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Bipolar Disorder and Antidepressant Associated Hypomania

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Abstract: The impact of antidepressant associated hypomania on monomanic depression and its relationship to bipolar disorder. This review attempts to investigate and review current research on bipolar disorder diagnosis, the neurobiological mechanisms of antidepressant-associated hypomania, risk factors, and how to manage the occurrence of this condition. Bipolar disorder is a widespread, debilitating, recurrent, variable-severity mental health condition in which the patient exhibits two different states and unpredictable mood switching. Mania, hypomania, mixed states, depression, and depression interspersed with moments of relative health are the stages of the disorder. Early identification of bipolar disorder can improve prognosis. Patients with monophasic episodes are uncommon, as the clinical manifestation of bipolar illness is unpredictable. Throughout their lives, individuals with bipolar disorder alternate between episodes of mania or hypomania and depression. Depressive episodes in bipolar disorder are referred to as bipolar depression, and the underlying core symptom is depressed mood, which are essentially identical to the diagnostic criteria and clinical symptoms of uniphasic depression, so there is a high risk of misdiagnosis during the initial visit. Patients often choose to seek specialist help during depressive episodes, and this can lead to a tendency to overlook whether a patient has bipolar disorder. Antidepressant monotherapy is contraindicated for hypomanic episodes. Antidepressants tend to induce hypomanic and manic episodes, a phenomenon known as antidepressant-associated hypomania (AAH). All antidepressant drugs may cause mania. One is drug induced mania; The other is considered a potential bipolar disorder. There is a high co-occurrence of psychiatric disorders, but only bipolar disorder, monophasic depression, and antidepressant-induced hypomanic episodes are discussed here.

Keywords: bipolar disorder, depression, major depressive disorder, unipolar depression, antidepressant-associated hypomania

1. Introduction

In recent years, there has been an increase in the amount of research on bipolar disorder and depression. The topic of depression has been divided into monophasic depression and bipolar depression, which refers to depressive episodes associated with bipolar disorder.

Bipolar disorder is a psychiatric disorder with a high relapse rate that requires patients to take medication for the rest of their lives. People suffering from bipolar disorder experience intense mood swings that last anywhere from a few days to a few weeks. These moods are classified as manic,

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hypomanic, or depressive. There are, however, usually periods of calm. Bipolar disorder is currently divided into three subtypes: Type I bipolar disorder, Type II bipolar disorder, and, only in recent years, cyclothymic disorder, which has been identified by some scholars as Type III bipolar disorder. Regarding the diagnosis and classification of Type III bipolar disorder, however, there is still some controversy. It is affects more than 1% of the world's population, regardless of nationality, race, or social standing, and the rates of death and disability are rising annually. Bipolar disorder's cognitive impairment contributes significantly to the mortality rate, particularly suicidal behavior. As the diagnosis of bipolar depression is very similar to that of monophasic depression, there is still a great deal of uncertainty in the diagnosis of bipolar disorder [1]. As a result, misdiagnosis is common, and some patients do not view the increase in energy and mood as a disorder and may even be more inclined to accept and acknowledge the occurrence of this state. For this disorder, no validated biomarkers have been identified.

Current research indicates that roughly half of all cases of bipolar disorder occur in people with major depressive disorder (MDD). Numerous patients demonstrate a transition from severe and markedly depressed mood to uncontrollable or even harmful and disruptive manic or hypomania episodes. In patients with major depressive disorder, 8.18 percent of antidepressant medication is correlated with the emergence of a manic response. However, there is still considerable clinical uncertainty regarding the diagnosis and comprehension of depressive episodes in bipolar disorder patients. How antidepressant-related mood transitions or the first manic episode following antidepressant use relate to the diagnosis of underlying bipolar disorder remains unclear [2].

A related study known as antidepressant-associated hypomania (AAH) is now a hot topic when it comes to the diagnosis of monophasic and bipolar depression. Antidepressants have a tendency to destabilise mood and may lead to manic or hypomanic episodes, a phenomenon known as AAH. The existence of this condition has led to controversy over the use of antidepressants in bipolar patients. Some reviews have defined AAH as the first manic episode in patients diagnosed with monophasic depression, shortly after receiving antidepressant medication, who have not been diagnosed or identified with any manic-related tendencies prior to taking the medication [3].

This literature review seeks to integrate and summarize recent research findings on bipolar disorder and hypomanic episodes induced by antidepressants.

