

A Review of Bipolar Disorder

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Abstract:

Bipolar disorder is a typical mental illness that affects people all over the world. It is also referred to as a manic depression. Bipolar disorder is a significant public health issue, and it is generally diagnosed many years after symptoms first appear. Norepinephrine, dopamine, and serotonin are three neurotransmitters that have been involved in mood disorders. Many drugs have been used for treatment mental disorders such as lithium and dopaminergic medications have been used to treat manic features of bipolar illness, while antidepressants are indicated during depressive episodes. Managing bipolar illness is a difficult task, even for psychiatrists, because of the disorder's frequent episodes, concomitant conditions, and lack of devotion to therapy.

Keywords —Bipolar disorder, depressive episodes, manic episode, treatment

I. INTRODUCTION

Mental disorders are extremely common throughout the world, particularly in low- and middle-income countries (LMICs) (1). The mental health conditions such as depression, schizophrenia, bipolar disorder and other psychotic disorder and intellectual disabilities are identified as priority mental and neurological disorders by the World Health Organization's Mental Health Gap Action Programme (mhGAP) (1). There is a significant functional impairment associated with these common mental disorders (CMDs), in addition to negative social and economic consequences (1). Depression and anxiety disorders, on their own, are estimated to cost the global economy approximately one trillion dollars per year on average. Despite the fact that CMDs are prevalent throughout the world, a higher proportion of people suffering from these health conditions live in LMICs (1, 2). In addition, in large population-based cohort study, depressed adults had a higher risk of cardiovascular diseases and mortality in economically varied environments

(2, 3). A global approach to lessen the burden of noncommunicable illnesses should increase understanding and awareness of these physical health concerns (2, 4). Mood disorders can be classified into 3 types that is frequently occurring which are major depressive disorder, dysthymia, and bipolar disorder (5). Bipolar disorder, also known as manic depression, is a mental health disorder that covers from a severe (mania or hypomania) to a lower one (depression). Episodes of bipolar may occur rarely or several times during the years (5). Beside the serious mood swings, manic depression disorder also affected the change in activity levels, how they respond and behaviour(6). This paper focused on discussing more deeply on the symptoms, causes, etiology, and medical treatment (pharmacological and psychosocial) of bipolar disorder (BD) as it is a severe illness and highly prevalent in our society, with top rates of suicidality and functional disability. Moreover, the aim of this paper is to argue the implications of these epidemiologic information to mental health practice.

II. MOOD DISORDERS

Major depressive disorder is the type that patients may be experiencing the loss of interest in their routine activities, the feeling of sadness or hopelessness, and other symptoms that may indicate depression (7, 8). Dysthymia is a persistent, low-grade state of depression or irritability which may last at least around 2 years (9, 10). In addition, the symptoms of dysthymia is similar to depression disorder (5, 11). The condition is known as bipolar disorder, a severe mental ailment characterised by alternating periods of depression, mania, and mixed states (6). About 1-2% of the population is affected by the condition. Bipolar II disorders appear to be more common in women than in men. Bipolar disorder is diagnosed according to the severity and frequency of episodes (6, 12). Furthermore, from what has been mentioned for the definition of bipolar, it can also be widely classified into three main groups.

Bipolar I disorder, also called manic-depressive illness, is a form of mental disease which must at least have one manic episodes and may or may not have a major depression afterwards which stay at least two weeks or even both of them (13). Manic episodes usually shown in the form of, for example, feeling extremely happy (euphoria), having risky behaviours, having decreased need of sleep, having a loud speech, and excessive spending (13, 14).

Bipolar II disorder is a type of bipolar disorder which is quite similar to the BD I disorder with mood swing up and down over time but less severe. This type simply referred to major depressive episodes and hypomanic episodes (13). During a hypomanic episode patient with this mental disorder may experience having exaggerated self-confidence, loud and rapid speech and having a lot of energy and a poor sleep (13). However, it is quite pleasant to be around during this episodes as these patient are often seem very happy and may give their positive mood to people around them (13, 14).

