manic/hypomanic symptoms are less common than depressed symptoms. Major depression with bipolar disorder can start suddenly or develop gradually over a period of weeks to months. Usually, episodes last a few months (23). inadequate personal hygiene, a messy appearance, hopelessness and despair, hesitation and pondering,

5.4. Mixed features :-

Mixed-characteristic mood episodes, such as major depression with mixed features, are periods of severe depression, bipolar mania, and hypomania that may also include symptoms of the opposite polarity (21). The literature also uses the terms dysphoric mania/hypomania, mixed episodes, mixed states, and mixed mania/hypomania (20).

Mixed-feature manic or hypomanic episodes are those who exhibit on most days of the episode, at least three of the following symptoms and who fit all the criteria for mania or hypomania (21):

- Reduced interest or enjoyment in the majority of activities
- Psychomotor retardation
- Depressed
- Lack of energy

6. DIAGNOSIS

A focused interview with the patient and their family members is helpful in reaching an accurate diagnosis because the longitudinal course of bipolar disease often differs from responses given in a cross-sectional interview context within the first year of beginning therapy, only 20% of individuals with bipolar illness who go through a depressive episode receive a bipolar disorder diagnosis. From the beginning of the sickness to the diagnosis, it often takes five to ten years. The most frequent differential diagnoses, aside from major depressive disorder and schizophrenia, include personality disorders, substance misuse, anxiety disorders, and, in children, oppositional defiant disorder and attention deficit hyperactivity disorder (ADHD). Bipolar disorder frequently co-occurs with

these conditions (24).

The majority of people Seek treatment for depression instead of mania or hypomania if you have bipolar spectrum disorder. The Depression and Bipolar Support Alliance was formerly known as the National Depressive and Manic-Depressive Association [NDMDA].recently surveyed its members and discovered that 60% of those with bipolar spectrum disorder sought therapy due to depression (25).

Symptoms of worry, trouble sleeping, and drug addiction were other causes. Hypomania is an unusual presentation for patients. They frequently seek medical assistance when manic due to family or legal authorities stepping in. Unfortunately, doctors frequently forget to inquire about a history of mania and mood fluctuations while evaluating patients with depression. As a result, bipolar spectrum illness is frequently overlooked for diagnosis.For example, in a study of 108 consecutive outpatients with anxiety or depression in a private family practice, for instance, just one person had a prior diagnosis, and 26% of them were diagnosed with bipolar spectrum disorder, with the majority having bipolar II illness. In a semistructured interview, individuals who had a history of hypomania were found to be bipolar II (26, 27).

They discovered that almost half of these individuals had bipolar II disease, and 72% of them had bipolar spectrum disorder. One-third of the sad group was represented by this. A recent According to a study, 37% of patients who went to an outpatient clinic within a year period had a manic or hypomanic episode but was mistakenly labeled with unipolar depression (28).

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) lists cyclothymic disorder, bipolar disorder not otherwise defined, bipolar I disorder, and bipolar II disorder (29). The episodes are characterized by mania, hypomania, mixed symptoms ,and sadsymptoms.

Patients with bipolar II disorder have had severe depressed and hypomanic episodes, whereas those with bipolar I disease have by definition undergone at least one manic episode. Secondary mania, which is described independently in the DSM-IV as substance-induced mania or mania related to a general medical condition, is mania that arises in individuals who are taking pharmaceuticals such as corticosteroids or antidepressants or who have a medical ailment. There are many complex differential diagnoses for bipolar disorder.

Even if a patient exhibits severe psychotic symptoms, a positive family history of mood disorders is predictive of a mood illness. Second, substance-related problems, impulsivity, recklessness, truancy, and other antisocial behaviors are linked to bipolar disorder. Therefore, it is necessary to distinguish the condition from other personality disorders, substance-related disorders, and antisocial personality disorder (30).

When making a differential diagnosis for those with unipolar depression, bipolar illness should always be taken into account. 3.9 percent of the 559 participants in the National Institute of Mental Health Collaborative Depression Study was ultimately diagnosed with bipolar I disorder, while 8.6 percent were diagnosed with bipolar II disorder. After two to eleven years of follow-up. Bipolar I illness was predicted by the severity of the depressive episode, the acute onset of depression, and psychosis. On the other hand, bipolar II disease was predicted by early onset age, higher drug abuse rates, disruption of psychosocial functioning, and a longer course (31).

