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RESEARCH ARTICLE
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A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF ORAL SODIUM VALPROATE VERSUS DIVALPROEX IN TREATMENT OF BIPOLAR DISORDER

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Abstract:
Background: Bipolar disorder is a prevalent psychiatric condition that significantly impacts the quality of life, characterized by recurring episodes of mania, hypomania, and depression. Sodium Valproate and Divalproex are two commonly prescribed mood stabilizers for managing bipolar disorder. This study aims to evaluate the efficacy and safety of these drugs in the treatment of bipolar disorder, given the limited data from Central India.
Methods: A prospective, observational study was conducted involving 110 patients diagnosed with bipolar disorder. Participants were divided into two groups: Group I received Sodium Valproate (500mg twice daily), and Group II received Divalproex (500mg twice daily). Treatment efficacy was measured using the Young Mania Rating Scale (YMRS) and Bipolar Depression Rating Scale (BDRS) at baseline, 6 weeks, and 8 weeks. The severity and causality of adverse drug reactions were assessed using the Hartwig Severity Scale and WHO UMC Causality Assessment Scale.
Results: Both drugs showed significant improvement in YMRS and BDRS scores over the 8-week period. Sodium Valproate resulted in a 53.39% reduction in YMRS and a 52.44% reduction in BDRS scores, while Divalproex showed slightly better efficacy with a 54.13% reduction in YMRS and a 53.33% reduction in BDRS scores. P value was calculated using the software Spss 30. Significant p value was found for each group. Both drugs were well tolerated, with mild adverse effects such as nausea and tremors being the most commonly reported.
Conclusion: Sodium Valproate and Divalproex are effective and safe options for managing bipolar disorder, with Divalproex showing a marginally better efficacy profile. These findings contribute to the understanding of bipolar disorder treatment in Central India and provide insights into the comparative effectiveness of these mood stabilizers

Keywords - Bipolar disorder, Sodium valproate, Divalproex, Mood stabilizers etc

INTRODUCTION

Mental health is a state of human tendency by which the people realises their abilities, can deal with the everyday stresses of life, can work productively, and may contribute to their community. This definition of mental health is not only limited to the absence of mental illness but also identifies

positive feelings and functioning as critical factors for mental well- being. Regarding well-being as a critical characteristic of mental health, it is difficult to reconcile with the many challenges & life situations in which well-being may even be unhealthy. **[1]**. Mental health has three critical components emotional well-being, psychological well-being, and social well-being. Various scholars use mental health concept, which includes both critical aspects of the WHO definition, i.e., positive emotions and positive productivity of work and identifies three components of mental health viz, emotional well-being, psychological well-being, and social well-being. The major components of emotional wellbeing are happiness, positive attitude, satisfaction and interest in life. **[2]** Mental health consists of three critical components biological, social and psychological. Various researchers found that mental illness and weak economic status are related. The relationship between poverty and mental disorders is universal and found across societies irrespective of levels of development. Hopelessness, insecurity, rapid social change, the risks of violence and disease are factors responsible for the vulnerability of poor people to mental illnesses.**[3]** Bipolar disorder is a common but a serious mental illness. In 2019, 40 million people experienced bipolar disorder worldwide.**[4]** In India, 13.5 million people had bipolar disorder. **[5]** Bipolar I disorder causes significant medical and psychiatric comorbidity, premature mortality, high levels of functional disability and reduced quality of life. The presence of a syndromic, hypomanic phase and a severe depressive episode characterises bipolar II disorder.**[6][7]** The majority of patients with bipolar I disorder are differently affected by depressive symptoms and episodes, even though some may exclusively experience manic or primarily manic episodes. Individuals suffering from bipolar depression experience higher rates of morbidity and death compared to those with bipolar mania. Additionally, depressed patients are more likely to experience psychosis, suicide, and inter- episode panic attacks. A person experiencing mania has an aberrant mood that might be expansive, soaring, and euphoric, or irritable and high on energy. Hypomania, which means "below mania," is a less severe form of the disorder. Unlike those experiencing a full manic episode, hypomanic are frequently perfectly functional and do not exhibit psychotic symptoms. Many people find that hypomania is a healthy state to be in, assuming it doesn't lead to depression or mania itself. (Goodwin, 2018). **[8]** Bipolar disorder patients have a 10 to 15 year shorter life expectancy due to an increased prevalence of medical co-morbidities such as diabetes, cardiovascular disease, metabolic diseases and they also have suicidal tendencies. (Schaffer et al., 2015). **[9]** The signs and symptoms of bipolar disorder are so diverse that they can be partially observed in almost all major mental disorders, making the Diagnosis difficult for psychiatrists.**[10][11]** Treating bipolar disorder should not be limited to short- term medication symptom relief; lifestyle modifications should be the main goal in order to reduce stress, stress sensitivity, and inflammation. Depending upon severity and pattern of episodes of Mania and depression, treatment can be done through psychological therapies (like behavioural activation ,cognitive behavioural therapy and interpersonal therapy) and/ mood stabiliser's medications such as Sodium valproate, lithium etc and antipsychotic medications such olanzapine, risperidone etc.**[12]** Sodium valproate is thought to reduce or prevent manic episodes by increasing the amount of a chemical called gamma-aminobutyric acid (GABA) in the brain. GABA blocks transmission across nerves in the brain and has a calming effect. **[13]** The first-generation antipsychotics work by inhibiting dopaminergic neurotransmission; their effectiveness is best when they block about 72% of the D2 dopamine receptors in the brain. Moreover, they inhibit histaminergic, cholinergic, and noradrenergic pathways. Second-generation antipsychotics function by inhibiting both the serotonin receptor antagonist and D2 dopamine receptors. The most often involved subtype of the serotonin receptor is 5-HT2A. **[14]** However published data comparing and evaluating the efficacy and tolerability of these two drugs in the treatment of Bipolar disorder in lacking in central India. This study was therefore designed to evaluate the efficacy and safety of Sodium valproate and Divalproex in Bipolar disorder

AIMS AND OBJECTIVES

AIMS - A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF SODIUM VALPROATE AND DIVALPROEX IN BIPOLAR DISORDER.

OBJECTIVES-

1. To study efficacy of Sodium valproate.
2. To study efficacy of Divalproex.
3. To analyze the severity and casualty of adverse drug reactions to Sodium valproate and Divalproex.

REVIEW OF LITERATURE

Bipolar disorder includes two or more episodes where patient experiences marked disturbances in their mood and energy levels; these disturbances can include mood elevation and increased energy and activity (hypomania or mania)or mood lowering and decreased energy and activity (depression). Bipolar disorder is defined as having recurrent bouts of either mania or hypomania.**[7]**

HISTORICAL BACKGROUND

From the classical Greek era to the DSM-5 and ICD-11, we examined the history of bipolar disorders. Aretaeus of Cappadocia, a Greek physician from the first century AD, may have been the first to characterise mania and melancholia as two distinct phenomenological phases of the same disease. France gave rise to the contemporary understanding of bipolar illnesses with the writings of Falret (1851) and Baillarger (1854).**[15][16]** However, Emil Kraepelin combined all forms of affective diseases into "manic-depressive insanity" in 1899; despite some resistance, Kraepelin's comprehensive idea was widely accepted. But in the 1960s, bipolar disorders came back into vogue because of Jules Angst, Carlo Perris, and George Winokur. These three individuals independently demonstrated the existence of clinical, familial, and course characteristics that support the differentiation between bipolar and unipolar disorders; they also confirmed a number of the Wernicke-Kleist-Leonhard school's related views. Over the past three decades, significant advancements have been made in the understanding of unipolar and bipolar disorders. These advancements include the revival of Kraepelin's mixed states, the concept of soft bipolar spectrum (Akiskal), the differentiation of schizoaffective disorders into unipolar and bipolar forms, and the cyclothymia and related affective temperaments identified by Kahlbaum and Hecker. **[17]** Melancholia was understood to be a general term that encompassed all types of silent insanity as early as the time of Hippocrates. It persisted into medieval times and Galenic medicine. It was associated, as the name suggests, with the Humoral hypothesis of causality and specifically with black bile. Kraepelin carried on and simplified the work of his predecessors in the nineteenth century and wrote a textbook that was published in multiple editions.In his early works, he mentioned a category called Involutional Melancholia, but in his later works, he returned to the term Manic-depressive category, which included all cases of Depression and all cases of Mania.**[19]** Adolf Meyer, a Swiss psychiatrist who led the Henry Phipps Psychiatric Clinic at Johns Hopkins University, abandoned the notion that mental illnesses were distinct diseases and instead saw all mental illnesses as reaction types, or the body's psychobiological response to stress.**[20]** This time, biological and psychological variables were considered. Some people arrived at the opinion that psychoses and neuroses are the two categories of mental diseases. Psychosis included severe mentally ill patients who were admitted to hospital had organic reasons. Others with less severe conditions that did not necessitate hospital admission were classified as having neuroses because they were more closely linked to psychological stress and could be treated psychologically. **[21]**