Cyclothymia or cyclothymic disorder is a mental disorder which may not be mild enough to realise any problem but actually they can affect patients' daily routine. Cyclothymia involves the episodes of hypomania and major symptoms which has many similarities to bipolar disorder but they are not

long-lasting compared to the episodes of hypomanic or major depressive disorder (5). These symptoms usually show up by having a periods of feeling low followed by periods of extreme happiness and because the periods of low mood do not lasts for long to recognise, most of the patients with cyclothymia disorder are untreated (15).

III. PATHOPHYSIOLOGY OF BIPOLAR DISORDER

Bipolar disorder is hereditary and researchers also found out that bipolar disorder and schizophrenia are genetically connected as they both share certain symptoms, but these can be distinguished by the abnormality in the systems of dopamine and serotonin and by our brain's pathology in the brain system which involved in controlling our emotion (13, 16). Psychosocial stressors, which refers to the event in your life that creates a huge amount of stress, this extremely influences the illness that relates to these vulnerabilities (17). In the group of psychiatric disorders, bipolar disorder is the most heritable and the most serious disorder (18). The concordance rates for 57% average in the identical twins however rates 14% for fraternal twins (19, 20). Approximately around 85% of the statistics used in the field of genetics that estimates the variation have been obtained (21, 22).

The risk of children with bipolar disorder parents to have a bipolar disorder is higher than those children with parents in good health (23). On the other hand, a child with bipolar disorder parents that is evolving a non-bipolar disorder psychiatric, such as Attention-deficit/hyperactivity disorder (ADHD) which is defined as a disorder that can be noticed when a person usually has some inattention and unfocused motor activity, is greater than the chance in a child with healthy parents (24). Hence, the probability according to a hereditary risk which is either through genetics or family background cannot surely assume that it is linked to a bipolar disorder symptoms (25).

Neurotransmitter which have received the most attention in studies of mood disorders are norepinephrine, dopamine, and serotonin (26-28). Depressive symptoms were associated with

norepinephrine and dopamine in a low levels, whereas mania was associated with norepinephrine and dopamine in a high level according to the original neurotransmitter models (29). Furthermore, both mania and depression have been associated with low serotonin levels which is a neurotransmitter that helps to controlling norepinephrine and dopamine. Initially, it was presumed that medical disorders could be attributed to abnormally high or low levels of neurotransmitters in the synaptic cleft (29, 30). However, the scientific proof does not wholly support these hypotheses, as the signalling cascade of drug responses indicates that changes in receptor sensitivity, rather than alterations in utter neurotransmitter levels, are more likely to be prosecuted for symptom stabilisation (31-33).

Many other distinct dopaminergic drugs have been considered to obtain manic symptoms in patients without bipolar disorder, including increasing of mood, energy, and talkativeness (34, 35). Even in the absence amount of dopamine binding to the receptors, amphetamine has a significant behavioural effect on people with bipolar disorder (36, 37). Additionally, approximately 10 per cent of people who had mania before will experience manic symptoms the following morning after a whole night lack of sleep (38, 39). Sleep deprivation may impair the dopamine receptors' ability to normalise their sensitivity (40, 41).

Neuroimaging studies indicate that mental health disorders are frequently associated with a decreased number of serotonin receptor sensitivity (42-44). Moreover, manipulating the tryptophan precursors to serotonin can challenge serotonin systems (44, 45). Consistent with the notion that decreased serotonin receptor sensitivity contributes to BD, individuals with a positive family history develop more cognitive deficits following a serotonin-depletion procedure than individuals without a family history (46). However, a procedure in one study used to boost serotonin levels, tryptophan loading, resulted in similar cognitive deficits in participants with a family history of depression versus those without a family history of depression (46, 47). These effects are consistent with

serotonergic system dysregulation, but the nature of that irregularity remains unknown.

IV. TREATMENT OF MANIA

Lithium is the most remarkable scientific evidence demonstrating efficacy in treating mania and preventing further occurrences. Most people suffered with bipolar disorder experience a remission of manic symptoms while taking lithium (48-50). Lithium's side effects do not occur without reason: gain of weight, sedation, gastrointestinal distress, increased thirst, muscle tremor, and kidney problems could be seen (51).

