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RELATION OF DEPRESSION AND MANIA IN BIPOLAR DISORDER AND ITS TREATMENT- AN INVESTIGATIONAL REVIEW

Biju G.B[1], Ashika P.L[2], John Stephen Raj[3], Mrs Pallavi singh[4], Dr.S. SATHESH KUMAR[*]

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Abstract

Bipolar disorder, formerly known as Manic depression is a mental illness marked by emotional highs (mania or hypomania) and lows (depression), which affects more than 1% of the world's population.Depression is common and harmful in children and adolescents, and it often heralds a chronic and repeated course of illness.Mixed mania was reported frequently in teenagers and individuals with a history of mania, particularly in females.In women, increasedYoung Mania Rating Scale(YMRS) core ratings resulted in a linear rise in depression load, and females were considerably more likely than males to suffer a greater number of depressive symptoms. Approximately half of the hypomanic and manic patients were also likely to meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) mixed feature specifies, with a considerable female predominance.In individuals with Bipolar II disorder (BD-II), as well as those who have a high number of mixed manic-depressive episodes and those who follow a Myotonic dystrophy type 1 (DM1) course pattern, there is a significant excess of depression.

KEYWORDS: BIPOLAR DISORDER,DEPRESSION,MANIA,RELATION OF DEPRESSION AND MANIA IN BD

[1,2,3,4]Pharm.D V[th] Year, School Of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced studies, Chennai-600117, Tamilnadu, India.

CORRESPONDING AUTHOR:Dr.S. SATHESH KUMAR[*]

Professor and head, Department of Pharmaceutics, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Chennai – 600117, Tamilnadu, India.

Email:sathesh2000@gmail.com

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INTRODUCTION

Depression within bipolar disease has been conceptualized in a variety of ways throughout the last 100 years, and the variations in conceptualization have been mirrored in basic changes in diagnostic nomenclature.[1]

Bipolar disorder, formerly known as Manic depression is a mental disease characterized by emotional peaks (mania or hypomania) and valleys (depression). The patient may present with symptoms like gloomy or hopeless depressed, and lose of interest or pleasure in most activities feel ecstatic, full of energy, or abnormally irritable. when your mood switches to mania or hypomania (a milder form of mania). Sleep, energy, activity, judgment, conduct, and the ability to think clearly can all be affected by mood fluctuations.[2]

A recommendation to a mental health professional may subsequently be made. Chronic illness that requires treatment for the rest of one's life. People who have multiple (four or more) episodes of mood shifts (rapid cycling) in a year may find it more difficult to recover [3]. Although medication is the major mode of treatment, psychotherapy or "talk" therapy is occasionally prescribed to assist avoid recurrence attacks. It can be treated with a variety of medications. The proposed treatment guidelines are based on the three primary phases of bipolar disorder: acute manic/mixed mood states, acute severe depression episodes, and lastly the continuation/maintenance phase. For most patients, avoiding antidepressants and taking two mood stabilizers has proven to be a successful method.[4]

Lithium, some anticonvulsants (valproate, carbamazepine), standard antipsychotics (eg, haloperidol, chlorpromazine), atypical antipsychotics (e.g., quetiapine, olanzapine, risperidone, ziprasidone, aripiprazole, clozapine), and benzodiazepines are the most commonly used medications in the acute setting (e.g., lorazepam, clonazepam).[5] The person's current and prior medication history, a need for rapid resolution of agitation and aggression, the characteristics of the manic episode, and the presence of rapid cycling, as well as the patient's own willingness to accept specific therapies and routes of administration, all influence the primary treatment choice. Oral medication should be used initially whenever feasible, however intramuscular injections are also an option.[6] This review focuses on depression in bipolar disorder, as well as the evidence on whether bipolar depression and unipolar depression have distinct aetiologies, symptoms, and courses.[1]

DEPRESSION:

Depression is common and harmful in children and adolescents, and it often heralds a chronic and repeated course of illness and impairment in adulthood [7]. Depression is linked to strained familial, peer, and romantic relationships, as well as lower educational attainment and socioeconomic level and a higher chance of suicide death. Kaslow and Thompson published the first evidence-based therapy (EBT) review in the area of child depression as part of the original 1998 special series in the Journal of Clinical Child Psychology [8]. The existence of a sad or irritable mood, followed by physical and cognitive alterations that significantly affect the individual's ability to function, is a common component of all depressive disorders [9]. A broad sense of melancholy, anhedonia, avolition, worthlessness, and hopelessness characterises depression. There are also cognitive and neurovegetative symptoms such as difficulties concentrating, memory changes, anorexia, and sleep abnormalities [10].