7. TREATMENT

7.1. Pharmacological:-

The key to effectively managing patients with BD is pharmacological medication. Reduction of symptoms is the aim for acute episodes, with complete remission being the ultimate goal. Preventing recurrent mood episodes is the goal of maintenance therapy. Among the drugs used to treat BD include mood stabilizers (including lithium, valproate, lamotrigine, and carbamazepine), atypical antipsychotics, and conventional antidepressants. The medications authorized by the US Food and Drug Administration (FDA) to treat the different phases of BD. The efficacy of intramuscular haloperidol and intravenous sodium valproate in treating acute manic individuals over

a two-week period was investigated in an open-label study. Bipolar illness treatment has advanced in the last ten years due to a number of studies on more recent therapies. Although the results in both groups were similar, patients treated with sodium valproate reacted faster, and 60% of patients in the haloperidol group experienced extrapyramidal symptoms (32).

Another trial was conducted on 120 mania patients to investigate the safety and efficacy of asenapine and olanzapine when used in combination with divalproex for six weeks. Clinical Global Impression-Bipolar scores and the Young Mania Rating Scale were shown to have significantly decreased in both groups, with the olanzapine group experiencing a larger drop than the asenapine group. While the asenapine group experienced tongue hypesthesia, the olanzapine group also experienced tremors, increased hunger and sleep, and greater weight gain (33).

Skin reactions were found to be 19.8% common in 125 patients with bipolar disorder receiving lithium medication participated in a retrospective cross-sectional study. Patients with therapeutic serum levels of lithium were more likely to have skin lesions, with acne or acneiform eruptions accounting for the majority of these lesions. Although changing the lithium dosage had no effect on the cutaneous lesions, these symptoms generally appeared during the first six months after starting lithium medication (34).

Another study looked at how often people with bipolar disorder who took lithium had skin problems and how their skin problems got worse over the course of a year. According to the study, the incidence was 38.46%, and the most prevalent forms were hair loss, acneiform eruption, and severe alopecia with pre-existing systemic lupus erythematosus. Individuals with early onset age and atypical characteristics, including a predominance of manic episodes over depressive ones, persistent symptoms, and mood-incongruent psychotic abnormalities, exhibited a diminished response to lithium (35).

60 bipolar disorder cases I patients participated in a randomized control experiment to assess the impact raising sodium chloride on lithium levels in the blood. Compared to the control group, which was instructed not to take any more salt, serum lithium changed far less in the intervention group, which got sachets of sodium chloride (1 g/day). Furthermore, a strong positive association was discovered between baseline serum lithium and aldosterone.

Sixty patients with euthymic bipolar disease who were receiving lithium and sodium valproate monotherapy had their cognitive capacities assessed. Patients Compared to individuals using lithium medication, those on sodium valproate monotherapy showed significantly lower attention, cognitive flexibility, verbal, visual, and delayed memory, as well as increased executive function deficits in response inhibition (51).

In order to show the safety and effectiveness of endoxifen (8 mg/day) in comparison to divalproex (1000 mg/day), a phase III multicentric, double-blinded trial was carried out on bipolar disorder I patients experiencing acute manic episodes with or without mixed characteristics. In patients with an early time to remission, endoxifen was found to be both safe and efficacious when compared to those on divalproex. In the Phase 3About 800 patients in the acute phase of bipolar depression were randomly assigned to receive either lithium (600–1800 mg/day), one of two doses of quetiapine (300 or 600 mg/day), or a placebo for eight weeks of monotherapy in the multicenter, randomized, double-blind, placebo-controlled EMBOLDEN study. Between baseline and Week 8 (the main objective), the mean Montgomery-Åsberg Depression Rating Scale (MADRS) total score dropped. Significantly higher than the placebo for both quetiapine dosages, but not for lithium. Additionally, both quetiapine dosages significantly reduced the mean MADRS total score compared to lithium. The Hamilton Depression Rating Scale (HAM-D), Clinical Global Impression-Bipolar Version (CGI-BP) severity and change scores, and Hamilton Anxiety Rating Scale were significantly improved in patients treated with quetiapine (both doses) but not lithium.when compared to placebo. Only over two thirds of individuals had serum levels of lithium that were at least 0.6 mEq/L.which may have contributed to the lack of a meaningful lithium treatment benefit shown in EMBOLDEN I (41).

