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PATHOPHYSIOLOGY, DIAGNOSIS AND TREATMENT OF I & II BIPOLAR DISORDERS – A DETAILED REVIEW

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ABSTRACT:

Bipolar disorder is a chronic and complex mood illness characterized by a combination of manic and depressive episodes. Manic depressive disorder is another name for bipolar disorder. Periods of mania, hypomania, psychosis, or sadness, as well as mood fluctuations, are all symptoms. Bipolar disorder sufferers experience a lot of mental health issues and medical problems.

Bipolar disorder is better treated if it is diagnosed and treated early. The occurrence of at least one lifetime manic episode is a required component of Bipolar 1 disorder. At least one hypomanic episode and one major depressive episode are required for Bipolar 2 disorder. Eighty percent of patients experience more than four episodes in their lives, and the duration between episodes is shorter as they get older. Suicide attempts are made by up to 50% of The Patients. Rapid cycling can be caused by a variety of factors, including biology Biological-rhythm, dysregulation, antidepressant or stimulant usage, hypothyroidism, and premenstrual and postpartum conditions.

In mixed states, manic episodes, and Bipolar 1 disorder, antidepressant monotherapy is contraindicated. Screening for suicidal thoughts and substance misuse, evaluating adherence to treatment, and identifying metabolic consequences of medication are all part of patient maintenance care. Body weight management decreases problems and improves lipid control. Patients and their support system should be educated about mood relapse, Suicidal ideation, and the effectiveness of early interventions to reduce complications.

In the current review we will be discussing the different types of bipolar disorders, its diagnosis, treatment and management practices.

Key Words: Primary Care, Bipolar Disorder, Managed Care, Mental Health, Psychological Stress.

INTRODUCTION:

Bipolar disorder is a mental illness that has been recognised since ancient times and is based on the idea of "mania," which originates from the Greek word "v," which means "madness" or "frenzy" [1]. Hippocrates, the father of medicine, recognised mania as a form of mental disorder. The term can even be found in early Greek literature, such as Homer's Iliad, where it refers to Achilles' uncontrollable rage at Agamemnon [2]. Philippe Pinel [3] created a variety of classifications for this sort of crazy (mania with delirious and non-delirious episodes), and this entity was intimately associated to psychosis throughout the nineteenth century. With the advent of anatomoclinic mentality in the mid-nineteenth century, somaticist tendencies in psychiatry began to emerge. In this context, Jacques-Joseph Moreau de Tours and Wilhelm Griesinger proposed that “madness” is caused by a structural change in the brain [4]. Finally, in this anatomoclinical environment, Emil Kraepelin developed the term manic-depressive psychosis at the end of the nineteenth century, distinguishing this condition from the so-called dementia praecox (schizophrenia) [5]. In the 1950s, Karl Leonhard proposed the notion of polarity in comprehending affective disorders [6], which was later included among the DSM diagnostic criteria in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (APA). As a result, unipolar patients who only have depressed episodes and bipolar patients who have a manic or hypomanic episode would exist [7].

Bipolar disorder had not gained the scientific and social acknowledgment it deserved until recently [8]. The lack of knowledge about its etiopathogenesis, the erroneous underestimation of its prevalence, and the status of therapeutic

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pseudo-orphanage had not been amended until almost two decades ago [9], compared to other psychiatric disorders—for example, major depression or schizophrenia—due to "scientific negligence." In fact, until the mid-1990s, when valproate's anti-manic efficacy was shown, lithium salts were the sole treatment option for these patients.

Bipolar disorder is a developing condition, according to current scientific study [9]. From a clinical standpoint, it has a high rate of morbidity and mortality [10]. Bipolar disorder was estimated to affect about 1% of the population in the well-known epidemiological studies Epidemiological Catchment Area Study (ECA) in 1981 and National Comorbidity Survey (NCS) in 1991, and its prevalence is currently estimated to be between 1% and 2% of the population over 20 years of age [11].

DEFINITION:

At least one lifetime manic or mixed episode characterizes bipolar I disorder, originally known as manic-depressive illness (Am. Psychiatry. Assoc. 2000). Cyclothymia is defined as a two-year period of changes in hypomanic and depressive symptoms that do not fulfil the DSM-IV criteria for a severe depressive episode or hypomania[12]. Patients with BD not otherwise described frequently have an illness that fulfils the minimum number of symptoms but does not meet the time requirements for a full manic, hypomanic, mixed, or depressed episode. The majority of research has been conducted on BD I disorder, which is the subject of this review.

