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Review Article

Bipolar Disorder: Diagnosis, Pathophysiology and Therapy

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Abstract

Bipolar disorder is a mental illness that causes dramatic shifts in a person's mood, energy and ability to think clearly. People with bipolar experience high and low moods-known as mania and depression-which differ from the typical ups-and-downs most people experience. People often undergo lack of energy to sometimes their energy levels touching the zenith. The person is sometimes in the feeling of sudden guilt and sometimes in the feeling of inflated self-esteem.

There are various symptoms that can be observed in a person and can be noted in order to diagnose the bipolar disorder in a person. Certain depression episodes prolong stress or anxiety, mania and hypomania can lead to bipolar disorder. The various neurological disorders can also be responsible for the cause of the disease. The neurotransmitter imbalance is one of the major causes of the bipolar disorder. Other major causes are the genetic and environmental factors which also lead to the formation of this syndrome in a person.

The need of absolute and perfect medication for the bipolar disorder is the foremost priority. No research or study could find out the exact treatment for the bipolar disorder. Treatment is usually lifelong and often involves a combination of medications and psychotherapy.

Keywords: *Bipolar Disorder; Stress; Mania; Hypomania; Depression; Catechol-O-methyltransferase*

Introduction

Bipolar disorder is a chronic, relapsing illness characterized by recurrent episodes of manic or depressive symptoms, with intervening periods that are relatively (but not fully) symptom-free [1]. It can commence during teenage or in beginning of adulthood. The mood ranges in a very unusual manner during bipolar disorder (Figure 1). It's on fall may occur later in life too. Bipolar Disorder (BD) is a severe and disabling condition characterized by recurrent episodes of depression, mania and mixed states often complicated by residual symptoms once the main episode has resolved [2].

The bipolar disorder has two major groups. They are bipolar disorder I and bipolar disorder II. Depression episodes and mania persists during bipolar disorder I. On the other hand in bipolar disorder II, hypomania and depression episodes prevail. Therefore, the main distinction between the 2 types is the severity of manic symptoms: full mania causes severe functional impairment, can include symptoms of psychosis, and often requires hospitalization; hypomania, by contrast, is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization [3]. The lifetime prevalence of BD-I is estimated at 1% of the adult population,

Figure 1: *Ranges of mood during bipolar disorder.*

and BD-II seems to affect about 0.4% of adults [4]. The lifetime prevalence of bipolar disorder in adults in the United States is reported to be 3.9% [1].

Treatment recommendations for BD emphasize the need for long-term psychopharmacological treatment combined with psychosocial interventions [5]. One of the fundamental obstacles in the prevention of BD is insufficient knowledge pertinent to causative, pathophysiological and protective factors. A greater understanding of how different etiologic factors interact to affect brain cells, circuits and structures is critical to the advancement of mood disorder prevention research [6]. Most patients with BD present initially to primary care providers, but- through a lack of resources or expertise-many do not receive an adequate evaluation for possible bipolar diagnosis [7]. Patients with BD are also likely to have other psychiatric and medical co-morbidities, and, therefore, rely on their primary care provider for holistic care [8].

The duration of mood episodes is highly variable, both between patients and in an individual patient over time, but, in general, a hypomanic episode may last days to weeks, a manic episode lasts weeks to months, and a depressive episode may last months to years [9]. This article discusses the pathophysiology of bipolar disorder and what all different therapies are there being used to deal with it. We shall discuss about different types of treatment that have evolved for the treatment of the Bipolar Disorder over the years and the procedures that are being followed along with them. We comprehensively study all the methods and known studies that have been developed in the treatment of this disorder.

Diagnosis of bipolar disorder

Patients with BD experience recurrent episodes of pathologic mood states, characterized by manic or depressive symptoms, which are interspersed by periods of relatively normal mood [10]. Primarily because unipolar depression (i.e. MDD) is more common than bipolar depression, and because bipolar depression lacks pathognomonic features, bipolar disorder is often incorrectly identified as MDD [11]. Among patients who are eventually diagnosed with bipolar disorder, approximately 70% reportedly had an initial misdiagnosis and more than 33% remained misdiagnosed for 10 years or more [12]. Women with bipolar disorder type II often face delay in diagnosis. The reason is that the hypomania symptoms are not common in them as compared to men.

There are certain categorical approaches that can be used to identify BD by examining the symptoms of mania or hypomania. Symptoms must be severe enough to impair function markedly or require hospital admission to prevent harm to self or others [13]. These

symptoms include:

- Not taking proper sleep
- Thinking too high of oneself
- Rapidly shifts between conversation topics
- Engage in movements that serve no purpose
- Garrulousness
- Too much distracted.

Screening each patient for a history of mania and hypomania (Figure 2) on their initial presentation of depressive symptoms is an early step toward the recognition of bipolar disorder [1]. Clinical screening can be supplemented with electronic health record (EHR)-based case findings, in which information collected by self-report or a healthcare assistant is entered into the EHR and is screened for possible indicators of bipolar disorder [14]. These tools help to ensure that the clinician recognizes patients who are more likely to have bipolar disorder, help assist in directing the clinical interview, and can encourage active follow-up for any emerging symptoms of bipolar disorder [15].

