Proceedings of the 5th International Conference on Education Innovation and Philosophical Inquiries
DOI: 10.54254/2753-7048/59/20241702

The Transition Between Depressive Episode and Manic Episode During the Treatment of Bipolar Disorder

Jingyun Liu[1,a,*]

[1]*Hebei Medical University, Shijiazhuang, Hebei, 050031, China*
a. j33442510@gmail.com
**corresponding author*

Abstract: Bipolar disorder (BD) is characterized by periodic alternations between depressive and manic episodes. It belongs to a complex group of severe and persistent conditions. This category includes bipolar I disorder (BDI) and bipolar II disorder (BDII). The definition of BDI hinges primarily on the manifestation of a syndromal manic episode. Conversely, BDII is characterized by the occurrence of both a syndromal hypomanic episode and a major depressive episode, which jointly constitute its defining features. BDI is the most common type in clinics. The duration of episodes and the time spent in the manic phases and depressive periods of bipolar disorder are not clearly defined for subtypes of the disorder. This paper analyzes the duration of manic episodes and depressive episodes in bipolar disorder, and explores the switch from major depression to bipolar depression. By analyzing and comparing the data and results in essays, it is still hard to tell the exact duration and the occurrence of the episodes. But the effects of drugs can be summarized during the treatment of bipolar disorders. At the same time, it discovers that during treatment of major depression, bipolar disorder occurs. In conclusion, the duration is different for different people, and it depends on many subjective influences. During treatment of major depression, the transition from major depression to bipolar depression will happen indeed, but the probability is very small. This research may provide a new concern that doctors and scientists should pay more attention to the treatment of such mental diseases and keep an eye on the switch.

Keywords: bipolar disorder, depression, mania, lithium

1. Introduction

Manic depression, which has recently superseded the term bipolar disorder, denotes a mental health condition that is primarily identified by drastic variations in mood. These fluctuations range from heightened emotional states, commonly referred to as mania or hypomania, to depressive lows, widely recognized as depression. Numerous types of bipolar and associated disorders exist, some of which may encompass mania, hypomania, and depression. These symptoms can lead to unpredictable changes in mood and behavior, causing distress and inconvenience in an individual's life.

The frequency of mood swings episodes can vary from infrequent occurrences to multiple instances annually. While the majority of individuals may encounter some emotional symptoms in the intervals between these episodes, there is a subset of individuals who may not experience any such symptoms at all. In a prolonging bipolar illness, without pharmacological interventions, the

DOI: 10.54254/2753-7048/59/20241702

duration of a manic or mixed episode is around several weeks and months, the average days are 3 months. Some episodes may only last for several days, the other episodes can last for more than 10 years. The early research suggested that episodes of depression are much longer than those of mania, but episode duration does not differ among BD diagnostic types.

Despite bipolar disorder being a lifelong condition, individuals can effectively manage their mood fluctuations and other symptoms by adhering to a comprehensive treatment plan. This condition is generally addressed through a combination of medication and psychological therapy. As for the drugs, lithium is used the most frequently, and is known as the gold standard.

It is well known that treatment of lithium will not let the transition happen, whereas transition to mania during treatment of bipolar depression, or transition to bipolar disorder during treatment of major depression may happen.