2. Bipolar Disorder

2.1. History of Bipolar Disorder

In 1851, the French psychiatrist Jean-Pierre Falret published an article describing a disorder he termed la folie circulaire, which is characterized by cycles of manic euphoria and depression. This is believed to be the earliest diagnosis of bipolar disorder ever recorded. Coincidentally, in 1854, Jules Baillarger, also a French psychiatrist, described a mental disorder that manifested as a double episode of mania and depression in a single patient, a phenomenon he regarded folie à double forme, which was regarded as hopeless and incurable at the time. These two psychiatrists have made the most significant contributions to the definition and diagnosis of modern bipolar disorder [4].

2.2. Risk Factor and Epidemiology for Bipolar Disorder

Bipolar disorder is a multifactorial disorder that includes severe mood disorders, neuropsychological deficits, immune and physiological changes, and functional impairment. As mentioned above, the etiology of the disorder is unclear, but in the last decade, a growing number of findings point to gene-environment interactions and cyclothymic as characteristics that possess a predisposition to bipolar disorder. The prevalence of bipolar disorder varies from country to country. Race, cultural variables, educational level, and diagnostic criteria may all play a role in explaining this disparity.

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Some studies have found that the prevalence of manic episodes and type 1 bipolar disorder is higher in men, while the prevalence of type 2 bipolar disorder is higher in women. The available research does not suggest a correlation between the prevalence of bipolar disorder and gender or ethnicity, however more women than men have the disease overall [1].

2.2.1. Environmental and Family Factors

Some studies suggest that genetic and environmental factors play a significant role in the pathogenesis of bipolar disorder and depression, although their causes remain unknown. Most studies acknowledge that genetic factors play a significantly larger role in bipolar disorder. Twin studies indicate a consistency of between 40% and 70% for monozygotes and a lifetime risk of 5 to 10% for close relatives of people with bipolar disorder, which is approximately seven times that of the general population [5]. Several research have indicated that relatives of people with bipolar disorder are more likely to develop monophasic depression than people with bipolar disorder themselves, indicating both a genetic risk and a rate of mental illness co-morbidity. Environment and family have significant variables in addition to genetics. Environmental variables including stress, sleep issues, alcoholism, or drug abuse can further exacerbate symptoms in those who are predisposed to them [5].

Childhood maltreatment is a high-risk environmental factor for bipolar illness, and that it is also largely responsible for the development of many other psychiatric disorders that manifest in adulthood. Bipolar disease has been demonstrated to be highly linked to childhood emotional neglect and physical, sexual, and emotional abuse. Compared to controls, those with bipolar disorder are four times more likely to have experienced emotional abuse. Abuse in childhood has even been linked to an increased incidence of depressive episodes and bipolar disorder, indicating a direct connection between childhood trauma and mental disease. Moreover, patients who have been physically or psychologically abused as children tend to exhibit more severe clinical symptoms, including more severe mood episodes, more frequent mood shifts, and even more frequent instances of suicide and substance abuse. Considered as a whole, childhood abuse reinforces its status as a probable cause of bipolar disorder and other severe mental disorders [5].

2.2.2. Genetic Factors

Generally, mood disorders were believed to be caused by imbalances in monoaminergic neurotransmitter systems, such as the 5-hydroxytryptaminergic, noradrenergic, and especially the dopaminergic neurotransmitter system in bipolar disorder. In general, it is believed that abnormalities in monoaminergic neurotransmitters induce mood disorders. systems, such as the

5-hydroxytryptaminergic, noradrenergic, and especially the dopaminergic neurotransmitter system, are implicated in bipolar illness. Other processes that may disrupt neuronal interconnectivity include mitochondrial failure and endoplasmic reticulum stress, neuroinflammation, oxidation, apoptosis, and epigenetic modifications, including histone and DNA methylation.

The advancement of technology enables researchers to study related genes. Multiple gene loci closely associated with bipolar disorder have been identified and characterized by some research; however, the mechanism by which the presence of these gene loci translates into disease risk remains to be investigated. Some studies have identified BDNF as a potential biomarker in relation to the pathogenesis of bipolar disorder, which has been strongly suspected to involve BDNF. The fact that BDNF plays a significant role in the neurodevelopment of the central nervous system makes it an intriguing possible gene linked to bipolar disorder. Bipolar disorder may be associated with Val66Met polymorphisms in the BDNF gene, according to some earlier research, in major part [6]. Numerous medications for bipolar disorder act on calcium channels or GABA receptors, indicating that the disease's neurobiology may be involved. However, additional research is ongoing.

