Section: Biomedical Sciences

Review Article

ROLE OF MOOD STABILIZER IN BIPOLAR DISORDER THERAPY – A PSYCHOLOGICAL EVALUATION

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ABSTRACT

Mood stabilisers are an important component of psychological therapeutics and have successfully transformed the treatment of affective bipolar illnesses. While several drugs are already in use and efficacy of psychotherapeutics like Carbamazepine, atypical antipsychotics, valproate, and verapamil have been studied recently for their efficacy, strong evidence substantiating the therapeutic effect of psychotherapeutic drugs is still missing. There is a conspicuous lack of data regarding the long-term effectiveness and protection of antipsychotic drugs, because even though pharmacotherapy is the cornerstone of bipolar illness treatment, it only provides temporary relief. Treatment with pharmaceutical therapy alone, is often falsely linked to low relapse rates, high recurrence rates, prolonged symptoms, and psychosocial impairment. In such scenario, bipolar-specific medicines are progressively being suggested as an important element of disorder treatment. The current psychotherapy data for people with bipolar disease are summarised in this paper. We examine the patient data on temper stabilizers' efficacy, effectiveness, utility, protection, and tolerability, in the context of Indian demography.

INTRODUCTION

Mood stabilizers are frequently used for treatment of bipolar disorder. To obtain a detailed understanding about the role of the mood stabilizers in bipolar disorder therapy, an understanding about the condition of bipolar disorder is essential. Bipolar disorder, which was formally known as “manic-depressive illness or manic depression” is a mental illness or condition that results in unusual shifts in mood, activity levels, energy, ability of performing daily activities, and concentration. There are primarily three types of bipolar disorder, Bipolar I disorder, Bipolar II disorder, and Cyclothymic disorder, which would be discussed in a detailed manner in the later part of the review. In all the mentioned three types of bipolar disorder, prominent changes in levels of activity, energy and mood can be noticed. Different categories of bipolar disorders are described in [Figure 1]. The changes in mood has been reported to vary from the duration of extremely elated and energized behaviour, denoted as “up,” (known as manic episodes”) which can also be irritable; to being very sad and hopeless, commonly termed as “down’, (known as depressive episodes). Another symptom often observed in such patients are hypomanic episodes, which can be explained as less severe manic periods.[1]

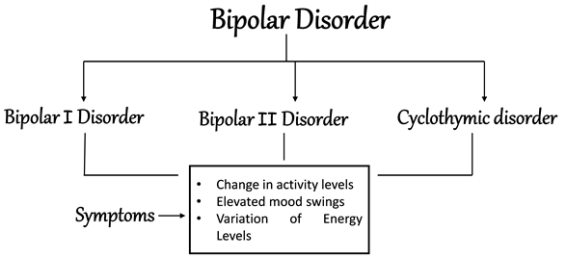

Figure 1: Different categories of bipolar disorders and associated symptoms.

For therapeutic management of the above-mentioned symptoms associated with bipolar disorder and for the treatment of this condition, mood stabilizers are often used as medications. With the help of these medications and associated treatments, mood swings related to the bipolar disorder can be reduced and depressive and manic episodes can be prevented. A detailed discussion on the functioning of these medications is provided in the later part of the paper. In the recent years, studies have focused on molecular genetic studies of bipolar disorder.

As an instance, in one of the studies conducted by Konradi et al. it has been observed that the expression of nuclear messenger RNA coding for mitochondrial proteins significantly reduced in the hippocampus among patients with bipolar disorder. The study

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further mentioned that subjects with bipolar disorder are characterized with prominent and extensive reduction in gene expressions which regulates the adenosine triphosphate-dependent process and oxidative phosphorylation of proteasome degradation.[2]

New discoveries have been also observed in regarding the use of lithium, "the prototype of mood-stabilizing drugs". Current research focusing on the use of lithium has shed new light on the neurobiology of bipolar disorder along with the evidences of neuroprotective, anti-suicidal, and immunomodulatory properties of lithium.[3] Thus, the study of the effects of mood stabilizers on the alterations of neurobiological pathways will contribute to advancement of recent research in the fields of therapeutic target identification for mood disorders along with the improvement of treatment response prediction.[4] The current review tries to encompass the details of recent research findings and the impact of different treatments of bipolar disorder in present scenario.