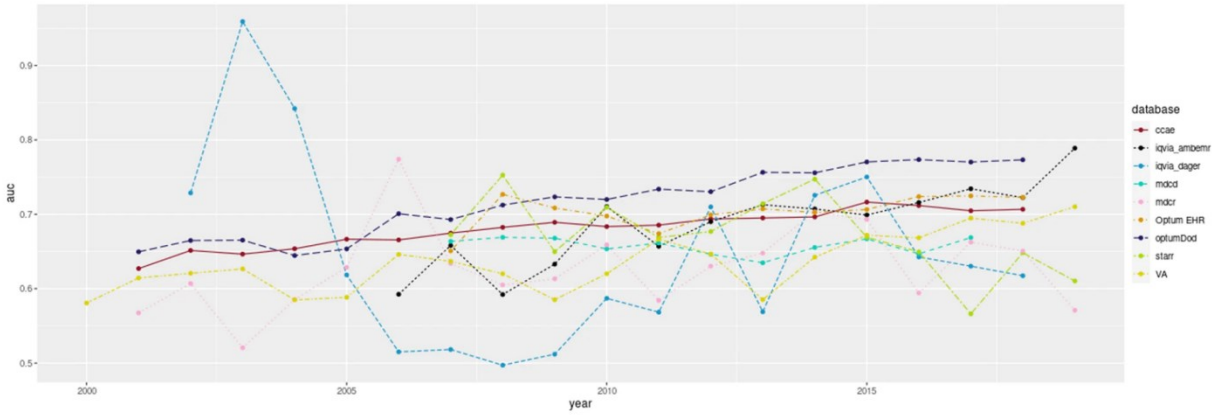
Western countries have conducted many studies. The interval between the onset of psychiatric disorders and the commencement of initial treatment, serving as a proxy for the duration of untreated illnesses, exhibited a marked elongation. So this study analyses the duration and the treatment, in order to focus on the development of bipolar disorder and make contributions to the prevention of the illness.

2. Duration of untreated bipolar disorder

Bipolar disorders represent a complex array of severe and persistent conditions, including bipolar I disorder. Patients with this disorder may have experienced at least one manic episode, which could be succeeded by hypomanic or major depressive episodes. In some cases, the presence of mania can lead to a distortion of reality perception. Moreover, bipolar II disorder is characterized by individuals who have encountered at least one significant depressive episode and one hypomanic episode, though they may never experience a full-blown manic episode. Regarding the cyclothymic disorder, patients typically experience a duration of at least two years, encompassing numerous episodes of hypomania, interspersed with intervals of depressive symptoms. This disorder is characterized by the recurrent nature of these mood fluctuations. When discussing alternative classifications, individuals who encounter bipolar and affiliated disorders that are often induced by specific substances like drugs or alcohol, or they may stem from medical conditions like stroke. These types of disorders demonstrate the multifaceted nature of mental health issues. And in this article, we will only talk about the BDI type.

People often can not recognize BD, and it is easy to be misdiagnosed. Owing to this, bipolar disorder often persists untreated for prolonged duration, resulting in suboptimal clinical outcomes, suicidal tendencies, a heightened risk of rapid cycling, and impaired functional capabilities. This underscores the importance of early intervention and management [1]. So it may be hard to tell when the beginning is. Numerous patients initially diagnosed with major depressive disorder (MDD) often undergo treatment with antidepressants, only to later be reclassified as having bipolar disorder. The implications of this misdiagnosis are the subject of widespread discussion. The exact nature of the relationship between MDD and bipolar disorder remains unclear, with some suggesting that MDD may be a comorbidity or an early stage of bipolar disorder. However, the existence of individual conversion predictors remains inconstant, hindering the timely recognition and treatment of bipolar disorder. To further investigate this issue, a model of (major depressive disorder)-(bipolar disorder) conversion was constructed and tested across a multinational network of patient databases. As illustrated in Figure 1, the model's conduction is evaluated in various databases (training) (validation) [2].

DOI: 10.54254/2753-7048/59/20241702



AUC—area under the curve. CCAE—IBM MarketScan Commercial Claims and Encounters Database (US), IQVIA_ambemr—IQVIA Ambulatory database for US, IQVIA_DAGER—IQVIA database for Germany, MDCD—IBM MarketScan Multi-State Medicaid Database, MDCR—IBM MarketScan Medicare Supplemental Database, Optum EHR—Optum de-identified electronic health record dataset, Optum claims—Optum De-Identified Clinformatics Data Mart Database, STARR—STAnford medicine Research data Repository, VA—US Veterans Administration database.

Figure 1: Performance of predictive model for one-year MDD-BD diagnosis conversion depending on a data recording year [2]

BD always has an acute or subacute onset, and happens at the end of spring and the start of summer. In the early studies, because of the particularity of phyciatric disease, such as the patients' physical health, the patients' growing environment and the subtypes of the illness, it was hard to conduct experiments and researches. Extant research frequently delves into demographic and clinical factors linked to the duration of untreated bipolar II disorder, encompassing variables such as female gender, early onset, depressive presentation, prolonged illness duration, suicide attempts, familial history of bipolar disorder (BD), and co-occurring anxiety disorders. Recent recommendations advocate for replacing the notion of duration of untreated illness with the duration of untreated bipolar disorder, aiming for a more precise conceptualization of the phenomenon [3].