EPIDEMIOLOGY:

Bipolar disorders were classified as the world's 12th most prevalent moderately to severely debilitating condition for any age group by the World Health Organization in 2004, with a lifetime prevalence of 4% in the United States [13]. Race, sex, or ethnicity have little bearing on bipolar illnesses. Although bipolar disorders can affect people of any age, they are more common in people under the age of 25. Bipolar I disorder begins around the age of 18 and bipolar II disorder at the age of 22.

Most research imply that BD I affects men and women equally, but some have found that males have a higher prevalence of manic episodes—and hence bipolar type 1--than females while females have a higher rate of bipolar type 2 [14].

Suicide rates among people with bipolar affective disorder have been found to be up to 20 times higher than in the general population, especially when bipolar disorder is untreated [15]. **ETIOLOGY:**

Bipolar affective disorder can be caused by a variety of factors [40]. Some of those are listed below:

Biological Factors:

Genetic Factors: When one parent has a mood disorder, the chance of bipolar disorder increases by 10% to 25%. Monozygotic twins have a 70-90 percent concordance rate, according to research. The greatest evidence supports a relationship between bipolar disorder and chromosomes 18q and 22q. Of all the psychiatric diseases, bipolar 1 disorder has the strongest hereditary relationship [16].

Neuroanatomy: Emotion control, response conditioning, and behaviour reaction to stimuli are all aided by the prefrontal cortex, anterior cingulate cortex, hippocampus, and amygdala.

Structural and Functional Imaging: In bipolar disorder, abnormal hyperintensities in subcortical regions, including the thalamus, basal ganglia, and periventricular area, signal repeated episodes and neurodegeneration.

Biogenic Amines: Dopamine, serotonin, and norepinephrine are among the neurotransmitters whose dysregulation has been linked to this condition; nevertheless, the data has yet to converge to reveal a genuine link [17].

Second Messengers: Mood stabilizers target G proteins, or guanine binding nucleoproteins. They bind to membrane receptors and produce second messengers such as cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) (cGMP)[18].

Hormone Regulation Imbalance: Mania is associated with adrenocortical hyperactivity. Chronic stress inhibits neurogenesis and neuroplasticity through lowering neurokinin brain-derived neurotrophic factor (BDNF)[19].

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Immunological Factors: Elevated levels of cytokines and interleukins over time are linked to clinical severity [20].

Psychosocial Factors:

In the context of BD, those with coexisting histrionic, obsessive-compulsive, or borderline personality traits are more likely to experience depressive episodes [21].

PATHOPHYSIOLOGY:

Bipolar affective disorder is supposed to be one of the most heritable mental diseases; nevertheless, a multifactorial paradigm in which genes and the environment interact dynamically with psychosocial stressors to induce this-phenomena is currently thought to be responsible [44]. Many small-effect alleles that overlap with schizophrenia (e.g., CACNA1C, TENM4, and NCAN) and that have been identified in genome-wide association studies contribute to the polygenic risk of bipolar disorder [22].