Depression is one of the most curable forms of mental illness. Between 80% and 90% of persons with depression react effectively to treatment in the long run [11].

Almost all patients get some improvement in their symptoms. A full diagnostic evaluation, including an interview and physical examination, should be conducted by a health expert prior to a diagnosis or therapy [12]. A hematological investigation may be required in some circumstances to ensure that the depression is not caused by a medical disease such as a thyroid problem or a vitamin deficit (Reversing the medical cause would alleviate the depression-likesymptoms) [13]. With the purpose of arriving at a diagnosis and planning a course of treatment, the examination will identify specific symptoms and study medical and family histories, as well as cultural and environmental factors [14].

MANIA:

Mania, often known as a manic phase, is a one-week or longer period in which a person's behaviour changes dramatically and impairs their functioning. Mania differs from hypomania in that hypomania does not result in a significant deficiency in social or occupational functioning and lasts at least four days rather than one week. Mania is distinguished by increased talkativeness, fast speech, a reduced need for sleep, racing thoughts, distractibility, an increase in goal-directed activity, and psychomotor agitation.[15]

Mania is a diagnostic criterion for bipolar I disorder, hence the epidemiology of bipolar I disorder includes information on the prevalence of mania. Bipolar disorder has a lifetime incidence of roughly 4%. Both men and women are equally vulnerable. Women, on the other hand, are significantly more likely to have multiple mood episodes in a given year.[16][17]

The clinical manifestation of a manic episode includeshaving alot of activity or energy feeling euphoric or exceedingly happiness or excitement.

Mania was initially treated with drugs such as lithium, valproic acid, and carbamazepine in bipolar I illness. The therapies concentrated on mood stabilisers and anticonvulsants that have demonstrated success in mood stabilisation. Today, the family of mood stabilisers includes various second-generation neuroleptics in addition to lithium and antiepileptics. A major meta-analysis of drugs used to treat acute mania revealed that atypical antipsychotics were more effective than mood stabilisers for this purpose, but not necessarily for bipolar disease maintenance.

Risperidone, olanzapine, and haloperidol are examples of some successful drugs. Lithium, quetiapine, and aripiprazole were also reported to be effective. Valproic acid, carbamazepine, and ziprasidone were more effective than placebo but less effective than their competitors. Gabapentin, lamotrigine, and topiramate had no effect on mania as compared to placebo. Clozapine and electroconvulsive therapy have shown numerous benefits in the treatment of treatment-resistant mania, but they are less often employed.

Bipolar disorder

Bipolar disorder is a recurrent chronic disorder characterised by fluctuations in mood state and energy. It affects more than 1% of the world's population irrespective of nationality, ethnic origin, or socioeconomic status. Bipolar disorder is one of the main causes of disability among young people, leading to cognitive and functional impairment and raised mortality. A high prevalence of psychiatric and medical co morbidities is typical in affected individuals. Accurate diagnosis of bipolar disorder is difficult in clinical practice because onset is most commonly a depressive episode and looks similar to unipolar depression.[18]

The recent advances in the acute and long-term treatment of bipolar illness are discussed, as well as prospective future therapy pathways. Overall, progress in drug treatment has been slow. Antipsychotic medications are useful in the acute treatment of mania; however,

their efficacy in the treatment of depression is mixed, with quetiapine having the best evidence. Despite their widespread usage, there is still a lot of doubt and debate concerning the use of antidepressants in the treatment of depression.[19]. The best evidence for long-term relapse prevention comes from lithium; the data for anticonvulsants like divalproex and lamotrigine is less solid, and there is a lot of ambiguity about antipsychotics' long-term benefits. Adjunctive psychological therapies have made significant progress in terms of development and evaluation.[20]. Combining psychological and pharmaceutical therapy can improve long-term maintenance and perhaps immediate stabilisation of depression.[21]. Future therapies should take into account both the neurobiological and psychological factors that underpin the illness.[22]. Psychoeducation and psychotherapy were also reported to be effective long-term strategies for bipolar illness patients, as well as their relatives or carers.[23]

RELATION OF DEPRESSION AND MANIA IN BIPOLAR DISORDER:

Mixed mania was seen frequently in teenagers and individuals who had previously had mania, particularly in females [5].The number of depressed symptoms experienced by those with a greater manic symptom load was likewise considerably higher. In women, increased YMRS core ratings resulted in a linear rise in depression load, and females were considerably more likely than males to suffer a greater number of depressive symptoms. Approximately half of the hypomanic and manic patients were also likely to meet the DSM-5 mixed feature specifier, with a considerable female predominance. In hypomanic and manic patients, the prevalence of agitation and irritability, both alone and combined, was a strong predictor of a larger depression load. Mania and depression should be viewed as complementary phases of manic-depressive diseases rather than antagonistic poles of bipolarity in future study.[25].