THE MODERN CONCEPT OF BIPOLAR DISORDER

Bipolar disorder is categorised in Mood disorders, which comes under the heading of Mental, Behavioural and Neurodevelopmental disorders in the INTERNATIONAL

CLASSIFICATION OF DISEASES (ICD)-11. (Version 02/2022) The ICD provides a common language that provides health professionals to share standardised information across the world.**[22]** Mood disorders refer to a subordinate grouping of Bipolar and Depressive disorders. Mood disorders are defined according to the mood episodes, their type and pattern over the course of time. Broadly there are following types of mood episodes-

1. Depressive episodes
2. Manic episodes.
3. Mixed episodes.
4. Hypomanic episode.

Depressive disorder includes the following-

1. Single episode depressive disorder.
2. Recurrent depressive disorder.
3. Dysthymic disorders.
4. Other specified Depressive disorders.

The DSM-5-TR is the first published revision of DSM-5 since its original publication in 2013. It was published in March 2022.It included many changes from DSM-5.**[23]**

Treatment of Bipolar Disorder

Although common, depression is treatable mental disorder. Bipolar disorder treatment mostly involves Medication, Psychotherapy, or both. If these treatments do not improve symptoms Deep Brain Stimulation Therapy may be considered.

For Bipolar disorder-Treatment begins with Psychotherapy alone, Medications may be needed if symptoms do not improve.

For moderate to severe cases of Bipolar disorder - Treatment begins with both Therapy and Medications.**[24]**

Psychotherapy

Also called talk therapy or counselling. It is teaching the patients suffering from Bipolar disorder, new ways of thinking and behaving and helps with changing habits which contribute to depression. Psychotherapy is given by medical trained profession who have license to do the same. They usually take session , which may be individualised or group sessions. Two effective psychotherapies to treat Bipolar disorder are-

1.Cognitive behavioural therapy.
2.Interpersonal therapy.**[25]**

PHARMACOTHERAPY OF BIPOLAR DISORDER

Medications commonly used to treat Bipolar disorder are referred to as mood stabilizers and atypical antipsychotics. Drug Treatment of Bipolar Disorder. Sodium valproate and divalproex or lithium is used as a mood stabilizer in Bipolar disorder. Sodium valproate and divalproex is preferred due to better side effect profile. Treatment with Li+ ideally is initiated in patients with acceptable renal function, typically defined as estimated glomerular filtration rate (eGFR) greater than 70 mL/min. Occasionally, patients with severe systemic illnesses are treated with Li+ provided that the indications are compelling, but the need for medications that pose potential kinetic problems often precludes Li+ use in those with multiple medical problems. Treatment of acute mania and the prevention of recurrences of bipolar illness in adults or adolescents are uses approved by the FDA. Li+ is the mood stabilizer with the most robust data on suicide reduction in bipolar patients (Baldessarini et al., 2019)**[26]**; 377 Li+ is also efficacious for augmentation in unipolar depressive patients who respond inadequately to antidepressant therapy and is also associated with a

5-fold reduction in suicidality in that population compared to nonlithium therapies.**[27]**

Pharmacotherapy of Mania.

The anticonvulsant VPA also provides antimanic effects, with therapeutic benefit seen within 3 to 5 days when loaded. The most common form of VPA is divalproex due to its lower incidence of GI and other adverse effects. Divalproex is initiated at 30 mg/kg given as single or divided doses in the first 24 h, and then titrated to effect based on the desired 12-h trough serum level. Trough serum concentrations of 90 to 120 µg/dL show the best response in clinical studies. With immediate-release forms of VPA and divalproex, 12-h troughs are used to guide treatment. With the extended-release divalproex preparation, the trough occurs 24 h after dosing. However, obtaining serum levels at night may be difficult in outpatient settings, so 12-h troughs are commonly used, bearing in mind that 12-h trough levels for sustained- release divalproex are 18% to 25% higher than the 24-h trough.**[28]** Divalproex lacks Li+'s risk for renal and thyroid adverse effects, but there is concern about its use in women of reproductive age related to risks of polycystic ovary syndrome and also the known mutagenic potential, which demands routine use of contraception (Anmella et al., 2019). **[29]** Divalproex is also associated with hyperammonemia due to effects on the carnitine shuttle and can induce thrombocytopenia and neutropenia. Given Li+'s superior efficacy for depressive episodes and for reduction in suicidal behavior, Li+ should be preferentially used for bipolar I prophylaxis unless there is a clear medical contraindication to initiation (e.g., baseline eGFR
<60 mL/min). Carbamazepine is effective for acute mania, but carbamazepine cannot be loaded or rapidly titrated over 24 h due to the development of adverse effects such as dizziness or ataxia, even within the therapeutic range (6–12 µg/dL). An extended-release form of carbamazepine is effective as monotherapy with once- daily dosing.Carbamazepine response rates are lower than those for VPA compounds or for Li+, with mean rates of 45% to 60% (Post et al., 2007).**[30]** Nevertheless, certain individuals respond to carbamazepine after failing Li+ andVPA. Initial doses are 400 mg/ day in two divided doses. While antipsychotics have proven efficacy as monotherapy for acute mania, population-based cohort studies indicate that relapse rates are high when used long term as monotherapy (Wingård et al., 2019). **[31]** Acute intramuscular forms of olanzapine and ziprasidone can be used to achieve rapid control of psychosis and agitation. Benzodiazepines are often used adjunctively for agitation and sleep induction, but use outside of acute hospital settings is discouraged due to concerns about tolerance and dependence. Li+ is effective in acute mania and can be loaded in those with normal renal function using three individual 10-mg/kg doses of a sustained- release preparation administered at 2-h intervals in the evening (Kook et al., 1985).**[32]**
Since Li+ has a 28-h t1/2 in the CNS there is no plausible reason for split daily dosing or routine use of sustained-release preparations. The sustained-release form is only used to minimize GI adverse effects (e.g., nausea, diarrhea) due to the lower Cmax and delayed peripheral tmax. Acutely manic patients may require higher dosages to achieve therapeutic serum levels, and downward adjustment may be necessary once the patient is euthymic. Efficacy following loading can be achieved within 5 days. When adherence with oral capsules or tablets is an issue, the liquid Li+ citrate can be used. A 300-mg dose of Li+ carbonate provides 56 mg of elemental Li+, which is equivalent to 8 mEq. Li+ citrate can be ordered in either milligram or milliequivalent doses, with most forms of the syrup containing 300 mg (or 8 mEq) per 5 mL.**[33]** Discontinuation of maintenance Li+ treatment in patients with bipolar I carries a high risk of early recurrence and of suicidal behavior over a period of several months, even if the treatment had been successful for several years. Recurrence is much more rapid than is predicted by the natural history of untreated bipolar disorder, in which cycle lengths average about 1 year. This risk may be moderated by slow, gradual removal of Li+; rapid discontinuation should be avoided unless dictated by medical emergencies.**[34]**

PHARMACOTHERAPY OF DEPRESSION

Medications commonly used to treat depression are referred to as Anti- depressants. In general, Antidepressants enhance Serotonergic or Noradrenergic transmission. The most commonly used medications, often referred to as second-generation anti-depressants are the SSRIs and SNRIs . These drugs are the ones who have improved safety and less toxicity compared to first- generation drugs, which include MAOIs and TCAs. **[35]**

First generation anti-depressants

They were the drugs first used to treat depression. They have direct effect on Adrenergic, Cholinergic, and Histaminergic receptors. These include MAOIs and TCAs.