3. The transition from major depression to bipolar disorder with antidepressant interventions

Depression, as commonly understood, is a mood disorder characterized by the persistent manifestation of symptoms such as depressed mood, profound sadness, and diminished interest in daily pursuits, to the extent that it significantly impairs an individual's normal functioning, encompassing their appetite, energy, concentration, and sleep patterns. And we usually call this illness a major depression, for it will be easier for us to distinguish the disorders from normal depression to bipolar depression. Actually there are no obvious differences between the former and the latter. The symptoms are normally the same. When someone is in an acute depressive episode, the symptoms may not be typical, that is to say, may not appear, such as a low mood, slowness of thinking and decreased willingness.

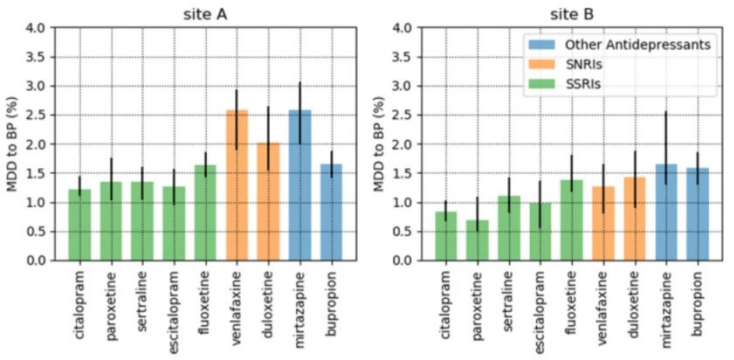
But the duration can be different. Generally speaking, the duration of bipolar depression should at least last for 2 weeks. As for bipolar mania, it can take at least 1 week. The patient may suffer manic episode for only once in the whole life, or it will repeat many times, which highly damages both the patient's physical and mental health.

A model was constructed to classify individuals with a high likelihood of transitioning from a depressive disorder diagnosis to a bipolar disorder diagnosis. This study integrated outpatient clinical data spanning both psychiatric and non-psychiatric practice networks. The participants

DOI: 10.54254/2753-7048/59/20241702

comprised 67,807 individuals who had been diagnosed with major depressive disorder or unspecified depressive disorder, with no prior history of bipolar disorder. Furthermore, these individuals had undergone treatment with at least one of the nine antidepressant medications in question [4]. This study can examine the transfer during the development of illness. The pathogenesis behind bipolar disorder, at the molecular level, can be described as the increase and decrease of serotonin, noradrennaline, dopamine and so on. For instance, increasing the concentration of noradrennaline is the principle of treatment for many antidepressants, but when it reaches one particular level, as the abnormal activity happens in the adrenal medulla, it releases too much noradrennaline, so the symptoms of mania will emerge.

The findings revealed that within three months of commencing antidepressant treatment, 636 individuals (1.49%) from Site A, out of a total of 42,547, and 289 individuals (1.14%) from Site B, out of 25,260, shifted from major depressive disorder to bipolar disorder. Generally, the transition rates were comparable across various antidepressants (Figure 2), with the highest rates noted among non-SSRIs. The transition rates across the two sites were 1.23% for SSRIs, 1.93% for SNRIs, and 1.73% for other antidepressants, demonstrating a significant difference (X2 (2df) = 37.98; p = 5.64e–09) [2]. So it is possible for patients with major depressive disorders to transfer to bipolar disorder during the treatment of antidepressants.



SNRIs serotonin and norepinephrine reuptake inhibitors, SSRIs selective serotonin reuptake inhibitors, MDD major depressive disorder, BP bipolar disorder.