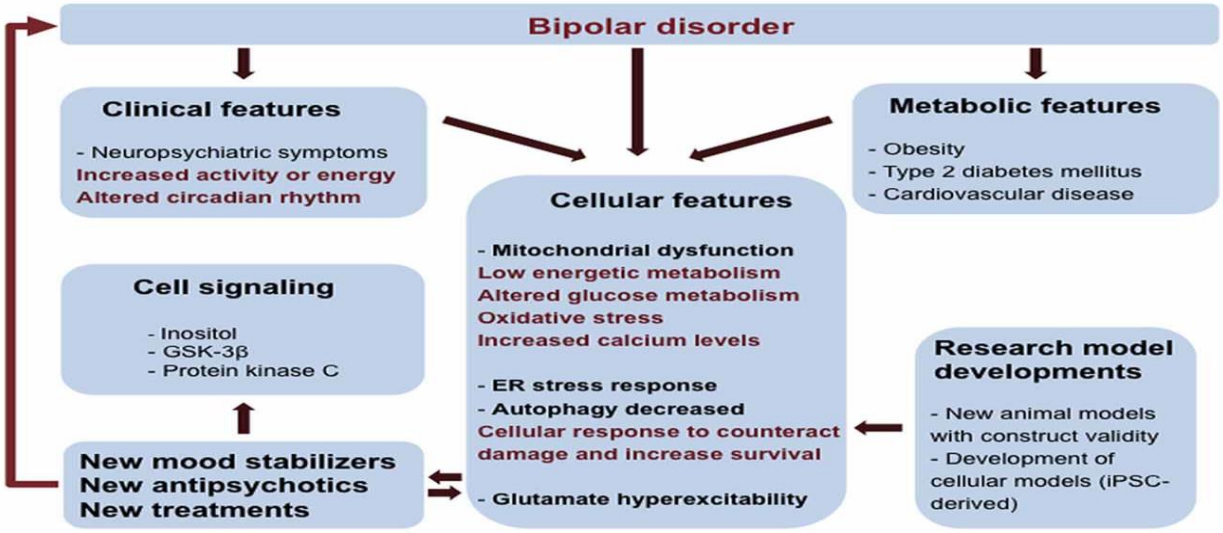

Figure 1: Pathophysiology of Bipolar disorder

Source: Frontiers | Molecular Mechanisms of Bipolar Disorder: Progress Made and Future Challenges | Cellular Neuroscience

DIAGNOSIS:

Correct diagnosis is difficult for healthcare professionals due to the significant number of concomitant diseases and differential diagnoses associated with bipolar disorder.

In a poll of bipolar patients who attend support groups run by the National Depressive and Manic–Depressive Association, 69 percent said clinicians misdiagnosed them at first, Before receiving a correct diagnosis, on average, 3.5 different diagnoses were received and 4 psychiatrists were consulted [23].Because bipolar disorder is a progressive illness, a prompt and accurate diagnosis is critical, and doctors should pay close attention to symptoms that may indicate a problem.

Patients with bipolar depression must have had at least one manic episode and be in a gloomy mood for the most of the day, practically every day, or have lost interest and pleasure in all activities (anhedonia); Weight loss, sleeplessness, psychomotor agitation or retardation, feelings of worthlessness or guilt, poor concentration, and recurring thoughts of death or suicidal ideation are all possible signs [24].

DIFFERENTIAL DIAGNOSIS:

Because the first episode of mood disruption in bipolar disease is frequently depression, not mania, and most patients seek therapy for depressed symptoms, diagnosing bipolar illness can be difficult [25]. Patients with bipolar

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disorder who are initially misdiagnosed face a longer wait for appropriate treatment and the danger of maltreatment with antidepressant monotherapy, which can increase the likelihood of recurrence and chronicity in this progressive condition. **ASSESSMENT:**

A variety of critical clinical and psychosocial concerns must be considered while evaluating a bipolar patient. The neuropsychiatric assessment, which includes a history and physical examination, is the most important tool. Due to the intricacy of the mood course in patients who have not been diagnosed, short histories (less than 30 minutes) may be a hazard. In most cases, further information from family, friends, or previous treatment locations is required. Except in patients with mood cycling from day to day, in a mixed episode, or otherwise on a very unstable trajectory, a distinction between episodic and chronic symptoms is useful. For manic episodes, screening measures can be utilized (e.g., the Mood Disorder Questionnaire [MDQ]), however they may be more useful in basic care settings. The MDQ consists of 13 yes/no questions, with seven positive responses requiring a comprehensive clinical evaluation [26].

It's also critical to catch instances of secondary mania, which was previously classified as a subtype of mania [27] but is now classified as either a substance-induced mania or a mania caused by a general medical disease.

HISTORY:

Symptoms:

- For a few days, there was less of a need for sleep without feeling weary.
- Sleep interruptions that cause a manic or hypomanic episode (e.g., shift work; childcare; travel; time change; change in season, especially spring and fall)
- Hypersomnia, increased hunger, psychosis, pathologic guilt, and labile mood are all symptoms of atypical depression.
- Constantly racing thoughts keep you from falling asleep.
- Irritability, impulsivity, and irrationality are all terms for the same thing.
- Periods of acute goal orientation or mood swings (irregular transitions from low to high).