Pharmacological research has recently concentrated on anticonvulsant efficacy. Although it was proved that carbamazepine had as good an effect on mania as lithium, additional studies have shown that carbamazepine is as effective as lithium for treating mania and is also as helpful as an adjunct to lithium for rapid-cycling patients (Denicoff et al. 1997). Its side effects, such as neurotoxicity, the elevation of liver enzymes, a decrease in sodium, and a depressed white blood cell count, restrict its utility. The beneficial effects of Divalproex appear to be about the same as that of lithium but with a fewer side effects (Bowden et al. 1994). Certain illnesses are mostly benefit from Divalproex therapy, mixed states, rapid cycling, and substance abuse, for example (48). In addition, patients with liver impairment required precaution when using carbamazepine and Divalproex since these drugs may increase liver enzymes and affect platelet counts (52, 53). Olanzapine has shown efficacy in treating both adult and paediatric mania (with particular effectiveness in mixed states and rapid cycling) and in the treatment of agitation connected with dementia (48). It is minimum as effective as, and in some studies, indeed more effective than lithium or divalproex in preventing manic or mixed-episode recurrences (48). Additionally, when used in conjunction with lithium and Divalproex, it enhances their long-term prophylactic effects (53). Other atypical antipsychotics have also shown efficacy in treating adult during manic episodes (e.g., Hirschfeld et al. 2004; Keck et al. 2003; Sachs et al. 2002, 2004). Quetiapine is helpful in adolescents with manic

symptoms (53). Regrettably, most atypical antipsychotics cause notable weight gain and sedation as the side effect (54).

V. TREATMENT OF DEPRESSION

Mood stabilizers are used in order to reduce mania (55). However, normal antidepressants are more common for healing depression in bipolar disorder and they must be used alone without mood stabilizers since they may lead to mania and rapid mood swings (56, 57).

Apparently, one study discovered that healing bipolar disorder depressions either by the mixture of taking a mood stabilizer and a selective serotonin inhibitor or the alternative of lithium and divalproex are equally efficacious (48, 53). According to these and other research, the number of researchers suggest the appropriate way of using antidepressants in patients. Even so, the latest study found out that the risk in developing depression into mania would be less in bipolar disorder patients who were treated with mood stabilizers and selective serotonin reuptake inhibitors effectively and also those patients should carry on taking antidepressants after remission in the period of six months (48, 50, 53).

The regulations of modern treatment only advise taking antidepressants in bipolar disorder depression in case that other agents have failed, and need to be taken together with mood stabilizers or atypical antipsychotics. Lamotrigine, one of an efficacious acute and maintenance treatment, used for bipolar disorder and depression (48). Furthermore, this medicine also helps slowing down the relapse in a six-month of rapid-cycling in bipolar disorder II patients who suffered from repeated depressions (13, 48). In the opposite way, the frequent side effects of Lamotrigine can include having a serious skin rash which happens in a small number of patients and also if it was unchecked this can develop to Stevens-Johnson syndrome through HLA-B genes (58, 59).

CONCLUSIONS

Mental disorders have a serious effect on our population and have given quite a lot of people in need and the humanity imperative to reduce

suffering and it is likely to increase every year. Bipolar disorder is a progressive, sometimes dangerous medical condition that often receives no attention and respect to control its course. Bipolar disorder may become more refractive and challenging to treat, like malignant conditions that are not timely handled. Thus, finding scalable mental health treatment to deal with this burden are really crucial for people all over the world. More appropriately and precisely, a fresh cycle of research, academic and public health care will be needed to treat this disease. Because this is unlikely to be reached quickly, specialists should obtain an early detection approach and efficient treatment.