Second generation anti-depressants

They have more selective action on Amine uptake, with no direct action on Cholinergic, Adrenergic and Histaminergic receptors. They show improved safety and less toxicity when compared to the first- generation anti-depressants.They include SSRIs and SNRIs. Anti- depressants are the drug of choice for depression. But they are also used for some other
disorders and have FDA approval for the same, for example anti-depressants are used to treat Obsessive- Compulsive disorder, Social Phobia, Panic Disorder, Generalised Anxiety Disorder (GAD) and Post-traumatic stress disorder (PTSD).**[36]**

Valproic Acid Chemistry

Valproic acid (n-dipropylacetic acid) is a simple branched-chain carboxylic acid. **[37]** Certain other branched-chain carboxylic acids have potencies similar to that of valproic acid in antagonizing pentylenetetrazol-induced convulsions. However, increasing the number of carbon atoms to nine introduces marked sedative properties. Straight-chain carboxylic acids have little or no activity.

Pharmacological Effects

Valproic acid is strikingly different from phenytoin and ethosuximide in that it is effective in inhibiting seizures in a variety of models. Like phenytoin and carbamazepine, valproate inhibits tonic hind limb extension in maximal electroshock and kindled seizures at nontoxic doses. Similar to ethosuximide, valproic acid at subtoxic doses inhibits clonic motor seizures induced by pentylenetetrazol. Its efficacy in various models reflects its effectiveness against absence, focal, and generalized tonic-clonic seizures in humans.

Mechanism of Action

Valproate is known to inhibit succinic semialdehyde dehydrogenase, leading to an increase in succinic semialdehyde, which acts as an inhibitor of GABA transaminase. This ultimately reduces GABA metabolism and increases GABAergic neurotransmission, enhancing inhibitory activity due to GABA being an inhibitory neurotransmitter. Additionally, valproate may contribute to cortical inhibition by directly suppressing voltage-gated sodium channels and indirectly through effects on GABA. **[38]** It has also been suggested that valproate impacts the extracellular signal-related kinase pathway (ERK).1 These effects appear to be dependent on mitogen- activated protein kinase (MEK) and result in the phosphorylation of ERK1/2. This activation increases the expression of several downstream targets, including ELK-1, which leads to higher levels of c-fos, growth cone-associated protein-43 (contributing to neural plasticity), the anti-apoptotic protein B-cell lymphoma/ leukemia-2, and brain- derived neurotrophic factor (BDNF), which is also involved in neural plasticity and growth. The resulting increased neurogenesis and neurite growth due to valproate are attributed to the effects of this pathway. An additional downstream effect of increased BDNF expression appears to be an increase in GABAA receptors which contribute further to increased GABAergic activity. **[39]** Another potential mechanism that may contribute to valproate's antiseizure actions involves metabolism of GABA. Although valproate has no effect on responses to GABA, it does increase the

amount of GABA that can be recovered from the brain after the drug is administered to animals. In vitro, valproate can stimulate the activity of the GABA synthetic enzme, glutamic acid decarboxylase, and inhibit GABA degradative enzymes, GABA transaminase, and succinic semialdehyde dehydrogenase. Thus far, it has been difficult to relate the increased GABA levels to the antiseizure activity of valproate. Finally, it is known that valproic acid is a potent inhibitor of histone deacetylase. Thus, some of its antiseizure activity may be due to its ability to modulate gene expression through this mechanism.**[40]**

Toxicity

The most common side effects are transient GI symptoms, including anorexia, nausea, and vomiting (~16%). Effects on the CNS include sedation, ataxia, and tremor; these symptoms occur infrequently and usually respond to a decrease in dosage. Rash, alopecia, and appetite stimulation have occasionally been observed, with some patients experiencing weight gain during chronic valproic acid treatment. Valproic acid has several effects on hepatic function; elevation of hepatic transaminases in plasma is observed in up to 40% of patients and often occurs asymptomatically during the first several months of therapy.A rare complication is a fulminant hepatitis that is frequently fatal (Dreifuss et al., 1989). **[41]**

Drug Interactions

Valproate inhibits the metabolism of drugs that are substrates for CYP2C9, including phenytoin and phenobarbital. Valproate also inhibits UGTs and thus inhibits the metabolism of lamotrigine and lorazepam. A high proportion of valproate is bound to albumin, and the high molar concentrations of valproate in the clinical setting result in valproate displacing phenytoin and other drugs from albumin. With respect to phenytoin in particular, valproate's inhibition of the drug's metabolism is exacerbated by displacement of phenytoin from albumin. The concurrent administration of valproate and clonazepam has been associated with the development of absence status epilepticus; however, this complication appears to be rare.**[42]**

Therapeutic uses

Valproate is a broad-spectrum ASD that is effective in the treatment of absence, myoclonic, focal, and tonic-clonic seizures. The initial daily dose usually is 15 mg/kg, increased at weekly intervals by 5 to 10 mg/kg per day to a maximum daily dose of 60 mg/kg. Divided doses should be given when the total daily dose exceeds 250 mg. **[43]**

Divalproex

It is the coordination compound of valproic acid with sodium valproate (1:1). Oral absorption is slower and bioavailability is the same as valproate. Gastric tolerance is better. Divalproex is primarily used in mania and bipolar illness, but may be employed in epilepsy in the same way as valproic acid. **[44]** Divalproex Also known as valproate or valproic acid, divalproex is an anticonvulsant drug that functions as a mood stabilizer and antiepileptic agent by enhancing the inhibitory effect of gamma-aminobutyric acid (GABA). This therapy reduces repetitive neuronal firing and can modulate inhibition and excitation within neuronal networks.**[45] [46] [47] [48]**

Other mood stabilizers :

Lithium: The mechanism of action for lithium's neuroprotective benefits is still being investigated. The current inositol depletion hypothesis suggests that lithium down regulates polyphosphoinositide signaling by acting as an uncompetitive inhibitor of inositol monophosphatase and inositol polyphosphate 1-phosphatase. This inhibition of neuronal excitation contributes to its effectiveness as a mood stabilizer.**[49] [50]**

Carbamazepine: Similar to other mood-stabilizing agents, carbamazepine has an additional specific mechanism of action in which it inhibits cAMP accumulation, leading to the down

regulation of the inositol transporter.**[51][52]**

Lamotrigine: An anticonvulsant like valproate, lamotrigine works by reducing the frequency (but not the amplitude) of excitatory postsynaptic currents in the CNS, decreasing glutamate release, and increasing both the frequency and amplitude of inhibitory postsynaptic currents, thereby enhancing GABA release. This results in decreased glutamate transmission and increased GABA transmission.

[53] In general, Antidepressants enhance Serotonergic or Noradrenergic transmission. The most commonly used medications, often referred to as second-generation anti-depressants are the SSRIs and SNRIs. These drugs are the ones who have improved safety and less toxicity compared to first- generation drugs, which include MAOIs and TCAs. Solanki et al conducted a study of efficacy and safety of Sodium valproate. 1- week open trial was conducted in the year 2004–2005 at the emergency ward of the Psychiatric Centre, SMS Medical College, Jaipur, in which 30 patients participated. This article is published on Indian journal of psychiatry. In the experimental group, 18 patients showed more than 50% decrease in YMRS scores and rest showed minimal decrease.