Lithium was found to be significantly less successful than extended-release quetiapine in improving sleep quality and managing depressive symptoms in bipolar depression patients throughout the course of an 8-week open-label, randomized study (36). An investigation that looked at the prescription patterns of mood stabilizers in 100

bipolar disorder patients found that carbamazepine was the least commonly prescribed, followed by valproate and lithium. In a research evaluating lithium adherence in bipolar disorder patients, it was discovered that adherence was far from optimal and that attitudes toward lithium and having family members present during mental health appointments were important predictors of adherence (37).

A research on the frequency of nonadherence and the variables linked to it in 150 individuals with bipolar illness in Kerela. It was shown that 82.7% had previously experienced noncompliance for at least one week, with the most frequent causes being a family's inadequate comprehension of the condition and a patient's unfavorable attitude toward the medication. Chauhan conducted a second research to investigate treatment opinions and their relationships between bipolar disorder and schizophrenia patients and their caretakers. Due to early withdrawals, the study found that total nonadherence rates rose over the first three months and then stabilized in both groups.Patients with schizophrenia and bipolar illness had both positive and negative views, although those who cared for Compared to other patients, those with schizophrenia showed more positive attitudes and were more knowledgeable (38).

One study found that low adherence was present in 60.6% of the 160 bipolar disorder patients in remission who were selected for the trial.Higher adherence to medicine was shown to be predicted with employment, fewer depressive episodes, more hospital days, and favorable drug attitudes in the same research. In order to determine the parameters influencing the treatment result for bipolar illness, 121 individuals with the disease who were followed up for six months participated in the study.According to the study, remission was negatively affected by early onset, treatment noncompliance, treatment delay, and living alone in bipolar disorder patients. Menon studied stable bipolar illness in a clinical setting. I tested whether providing short message service (SMS) reminders twice a week for three months improved medication adherence in patients on maintenance medication. The study found that while the SMS intervention improved treatment attitudes and quality of life outcomes, it did not enhance medication adherence or attitudes toward medicine at the conclusion of the treatment period (39, 40).

7.2. Nonpharmacological:-

Numerous non pharmacological therapies, including as neuromodulation methods and psychosocial approaches, are also commonly employed in addition to pharmaceutical treatments. To describe the clinical characteristics and outcomes of bipolar individuals undergoing electroconvulsive therapy (ECT), Bharadwaj (42) Carried out a retrospective analysis spanning ten years. It was shown that 18% of all ECT patients had a bipolar disorder diagnosis, with mania with psychotic symptoms being the most prevalent symptom. Patients Over 90% of patients in both the mania and depression groups reported a response rate, with severe depression and psychotic symptoms having the highest reaction rate. Approximately 10% of manic patients and 22% of depressed patients experienced aches and pains following the operation. A different study that looked at the clinical and sociodemographic traits of 178 bipolar disorder patients receiving treatment with ECT between 2016 and 2020, 63.5% of them had bipolar depression, while the remaining patients experienced mania or mixed episodes. Most of the patients exhibited clinical response, with only a small percentage of them experiencing complications (43).

The study examined the antidepressant advantages and cognitive adverse effects of intravenous ketamine infusion in individuals with severe depression (bipolar or unipolar).Versus electroconvulsive therapy. For severe depression, this trial found that ECT was more effective than ketamine after six therapy sessions (44).

Tikka evaluated the effectiveness and safety of therapeutic transcranial magnetic stimulation (rTMS) through a meta-analysis and comprehensive review of Indian literature for a range of neuropsychiatric diseases. Although there were a few unusual side effects noted, the research indicated that active rTMS was a highly successful enhancing therapy for treating mania and sadness, including bipolar and unipolar depression. In a study on the effectiveness of new continuous theta burst stimulation (cTBS) targeting the right dorsolateral prefrontal cortex in bipolar depressive patients (n = 19), there was no statistically significant difference between the active and sham cTBS groups (45, 46). In order to assess the impact of Family-focused Nursing Interventions (FFNI) on functional improvement, 149 bipolar disease patients took part in a randomized control study. When combined

with conventional psychiatric treatment for bipolar disease, this study indicated that FFNI considerably improved the patients' functioning capacities when compared to the control group (32).

A mood stabilizer as an adjuvant; C a combination treatment involving an antipsychotic, antidepressant, or another mood stabilizerX, recommended but not FDA-approved; M, monotherapy; RLAI, long-acting injectable risperidone.

7.3. Mood stabilizers:-

The first medication to be used to treat BD was lithium. Lithium still plays a significant role today despite its several drawbacks, characteristics include ineffectiveness un treating bipolar depression, a brief therapeutic window, and a delayed onset of action in treating acute mania.Comparing lithium + optimized tailored treatment versus optimized personalized treatment alone, a research that decreased the amount of lithium (to make it more tolerable) found no advantages (47).