Bipolar disorder: A raised concern in the world of psychological disorder

Bipolar disease (BD) is a long-term mental condition that can have severe consequences for sufferers and their families. The most severe form of the disorder is Bipolar I Disorder, a disorder that affects about one percent of people at some point or other in their lives. The lifetime occurrence of all the varieties of the disease, commonly known as the "bipolar spectrum disorders", is estimated to persist among five percent of the overall population across the globe. According to Ganguli, "the national rate of affective disorder in India is 34 per 1,000 people".[5] Bipolar disorder is the 6th most significant cause of medical disability in people from the age of 15 to 44 around the world. Unemployment, work-related challenges, and interpersonal problems are linked to the same.[6]

BD is a severe psychiatric condition that has a lifetime prevalence of 1-3 %.[7] In their mid-20s, an adult with the disease can expect to miss 9 yrs of life, 12 years of normalhealth, and 14 years of work activity. Furthermore, the disorder exerts severe psychosocial consequences, such as impairment. Because of the hereditary nature of bipolar disease, pharmacological treatment has been prioritised, but only around 60% of bipolar patients react to lithium or anticonvulsants alone. Furthermore, even when treated with standard medications, only 40% of patients, approximately, remain free of disease recurrence for two to three years. Even though compelling episodes are often absent post-treatment, many patients exhibit considerable sub-syndromal symptoms, particularly depression. Psychosocial variables in bipolar disorder are thought to account for up to 30% of the diversity in outcomes.[8] These figures, as well as the quality of life and the cost of care, can be improved by integrating psychological therapies with routinely used pharmacological regimens. Adherence is a critical factor in how well a patient responds to treatment for any ailment. Weak adherence may jeopardise the therapeutic interaction.[5] A cross-sectional investigation of therapeutic insight in 435 bipolar disorder patients and two markers of medication adherence indicated that twenty-seven percent of the patients showed deprived devotion based on missing doses and forty-six percent exhibited similar symptoms based on the Morisky medication scale. Poor adherence to care might lower the quality of life and cause impairment.

Types of Bipolar Disorder (BD)

As mentioned previously in this review, there are 3 kinds of bipolar disorders, each of which is characterised by mood, energy, and behaviour swings regularly. Manic episodes range from delighted, euphoric, and energetic activities or high activity levels to extremely sad, "down," hopeless, or low levels of activity (depression episodes). Patients with the illness may have a standard "euthymic" mood or a state of living without mood disturbances that alternate with depression. A diagnosis is made when a person experience 4 or more than 4 "rapid cycling" spells of mania or depression in a year.[9]

Manic episodes that persist for at least 7 consecutive days (most of the day, almost every day) or are so intensive that hospital admission is necessary, are signs of 'Bipolar I Disorder'. Patients often show separate bouts of depression that last for at least two weeks. It is possible to undergo mood disorder episodes with mix of traits that can be depression and manic symptoms at the same time. According to epidemiological research, bipolar type I has a lifetime frequency of around one percent in the general population.[10]

'Bipolar II Disorder' is characterised by a sequence of sad and hypomanic events andfull-blown manic episodes are absent.[11]

Cyclothymic illness is characterised by hypomanic and depressive symptoms that are persistent but not severe are categorised as hypomanic or depressive episodes (also called cyclothymia). Adults experience symptoms for at least two years, although children and teenagers only experience symptoms for a year.

Beside these 3 types of the bipolar disorder, there are other prevalent psychological disorders, termed as disorders of Bipolar illness and others (Other Bipolar and Related Disorders), which shows specified and undefined symptoms similar tobipolar illness symptoms, but these disorders do not fit into any recognised categories.