Figure 2: Bipolar rates among all index prescriptions between 2008 and 2017 for different antidepressant categories [2]

Despite efforts in treatment, patients suffering from bipolar disorder can unexpectedly shift directly from episodes of profound depression into manic, hypomanic, or mixed states, regardless of the absence of antidepressant medication. Unfortunately, the intricate interplay of factors that contribute to such transitions in clinical settings is still not fully grasped. In a prior investigation, survival analysis was employed to scrutinize the duration leading to the emergence of manic, hypomanic, or mixed states among 2166 individuals with bipolar I and II disorders who were experiencing a major depressive episode. Before achieving remission, a substantial proportion of 21.3% (461/2166) of subjects experiencing a major depressive episode transitioned to a manic/hypomanic or mixed state. Among those who received antidepressant treatment during the episode, 19.6% (289/1475) also experienced such a transition. Notably, the severity of manic symptoms was positively correlated with the likelihood of manic transition, regardless of antidepressant use. Interestingly, three factors emerged as differential predictors: a history of suicide attempts, an earlier age of onset, and the bipolar subtype. These results underscore the possibility that certain clinical characteristics may heighten the risk of transitioning from depression to mania, yet these factors are not exclusively confined to patients undergoing antidepressant

DOI: 10.54254/2753-7048/59/20241702

therapy. While these individuals may be predisposed to such transitions, a range of variables including individual variations, nursing practices, and living environments also play a role in influencing this switch.

Kraepelin noted that individuals afflicted with bipolar disorder were capable of transitioning directly from depressive states to manic or mixed episodes, without an intervening phase of euthymia [5]. As mentioned before, mania is a mental health condition characterized by intense and persistent feelings of elevated mood, energy, and activity, which can be seen as the opposite of depression. Individuals enduring manic episodes may exhibit rapid thought processes, diminished sleep requirements, and engage in impulsive behaviors such as excessive spending or partaking in high-risk activities. There may be no transitional process between the two episodes of bipolar disorder. Mania can be described as a key feature of bipolar disorder, where individuals alternate between episodes of mania and depression. Early studies suggested that the risk of transitioning to mania may increased by the treatment of monoaminergic antidepressents, or the frequency of cycling may be increased. Prior investigations into patients who is untreated by antidepressant with bipolar disorder, encompassing individuals who were not prescribed mood stabilizers, revealed that a direct transition into manic episodes occurred in approximately 50% of the studied cases [6].

In essence, the study's conclusions highlight that a direct shift to manic episodes is a common occurrence during major depressive episodes among individuals with bipolar disorder. This phenomenon is linked to various risk factors that transcend mere manic or mixed symptoms [7]. Notably, these factors seem to be non-specific to treatment modalities, as they are not exclusively associated with antidepressant therapy. As a result, rigorous monitoring is imperative for all bipolar patients undergoing treatment for depressive episodes.

4. Lithium: preferred medication for bipolar disorder treatment

Bipolar disorder exhibits a notable association with various cellular abnormalities and psychiatric comorbidities, posing a high risk of suicide. The flow of sodium in the body is influenced by lithium through nerve and muscle cells. Sodium contributes to excitement or mania, where manic symptoms encompass rapid speech patterns, hyperactivity, impaired judgment, diminished sleep requirements, aggression, and irritability.

Ever since lithium's capacity to stabilize mood was discovered in 1949 [8], the compound has been extensively employed as the primary therapeutic approach for individuals with BD. Lithium demonstrates efficacy in managing severe episodes of disorders, and it mitigates the likelihood of potential future relapses of manic episodes and depressive states. Additionally, it has been demonstrated to reduce the risk of suicide. In spite of these favorable attributes, the potency of lithium varies greatly, with approximately 30% of treated patients exhibiting a positive response, while over 30% experience no discernible clinical improvement [9]. Moreover, while some patients exhibit significant enhancement with lithium treatment, others prove unmanageable under its administration.

The study is centered on the polygenetic level, as genetic factors are believed to play a crucial role in the individual response to lithium. In their latest study, the researchers adopted a polygenic score (PGS) modeling approach to uncover associations between an inadequate response to lithium and a significant genetic predisposition for major depression, schizophrenia, or a combined meta-PGS encompassing both disorders. Their results were based on the analysis of ConLi+Gen data derived from 2,367 European-descent patients with bipolar disorder who had been through treatment of lithium for at least six months. In total, 660 patients (27.9%) exhibited a favorable response to lithium therapy. Among the 2,362 individuals evaluated for bipolar disorder classification, the majority (80.0%) of the participants were diagnosed with Bipolar Disorder Type I. These patients presented with concurrent comorbid conditions, such as psychotic symptoms,

DOI: 10.54254/2753-7048/59/20241702

alcohol dependency, panic attacks, and obsessive-compulsive symptoms [10]. In conclusion, people with BDI have a greater response to lithium, though the total amount is not as positive as we expected.