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A number of genes and environmental factors have been found to interact to cause bipolar disorder, and as genetic research techniques continue to advance, more and more associations are being discovered, with many different genes and environmental interactions leading to an increased propensity to cause bipolar disorder. However, additional research and understanding of the specific causes of this condition are still required to more effectively implement interventions and treatments.

2.3. Diagnosis of Bipolar Disorder

There are three distinct types of bipolar disorder, each representing a distinct tendency to experience episodes. Regardless of type, sufferers exhibit an unpredictable, erratic mood swing between two extreme emotions.

Type I Bipolar Disorder

Typically, type I bipolar disorder is diagnosed when a person shows manic episodes, even though at this stage the person does not exhibit symptoms of a depressive episode. However, type I bipolar disorder is defined because the majority of patients will eventually exhibit depressed episodes. Some patients with type I bipolar disorder also experience depressive episodes, however these are often milder and shorter in duration than manic episodes, as well as times of relative emotional stability and neutrality [7].

The following are typical symptoms of a manic episode:

• The patient feels significantly more energized and at an incredibly high level compared to previously, and he or she appears to have an endless supply of energy. Feel even more potent than everyone else.

• Reduced need for sleep, requiring extremely little sleep, or even going days without sleep while being energetic.

• There is a discernible rise in speaking velocity and an influx of unrestrained thoughts.

• Increased irritability, restlessness, and hazardous behavior.(High-risk sexual behavior, unrestrained spending, disputes and even physical altercations with other individuals).

• Feeling very complacent and happy. Even patients who have been diagnosed still feel completely healthy at this time and do not need any medical assistance.

When these symptoms grow severe enough to interfere with work, education, and daily life, early treatment is necessary to guarantee the patient's and others' safety.

Type II Bipolar disorder

A patient must have experienced at least one severe depressive episode and one hypomania episode in order to be diagnosed with Type II bipolar disorder. This means that, in contrast to Type 1, which can be diagnosed even if only one symptom is manic, Type 2 must have periods of both mania and depression in order to be identified as Type 2 bipolar disorder. In general, Type 2 bipolar disorder is more likely to be characterized by sever depressive episodes, while manic symptoms are typically modest [7].

However, the diagnostic criteria for depressive episodes in bipolar disease are remarkably similar to those for unipolar depression, and that is reason about many people with Type 2 bipolar disorder are incorrectly diagnosed with unipolar depression. The majority of individuals with this disease will seek treatment after experiencing a significant depressive episode, as hypomania typically has no effect on life, school, or work, and can even boost learning and productivity and make the patient feel happier [8].

Type III Bipolar disorder

Also called cyclothymia. Type III bipolar disorder is not its official term because it has not yet been identified as a genuine mental illness. It is less severe than type I bipolar disorder and type II bipolar disorder because the severity of depression and mania is significantly less than that of

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clearly-defined bipolar disorder and neither the duration nor the severity of the attack is sufficient to meet the diagnostic criteria [9].

Currently, some feel that cyclothymic is a subtype of bipolar illness marked by chronic symptoms comparable to those of mild depression and hypomania. Cyclothymic is a psychopathological risk factor that may increase the likelihood of developing bipolar disorder types I and II in the future [10].

2.4. Treatment for Bipolar Disorder

Early detection and therapeutic intervention for bipolar disorder can improve the prognosis, and after treatment, the majority of individuals are able to maintain a relatively stable mental state. As with the majority of mental diseases, the maintenance of bipolar disorder involves medication and psychotherapy. Medication is an essential component of the treatment for bipolar disorder, as it helps patients

maintain a more stable mental state for social reintegration,the risk of medical and cardiovascular diseases, such as diabetes or metabolic syndrome, and the associated mortality rate are several times higher for people with bipolar disorder than for those with other mental disorders or the general population. Psychotherapy, on the other hand, can improve patients' incorrect perceptions, assist them in returning to their daily lives and work, assist them in coping with their illness, and improve their medication compliance. The use of modified electroconvulsive therapy (MECT) may potentially be considered for more severe and extreme instances. Lithium carbonate and valproate are the most often used medications to treat bipolar disorder. These medications assist patients maintain a stable mood and eliminate extreme highs and lows [11]. Due to the high incidence of relapse associated with bipolar disorder, continuing preventative treatment is frequently advised in clinical practice, even if the patient has significantly improved [11]. Therefore, long-term medication use necessitates regular monitoring of blood glucose, blood lipids, and liver and kidney functions [2].