FAMILY AND PSYCHOSOCIAL ISSUES:

Family history:

- A relative who suffers from bipolar illness.
- There are multiple relatives who have one or more of the following: Anxiety, panic disorder, depression, obsessive-compulsive disorder, attention-deficit/hyperactivity disorder.
- Multiple suicide attempts, incarceration, and drug or alcohol misuse in the family.

Personal history:

- Several divorce.
- Previous episodes of depression, particularly those with a young onset (age 13 or younger) or seasonal variation.
- Three or more antidepressant studies yielded no results.
- Problems with the law or finances.
- Suicide attempt.
- Abuse of drugs or alcohol.
- Job loss on a regular basis.
- Antidepressant, steroid, or other medicine intolerance, particularly if it induced agitation or mania.
- Previous mania or hypomania experiences.

TREATMENT:

Psychosocial therapies, as well as pharmacotherapy, are used to treat Bipolar disorder.

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Treatment of Mania:

Lithium and chlorpromazine trials were pioneering in the 1970s, followed by a focus on antiepileptics (e.g., valproate and carbamazepine) in the 1980s and 1990s. There are few trials that directly compare the efficacy of different second-generation antipsychotics, but a mixed treatments meta-analysis compared 13 agents studied in 68 randomised controlled trials (16 073 participants)[28].

Treatment of bipolar depression:

The treatment of bipolar depression is a major challenge, with few proven treatments and significant controversy surrounding the role of antidepressant drugs. Authors of guidelines and consensus statements on this topic frequently wonder why antidepressants are so widely used despite scant evidence of efficacy. With few proven treatments and significant controversy surrounding the role of antidepressant drugs, treating bipolar depression is a major challenge[29].

There is very little evidence of effective strategies for patients who do not respond to first-line therapies. A recent review of strategies found only seven small trials: one for ketamine, one for pramipexole, one for lamotrigine, and one for risperidone, and two for modafinil and electroconvulsive therapy [30].

Treatment for long-term maintenance:

Lithium, which was first introduced by John Cade in 1949, is still the most well-established long-term treatment for bipolar disorder. Despite the fact that the metal has been used in clinical trials for over 50 years, the most convincing evidence of long-term efficacy comes from randomised clinical trials in which lithium was used as an active comparator.

Lithium is the only known anti-suicidal treatment with randomised evidence of a more than 50% reduction in the risk of suicide.

Bipolar disorder psychosocial treatments:

Treatment guidelines are increasingly recommending that pharmacotherapy be combined with targeted psychotherapy for the best management of bipolar disorder. This approach has shown clinical benefits in a recent randomised trial in Denmark.

Psychosocial interventions for bipolar disorder all have the same goals:

- Improve your ability to recognise and intervene early when warning signs of recurrence appear.
- Increase understanding of the illness.
- Improve adherence to medication regimens
- Improve your ability to cope with environmental stressors linked to symptoms.
- Stabilize sleep and wake cycles, as well as other daily routines[31].

Adjunctive psychotherapy in acute treatment

- Family focussed therapy
- Cognitive behavioural therapy
- Interpersonal and social rhythm therapy
- Group psychoeducation
- Functional remediation
- Systemic care management