[54] Muzina et Al, done similar study of safety and efficacy of Divalproex in Bipolar disorder. Patient showed 50% reduction in YMRS and BDRS score within 8 weeks of treatment. Nausea, Constipation, dry mouth, and cramps were the most common side effects.**[55]**

MATERIALS AND METHOD

A. INCLUSION CRITERIA

- All patients aged between 18 to 60 years undergoing treatment of Bipolar disorder at Department of Psychiatry, Gandhi Medical College, Bhopal during the studyperiod.
- Patient giving consent for the study.
- Patients receiving either Sodium valproate or Divalproex for Bipolar disorder.
- Both Male and Females.

B. EXCLUSION CRITERIA

- Patients who refuse to give consent.
- Pregnant Females.
- Lactating Females.
- Those with other co-morbid diseases

M.MATERIALS

1.Tablet Sodium valproate
2.Tablet Divalproex
3.Proforma
4.Validated consent form

D. METHODOLOGY

This study was conducted at Gandhi medical college and associated Hamidia Hospital Bhopal, Madhya Pradesh in the Department of Psychiatry. It is a Tertiary care teaching Hospital. The study was Prospective, Observational, and was conducted for a duration of 15 Months. Approval from Institutional ethics committee was obtained before the study. Patients were diagnosed and treated by the clinicians, and we observed their treatment responses. Both the drugs, Sodium valproate and Divalproex was prescribed to the patients according to the practicing guidelines by the treating Psychiatrist. Sodium valproate was given in the dose of 500 mg twice a day at baseline. The dose was gradually monitored and changed accordingly by the treating Psychiatrist depending upon the patient's response to the treatment. In this study we found that Sodium valproate was given in the initial of 500 mg in cases of mild cases of Bipolar disorder, while in majority of severe cases of Bipolar disorder it was started from 1000 mg itself. Divalproex was given in the dose of 500 mg twice a day at baseline. The dose was gradually monitored and changed accordingly by the treating Psychiatrist depending upon the patient's response to the treatment. In this study we found that

Divalproex was given in the initial of 500 mg in cases of mild cases of Bipolar disorder, while in majority of severe cases of Bipolar disorder it was started from 1000 mg itself. Data about patient's demographic details and clinical symptoms were obtained on case sheet by interviewing patients and Hamilton Rating Score sheet was filled according to their responses. Sixty-four patients who were suffering from depression and who met the inclusion and exclusion criteria were registered for the study after taking their written informed consent. The patients were interviewed Young Mania Rating Scale (YMRS) and Bipolar depression rating scale was filled according to their responses on the day of registration, that is, on the day of beginning the treatment. This day is considered as day 0. Then on follow up of the patients, their responses were again noted and accordingly the Young Mania Rating Scale (YMRS) and Bipolar depression rating scale Scores were filled for them on 6th week and 8th week of their treatment with the drug. Patients were asked about any adverse event and tolerability of the drug was assessed on the basis of Hartwig severity scale and WHO UMC causality assessment scale.

TOLERABILITY ASSESSMENT

On each visit patients were interviewed and asked about any adverse event after taking the prescribed drug. Severity of the adverse effect was judged based on ADR severity assessment scale (modified Hartwig and Siegel scale) which classifies ADR into mild, moderate, and severe.Causality assessment was done for individual cases by using WHO UMC scale.

ADR FORM

Latest edition (1.4) of ADR form was filled during ADR reporting.

STATISTICALANALYSIS OF DATA

The collected data was entered in Microsoft excel, Numbers, Google sheets and analyzed using Spss 23.0. The Qualitative data was expressed as percentage while the Quantitative data was expressed as mean and standard deviations were obtained. Then using paired t test, the p-value was obtained for mean YMRS and BDRS score on day 0, 45 and 60 of the study for both the drugs.

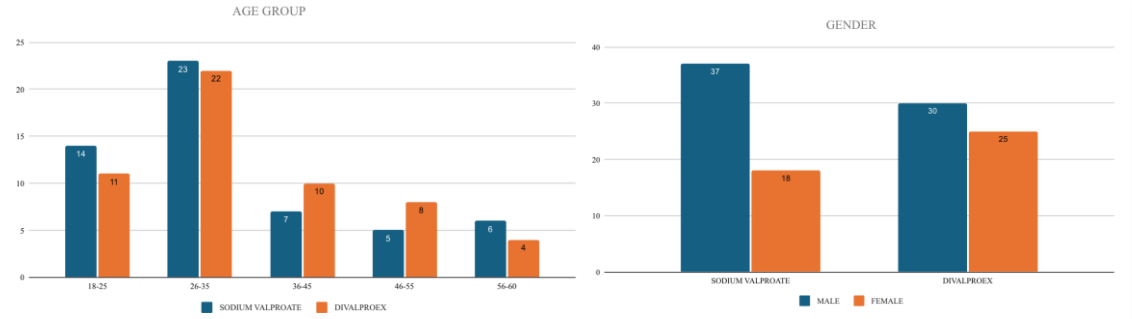
OBSERVATION AND RESULTS

During the study period a total of 110 patients were registered and monitored for a period of 0, 6th and 8th weeks. Two groups were made, one of Sodium valproate and other of Divalproex. In Sodium valproate group there were a total of 55 patients who were monitored throughout their treatment period. While in Divalproex group there were 55 patients who were too monitored throughout their treatment course.

Demographic characteristics - AGE

In Sodium valproate group the mean age of the patients was found to be 33.98 years with SD of 11.43 and in the Divalproex group the mean age of the patients was found to be 33.57 years with SD 11.57 as shown in the figure 5.1.

Figure-5.1: Age Group; Figure-5.2 : Gender



GENDER

Out of the total 110 patients, 55 received Sodium valproate and 55 received
Divalproex. In the Sodium valproate group there were total of 37 males (68%) and 18 females (32%) While in Divalproex group there were 30 males (54.2%) and 25 females (48.8%) as depicted in figure 5.2.

FAMILY AND ADDICTION HISTORY

Out of total 110 patients recorded, 34 had a family history of bipolar disorder.These patients had bipolar disorder in their first-degree family member.

- Most of the patients found in the study were married. Due to social withdrawal and many other

factors, majority of the patients were not working in any profession. Urban population was found in the study. Smoking was the most common addiction found in my study. As shown in the figures 5.3, 5.4 and 5.5 respectively.

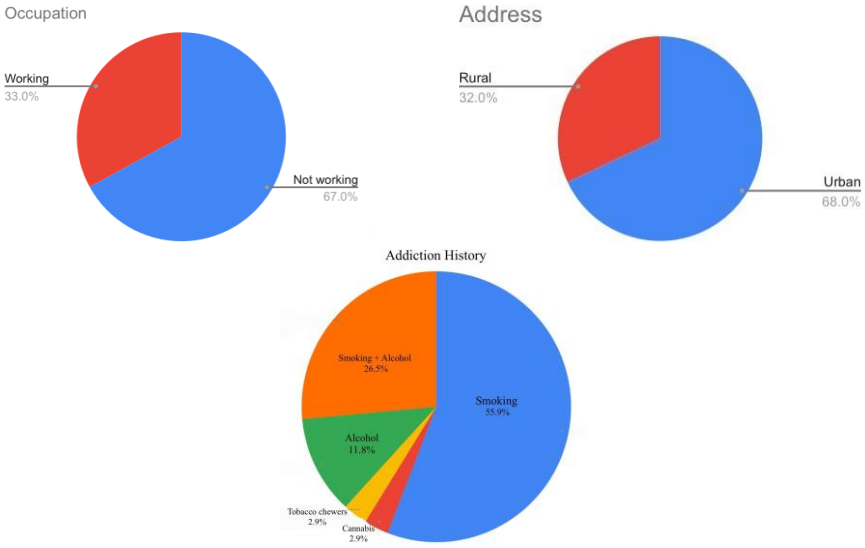


Figure-5.3 : Occupation ; Figure-5.4 :Address ; Figure-5.5 : Addiction history

DOSE AND FREQUENCY

Hospitalized patients were prescribed 1000mg and OPD patients were given 500mg of Sodium valproate and Divalproex by the physician respectively. Patients admitted in the hospital were given once a day dose (OD) 1000mg while OPD and follow-up patients were prescribed with twice a day (BD) 500mg. Duration of the treatment of most of the patients were 1month followed by 15 days or even 1 week. These results are shown in Table 5.1 and in figure 5.6 and 5.7.