Even when just manic core items are evaluated and overlapping items with depression are deleted, the frequency of depressive symptoms in hypomanic participants validates our prior findings that mixed hypomania is widespread in patients with hypomania symptoms, especially in women.According to the available data, depressive symptoms co-occurred with mania in 10% to 30% of individuals [26]. In this investigation, 40% of patients with (hypo-) manic episodes were screened out MFS using CUDOS-C (score 12), which was similar to earlier data (3538%) and higher than the rate of 18% identified by clinicians using normal psychiatric interview [27]. According to Hergueta and Weiller (2013), psychiatrists identified MFS in 46.5 percent of manic patients using DSM-5 criteria, while the proportion of MFS climbed to 58.6 percent using the MINI-M questionnaire[28]. The differences might be due to the latter study's tougher criteria for recruited patients (e.g., bipolar I disorder and manic episode) and physicians' clinical experience. (Certified for three to thirty years and treated at least 15 bipolar I disorder patients each month) [29]. Overall, these screening techniques can assist clinicians recognise mixed traits in depression and bipolar illness. Mixed depression, defined as an IDS-C score of 15 and a YMRS score of >2, was also discovered in a prior report on the SFBN cohort.[30]

The majority of people with bipolar disorder spend three times as much time in depressive phases as they do in manic ones. The number of depressed symptoms experienced by subjects with a higher manic symptom load was likewise significantly higher [31]. In hypomanic and manic patients, the prevalence of agitation and irritability, both alone and combined, was a strong predictor of a larger

depression load. Mania and depression should be viewed as complementary phases of manic-depressive diseases rather than antagonistic poles of bipolarity in future research [32].

According to the findings, people with BD had a larger impairment of insight during mania than during depression or euthymia [33]. In comparison to those suffering from depression or euthymia, people suffering from mania have less understanding into the efficiency of treatment and the societal ramifications of the disease, according to other studies [34]. The current investigation found no differences between depression and euthymia in relation to the first three categories as wel [35]. In previous investigations, insight was also reported to be preserved during the depressive phase of BD. These findings support the theory that people with mania have a harder time recognising their symptoms than those with depression [36].

Alan C. Swann, MD et al (2008)., conducted a study among depression and mania in bipolar disorder, they concluded that depression and mania both - Impulsivity appears to be linked to depressive and manic symptoms in distinct ways. With either depression or mania, attentional cognitive impulsivity rises; motor impulsivity rises with mania, while no planning impulsivity rises with depression. In mania, impulsivity was significantly linked to hyperactivity, whereas in depression, it was linked to despair or anhedonia. Possibility of a greater link between subjective emotion and motivation or activity.[37]

The link between sleep problems and mood in children and adolescents is complicated. Sleep issues are common before, during, and occasionally after an episode of unipolar depression or bipolar illness, and they can play a significant influence in how they manifest. In depression and bipolar illness, the prevalence of sleep disorders such as insomnia, CRDs, and sleep apnea is greater than in the general population, yet these diagnoses are frequently ignored and no special therapy is provided. Treatment of both the emotional and particular sleep disorders would be included in a multi-modal approach. The term "sleep disruption" is not a medical term. More long-term research with subjective and objective sleep metrics are needed to enhance treatment and the nature of the mood-sleep link. The influence of specialised therapy for sleep disturbances on the long-term prognosis of emotional disorders is of particular concern. Clinicians must determine if better nights consistently lead to better days [38].

In children and teenagers, mixed states are highly common. Nonetheless, approaches for measuring them vary, and further research is needed to confirm diagnostic consistency. Furthermore, substantial rates of comorbidity with typical child mental disorders characterise mixed states. In this specific research, the response to pharmacological therapy and the function of psychopathological features have not received much attention, indicating prospective exploratory targets. To summarise, mixed moods should be examined in infancy and regarded a key component of paediatric BD, in contrast to the popular belief that mood disorders exclusively swing from depression to mania. [39]

TREATMENT FOR BIPOLAR DISORDER

Treatment options:

1) Pharmacotherapeutic options:

Mood stabilizers have historically been the mainstay of therapy for bipolar disorder. Agents include lithium, valproic acid and its derivatives (divalproex sodium), and carbamazepine. Recent literature has supported the use of atypical antipsychotics as monotherapy or adjunctive treatments in bipolar mania.