The lifetime prevalence of spectrum of bipolar diseases was 2.4 percent, according to a thorough survey of eleven nations, with 0.6 percent for 'bipolar type I' and 0.4 percent for 'bipolar type II'. [12] The actual cause for the same is unknown but the research indicates that there exists no single cause for BD. The development of the bipolar disorder is thought to be influenced by various factors. Bipolar disorder is frequently handed down through families. Research indicates that this is primarily attributable to genetic heredity and mutations in specific genes contribute to the onset of the illness. It is difficult to single out a

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particular gene responsible for this disorder, as there are multiple factors associated. According to one study comparing identical twins, it was observed that while one twin acquired bipolar disorder, the other twin does not necessarily develop the disease.[13] Although having a parent or sibling carrying the illness enhances the chances of genetical inheritance, there are many people with a family history of bipolar disease who did not inherit the same. Currently, researchers have reported that people with bipolar disorder and other psychiatric diseases have different brain structures and functions as compared to people who do not.[14] Understanding the nature of these structural changes in brain can aid clinicians to better understand the onset of bipolar disorder and prescribe beneficial treatment options in the future for an individual with the bipolar order. Symptoms are employed to determine a diagnosis rather than brain imaging or other diagnostic procedures.[15]

Despite breakthroughs in biological psychiatry research methods and recent data on the processes of mood stabiliser activity, the pathophysiology of BD remains unknown. The early theories on the pathophysiology of BD focused on the neurotransmission system of 'biogenic amines'. The behavioural and physiological characteristics of the disease are complicated, and it is highly likely that a network of interconnected brain circuits is involved.[16] The 'limbic-striatal circuits of the prefrontal cortex' controls many behavioural aspects of mood disorders, and monoaminergic systems are known to exhibit a widespread effect on the limbic-striatal circuit. Due to this feature, monoaminergic systems have attracted a lot of attention in neurobiological research on mood disorders. Further, depression and mania have long been thought to be caused by a decrease in transmitter transport in the presynaptic neuron or synaptic vesicles (SV). Synaptic vesicles (SV), which function as "buffer systems", would be unable to perform correctly, resulting in neurotransmitter shortages and overflow.[17] As a result of the increased transmitter variation in the synaptic cleft (SC), mood swings may occur.

On the other hand, BD models that focus on a 'single neurotransmitter or neuromodulator system' are unable to explain the disorder's diverse medical manifestations fully. According to research, several systems interact to regulate mood, and the most successful drugs maintain the efficient balance between the several interactive systems rather than targeting a single neurotransmission system.[18] Appetite, sleep, weight of the body, and libido, all 'neurovegetative behaviours' that are frequently impaired in mood disorders, necessitate complex links between semi-independent brain systems. Autopsy reports of people with BD revealed presence of considerably fewer glial cells (GC) in the prefrontal cortex and limbic system, as well as less neuronal cells in the prefrontal cortex and hippocampus, which also matched results of neuroimaging.[19] Pharmacological studies in various neurotoxicity models have also shown that mood stabilisers have neuroprotective properties. The therapeutic activity of these drugs, according to current research, includes the modulation of intracellular signalling networks, second messengers, and gene expression.

Recent research into the pathogenesis and treatment of mood disorders has turned from neurotransmitters and cell surface receptors to intracellular signalling networks. Cellular signalling pathways with several components interact at multiple levels, resulting in complex signalling networks that allow cells to receive, process, and respond to internal and external stimuli. These signalling networks allow for the integration of signals over numerous time points as well as the development of diverse outputs based on the strength and duration of the input signals. In addition, these signalling networks control complex feed-forward and feedback loops.