5. Conclusion

To sum up, the duration of untreated bipolar disorder, mainly BDI, and depressive episodes are around 2 weeks, and it is hard to tell the exact time of a manic episode. Some can be short, like more than 1 week or up to 1 month, others can be long, like for more than one year. Mixed states are often accompanied, which seriously damage both the patients' physical health and mental health. Due to the misdiagnosis, it is confusing that bipolar depression is usually considered a major depression, hence, the duration of manic and depressive episodes will be difficult to identify.

During the treatment of major depression, there is the possibility that under the intervention of antidepressants, the major depression may switch to bipolar disorder. As for the treatment of BD, lithium is the first choice and gold standard. Those phenomenons can be monitored during the lithium response. There was little evidence showing it may lead to the conversion, but several models were built to identify the change in patients' behaviors and the concentration of substances. One in three individuals who suffer from BD can see the change.

Little is known about the exact duration, the transition from mania to depression, or the transition from major depression to bipolar disorder, the effects of antidepressants or lithium, but we still summarize that it is essential for doctors or researchers to pay more attention to the symptoms of patients who suffers from BD or MDD. So it would be easier for medical workers to prevent the conversion, finally, to release the pain and burden of patients.

References

[1] *Zhang, L., Yu, X., Fang, YR. et al. (2017) Duration of untreated bipolar disorder: a multi-center study. Sci Rep 7, 44811. https://doi.org/10.1038/srep44811*

[2] *Nestsiarovich, A., Reps, J.M., Matheny, M.E. et al. (2021) Predictors of diagnostic transition from major depressive disorder to bipolar disorder: a retrospective observational network study. Transl Psychiatry 11, 642. https://doi.org/10.1038/s41398-021-01760-6*

[3] *Pradier, M.F., Hughes, M.C., McCoy, T.H. et al. (2021) Predicting change in diagnosis from major depression to bipolar disorder after antidepressant initiation. Neuropsychopharmacol. 46, pp.455–461. https://doi.org/10.1038/s41386-020-00838-x*

[4] *Perlis, R., Ostacher, M., Goldberg, J. et al. (2010) Transition to Mania During Treatment of Bipolar Depression. Neuropsychopharmacol 35, 2545–2552. https://doi.org/10.1038/npp.2010.122*

[5] *Kraepelin E (1899). Psychiatry: A Textbook for Students and Physicians, Sixth Edition. Translated by Helga Metoui. (Originally published as Psychiatrie. Ein Lehrbuch fur Studierende und Arzte. Leipzig: Johann Ambrosius Barth, 1899). Science History Publications: Canton, MA.*

[6] *Calabrese JR, Rapport DJ, Kimmel SE, Shelton MD (1999). Controlled trials in bipolar I depression: focus on switch rates and efficacy. Eur Neuropsychopharmacol 9 (Suppl 4): S109–S112.*

[7] *Frye M.A., Helleman G., McElroy S.L., Altshuler L.L., Black D.O., Keck Jr PE et al. (2009). Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. Am J Psychiatry 166: 164–172.*

[8] *Cade J.F. (1949) Lithium salts in the treatment of psychotic excitement. Med J Aust. 2:349–52.*

[9] *Garnham J., Munro A., Slaney C., Macdougall M., Passmore M., Duffy A., et al. Prophylactic treatment response in bipolar disorder: results of a naturalistic observation study. J Affect Disord. 2007;104:185–90.*

[10] *Amare, A.T., Thalamuthu, A., Schubert, K.O. et al. Association of polygenic score and the involvement of cholinergic and glutamatergic pathways with lithium treatment response in patients with bipolar disorder. Mol Psychiatry 28, 5251–5261 (2023). https://doi.org/10.1038/s41380-023-02149-1*