REFERENCES

1. Keynejad R, Spagnolo J, Thornicroft G. WHO mental health gap action programme (mhGAP) intervention guide: updated systematic review on evidence and impact. *Evidence-Based Mental Health*. 2021.
2. Rajan S, McKee M, Rangarajan S, Bangdiwala S, Rosengren A, Gupta R, et al. Association of symptoms of depression with cardiovascular disease and mortality in low-, middle-, and high-income countries. *JAMA psychiatry*. 2020;77(10):1052-63.
3. Silverman ME, Reichenberg A, Savitz DA, Cnattingius S, Lichtenstein P, Hultman CM, et al. The risk factors for postpartum depression: A population - based study. *Depression and anxiety*. 2017;34(2):178-87.
4. Stapelberg NJC, Neumann DL, Shum D, Headrick JP. Health, pre-disease and critical transition to disease in the psycho-immune-neuroendocrine network: Are there distinct states in the progression from health to major depressive disorder? *Physiology & behavior*. 2019;198:108-19.
5. Sekhon S, Gupta V. *Mood disorder*. 2020.
6. Müller JK, Leweke FM. Bipolar disorder: clinical overview. *Medizinische Monatsschrift Fur Pharmazeuten*. 2016;39(9):363-9.
7. Trivedi MH. Major Depressive Disorder in Primary Care: Strategies for Identification. *The Journal of clinical psychiatry*. 2020;81(2).
8. Knight MJ, Baune BT. Cognitive dysfunction in major depressive disorder. *Current opinion in psychiatry*. 2018;31(1):26-31.
9. Ishizaki J, Mimura M. Dysthymia and apathy: diagnosis and treatment. *Depression research and treatment*. 2011;2011.
10. Schramm E, Klein DN, Elsaesser M, Furukawa TA, Domschke K. Review of dysthymia and persistent depressive disorder: history, correlates, and clinical implications. *The Lancet Psychiatry*. 2020;7(9):801-12.
11. MacQueen G, Santaguida P, Keshavarz H, Jaworska N, Levine M, Beyene J, et al. Systematic review of clinical practice guidelines for failed antidepressant treatment response in major depressive disorder, dysthymia, and subthreshold depression in adults. *The Canadian Journal of Psychiatry*. 2017;62(1):11-23.
12. Bayes A, Parker G, Paris J. Differential diagnosis of bipolar II disorder and borderline personality disorder. *Current psychiatry reports*. 2019;21(12):1-11.
13. Karanti A, Kardell M, Joas E, Runeson B, Pålsson E, Landén M. Characteristics of bipolar I and II disorder: a study of 8766 individuals. *Bipolar disorders*. 2020;22(4):392-400.
14. Bobo WV, editor *The diagnosis and management of bipolar I and II disorders: clinical practice update 2017* 2017: Elsevier.
15. Perugia G, Hantouche E, Vannucchia G. Diagnosis and treatment of cyclothymia: the "primacy" of temperament. *Current neuropharmacology*. 2017;15(3):372-9.
16. Benazzi F. Mood patterns and classification in bipolar disorder. *Current Opinion in Psychiatry*. 2006;19(1):1-8.