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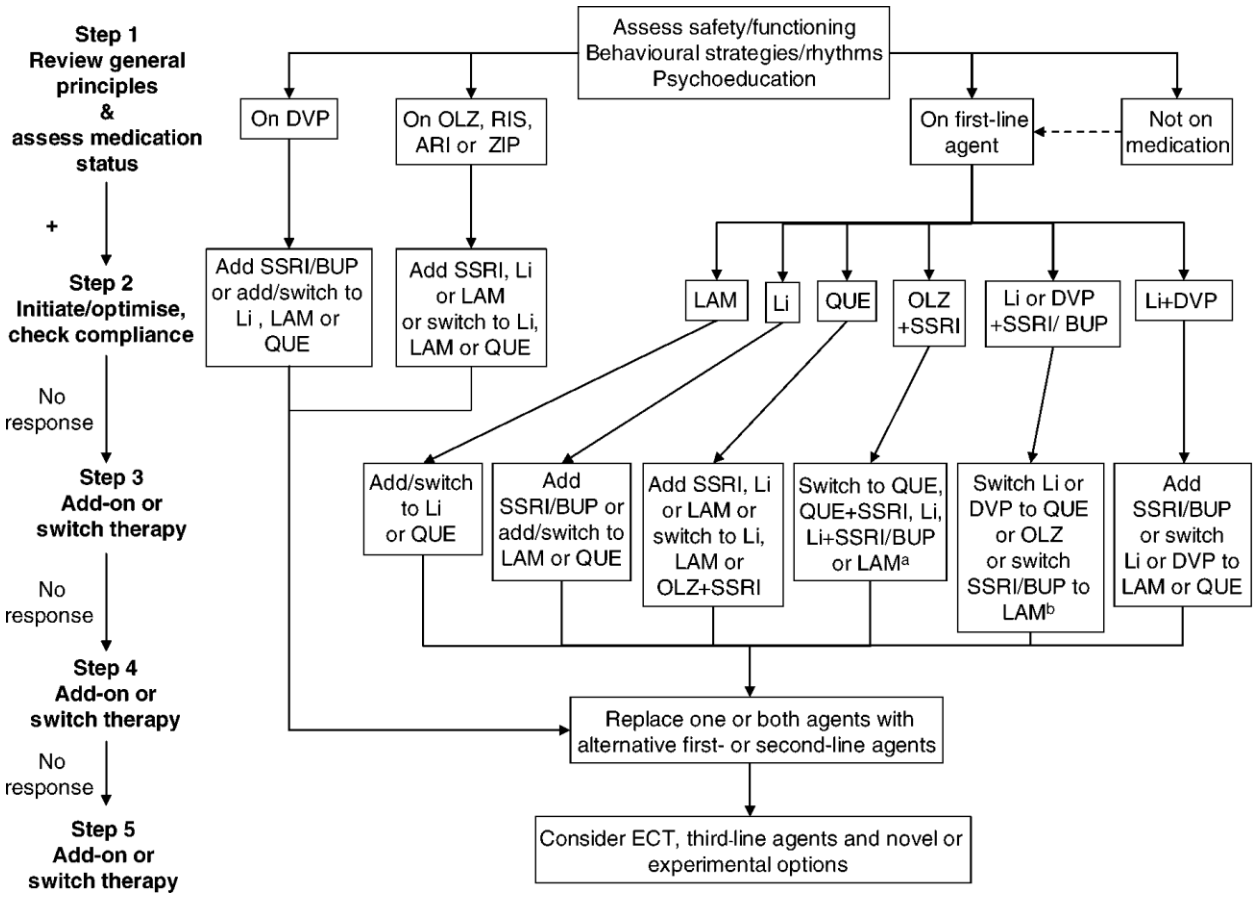

Figure 2: Pharmacotherapy of bipolar disorder

Source: Cambridge university press: Practical treatment guidelines for bipolar disorder chapter 5

MANAGEMENT:

The first stage in bipolar affective disorder treatment is to establish the diagnosis of mania or hypomania and characterize the patient's mood state, as treatment approaches for hypomania, mania, depression, and euthymia differ substantially. Medical and mental comorbidities, previous or current therapies, treatment response or side effects in patients and families, and the patient's willingness to be treated are all factors that might influence pharmacological and psychological methods[32].

Lithium treatment reduces mania in 50 percent to 70 percent of individuals. Lithium, on the other hand, has a limited therapeutic index, thus serum lithium levels should be closely monitored. Carbamazepine and valproic acid are anticonvulsants with a mood-stabilizing effect that are also used to treat acute manic episodes in many situations.

Electroconvulsive therapy is the most effective treatment for mania in a pregnant woman with treatment-resistant acute mood episodes such refractory depression or acute life-threatening mania, especially in patients with psychotic or catatonic characteristics[32].

COMPLICATIONS:

Bipolar affective illness progresses over time and has an impact on the patient's cognitive and functional areas as well as their physical health. Although numerous cognitive and neuroimaging investigations have found that people with bipolar illness had normal or even higher cognition before diagnosis, bipolar disease has been linked to severe neurocognitive impairments in all mood states, including remission[33].Patients with bipolar illness experience

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significant changes in their physical health in addition to their cognitive and functioning.