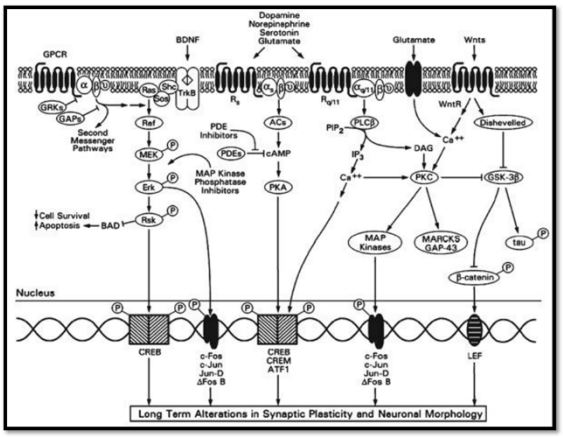

Figure 2: Long term alteration in synaptic plasticity

Diagnosis of Bipolar Disorder

Diagnosis of bipolar disorder requires a rigorous evaluation from a certified psychiatrist in order to rule out other problems. The diagnosis is performed by the medical practitioner by closely observing the symptoms exhibited by the individual and the severity of BD is determined by noting the intensity, duration, and frequency of the alleged symptoms.

Bipolar disorder is not often diagnosed when there are "mood swings" from day to day or moment to moment. Instead, having bouts of unusually elevated or irritable mood that are accompanied by increases in energy, insomnia, and rapid thinking or speaking is what determines the onset of BD. Utilizing precise criteria from the "Diagnostic and Statistical Manual of Mental Disorders", often known as the DSM-5, the patient's symptoms are thoroughly evaluated. Before being diagnosed with bipolar disease, some people have suffered for years.[20] This may be because the illness has symptoms with various mental problems The signs of the BD might be noticed by the close relatives of the patients but remain unrecognisable due to to lack of medical expertise. The symptoms can be components of a broader issue, such as schizophrenia or unipolar depression.[21] People with a bipolar illness often have other health issues,

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making it harder for doctors to diagnose the disease.[22]

Bipolar Disorder and The New Psychiatry

Diagnostic classifications from the nineteenth century still dominate psychiatry and the treatment is performed with medications discovered decades ago. The treatment of BD till date is based on symptom clusters rather than the biological markers. Even though the nomenclature has changed, the core qualities, evaluation procedure and treatment strategies have primarily remained the same.[29] Additionally, its well-established high heritability and lack of actual grip on its causes and underlying biology have played a crucial role in this stagnation.[29] Although alteration of anatomical and functional brain connectivity has been reported, as well as changes in oxidative stress, functioning of mitochondria, soreness, circadian rhythms, and dopamine markers have been reported, combining these disparate data, and separating the primary changes from the secondary ones remains a challenge. The situation is gradually but steadily improving. Although there has been much improvement in the current knowledge of the ailment and how it is diagnosed and treated, optimism is tempered by the presence of many difficulties. The first risk genes have been discovered, and their repercussions are now described along with the development of technologies that can improve or redefine the phenotype of BD.[23] These developments demonstrate the advances in genetics, neuroscience, and modern technology are ushering in a new age in psychiatry.

Mood stabilizers

Psychopharmacology has changed the way serious mental illnesses are defined and treated. Psychopharmacological medications have aided in neurobiological understanding of several psychiatric diseases and significantly reduced relapse rates, symptom-free periods, patient quality of life, and the burden placed on patients and their families.[24] Typical antipsychotics and electroconvulsive therapy were utilised before lithium to treat BD.[25] Many drugs, however, have been evaluated as mood stabilisers over the years and proved to be beneficial, although the definition of a mood stabiliser is yet to be determined. Psychopharmacological research on mood stabilisers in India has lagged as compared to the West. However, studies have shifted from case studies to multicentric double blind controlled trials. After its debut in India in the late 1960s, 'lithium' gained a lot of scientific interest in the 1970s and 1980s, with most of the studies concentrating on open trials to test its effectivity in various illnesses (mostly mood disorders) and to understand its side effects.[23] Numerous early modest double-blind trials that found 'lithium' to be superior to 'placebo', supported lithium usage in the treatment of depression; nevertheless, most of these studies had methodological problems.[23] In the only recent, well-done 'RCT (EMBOLDEN I)', quetiapine was better than placebo at treating acute depression.