17. Shapero BG, Weiss RB, Burke TA, Boland EM, Abramson LY, Alloy LB. Kindling of life stress in bipolar disorder: Effects of early adversity. *Behavior therapy*. 2017;48(3):322-34.
18. Prata DP, Costa-Neves B, Cosme G, Vassos E. Unravelling the genetic basis of schizophrenia and bipolar disorder with GWAS: A systematic review. *Journal of psychiatric research*. 2019;114:178-207.
19. Alda M. Bipolar disorder: from families to genes. *The Canadian Journal of Psychiatry*. 1997;42(4):378-87.
20. Sawada T, Chater TE, Sasagawa Y, Yoshimura M, Fujimori-Tonou N, Tanaka K, et al. Developmental excitation-inhibition imbalance underlying psychoses revealed by single-cell analyses of discordant twins-derived cerebral organoids. *Molecular psychiatry*. 2020;25(11):2695-711.
21. McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Archives of general psychiatry*. 2003;60(5):497-502.
22. Stahl EA, Breen G, Forstner AJ, McQuillin A, Ripke S, Trubetsky V, et al. Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nature genetics*. 2019;51(5):793-803.
23. Arman S, Salimi H, Maracy MR. Parenting styles and psychiatric disorders in children of bipolar parents. *Advanced biomedical research*. 2018;7.
24. Weibel S, Menard O, Ionita A, Boumendjel M, Cabelguen C, Kraemer C, et al. Practical considerations for the evaluation and management of Attention Deficit Hyperactivity Disorder (ADHD) in adults. *L'encephale*. 2020;46(1):30-40.
25. Yee CS, Hawken ER, Baldessarini RJ, Vázquez GH. Maintenance pharmacological treatment of juvenile bipolar disorder: review and meta-analyses. *International Journal of Neuropsychopharmacology*. 2019;22(8):531-40.
26. Wei S-Y, Tseng H-H, Chang HH, Lu T-H, Chang WH, Chiu NT, et al. Dysregulation of oxytocin and dopamine in the corticostriatal circuitry in bipolar II disorder. *Translational psychiatry*. 2020;10(1):1-8.
27. Kim S-Y, Kim H-N, Jeon SW, Lim W-J, Kim SI, Lee YJ, et al. Association between genetic variants of the norepinephrine transporter gene (SLC6A2) and bipolar I disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2021;107:110227.
28. Yatham LN, Vieta E, McIntyre RS, Jain R, Patel M, Earley W. Broad efficacy of cariprazine on depressive symptoms in bipolar disorder and the clinical implications. *The Primary Care Companion for CNS Disorders*. 2020;22(5).
29. Mizziou S, Tsitsipa E, Moysidou S, Karavelas V, Dimelis D, Polyzoidou V, et al. Psychosocial treatment and interventions for bipolar disorder: a systematic review. *Annals of general psychiatry*. 2015;14(1):1-11.
30. Pearlson GD. Etiologic, phenomenologic, and endophenotypic overlap of schizophrenia and bipolar disorder. *Annual review of clinical psychology*. 2015;11:251-81.
31. Shen W, Wang Q-W, Liu Y-N, Marchetto MC, Linker S, Lu S-Y, et al. Synaptotagmin-7 is a key factor for bipolar-like behavioral abnormalities in mice. *Proceedings of the National Academy of Sciences*. 2020;117(8):4392-9.
32. Jones GH, Rong C, Shariq AS, Mishra A, Machado-Vieira R. Intracellular signaling cascades in bipolar disorder. 2020.
33. Spiliotaki M, Salpeas V, Malitas P, Alevizos V, Moutsatsou P. Altered glucocorticoid receptor signaling cascade in lymphocytes of bipolar disorder patients. *Psychoneuroendocrinology*. 2006;31(6):748-60.
34. Lopachev A, Volnova A, Evdokimenko A, Abaimov D, Timoshina Y, Kazanskaya R, et al. Intracerebroventricular injection of ouabain causes mania-like behavior in mice through D2 receptor activation. *Scientific reports*. 2019;9(1):1-13.
35. Yu X, Ba W, Zhao G, Ma Y, Harding EC, Yin L, et al. Dysfunction of ventral tegmental area GABA neurons causes mania-like behavior. *Molecular Psychiatry*. 2020:1-16.
36. Lappin JM, Sara GE. Psychostimulant use and the brain. *Addiction*. 2019;114(11):2065-77.
37. Stuhec M, Lukić P, Locatelli I. Efficacy, acceptability, and tolerability of lisdexamfetamine, mixed amphetamine salts, methylphenidate, and modafinil in the treatment of attention-deficit hyperactivity disorder in adults: a systematic review and meta-analysis. *Annals of Pharmacotherapy*. 2019;53(2):121-33.
38. Sikkens D, Riemersma-Van der Lek RF, Meesters Y, Schoevers RA, Haarman BCM. Combined sleep deprivation and light therapy: Clinical treatment outcomes in patients with complex unipolar and bipolar depression. *Journal of affective disorders*. 2019;246:727-30.