Antidepressant monotherapy is not permitted in people diagnosed with Type 1 or Type 2 bipolar disorder. The treatment of bipolar depression remains a major issue for psychiatrists, and the use of antidepressants is the subject of great disagreement.

3. Antidepressant Associated Hypomania (AAH)

In a recent article, the authors identified AAH as the onset of symptoms of mania or hypomania shortly after a patient is treated with antidepressants as monophasic depression or with increased doses of medication, in the absence of a previous diagnosis of bipolar disorder [3]. The scientists determined that AAH is more prevalent among women, younger individuals, and those with a family history of the disorder. Similar to stimulants, antidepressants have a propensity to destabilize mood, resulting in hypomania in several instances. Approximately one-quarter to one-third of individuals with bipolar illness may be predisposed to bipolar disorder brought on by antidepressants. Bipolar disorder is strongly inherited in patients with the disease [11].

AAH is defined as a pharmacogenic, reversible condition that decreases or disappears after discontinuation of medication; whose manic symptoms occur only when treated with antidepressants; classified as one of the three major subtypes of bipolar disorder; where the antidepressant converts monophasic depressive disorder into bipolar disorder; and has an underlying predisposition to bipolar disorder or is only a coincidental phenomenon, unrelated to antidepressant treatment [3].

3.1. Antidepressants

An link between antidepressants and manic episodes has been demonstrated by preliminary research. In one article, the manic conversion rate with antidepressants in monophasic depression was 0.4%-11%; in bipolar depression, the manic conversion rate with antidepressants was as high as

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2.2%-70%; and in the placebo group, it was 0.21-0.9%. It is evident that the use of antidepressants considerably increases the likelihood of depressed patients experiencing manic episodes [12]. In previous research, SSRI antidepressants appeared to increase the risk of mania in patients with monophasic depression by two to three times relative to placebo, whereas tricyclic antidepressants appeared to increase the conversion to bipolar depression by two to three times relative to placebo [13].

Presently, the incidence of AAH with SSRIs is quite low, but research on the probability of mania induced by pentazocine norepinephrine reuptake inhibitors are scarce, with only one study indicating 0.15% likelihood of conversion to mania in patients treated with citalopram [14]. Due to the numerous controversies surrounding the diagnosis of bipolar subtypes, the treatment of bipolar depression, and the limits of numerous research, it is currently impossible to create information that is both comprehensive and reliable. In general, however, selective, more targeted drugs like SSRIs are less likely to cause AAH, whereas antidepressants that target numerous monoamine systems are more likely to cause AAH [3].

3.2. Neurobiology

At now, it is believed that the emergence of AAH is due to the potential for unconscious activation of the dopamine system. A manic state is generated when stimulant-like effects occur. On the other side, some antidepressants may lose their specificity following prolonged usage or increased dosage, resulting in mania or a continuous state of elevated mood in patients. Reducing or discontinuing the drug's use, or adding a mood stabilizer such as lithium, is the primary course of action in this scenario [15].

3.3. Treatment of AAH

As AAH in some patients may be caused by a pharmacogenic side effect of an antidepressant (e.g., related to the dose or duration of medication), AAH caused by a drug-induced state is not entirely consistent with a conventionally diagnosed bipolar disorder. Therefore, when dealing with patients who are strongly suspected of having AAH, it is essential to reconsider and determine whether the patient has an unrecognized predisposition to bipolar disorder and to rule out the possibility of previous manifestations of manic symptoms or cyclothymic disorder. Also worthy of consideration are environmental disturbances, alcohol or drug dependence, and sleep disorders. Identification of important risk factors and the correct use of mood stabilizers (especially lithium) can minimize the unsettling side effects of antidepressant use in patients with this tendency or who have been identified as having bipolar disorder [11].

4. Conclusions

Concerning how to accurately diagnose bipolar disorder and differentiate between cyclothymic disorder and pharmacogenetic bipolar disorder, there is still considerable uncertainty and controversy. When interacting with potential patients, researchers need to conduct additional research, and clinicians need to exercise greater care and attention. Any of the currently available antidepressants may cause monophasic depression to convert to bipolar disorder; however, the probability of bipolar disorder varies between different types of antidepressants acting in different populations, and the clinical presentation of patients with AAH is very similar to that of patients with bipolar disorder, thereby increasing the possibility of misdiagnosis. Therefore, additional research and discussion are required to determine whether AAH should be recognized as a new subtype of bipolar disorder or discussed as a separate disorder.

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