On the other hand, lithium monotherapy did not differ much from placebo when it came to reducing ratings of depressive symptoms. In this study, the median serum lithium level was at the lower end of the recommended range (0.6 mEq/L), and thirty-five percent of patients had blood levels below that.[26] For the best antidepressant effects, serum levels may need to be higher, but this increases the risk of side effects. Still, there is evidence that lithium does more than stopping mania from coming back. It also stops depression from coming back and lowers the risk of suicide in people with bipolar disorder. The efficacy of different mood stabilisers as observed in different clinical trials are listed in [Table 1].

Mood (in) stability is a continuous trait that can be found in healthy people to varying degrees. It is a valuable attribute for studies aiming to understand the mechanisms underpinning mood regulation in general, and it is being employed in a variety of ways. For example, from a machine viewpoint, models showing mood instability interaction with reward sensitivity to obtain change in output can be observed. It is also possible to determine if changes in brain activity recorded with functional MRI and magnetoencephalography at various temporal resolutions are associated with mood instability.[27] Statistical analysis can also aid in the understanding of the links between mood swings and other factors such as environmental exposures and behavioural variables. Many other medical illnesses like borderline personality disorder (BPD), attention deficit disorder (ADD), schizophrenia and mood disturbance are frequent as in BD.

Table 1: Various mood stabilizers and associated findings from clinical trials

S. No	Mood stabilizers	Clinical trials	References
1.	Lithium	Lithium is the first medicine that has been used to treat the disease by balancing the mood. It is effective in treating acute episodes of either polarity and stopping episodes of either polarity from happening or coming back. .	[28]
2.	Divalproex/valproate	It has been shown to help people with acute mania and mixed episodes. There is not as much evidence that it helps with acute depression as there is for lithium.	[29]
3.	Lamotrigine	Much research has been done on the role of lamotrigine in treating BPAD, and it is effective in treating bipolar depression and stopping relapses.	[30]
4.	Carbamazepine	Carbamazepine has been shown to work well for treating and preventing relapses in people with acute bipolar mania.	[31]27

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		Before giving carbamazepine, the doctor should look at the patient's history of blood problems and liver problems.	

It has been demonstrated that mood stabilisers alter the activity of enzymes, ion channels, G protein coupled receptors, the turnover of arachidonic acid, and intracellular pathways involved in synaptic development and neuroprotection.[32] Many "neurotransmitter and neuromodulator systems," including the serotonergic, cholinergic, monoaminergic, and GABAergic systems, were the subject of early investigations that described lithium's effects. One of the most widely accepted theories postulated that lithium interfered with the sodium-potassium electrogenic pump, and that the direct consequences of this change on synaptic transmission caused the observed secondary effects in certain neurotransmitter systems.[33] According to more recent research, bipolar illness and other mood disorders impact intracellular signalling cascades that impede structural and functional brain development and change glutamatergic neurotransmission.[34] Anticonvulsant mood stabilisers have also been shown to have direct impacts on neuronal transmission.[35] By improving voltage-gated sodium channel inactivation, valproate reduces high-frequency action potential firing and, inadvertently, improves GABAergic activity. Lithium has been shown in both preclinical and clinical investigations to have "neurotrophic and neuroprotective effects", and more recent studies have identified particular functions for lithium in the activation of pertinent intracellular signalling cascades.[36] The "neurotrophin brain-derived neurotrophic factor" (BDNF) and the neuroprotective protein B-cell lymphoma/leukemia-2 are both upregulated in response to lithium (Bcl-2). Lithium has been demonstrated to directly inhibit several enzymes at a therapeutically useful doses. These include "fructose 1,6-bisphophatase, glycogen synthase kinase 3 (GSK3), inositol monophosphatase (IMPase), inositol polyphosphate a-phosphatase, bisphosphate 3′-nucleotidase, and phosphoglucomutase".[37]