Table- 5.1 : Dose

Duration	Sodium valproate (50) Number of		Divalproex (50) Number of	
Baseline	55	0	55	0
week 0	43	500	46	500
(IPD)	12	1000	9	1000
Week 6	53	500	52	500
Week 8	48	500	49	500

3. YOUNG MANIA RATING SCALESCORE

• In Sodium valproate group the mean Young mania rating scale score on day 0 i.e., the day of registration was found to be 21.95 with SD of 3.97.

• This score reduced to 14.77 with SD 3.99 and 10.23 with SD of 3.41 on6th week and 8th week respectively.

• So, the mean percentage reduction in YMRS score at the end of 6th week was found to be 32.71%.

• The score reduced to 10.23 at the end of 8th week of the treatment.

• So the mean percentage reduction in YMRS Score at the end of 8th week was found to be 53.4%.

BIPOLAR DEPRESSION RATING SCALE SCORE

• In Sodium valproate group the mean Bipolar depression rating scale score on day 0 i.e., the day of registration was found to be 21.51 with SD 4.20.

• This score reduced to 14.07 with SD 4.31 and 10.23 with SD of 3.61 on6th week and 8th week respectively.

• So, the mean percentage reduction in BDRS at the end of 6th week was found to be 20.85%.

• The score reduced to 10.23 at the end of 8th week of the treatment

• So, the mean percentage reduction in BDRS Score at the end of 8th week was found to be 52.44 %.

SODIUM VALPROATE GROUP

Table-5.2: Mean, Standard deviation				
DRUG NAME = SODIUM VALPROATE				
SCORE	N	Minimu	Maximum	Mean ± SD
Young Mania rating scale score on day 0	55	10.0	28.0	21.95 ± 3.97
Follow up - Young Maniarating scale score on 6th week	53	6.0	26.0	14.77 ± 3.99
Follow up -Young Mania rating scale soreon 8th week	48	6.0	19.0	10.23 ± 3.41

Table-5.3 Mean, Standard deviation, t value, P value and conclusion				
Drug name = Sodium valproate	M e a n ± SD	t value	p valu e	Conclusion
Young Mania rating scale score on day 0	21.95 ±3.97	9.46	0.001	Significant
Young Mania rating scale score on 6th week	14.77 ±3.99			
Young Mania rating scale score on day 0	21.95 ±3.97	16.61	0.001	Significant
Young Mania rating scale score on 8th week	10.23 ±3.41			
Young Mania rating scale score on 6th week	14.77 ±3.99	6.41	0.001	Significant
Young Mania rating scale score on 8th week	10.23 ±3.41			

Table-5.4 Mean, Standard deviation				
DRUG NAME = SODIUM VALPROATE				
SCORE	N	Minimum	Maximum	Mean ± SD
Bipolar dep ression rating scale score on day 0	55	10.0	27.0	21.51 ± 4.20
Follow up -Bipolar depression rating scale score on 6th week	53	7	25	14.07 ± 4.31
Follow up -Bipolar depression rating scale soreon 8th week	48	6.0	20	10.32 ± 3.61

Table-5.5 Table-5.3 Mean, Standard deviation, t value, P value and conclusion				
Drug name = Sodium valproate	**Mean ± SD**	**t valu e**	**p valu e**	**Conclusion**
Bipolar depression rating scale score on day 0	21.51 ±4.20	9.17	0.001	Significant
Bipolar depression rating scale score on 6th week	14.07 ±4.31			
Bipolar depression rating scale score on day 0	21.51 ±4.20	14.98	0.001	Significant
Bipolar depression rating scale score on 8th week	10.32 ±3.61			
Bipolar depression rating scale score on 6th week	14.07 ±4.31	4.95	0.001	Significant
Bipolar depression rating scale score on 8th week	10.32 ±3.61			

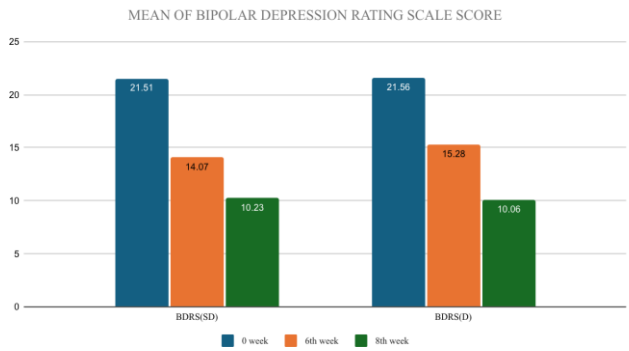
DIVALPROEX

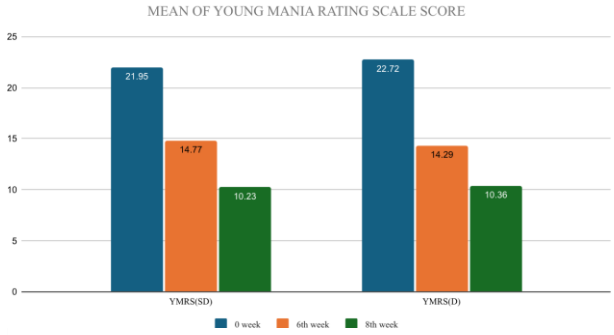
YOUNG MANIA RATING SCALE SCORE

- In Divalproex group the mean Young mania rating scale score on day 0 i.e the day of registration was found to be 22.72 with SD of 5.04.
- This score reduced to 14.29 with SD 3.10 and 10.36 with SD of 2.86 on6th week and 8th week respectively.
- So, the mean percentage reduction in YMRS score at the end of 6 weeks was found to be 37.12%.
- This score reduced to 10.36 at the end of 8th week of the treatment.
- So, the mean percentage reduction in YMRS Score at the end of 8 weeks was found to be 54.41%

BIPOLAR DEPRESSION RATING SCALE SCORE

- In Divalproex group the mean Bipolar depression rating scale score on day 0 i.e., the day of registration was found to be 21.56 with SD 5.51.
- This score reduced to 15.28 with SD 4.70 and 10.06 with SD of 3.33 on6th week and 8th week respectively.
- So, the mean percentage reduction in BDRS score at the end of 6th week was found to be 29.12 %.
- The score reduced to 10.73 at the end of 8th week of the treatment
- So, the mean percentage reduction in BDRS Score at the end of 8th week was found to be 53.33 %.





DIVALPROEX GROUP

Table-5.6 Mean, Standard deviation				
DRUG NAME = DIVALPROEX				
SCORE	**N**	**Minimum**	**Maximum**	**Mean ± SD**
Young Mania rating scale score on day 0	55	11.0	29.0	22.72 ± 5.04
Follow up -Young Mania rating scale score on 6th week	52	9.0	26.0	14.29 ± 3.10
Follow up -Young Mania rating scale sore on 8th week	49	7.0	23.0	10.36 ± 2.86

Table-5.7 Table-5.3 Mean, Standard deviation, t value, P value and conclusion				
DRUG NAME = DIVALPROEX	**Mean ± SD**	**t valu e**	**p valu e**	**Conclusion**
Young Mania rating scale score on DAY 0	22.72 ±5.04	14.97	0.001	Significant
Young Mania rating scale score on 6th week	14.29 ±3.10			
Young Mania rating scale score on DAY 0	22.72 ±5.04	22.39	0.001	Significant
Young Mania rating scale score on 8th week	10.36 ±2.86			
Young Mania rating scale score - on 6th week	14.29 ±3.10	9.78	0.001	Significant
Young Mania rating scale score - on 8th week	10.36 ±2.86			

Table-5.8 Mean, Standard deviation

DRUG NAME = DIVALPROEX				
SCORE	**N**	**Minimum**	**Maximum**	**Mean ± SD**
Bipolar depression rating scale score on day 0	55	11.0	31	21.56 ± 5.51
Follow up -Bipolar depression rating scale score on 6th week	52	9	27	15.28 ± 4.70
Follow up -Bipolar depression rating scale sore on 8th week	49	7.0	25	10.06 ± 3.33

Table-5.9 Mean, Standard deviation, t value, P value and conclusion

DRUG NAME = DIVALPROEX	**Mean ± SD**	**t value**	**p valu e**	**Conclusion**
Bipolar depression rating scale score on DAY 0	21.56 ±5.51	9.1	0.001	Significant
Bipolar depression rating scale score on 6th week	15.28 ±4.70			
Bipolar depression rating scale score on DAY 0	21.56 ±5.51	18.85	0.001	Significant
Bipolar depression rating scale score on 8th week	10.06 ±3.33			
Bipolar depression rating scale score on 6th week	15.28 ±4.70	9.48	0.001	Significant
Bipolar depression rating scale score on 8th week	10.06 ±3.33			

Statistical analysis were depicted in the tables where p value is calculated for YMRS and BDRS score on day 0 and 6th week, day 0 and 8th week, 6th week and 8th week. All these values are found to be significant.