The most popular mood stabilizer is sodium valproate. Although it outperformed a placebo as an acute medication in the largest research and had a quicker start of action than lithium, there is less data supporting its effectiveness as a mania maintenance treatment. Acute mania can be effectively treated with carbamazepine, according to placebo-controlled trials. The majority of patients respond well to carbamazepine, according to a naturalistic research conducted over an average of ten years in the absence of long-term controlled investigations. When it comes to stopping BD depressive episodes from happening again, lamotrigine is better than the other mood stabilizers. Additionally, lamotrigine has been studied as a therapy for acute bipolar depression. Albeit there is less strong evidence to support its efficacy. In a study on acute mania, lamotrigine did not significantly differ from a placebo (48).

Long-term mood stabilizer use is impacted by a number of safety and tolerability issues. Lithium requires routine blood level monitoring because of its limited therapeutic window. Thyroid toxicity and increasing renal failure are possible side effects of lithium. Every six months following the initial evaluation, it is recommended to re-evaluate thyroid and kidney functions to make sure they are operating appropriately. Tremors and The most frequent side effects of lithium are gastrointestinal issues such as diarrhea, vomiting, and nausea. Hepatotoxicity is the most common major side effect of valproate (risk: 1/20,000). Nausea, dizziness, somnolence, lethargy, infection, tinnitus, and cognitive impairment are other potential adverse effects. Hematologic problems during valproate therapy include low white blood cell counts, low platelet counts, and occasionally bone marrow suppression need to be closely watched. The use of carbamazepine is limited due to its association with worse tolerability during rapid dose titration and may interact with other psychiatric and nonpsychiatric drugs. About 10% of people get a benign rash when using carbamazepine and the drug carries an FDA boxed warning for agranulocytosis and aplastic anemia. The well-tolerated drug in this family, lamotrigine, can cause a rash that resembles a Stevens-Johnson rash. In particular, lamotrigine has been studied in connection with the production of prenatal cleft palates, the results are still inconclusive. Teratogenic consequences may result from pregnancy-related exposure to lithium, carbamazepine, and valproate (49).

7.4. Atypical antipsychotics:-

The modern era of psychopharmacology produced the atypical antipsychotics, all of which have been investigated in BD treatment randomized controlled trials. All licensed atypical antipsychotics, often known as "second-generation" antipsychotics, have a controllable safety profile and are effective in treating acute bipolar mania. Only a small number conversely, atypical antipsychotics have demonstrated potential in the management of acute bipolar depression.
The only medication that has shown promise as a stand-alone treatment for acute depressive episodes in BD I or BD II is quetiapine (both immediate-release [IR] and extended-release [XR] versions). Acute depressive episodes of BD I have been successfully treated with a fixed-dose combination of olanzapine and fluoxetine. Furthermore,

the FDA recently approved lurasidone for use in BD I as a stand-alone treatment or as an adjuvant medication (with valproate or lithium), but not in BD II.

Aripiprazole, olanzapine, quetiapine (IR and XR), risperidone long-acting injectable (LAI), and ziprasidone are among the FDA-approved atypical antipsychotics for the treatment of BD I. These drugs can be used as supplemental therapy in addition to mood stabilizers or as stand-alone treatments. Aripiprazole, olanzapine, quetiapine (IR and XR), and risperidone LAI monotherapy significantly outperformed placebo in treating manic or mixed episodes, according to a recent meta-analysis of trials utilizing atypical antipsychotics used for maintenance treatment. Additionally, quetiapine by itself showed notable efficacy in stopping the recurrence of depressive episodes.

Atypical antipsychotics' safety and tolerance profiles in BD patients have been thoroughly documented. As a group, these medications are associated with a number of safety issues, including extrapyramidal side effects (EPS), sedation/somnolence, and metabolic consequences (such as weight gain, hyperglycemia, and dyslipidemia). The proportional risk of these side effects varies among the various atypical antipsychotics.

For instance, quetiapine and risperidone are considered to be in between olanzapine and ziprasidone in terms of the possibility of negative metabolic effects. Furthermore, in contrast to monotherapies, adjunctive therapies that mix atypical antipsychotics with additional drugs (mainly mood stabilizers) have a higher risk of side effects. Regular patient monitoring is essential since atypical antipsychotics have a propensity to negatively impact weight, cholesterol levels, and other metabolic indicators (50).