According to the NIMH (National Institute of Mental Health) Research Domain Criteria, it is a trans-diagnostic construct. Treatments that affect mood disturbance, as well as the causes and processes of mood disturbance, are likely to have biological and behavioural consequences that extend beyond BD.[38] With the finding of the first genome-wide significant loci, mood disturbance is now a heritable trait in the overall population.[39] It would be fascinating to examine how closely the risk regions for instability of mood corresponds to those for BD and other disorders involving mood instability and examine the linked chemicals and pathways. Furthermore, essential characteristics of mood instability (such as regularity, amplitude, or behavioural effect) may vary enough between disorders to aid in gaining traction on the underlying neural mechanisms, thus providing additional clues to the biological basis of these diseases, and leading to classification refinements.[40]

Improved classification refinements of mood disorders can make the screening of potential BD medications more rapid and economical as compared to the traditional clinical studies, which often focuses on the treatment or prevention of depressed or manic episodes and require lengthy follow-up periods.[41] In unipolar depression, swift effects on emotional processing predict final therapeutic comeback, and early mood stabilisation can be used to predict therapy success. Furthermore, antidepressants immediately impact the emotional processing in both euthymic and depressed population; similarly, novel BD treatments, such as newer VGCC-acting medicines, could be tested in depressed people who have not been diagnosed.[42] Second, mood stabilisation can be effective in and of itself and prevent clinical bouts of depression and mania because mood disturbances predict bad functional recovery in the illness and worse outcomes of many kinds, due to mood swings.[42]

Alternative treatments of BD

Alternative treatments to assist bipolar symptoms may be beneficial for some people. People with severe symptoms may benefit from electroconvulsive therapy (ECT), a sort of brain stimulation treatment.[43] This sort of therapy is usually considered only when other therapies (such as medicine or psychotherapy) have failed to improve a patient's condition or when a speedy reaction is required, such as in the situation of suicide risk or catatonia (inability to respond).[44]

Regular exercises like running, swimming, or bicycling can help with melancholy and anxiety, enhance sleep, and is suitable for the heart and brain. However, a proper workout routine or changes in a workout routine should be only adapted after consultation with concerned medical practitioner.

Keeping a life record that captures symptoms of everyday mood, medications, sleep cycles, and life events might help in better control as well as improved management BD [45]. There has not been much research done on the effects of herbal or natural supplements on bipolar disorder. Uses of herbal medications or supplements should be undertaken after authorization from a doctor, as the herbal treatments might cause serious side effects or potentially fatal drug reactions, when used in combination with certain drugs and supplements.[46]

Other Mood-Stabilizing Drugs

Antipsychotic medications are also commonly used for treating BD patients. To aid with mania symptoms, a patient can be adviced consume them independently or in combination with mood stabilisers Some common anti-psychotic drugs used for this purpose are Haloperidol (Haldol), Loxapine (Loxitane) or loxapine, Risperidone (Risperdal).

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Besides these commonly sed anti-psychotics, current generation of antipsychotic drugs, including Aripiprazole, Asenapine (Saphris), Cariprazine (Vraylar), Lurasidone (Latuda), Olanzapine (Zyprexa), Quetiapine fumarate (Seroquel), Ziprasidone (Geodon) are also being prescribed

These drugs can be consumed solely by itself or in combinations, for example, combinations like Lithium + Divalproex, Lithium + carbamazepine, Mood-stabilizing medication + antidepressants can be used.

Side Effects of Drugs

Medicines for bipolar disorders can also exhibitadverse side effects. These effects may vary based on the medicine the patient is taking. The side effects may include tremors, nausea, loss of hair, sexual problems, and weight gain.

Some drugs can impact the number of platelets or white blood cells in the human body and the liver function efficiency. Ziprasidone, an antipsychotic medicine, has been related to 'DRESS syndrome' (drug response with eosinophilia and systemic symptoms), an uncommon but severe skin reaction (Geodon).[47]

The adverse effects of the drugs generally sustain for a few weeks, after which the symptoms generally start fading. The patient should be continuously under medical monitoring to avoid any unprecedented circumstances. In case of persisting side effects, the doses of the drugs can adjusted or even the prescription can be changes to alleviate the adverse effect of the drugs.