Agents for the treatment of depressive episodes in patients with bipolar remain more limited, with data supporting the use of lithium, lamotrigine, quetiapine, and olanzapine-fluoxetine.[40]

Lithium:

Lithium is indicated for the acute and chronic treatment of mania. Lithium may also be effective in the treatment of mixed episodes and depressive episodes. Between 60% and 100% of lithium is absorbed from the GIT. The extent of absorption is not affected by food. The rate of absorption changes depending on the formulation. Lithium is not highly protein bound. Lithium is eliminated primarily through the Renal. Changes in renal function can significantly affect the clearance of lithium.

MECHANISM OF ACTION: For lithium is currently unknown, although several theories exist.

(a) Lithium is thought to help correct desynchronized biological rhythms in patients with bipolar disorder.

(b) Lithium may affect membrane stabilization.

(c) Lithium may augment homeostasis by enhancing the function of secondary messenger systems, especially cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), and phosphatidylinositol.

(d) Lithium can inhibit NE release and accelerate its metabolism.

(e) Lithium may reduce receptor sensitivity and elevate presynaptic reuptake of NE and 5-HT.

With a therapeutic range of 0.5 to 1.0 mEq/L, lithium has a narrow therapeutic index. Toxicity is related to levels greater than 1.5 mEq/L. Acute mania patients often require amounts at the upper end of the therapeutic range than those on maintenance medication. Bipolar depression patients require a level of 0.8 mEq/L. If patients are clinically stable, maintenance lithium levels can be as low as 0.6 mEq/L. [41]

(a) Patients are often started on 300 mg of lithium twice a day and titrated up in 300 mg increments as needed to achieve therapeutic effects while minimizing toxicity. Once a patient has been stabilized on medication, he or she might be switched to a long-acting formulation.

(b) Consider patient-specific factors such as age, weight, and renal function.

(c) Serum concentrations should be checked 5 days after starting therapy or modifying doses. In individuals with potential toxicity or impaired renal function, A levels might be tested after 3 days of therapy. Levels should be measured 12 hours after the dose, which should be done in the morning before the first dose of the day. Extended-release lithium patients may have a 12-hour trough level that is 12% to 33% greater than regular-release lithium.

(d) Once a patient is stabilised, follow-up lithium levels can be done less regularly (every 6 to 12 months) and are determined by the patient's clinical situation.[42]

Valproic acid (VPA):

VPA is indicated in the acute and chronic treatment of mania. VPA may also be effective in the treatment of hypomania, mixed disorders, and rapid cycling.[43]

The mechanism of action of VPA is not completely understood. VPA's efficacy is assumed to be connected to its capacity to boost GABA levels.

There are numerous formulas: There is a VPA. VPA is available in the forms of valproic acid (Depakene) capsules and syrup, divalproex sodium delayed-release tablets (Depakote) and extended-release tablets (Depakote ER), and valproate intravenous solution (Depacon).[44]

Dose: VPA is typically started at 20 to 30 mg/kg/day in divided dosages for inpatients and 250 mg three times daily for outpatients. The current therapeutic range

(50 to 125 g/mL) was developed for the treatment of seizure disorders and has not been proven to be effective in bipolar disorder. When transitioning from an immediate-release formulation to an extended-release formulation, the bioavailability is reduced by 15% to 25%, necessitating a 25% dose increase.

(a) Levels can be measured after 3 to 5 days of therapy. These should be trough readings collected 12 hours after dosage. In clinically stable individuals, VPA levels can be monitored less regularly (every 6 to 12 months).
(b) Patients who do not respond clinically after 4 to 6 weeks of treatment with VPA values of 80 to 120 g/mL may be classed as VPA therapy failures. [44]

Interactions between medications Multiple medication interactions are possible with VPA. Because VPA is highly protein bound in the body, levels can rise in the presence of another highly protein-bound medicine. VPA is also a substrate and inhibitor of the cytochrome P450 isoenzyme 2C9, which may raise the levels of other drugs processed by this iso-enzyme. [45]

Carbamazepine (CBZ):

CBZ is indicated in the acute treatment of mania but is considered to be a second-line agent owing to its numerous adverse effects and medication interactions.[46]

The mode of action of CBZ is not totally understood; nevertheless, it is hypothesised that its success in bipolar illness is due to its effects on GABA and G protein-linked second messenger systems, such as cAMP. [47][48]

Dosage of CBZ should be started at 200 to 600 mg/day in divided doses, then raised by 200 mg/day to the normal levels of 800 to 1000 mg/day.

(a) For seizure disorders, a therapeutic range of 4 to 12 g/mL has been described. Although the relationship between this range and efficacy in bipolar disorder has not been thoroughly proven, it is utilised to limit negative effects.