7.5. Conventional antidepressants:-

When treating BD, the proper use of conventional antidepressants is a contentious issue. The main problem with treating bipolar depression patients only with antidepressants is that they may cause a transition to mania or hypomania. According to estimates, this phenomena occurs in 3% to 15% of cases (51). The effectiveness of antidepressant maintenance medication in avoiding recurrence is still unknown. It is recommended to combine standard antidepressants with either an atypical antipsychotic or a mood stabilizer. Additionally, the antidepressant dosage should be gradually lowered once the incident has subsided (52).

Current guidelines suggest using bupropion or selective serotonin reuptake inhibitors (SSRIs) because they are less likely to provoke a manic transition than tricyclics or selective serotonin-norepinephrine reuptake inhibitors (SNRIs). Despite the absence of complete consensus, antidepressant monotherapy should be avoided in people with BD I and BD II who have two or more contemporaneous core manic symptoms. Additionally, those using antidepressants should not use them at all. Therapy for a mixed episode or who are experiencing rapid cycling.

7.6. Psychosocial treatments:-

There is a growing acknowledgement of the importance of psychosocial therapies in the treatment of BD, including instructive and supportive group therapies and individual psychotherapies. Common elements of psychosocial treatments include disease education and an emphasis on self-care and adherence to treatment. It is noteworthy that, among the psychosocial treatments, group psychoeducation for patients and caregivers has the most robust evidence supporting its effectiveness. This method’s long-term advantages consist of fewer days spent in the hospital and fewer days with symptoms (53).

Other successful psychotherapies include BD-specific cognitive behavioral psychotherapy and interpersonal and social rhythm treatment. Since interpersonal and social rhythm therapy is predicated on the idea that circadian rhythm disruptions are a basic feature of mood disorders, its goal is to help patients establish more regular daily routines. These treatments can help patients identify triggers for mood disorders, improve medication adherence, and create early intervention methods. Relapse rates have been shown to significantly decline when BD-specific supplementary psychotherapies are used with medication.

7.7. Electroconvulsive therapy and novel treatments for mania:-

Patients who cannot tolerate first-line drugs, are pregnant, or do not respond to more conventional therapies may be eligible for electroconvulsive therapy (ECT). After undergoing ECT, over 80% of patient's exhibit noticeable improvement, indicating its quick effectiveness in treating acute mania (54). It has been shown in prospective trials to be just as successful as or more successful than medication; one study found that 54% of patients who were resistant to treatment responded to it. For most people, ECT is the safest and most effective treatment. experiencing depression or mania during the first trimester of pregnancy. Rehospitalization rates decreased when monthly maintenance ECT was administered for two years to 22 patients with intractable bipolar illness in an uncontrolled study (55).

Alternative therapies are offered for patients who cannot tolerate first-line medicines or who do not react to regular treatments. When treating refractory bipolar disease, clozapine works better for those with bipolar mania than for people who experience rapid cycling or bipolar depression. It is possible to employ calcium channel antagonists as a substitute for conventional therapies (56).

Gabapentin, which the FDA has recently authorized for use as an adjunct treatment of partial seizures, is a novel therapy for bipolar disorder. Gabapentin increases gaba-ergic transmission. It has a half-life of five to seven hours, is thought to be safe and well tolerated, and is virtually entirely eliminated by the kidneys. The FDA has designated gabapentin as a category C medication for pregnant patients, meaning that its teratogenic risk is less than that of common first-trimester medications (57).

The range of doses used to treat bipolar illness with gabapentin is currently unknown. The daily dosage for people with seizures is 900–1,800 mg divided into three doses. Ataxia, fatigue, and drowsiness are typical adverse effects. 18 of the 28 bipolar disorder patients in a naturalistic case series who received gabapentin in addition to a mood stabilizer and antipsychotic drug showed a mild to notable response. They took 539 mg of gabapentin on average each day. Randomized controlled trials for gabapentin monotherapy have not been published (58).

Lamotrigine, which has recently received FDA approval for use as an adjunct treatment for partial seizures, represents another new option for treating bipolar disorder. The release of glutamate is reduced by lamotrigine. It is categorized has a half-life of 24 to 30 hours, is processed by the liver, and is an FDA category C drug for expectant mothers. Due of side effects such as headache, dizziness, somnolence, double vision, and rash (which seldom involves Stevens-Johnson syndrome), the dosage ought to be progressively changed over the course of two to four weeks.