The above tables (5.2 to 5.9) shows mean YMRS and BDRS score value on baseline i.e. day 0, 6th week and 8th week and their pictorial presentation is depicted in figure 5.8 and 5.9.

ADR REPORTED

Few side effects were seen in the study participants as seen in the table belowand their pictorial presentation is given in table 5.10 and 5.11

Figure - 5.8; Figure : 5.9

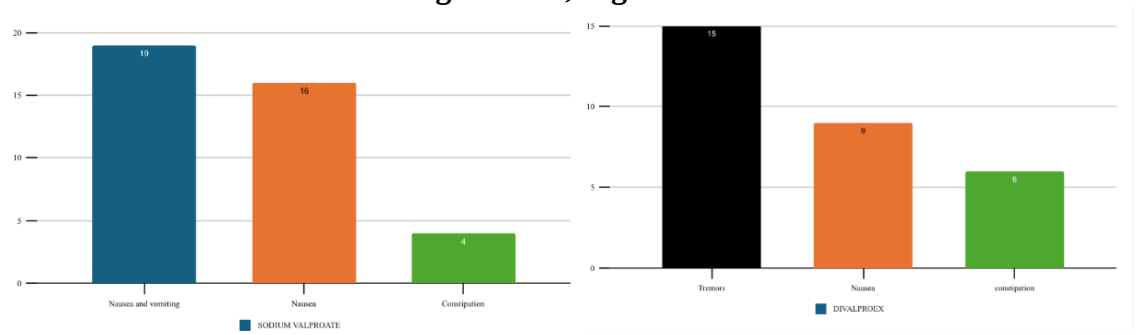


Table-5.10 Adverse drug reaction of SD and D

ADR	SODIUM VALPROATE(SD)	DIVALPROEX(D)
1	Nausea and Vomiting (19)	Tremors (15)
2	Nausea (16)	Nausea (9)
3	Constipation (4)	Constipation (6)

SEVERITYASSESSMENT

On evaluation of the severity of the ADR's by Hartwig scale, it was evident that most of the ADR's reported in this study were of Mild severity. Details of the severity assessment is given in the table below-

Table-5.11 Severity assessment done by Hartwig scale

TYPE	NUMBER OF ADR's
MILD	69
TOTAL	69

CAUSALITYASSESSMENT

Causality assessment was done for individualised cases by using WHO- UMC, and in most of the cases causality was found to be POSSIBLE.Details of the causality assessment in given in the table below.

Table-5.12 Causality assessment by WHO-UMC

TYPE	NUMBER OFADR's	PERCENTAGE
POSSIBLE	69	62.72%
TOTAL	69	

DISCUSSION

In central India, there is limited data of study of efficacy and safety of Sodium valproate and Divalproex, so we aimed to analyse the efficacy of these two commonly used drug in the treatment of depression. Our study was conducted in Department of Psychiatry and Pharmacology, in Gandhi medical college, Hamidia hospital, Bhopal, Madhya Pradesh. 110 patients who gave consent and were in accordance with the inclusion criteria's, were registered and followed for the period of study duration i.e. 8 weeks. After taking informed consent, patients were interviewed and their

responses were filled accordingly. They were asked questions related to YMRS and BDRS scale and responses were noted. The day of registration was considered as the day 0. Subsequent follow up was done on day 0, 6th week and 8th week. YMRS and BDRS score was filled on each follow up. Efficacy of the mood stablizers was studied based on their scores. Patients were questioned about any adverse events and side effects were than noted for evaluating the tolerability of both the drugs. The YMRS and BDRS score measured on day of registration was considered the baseline score. Patient were followed up on 6th week and 8th week. Improvement in the scores were noted and mean percentage reduction was calculated for each day. We found significant improvement (reduction more than 50%) at the end of 8th week of the treatment. P value was calculated for these mean YMRS and BDRS score on day 0 and 6th week, 0 and 8th week, 6th week and 8th week. P value was calculated using the software Spss 30. Significant p value was found for each group. Our study revealed that Bipolar disorder is common in the age group of 18-35 years which was similar to previous studies conducted by Soni et al and Ajitabh et al. **[56]** The mean age was found to be 33.97 years with SD of 11.43 in Sodium valproate group and 33.57 year with SD 11.57 in Divalproex group which was similar to previous studies conducted by Baldessarini RJ et al and Bolzani L et al. **[26]** In the present study we also found that the prevalence of Bipolar disorder was higher in males. A total of 67 females were there, which was 60.90% of the study population. This result was similar to the studies conducted by Hochman et al. **[57] [58]** Out of total 110 patients recorded, 34 had a family history of bipolar disorder. These patients have first-degree family member. **[59]** In this study we found that the patients treated with Sodium valproate reported nausea and vomiting (n=19) and Nausea(n=16) Constipation(n=4). Nausea was also reported as adverse event in the study population treated with Sodium valproate in the study conducted by Delage et al. **[60]** While in Divalproex group, tremors (n=15), nausea(n=9) and Constipation(n=6)and were the reported side effects. Sedation was also reported adverse event in the study conducted by Delage et al. **[60]** Also, all patients who were registered were Normotensive, Non-diabetic and had normal Blood Pressure. During the course of the study, some patients reported adverse events like nausea, fatigue, tremors, constipation etc. All reports came out to be within normal limits. Young mania rating scale and Bipolar depression rating scale score was filled on each visit of patients and, in this study we found a highly significant improvement in YMRS and BDRS score reduction at the end of 6th and 8th week. In Sodium valproate group, the mean percentage reduction in YMRS score was found to be 32.71% on 6th week, while this reduction increased to 53.39 % on 8th week of the treatment. In Sodium valproate group, the mean percentage reduction in BDRS score was found to be 20.85% on 6th week, while this reduction increased to 52.44 % on 8th week of the treatment. These studies have similar results as conducted previously by Talaei A et Al, Chaurasia et Al, Shansis et Al**[54] [61] [62] [63]** In Divalproex group, the mean percentage reduction in YMRS score was found to be 37.12 % on 6th week, while this reduction increased to 54.13 % on 8th week of the treatment. In Divalproex group, the mean percentage reduction in BDRS score was found to be 29.14% on 6th week, while this reduction increased to 53.33 % on 8th week of the treatment. These studies have similar results as conducted previously by Shansis et Al, Bowden et Al and Young et Al.**[63] [64] [65]** A 50% reduction in YMRS and BDRS score is considered to be significant improvement. This 50% reduction has been a common definition of response in trials assessing the efficacy of Antimanic drugs. On evaluation of the severity of the ADR's by Hartwig et al., scale, it was evident that the ADR's reported in this study were of Mild severity. **[66]** Causality assessment was done for individualised cases by using WHO-UMC and causality was found to be POSSIBLE.

CONCLUSION

Overall, the present study was designed to evaluate the efficacy and safety of Sodium valproate and Divalproex in Bipolar disorder.