NIMH (National Institute of Mental Health) Approach of Addressing Bipolar Disorder

The investigations on bipolar illness are conducted and funded by 'National Institute of Mental Health (NIMH)', which aids in the development of new treatments and enhances the understanding of the condition's causes. Bipolar disorder and its underlying biology are still being studied, as well as the brain activity and the symptoms in children and adolescents with the disease and health and behavioural family history are also b researched systematically.[48]

Bipolar disorder treatments are beneficial, but a strict regimen must be put in place to follow the doctor's instructions and the medications should not be discontinued with the instructions of the concerned medical advisor. Abrupt termination of medication or irregular consumption of the medications can be potentially dangerous.

Also, it has been reported that rteatment alone may not be enough to avoid the recurrence of symptoms during mood episodes.[49] Most people benefit from maintenance therapy between the mood episodes because it lessens the frequency and the intensity of mania and depression.

Management of Bipolar Disorder

The patient's family doctor and psychiatrist should establish a productive and collaborative partnership since bipolar disease is chronic and has an influence on the entire family.[50] An agreed-upon manner of communication with a frequency that suits each doctor's demands is necessary for informed collaboration. When the symptoms of bipolar illness first appear, the family doctor may advise to consult a psychiatrist for a differential diagnosis and treatment advice. In many cases, the psychiatrist oversees initial medications and manages the preliminary stages, till the clinical pattern of the patient is identified.[51] Both physicians should keep an eye on the patient throughout the follow-up for indications of psychosis, mood swings, aggressiveness, and self-harming behaviours.[52] The physicians can renegotiate responsibility for ongoing care with the patient and amongst themselves, when the patient's disease stabilises and the therapeutic management is in place. The psychiatrist may not need to see the patient as frequently as before once the condition has been stabilised, though this will depend on several factors like, the patient's adherence to the treatment regimen, the severity of their illness, their need for medication, their need for ongoing psychotherapy, and the patterns of care in their geographic area.[53] It is crucial that the patient's family doctor and psychiatrist work together to coordinate medication recommendations and follow-up laboratory testing for figuring out the blood drug levels in blood.[54] A family doctor, psychiatrist, or psychologist may provide counselling or family therapy as additional crucial management components.

In significant cases, BD treatment is separated into two stages, acute phase treatment or maintenance treatment. Acute phase treatment or APT focuses on the management of acute mood crises (manic, hypomanic, or depressive),[55] whereas the maintenance treatment (MT) aims to prevent acute episodes from recurring. Each phase has its own set of therapeutic requirements, and existing pharmacotherapies have shown varying degrees of efficacy depending on the stage of the illness.[56] Given the likelihood of medication with clinical significance, interactions associated with drugs used to treat bipolar disorders, regular communication between health care providers regarding changes in prescribed and over-the-counter drugs is crucial.[57] For example, when lithium is coupled with regularly used medications such as nonsteroidal anti-inflammatory medicines and various antihypertensive treatments, lithium levels and toxicity risk can arise.[58] Hence, stringent efficiency is required while designing a treatment plan for BD.

CONCLUSION

Treatment of BD had commonly used mood stabilizers as the prime medication and antidepressant drugs are being widely prescribed despite a lack of compelling evidence of their effectiveness.[59] For all stages of the disease, polypharmacy remains the norm in most patients.

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While choosing the treatment plan for bipolar depression, 'it is crucial to weigh the advantages and disadvantages of the therapeutic regimen. The medicines discussed in this review differ significantly in adverse effect profile, tolerance, and acceptability. It is impossible to stress the importance of uniquely treating each case and including the patient in the treatment process. Despite the substantial clinical and societal repercussions of bipolar depression, thorough research of its therapeutic plan is limited. The current scenario demands for more significant research into innovative drugs and therapeutic techniques, as well as more consistent and optimal trial designs. This will lead to the increase of the availability of an evidence-based treatment arsenal for bipolar depression and will allow for more accurate treatment in comparison to the currently available therapeutic management plans of BD.

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