For patients experiencing seizures, the recommended daily dosage is 300 to 500 mg, split into two separate doses. There are significant medication interactions, since valproate increases the half-life of lamotrigine by two to three times while carbamazepine, phenobarbital, and phenytoin decrease it by over fifty percent. 82% of patients A study involving 67 patients with refractory bipolar disorder who received both a mood stabilizer and an antipsychotic medication found that 76% of those with manic symptoms and 76% of those with depressive symptoms responded moderately to markedly to lamotrigine treatment (59). There were no randomized controlled studies available at the time of this assessment. Examining its usage as a monotherapy.

8. COMPLICATION AND PROGNOSIS

PROGNOSIS:-

Worldwide, bipolar disorder ranks among the ten leading causes of disability. Bipolar disorder sufferers "experienced a reduced life expectancy compared to the general population, resulting in an approximate loss of 13 years of potential life," according to a new meta-analysis. Furthermore, compared to persons with common mental health problems including sadness and anxiety, those with bipolar disorder experienced a more pronounced loss in longevity. Furthermore, compared to women with bipolar disorder, men with the illness had a much shorter life expectancy (60).

Ultimately, an individual's prognosis is influenced by numerous factors that are actually within their control: appropriate medications; correct dosages for each medication; a well-informed patient; a productive relationship with a capable physician; a therapist who is skilled, encouraging, and caring; a family or partner who provides support; and a balanced lifestyle that involves stress regulation, consistent physical activity, and regular sleep patterns.Other factors contributing to a favorable prognosis are clearly present, including a heightened awareness of minor fluctuations in energy levels, mood, sleep patterns, and eating habits, as well as collaborating with one's physician to devise a strategy for addressing subtle changes that could signal the onset of a mood swing. For some individuals, maintaining a record of their moods proves helpful in forecasting fluctuations (64).

According to a meta-analysis, the all-cause mortality rate for BD patients is twice the expected rate for the general population. Natural fatalities in BD were more than 1.5 times higher, with "nearly double risk of deaths from circulatory diseases (heart attacks, strokes, etc.) and three times the risk of deaths from respiratory illnesses (COPD, asthma, etc.)." The probability of suicide increased by over 14 times, while the likelihood of other violent deaths increased by roughly 4 times, making unnatural deaths around seven times as prevalent than the overall population.

Both genders had comparably high mortality rates from all factors evaluated. The suicide incidence among people with bipolar disorder is roughly 20 to 30 times greater than that of the general population, according to a more recent systematic review (61).

COMPLICATIONS :-

Bipolar disorder significantly raises the chance of dying young, primarily due to medical comorbidities such endocrine, respiratory, and cardiovascular disorders as well as elevated suicide risks (62). The fact that more than half of the patients are obese or overweight doesn't seem to be related to the weight-promoting medications they take. The metabolic syndrome criteria, which raise the risk of stroke and heart disease, are met by about 33% of people with bipolar disorder.

Moreover, there is a higher prevalence of attempted suicides in patients who have metabolic syndrome alongside other conditions. Overweight and obesity, when comorbid, correlate with a more severe progression of the condition, an elevated lifetime incidence of depressive and manic episodes, a diminished efficacy of pharmacotherapy, and an increased risk of suicide. Bipolar disorder is also linked with migraine. In patients with BD, psychiatric comorbidity occurs in 50 to 70% of cases. Of those with the diagnosis, 30% to 50% fit the criteria for alcohol and other 70% to 90% of those with substance use problems meet the criteria for panic disorder, social anxiety disorder, or generalized anxiety disorder. Patients with bipolar disorder who also had mental comorbidities have a worse quality of life, more frequent manic and depressive episodes, and a more severe course of the condition (63).

Ten to twenty percent of those with BD also have binge eating disorder, and up to half of those with BD also have a comorbid personality condition, particularly borderline personality disorder. This results in higher incidence of alcohol and drug use problems, mood episodes, and suicidality (16).

If discontinuing medication or using it incorrectly can result in a recurrence of your symptoms and lead to the following complications:

- Abuse of alcohol and/or drugs
- Issues concerning interpersonal connections, employment, and monetary matters
- Patients with suicidal thoughts and behaviors are still at risk of committing suicide. It is believed that patients who are coming out of depression have a higher risk of suicide. bipolar disorder increases men's suicide risk.
- Homicide might frequently display extremely demanding and ostentatious traits during the manic phase. These people have the potential to become murderous by acting on their delusions.

Bipolar disorder type I is linked to a lower quality of life as measured by utility-based health-related quality of life and health utility. Individuals suffering from depression saw the biggest drop in quality of life (21)

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