Young mania rating scale for mania and for bipolar depression Bipolar Depression Rating Scale Score was used to evaluate the efficacy of both the drugs. Patients were interviewed and according

to their responses the YMRS and BDRS scores were filled on day 0, that is the day of starting the treatment.

Follow-up was done on 6th week and 8th week of the treatment. In Sodium valproate group, the mean percentage reduction in YMRS score was found to be 32.71% on 6th week, while this reduction increased to 53.39 % on 8th week of the treatment. In Sodium valproate group, the mean percentage reduction in BDRS score was found to be 20.85% on 6th week, while this reduction increased to 52.44 % on 8th week of the treatment.

In Divalproex group, the mean percentage reduction in YMRS score was found to be 37.12 % on 6th week, while this reduction increased to 54.13 % on 8th week of the treatment.

In Divalproex group, the mean percentage reduction in BDRS score was found to be 29.14% on 6th week, while this reduction increased to 53.33 % on 8th week of the treatment.

A 50% reduction in YMRS and BDRS score is considered to be significant improvement. This 50% reduction has been a common definition of response in trials assessing the efficacy of mood .stabiliser drugs So, in the present study the percentage reduction on 6th week and 8th week, for both the drugs is found to be significant. No serious side effect was found in all the patients who were treated with the two drugs. In this study we found that the patients treated with Sodium valproate reported nausea and vomiting (n=19) and Nausea(n=16) Constipation (n=4). While in Divalproex group, Tremors (n=15), Nausea (n=9) and Constipation (n=6) and were the reported side effects. So, we conclude that the efficacy and safety of both Sodium valproate and Divalproex is found to be nearly same with little better results with Divalproex.

Conflict of interest - There was no conflict of interest.

BIBLIOGRAPHY

1. Galderisi S, Heinz A, Kastrup M, Beezhold J, Sartorius N. Toward a newdefinition of mental health. World Psychiatry. 2015 Jun;14(2):231-3.
2. Health and well-being. (n.d.). Who.int. Retrieved June 24,2024, from health-and-well-being
3. Patel V, Kleinman A. Poverty and common mental disorders in developing countries. Bull World Health Organ. 2003;81(8):609-15
4. Institute of Health Metrics and Evaluation. Global Health Data Exchange(GHDx), (https:// vizhub.healthdata.org/gbd-results/, accessed 14 May 2022)
5. Sagar R, Dandona R, Gururaj G, Dhaliwal RS, Singh A, Ferrari A, Dua T,Ganguli A, Varghese M, Chakma JK, Kumar GA. The burden of mental disorders across the states of India: the Global Burden of Disease Study 1990–2017. The Lancet Psychiatry. 2020 Feb 1;7(2):148-61.
6. ICD-10 version:2016. (n.d.). Who.int. Retrieved May 9, 2024, fromhttps:/icd.who.int/ browse10/2016/en#/F30-F39
7. Sentissi O, Popovic D, Moeglin C, Stukalin YB, Mosheva M, Vieta E,Serretti A, Souery D. Predominant polarity in bipolar disorder patients:the COPE bipolar sample. Journal of affective disorders. 2019 May 1;250:43-50.
8. Goodwin, G.. 2018. Hypomania: What's in a name? Br. J. Psychiatry 181.94-95. Gordovez, F.J.A., McMahon, F.J.. 2020, Y the geneties of bipolar disorder. Mol. Pyvchuatrs 25. 544-559.
9. Schaffer A, Isometsä ET, Tondo L, H Moreno D, Turecki G, Reis C, Cassidy F, Sinyor M, Azorin JM, Kessing LV, Ha K. International Societyfor Bipolar Disorders Task Force on Suicide: meta-analyses and meta- regression of correlates of suicide attempts and suicide deaths in bipolar disorder. Bipolar disorders. 2015 Feb;17(1):1-6.
10. Rantala MJ, Luoto S, Borráz-León JI, Krams I. Bipolar disorder: An evolutionary psychoneuroimmunological approach. Neuroscience & Biobehavioral Reviews. 2021 Mar 1;122:28-37.
11. Post RM. The impact of bipolar depression. Journal of ClinicalPsychiatry. 2005 Jan 1;66(5):5.
12. Sodium valproate: medicine to treat epilepsy and bipolar disorder. (n.d.).nhs.uk. Retrieved May 8, 2024, from https://www.nhs.uk/medicines/ sodium-valproate/

13. Godman B, Grobler C, Van-De-Lisle M, Wale J, Barbosa WB, Massele A,Opondo P, Petrova G, Tachkov K, Sefah I, Abdulsalim S. Pharmacotherapeutic interventions for bipolar disorder type II: addressing multiple symptoms and approaches with a particular emphasis on strategies in lower and middle-income countries. Expert opinion on pharmacotherapy. 2019 Dec 12;20(18):2237-55.
14. Chokhawala K, Stevens L. Antipsychotic Medications. [Updated 2023Feb 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from:
15. Falret JP. Circular madness or form of mental illness characterized by theregular alternation of mania and melancholy. Bull Acad Med (Paris). 1851.
16. Baillarger J. Madness in two forms. Ann med psychol. 1854;6:367-91.
17. Akiskal HS. Subaffective Disorders: Dysthymic, Cyclothymic and Bipolar II Disorders in the "; Borderline" Realm. Psychiatric clinics. 1981Apr 1;4(1):25-46.
18. Angst J, Marneros A. Bipolarity from ancient to modern times:: conception, birth and rebirth. Journal of affective disorders. 2001 Dec1;67(1-3):3-19.
19. Mason BL, Brown ES, Croarkin PE. Historical underpinnings of bipolardisorder diagnostic criteria. Behavioral Sciences. 2016 Jul 15;6(3):14.
20. Lamb S. Social skills: Adolf Meyer's revision of clinical skill for the newpsychiatry of the twentieth century. Medical history. 2015 Jul;59(3):443-64.
21. Paykel ES. Basic concepts of depression. Dialogues in clinicalneuroscience. 2008 Sep 30;10(3):279-89.
22. Özdemir O, Coşkun S, Mutlu EA, Özdemir PG, Abdullah AT, Yilmaz E, Keskin S. Family history in patients with bipolar disorder.Archives of Neuropsychiatry. 2016 Sep;53(3):276.
23. 2024 ICD-10-CM diagnosis code F31.30. (n.d.). .Retrieved June 18, 2024, from Codes/F01-F99/F30-F39/F31-/F31.30
24. Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. The lancet. 2013May 11;381(9878):1672-82.
25. Novick DM, Swartz HA. Evidence-based psychotherapies for bipolardisorder. FOCUS, A Journal of the American Psychiatric Association.2019 Jul;17(3):238-48.
26. Baldessarini RJ, Bolzani L, Cruz N, Jones PB, Lai M, Lepri B, Perez J, Salvatore P, Tohen M, Tondo L, Vieta E. Onset-age of bipolar disorders atsix international sites. J Affect Disord. 2010 Feb;121(1-2):143-6. doi: 10.1016/j.jad.2009.05.030. Epub 2009 Jun 28. PMID: 19560827.
27. Fountoulakis KN, Tohen M, Zarate CA Jr. Lithium treatment of Bipolardisorder in adults: A systematic review of randomized trials and meta- analyses. Eur Neuropsychopharmacol. 2022 Jan;54:100-115. doi: 10.1016/j.euroneuro.2021.10.003. PMID: 34980362; PMCID: PMC8808297.
28. Angus-Leppan H, Arkell R, Watkins L, Heaney D, Cooper P, Shankar R.New valproate regulations, informed choice and seizure risk. Journal of Neurology. 2024 Jun 19:1-6.
29. Anmella G, et al. Expert advice on the management of valproate inwomen with bipolar disorder at childbearing age. Eur Neuropsychopharmacol, 2019, 29:1199–1212.
30. Post RM, et al. Thirty years of clinical experience with carbamazepine in the treatment of bipolar illness: principles and practice. CNS Drugs, 2007,21:47–71.
31. Wingård L, et al. Monotherapy vs. combination therapy for post maniamaintenance treatment: a population based cohort study. Eur Neuropsychopharmacol, 2019, 29:691–700.
32. Kook KA, et al. Accuracy and safety of a priori lithium loading. J ClinPsychiatry, 1985, 46:49–51
33. Awan S, Abelleira A, Khehra L, Hieber R. Undetectable serum lithium concentrations after coadministration of liquid lithium citrate and applejuice: A case report. Mental Health Clinician. 2021 Jan 1;11(1):27-30.
34. Brunton LL, Knollmann BC, editors. Goodman & Gilman's the pharmacological basis of therapeutics. Fourteenth edition. New York:McGraw Hill; 2023. 1 p.
35. Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-