CONCLUSION:

Bipolar disorder is a major public health issue that is linked to a high rate of morbidity and mortality. Treatment is complicated due to a number of issues, including mood swings and their implications on patient well-being, treatment non-adherence, and co-occurring psychiatric diseases. Mania, despair, and other episodes have their own set of guidelines. Randomized studies are being conducted on a variety of pharmacologic and psychosocial therapies. Primary care providers see the majority of patients with mental illness and depression. Because bipolar depression is frequently misdiagnosed as unipolar depression, it's important to keep an eye out for signs that could indicate bipolar vs unipolar depression. By carefully assessing presenting symptoms, you can enhance diagnostic accuracy and avoid unnecessary antidepressant monotherapy. To improve patient outcomes, medical and mental comorbidities, which add to the complexity of bipolar disorder treatment, must be treated. Bipolar depression has a higher burden of disease than bipolar mania because of the amount of time spent sick, the higher level of functional impairment, and the restricted number of authorized treatment choices. Given the degenerative nature of bipolar depression and its significant unmet requirements, prompt diagnosis and appropriate treatment are critical. The patient, the doctor, and the patient's family/caregivers should work together to provide clinical treatment for patients with bipolar disorder.

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REFERENCES:

1. Liddell H.G., Scott R. A Greek-English Lexicon. Clarendon Press; Oxford, UK: 1940. [Google Scholar]
2. Young J.W., Henry B.L., Geyer M.A. Predictive animal models of mania: Hits, misses and future directions. Br. J. Pharmacol. 2011;164:1263–1284. doi: 10.1111/j.1476-5381.2011.01318.x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
3. Pinel P. Nosographie Philosphique ou La Methode De L'analyse Appliquee a La Medecine. 6th ed. Brosson; Paris, France: 1818. [Google Scholar]
4. Huertas R. El saber psiquiátrico en la segunda mitad del siglo XIX: La somatización de la enfermedad mental. Historia 16. 1993;18:66–73. [Google Scholar]
5. Kraepelin E. Psychiatrie. Ein Lehrbuch Für Studirende Und Aerzte. Sechste, Vollständig Umgearbeitete Auflage. Volume 2 Barth; Leipzig, Germany: 1899. [Google Scholar]
6. Leonhard K. Aufteiling der Endogenen Psychosen und Ihre Differenzierte Aetiologie. Akademie-Verlag; Berlin, Germany: 1957. [Google Scholar]
7. American Psychiatric Association . Diagnostic and Statistical Manual of Mental Disorders. 4th ed. American Psychiatric Association; Washington, DC, USA: 1994. [Google Scholar]
8. Del Porto J.A. Bipolar disorder: Evolution of the concept and the current controversies. Rev. Bras. Psiquiatr. 2004;26:3–6. doi: 10.1590/S1516-44462004000700002. [PubMed] [CrossRef] [Google Scholar]
9. López-Muñoz F., Vieta E., Rubio G., García-García P., Alamo C. Bipolar disorder as an emerging pathology in the scientific literature: A bibliometric approach. J. Affect. Disord. 2006;92:161–170. doi: 10.1016/j.jad.2006.02.006. [PubMed] [CrossRef] [Google Scholar]
10. Bauer M., Pfenning A. Epidemiology of bipolar disorders. Epilepsia. 2005;46:8–13. doi: 10.1111/j.1528-1167.2005.463003.x. [PubMed] [CrossRef] [Google Scholar]
11. Goodwin F.K., Jamison K.R., editors. Manic-Depressive Illness. Oxford University Press; New York, NY,

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

USA: 1990. [Google Scholar]

12. Vieta E. Mood stabilization in the treatment of bipolar disorder: Focus on quetiapine. Hum. Psychopharmacol. Clin. Exp. 2005;20:225–236. doi: 10.1002/hup.689. [PubMed] [CrossRef] [Google Scholar]

13. Tamayo J.M. Diferencias terapéuticas de los medicamentos para el tratamiento de los trastornos bipolares: Siete años después. Actas Esp. Psiquiatr. 2011;39:312–330. [PubMed] [Google Scholar]

14. De Lima M.S., Tassi J., Novo I.P., Mari J.J. Epidemiology of bipolar disorders. Rev. Psiquiatr. Clin. 2005;32:15–20. doi: 10.1590/S0101-60832005000700003. [CrossRef] [Google Scholar]