39. Barbini B, Colombo C, Benedetti F, Campori E, Bellodi L, Smeraldi E. The unipolar-bipolar dichotomy and the response to sleep deprivation. *Psychiatry Research*. 1998;79(1):43-50.
40. Sardi NF, Tobaldini G, Morais RN, Fischer L. Nucleus accumbens mediates the pronociceptive effect of sleep deprivation: the role of adenosine A2A and dopamine D2 receptors. *Pain*. 2018;159(1):75-84.
41. Volkow ND, Tomasi D, Wang G-J, Telang F, Fowler JS, Wang RL, et al. Hyperstimulation of striatal D2 receptors with sleep deprivation: Implications for cognitive impairment. *Neuroimage*. 2009;45(4):1232-40.
42. Ananth M, Bartlett EA, DeLorenzo C, Lin X, Kunkel L, Vadhan NP, et al. Prediction of lithium treatment response in bipolar depression using 5-HTT and 5-HT 1A PET. *European journal of nuclear medicine and molecular imaging*. 2020:1-12.
43. Jones MT, Strassnig MT, Harvey PD. Emerging 5-HT receptor antagonists for the treatment of Schizophrenia. *Expert opinion on emerging drugs*. 2020;25(2):189-200.
44. Reiche S, Hermle L, Gutwinski S, Jungaberle H, Gasser P, Majič T. Serotonergic hallucinogens in the treatment of anxiety and depression in patients suffering from a life-threatening disease: A systematic review. *Progress in neuro-psychopharmacology and biological psychiatry*. 2018;81:1-10.
45. Lieberman HR, Agarwal S, Fulgoni Iii VL. Tryptophan intake in the US adult population is not related to liver or kidney function but is associated with depression and sleep outcomes. *The Journal of nutrition*. 2016;146(12):2609S-15S.
46. Sobczak S, Riedel WJ, Booij I, Rot MAH, Deutz NEP, Honig A. Cognition following acute tryptophan depletion: difference between first-degree relatives of bipolar disorder patients and matched healthy control volunteers. *Psychological medicine*. 2002;32(3):503-15.
47. Riedel WJ, Sobczak S, Schmitt JAJ. Tryptophan modulation and cognition. *Developments in Tryptophan and Serotonin Metabolism*. 2003:207-13.
48. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Bond DJ, Frey BN, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar disorders*. 2018;20(2):97-170.
49. Mosolov S, Born C, Grunze H. Electroconvulsive Therapy (ECT) in Bipolar Disorder Patients with Ultra-Rapid Cycling and Unstable Mixed States. *Medicina*. 2021;57(6):624.
50. Papiol S, Schulze TG, Alda M. Genetics of lithium response in bipolar disorder. *Pharmacopsychiatry*. 2018;51(05):206-11.
51. Gitlin M. Lithium side effects and toxicity: prevalence and management strategies. *International journal of bipolar disorders*. 2016;4(1):1-10.
52. Amponsah SK, N'guessan BB, Akandawen M, Aning A, Agboli SY, Danso EA, et al. Effect of Cellgevity® Supplement on Selected Rat Liver Cytochrome P450 Enzyme Activity and Pharmacokinetic Parameters of Carbamazepine. *Evidence-Based Complementary and Alternative Medicine*. 2020;2020.
53. Young RC, Mulsant BH, Sajatovic M, Gildengers AG, Gyulai L, Al Jurdi RK, et al. GRI-BD: a randomized double-blind controlled trial of lithium and divalproex in the treatment of mania in older patients with bipolar disorder. *American Journal of Psychiatry*. 2017;174(11):1086-93.
54. Barton BB, Segger F, Fischer K, Obermeier M, Musil R. Update on weight-gain caused by antipsychotics: a systematic review and meta-analysis. *Expert opinion on drug safety*. 2020;19(3):295-314.
55. Solmi M, Fornaro M, Ostinelli EG, Zangani C, Croatto G, Monaco F, et al. Safety of 80 antidepressants, antipsychotics, anti - attention - deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta - review of 78 adverse effects. *World Psychiatry*. 2020;19(2):214-32.
56. Safer DJ. Mood swing and mood stabilizer: how specific are these terms? *Bipolar disorders*. 2010;12(7):685-90.

57. Goldberg JF, Garno JL, Leon AC, Portera L. Rapid titration of mood stabilizers predicts remission from mixed or pure mania in bipolar patients. *The Journal of clinical psychiatry*. 1998;59(4):0-.
58. Sabourirad S, Mortezaee R, Mojarad M, Eslahi A, Shahrokhi Y, Kiafar B, et al. Investigating the association of Lamotrigine and Phenytoin - induced Stevens - Johnson syndrome/Toxic Epidermal Necrolysis with HLA - B* 1502 in Iranian population. *Experimental Dermatology*. 2021;30(2):284-7.
59. Inaba T, Sogawa R, Mizoguchi Y, Tateishi H, Kunitake Y, Kato TA, et al. Lamotrigine Rechallenge in Treatment-Resistant Bipolar Disorder. *The primary care companion for CNS disorders*. 2018;20(2).