analysis of efficacy and tolerability. Journal ofaffective disorders. 2000 Apr 1;58(1):19-36.
36. Hillhouse TM, Porter JH. A brief history of the development of antidepressant drugs: from monoamines to glutamate. Experimental andclinical psychopharmacology. 2015 Feb;23(1):1.
37. PubChem. (n.d.). Valproate Sodium. nih.gov. Retrieved June 15, 2024,from https://pubchem.ncbi.nlm.nih.gov/compound/Valproate-Sodium
38. El-Habr EA, Dubois LG, Burel-Vandenbos F, Bogeas A, Lipecka J, Turchi L, Lejeune FX, Coehlo PL, Yamaki T, Wittmann BM, Fareh M. Adriver role for GABA metabolism in controlling stem and proliferative cell state through GHB production in glioma. Acta neuropathologica. 2017 Apr;133:645-60.
39. Rosenberg G. The mechanisms of action of valproate in neuropsychiatric disorders: can we see the forest for the trees?. Cellular and Molecular LifeSciences. 2007 Aug;64(16):2090-103.
40. Yamada MK, Nakanishi K, Ohba S, Nakamura T, Ikegaya Y, Nishiyama N, Matsuki N: Brain-derived neurotrophic factor promotes the maturationof GABAergic mechanisms in cultured hippocampal neurons. J Neurosci.2002 Sep 1;22(17):7580-5
41. Dreifuss FE, et al. Valproic acid hepatic fatalities. II. U.S. experiencesince1984. Neurology, 1989, 39:201–207.
42. Khandelwal A, Mahajan C, Prabhakar H. Anti-epileptic drugs (AEDs). Pharmacology in Clinical Neurosciences: AQuick Guide. 2020:173-256.
43. Brunton LL, Knollmann BC, editors. Goodman & Gilman's the pharmacological basis of therapeutics. Fourteenth edition. New York:McGraw Hill; 2023. 1 p.
44. KD Tripathi Essentials of Medical Pharmacology, 8th edition, pageno.444-445, Jaypee Brothers: New Delhi, 2018.
45. Löscher W. Basic pharmacology of valproate: a review after 35 years ofclinical use for the treatment of epilepsy. CNS Drugs.2002;16(10):669-94
46. Faingold CL, Browning RA. Mechanisms of anticonvulsant drug action. II. Drugs primarily used for absence epilepsy. Eur J Pediatr. 1987Jan;146(1):8-14.
47. PubChem. (n.d.-a). Divalproex Sodium. nih.gov. Retrieved June 15, 2024,from https://pubchem.ncbi.nlm.nih.gov/compound/Divalproex-Sodium
48. Davis LL, Williams R, Cates M. Divalproex sodium in the treatment ofadults with bipolar disorder. Expert Review of Neurotherapeutics. 2004May 1;4(3):349-62.
49. Berridge MJ, Downes CP, Hanley MR. Neural and developmental actionsof lithium: a unifying hypothesis. Cell. 1989 Nov 03;59(3):411-9.
50. Kerr F, Bjedov I, Sofola-Adesakin O. Molecular Mechanisms of LithiumAction: Switching the Light on Multiple Targets for Dementia Using Animal Models. Front Mol Neurosci. 2018;11:297.
51. Lubrich B, van Calker D. Inhibition of the high affinity myo-inositol transport system: a common mechanism of action of antibipolar drugs?Neuropsychopharmacology. 1999 Oct;21(4):519-29.
52. Chen G, Pan B, Hawver DB, Wright CB, Potter WZ, Manji HK. Attenuation of cyclic AMP production by carbamazepine. J Neurochem.1996 Nov;67(5):2079-86.
53. Cunningham MO, Jones RS. The anticonvulsant, lamotrigine decreases spontaneous glutamate release but increases spontaneous GABA releasein the rat entorhinal cortex in vitro. Neuropharmacology. 2000 Aug 23;39(11):2139-46.
54. Solanki RK, Singh P, Khandelwal R, Midha A. Efficacy and tolerabilityof injectable sodium valproate in patients with mania. Indian Journal ofPsychiatry. 2006Apr 1;48(2):118-20.
55. Muzina, D. J., Gao, K., Kemp, D. E., Khalife, S., Ganocy, S. J., Chan, P.K.,Serrano, M. B., Conroy, C. M., & Calabrese, J. R. (2011). Acute efficacysof divalproex sodium versus placebo in mood stabilizer– naive bipolar I orII depression: Double-blind, randomized, placebo-controlled trial. TheJournal of Clinical Psychiatry, 72(06), 813–819.
56. Soni A, Singh P, Kumar S, Shah R, Batra L, Verma M. Role of age at onset in the clinical presentation of bipolar disorder in Indian population.Industrial psychiatry journal. 2021 Jan

1;30(1):41-6.
57. Bipolar disorder. (n.d.). National Institute of Mental Health (NIMH).Retrieved June 19, 2024, from
58. Hochman E, Valevski A, Onn R, Weizman A, Krivoy A. Seasonal patternof manic episode admissions among bipolar I disorder patients is associated with male gender and presence of psychotic features. Journal of affective disorders. 2016 Jan 15;190:123-7.
59. Antypa N, Serretti A. Family history of a mood disorder indicates a moresevere bipolar disorder. J Affect Disord. 2014 Mar;156:178-86. doi: 10.1016/j.jad.2013.12.013. Epub 2013 Dec 18. PMID: 24439249
60. Delage C, Palayer M, Etain B, Hagenimana M, Blaise N, Smati J, Chouchana M, Bloch V, Besson VC. Valproate, divalproex, valpromide:Are the differences in indications justified?. Biomedicine & Pharmacotherapy. 2023 Feb1;158:114051.
61. Talaei A, Dastgheib MS, Soltanifar A, Mokhber N, Akhondzadeh S, Afzaljavan F. Oxcarbazepine versus sodium valproate in treatment ofacute mania: a double-blind randomized clinical trial. International Clinical Psychopharmacology. 2022 May 1;37(3):116-21..
62. Chaurasia L, Shah SK, Chetty SM. Efficacy of Sodium Valproate and Olanzapine in treating bipolar affective disorder'mania'at a tertiary carehospital in Nepal: A comparative study. Janaki Medical College Journalof Medical Science. 2016;4(1):27-35.
63. Shansis FM, Reche M, Capp E. Evaluating response to mood stabilizersin patients with mixed depression: a study of agreement between three different mania rating scales and a depression rating scale. Journal of Affective Disorders. 2016 Jun 1;197:1-7.
64. Bowden CL, Mosolov S, Hranov L, Chen E, Habil H, Kongsakon R, Manfredi R, Lin HN. Efficacy of valproate versus lithium in mania ormixed mania: a randomized, open 12-week trial. International clinicalpsychopharmacology. 2010 Mar 1;25(2):60-7.
65. Young RC, Mulsant BH, Sajatovic M, Gildengers AG, Gyulai L, Al JurdiRK, Beyer J, Evans J, Banerjee S, Greenberg R, Marino P. GERI-BD: a randomized double-blind controlled trial of lithium and divalproex in thetreatment of mania in older patients with bipolar disorder. American Journal of Psychiatry. 2017 Nov 1;174(11):1086-93.
66. Why causality assessment. (n.d.). The use of the WHO-UMC system for standardised case causality assessment. who-umc.org. Retrieved June 17,2024, from https://who-umc.org/media/164200/who-umc- causality assessment_newlogo.pdf