(b) Levels can be collected 5 to 7 days after starting treatment. CBZ concentrations in the body will decline after auto-induction, therefore levels should be monitored for the next few weeks.

(c) Patients who do not respond clinically after 4 to 6 weeks of treatment with CBZ doses of 6 to 12 g/mL may be classed as CBZ therapy failures. [47]

Lamotrigine:

Lamotrigine. Is indicated in the maintenance treatment of bipolar disorder with the benefit in preventing depressive episode relapse. Lamotrigine may be effective in rapid-cycling bipolar patients. Lamotrigine has mixed evidence regarding its use in acute depressive episodes.[49]

The mechanism of action of lamotrigine is not fully understood. It is now assumed to be related to its capacity to inhibit glutamate and aspartate release by inhibiting sodium channels. [50]

Dosage of Lamotrigine should be started at low doses (25 mg/day) and gradually raised by 25 mg every 1 to 2 weeks due to the possibility of rash. Lamotrigine should be used twice daily in amounts of more than 50 mg. The typical dosing range is 50 to 300 mg/d. Because of a substantial pharmaceutical interaction, patients taking lamotrigine with VPA should cut the dose in half. Patients using lamotrigine with carbamazepine should start at 50 mg/d since carbamazepine increases lamotrigine clearance. [51]

Atypical antipsychotics:

Atypical antipsychotics have recently been the subject of multiple studies in the treatment of bipolar disorder. All atypical antipsychotics except clozapine, iloperidone, and lurasidone are approved for the treatment of bipolar disorder. Olanzapine and quetiapine are approved for maintenance treatment in bipolar.

Olanzapine is available in a formulation with fluoxetine (Symbyax), and quetiapine is approved for depressive episodes. Olanzapine and aripiprazole are available in intramuscular injections approved for the treatment of agitation associated with bipolar mania.[52]

Additional anticonvulsants:

Oxcarbazepine is a medication structurally similar to carbamazepine but with fewer adverse effects. It is postulated to have similar therapeutic effects in bipolar disorder to carbamazepine; however, studies demonstrating its efficacy are limited. It currently is recommended only in combination with other mood stabilizers.[53]

Antidepressants:

Antidepressants should be used cautiously in patients with bipolar disorder because of the risk of inducing mania. When possible, patients should be receiving mood stabilizers at goal doses before initiating antidepressants and should be cautiously monitored. Bupropion and paroxetine have been associated with less risk of inducing mania than other antidepressants and may be preferable.[54]

Benzodiazepines:

Benzodiazepines may be useful adjuncts to primary treatment in reducing agitation, anxiety, and insomnia. Benzodiazepines should be discontinued once the primary treatment is stabilized because benzodiazepines are ineffective in treating bipolar disorder. Lorazepam is available in an intramuscular formulation, which may be useful in acute agitation.[55]

Treatment duration/phases:

The treatment of bipolar disorder is structured similarly to that of depression with acute, continuation, and maintenance phases. Maintenance treatment is strongly recommended for all patients with bipolar disorder, especially those with a family history. [56]

Treatment augmentation:

a. Patients with no or partial response to monotherapy may receive combination therapy with two agents. Agents that can be combined include lithium, VPA, and atypical antipsychotics. Atypical antipsychotics, if used, should be combined with either VPA or lithium and not combined with another atypical antipsychotic.

b. For depressive episodes, lamotrigine may be combined with another mood stabilizer as first-line therapy, and the olanzapine–fluoxetine combination product is a second-line option.[57]

Treatment options in pregnancy:

Multiple agents used in the treatment of bipolar disorder have been associated with birth defects.

(1) Lithium, VPA, and CBZ are pregnancy category D medications.

(2) Lithium has been associated with birth defects, primarily in the first trimester.

(3) VPA and CBZ should be used during pregnancy only if the benefits outweigh the risks. If the decision is made to use these medications during pregnancy, folic acid should be given to minimize the risk of defects. [58]

(4) Lamotrigine and oxcarbazepine are pregnancy category C medications.[59]

CONCLUSION

Bipolar illness is a common mental disorder characterised by emotional instability and cognitive deficits, particularly during mood swings. The neurophysiology of bipolar disorder appears to be influenced by abnormalities in the ALN and adjacent brain areas.This pattern of morbidity distribution was discovered long before contemporary antimanic, antidepressant, and mood-stabilizing drugs were introduced, therefore it is unlikely to be replicated. wholly due to current therapies. In

individuals with BD-II disease, as well as those who have a high number of mixed manic-depressive episodes and those who follow a DMI course pattern, there is a significant excess of depression among the less well-known findings.

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