15. Merikangas K.R., Akiskal H.S., Angst J., Greenberg P.E., Hirschfeld R.M., Petukhova M., Kessler R.C. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch. Gen. Psychiatry. 2007;64:543–552. doi: 10.1001/archpsyc.64.5.543. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

16. Fountoulakis K.N., Kasper S., Andreassen O. Efficacy of pharmacotherapy in bipolar disorder: A report by the WPA section on pharmacopsychiatry. Eur. Arch. Psychiatry Clin. Neurosci. 2012;262:S1–S48. doi: 10.1007/s00406-012-0323-x. [PubMed] [CrossRef] [Google Scholar]

17. Vos T., Flaxman A.D., Naghavi M., Global Burden of Disease Study 2010 Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2163–2169. doi: 10.1016/S0140-6736(12)61729-2. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

18. Vieta E. Managing Bipolar Disorder in Clinical Practice. Current Medicine Group Ltd.; London, UK: 2007. [Google Scholar]

19. Novick D.M., Swartz H.A., Frank E. Suicide attempts in bipolar I and bipolar II disorder: A review and meta-analysis of the evidence. Bipolar Disord. 2010;12:1–9. doi: 10.1111/j.1399-5618.2009.00786.x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

20. Dilsaver S.C. An estimate of the minimum economic burden of bipolar I and II disorders in the United States. J. Affect. Disord. 2011;129:79–83. doi: 10.1016/j.jad.2010.08.030. [PubMed] [CrossRef] [Google Scholar]

21. López-Muñoz F., Álamo C., Domino E.F. History of Psychopharmacology (4 Volumes) NPP Books; Arlington, TX, USA: 2014. [Google Scholar]

22. World Health Organization. The global burden of disease: 2004 update. Part 3: disease incidence, prevalence and disability. http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/. Accessed May 19, 2011.

23. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication [published correction appears in Arch Gen Psychiatry. 2007;64(9):1039]. Arch Gen Psychiatry. 2007;64(5):543–552.

24. Hirschfeld RMA, Bowden CL, Gitlin MJ, et al. Practice guideline for the treatment of patients with bipolar disorder (revision) [April 14, 2006];Am J Psychiatry. 2002 159(Suppl):1–35. Available at: www.psych.org/psych_pract/treatg/pg/prac_guide.cfm. [Google Scholar].

25. Weissman MM, Leaf PJ, Tischer GL, et al. Affective disorders in five United States communities. Psychol Med. 1988;18:141–53. [PubMed] [Google Scholar].

26. Hirschfeld RMA, Holzer C, Calabrese JR, et al. Validity of the mood disorder questionnaire: A general population study. Am J Psychiatry. 2003;160:178–80. [PubMed] [Google Scholar].

27. Kessler RC, Bergland P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:593–602. [PubMed] [Google Scholar].

28. Hirschfeld RM. Bipolar spectrum disorder: improving its recognition and diagnosis. J Clin Psychiatry. 2001;62(Suppl 14):5–9. [PubMed] [Google Scholar].

29. Lish JD, Dime-Meenan S, Whybrow PC, et al. The National Depressive and Manic-Depressive Association (DMDA) survey of bipolar members. J Affect Disord. 1994;31:281–94. [PubMed] [Google Scholar].

30. Merikangas KR,Jin R,He JP,Kessler RC,Lee S,Sampson NA,Viana MC,Andrade LH,Hu C,Karam EG,Ladea M,Medina-Mora ME,Ono Y,Posada-Villa J,Sagar R,Wells JE,Zarkov Z, Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Archives of general psychiatry. 2011 Mar; [PubMed PMID: 21383262].

31. Tsuchiya KJ,Byrne M,Mortensen PB, Risk factors in relation to an emergence of bipolar disorder: a systematic review. Bipolar disorders. 2003 Aug; [PubMed PMID: 12895201].

32. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication [published correction appears in Arch Gen Psychiatry. 2007;64(9):1039]. Arch Gen Psychiatry. 2007;64(5):543–552.

33. Parikh SV, LeBlanc SR, Ovanessian MM. Advancing bipolar disorder: key lessons from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Can J Psychiatry. 2010;55(3):136–143.