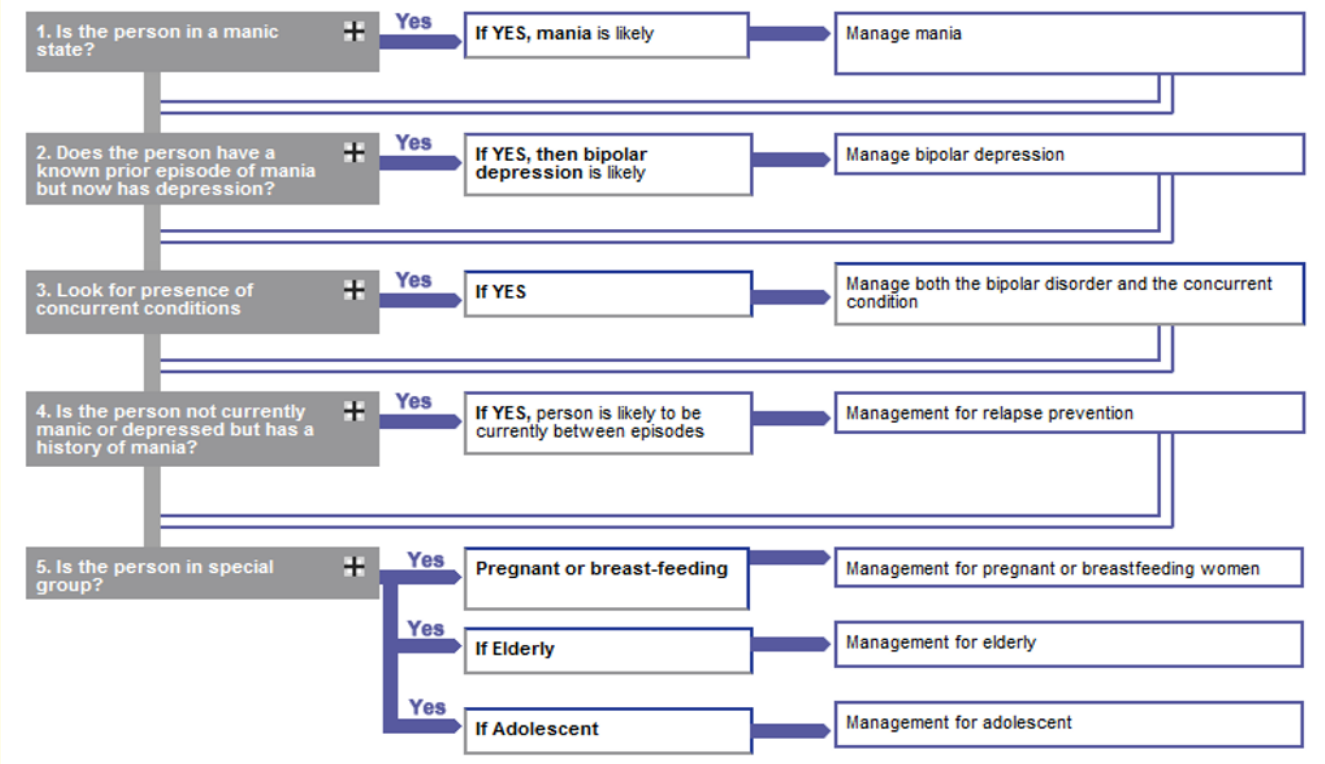

Figure 2: *Identification of bipolar disorder (Source: https://www.paho.org/mhgap/en/bipolar_flowchart.html?reload).*

Certain symptoms of depression can also be used to identify the BD in an individual. Symptoms must be severe enough to cause significant distress or impairment in social, occupational or other important areas of functioning [13]. Some of the depression symptoms include:

- Lack of sleep.
- Very little or negligible involvement in mot activities.
- Mood is depressed.
- Weight loss or gain, irrespective of any significant medical issue.
- Not feeling worthy of oneself.
- Lack of sleep.
- Feeling restlessness or fatigue.
- Not being able to take decisions properly.
- Feeling of too much guilt.
- Attempts of suicide or having thoughts of death.

If at least four mood episodes occur within a year in a person then it is known as "rapid cycling". It is necessary to diagnose rapid cycling in a person as they respond less to the treatment. They need immediate special care and should be marked as 'red flag'.

Pathophysiology of bipolar disorder

The pathophysiology of BD is still not completely known. Genetic studies show that BD is a heritable disorder. Heritability estimates as high as 85% have been obtained [16]. BD Parents have four times more tendency to transmit BD disorder in their children than the normal parents. However, the risk to children of BD parents of developing a non-BD psychiatric disorder (for example, attention deficit hyperactivity disorder) is 2.7 times greater than the risk to children of healthy parents [17]. Thus, a proportion of the familial risk (through either genetics or family environment) is not specific to BD illness [18]. Adoption studies, although few in number, confirm the importance of heritability in BD and unipolar depression [19].

Although once thought genetically distinct, new research indicates a partial overlap in the susceptibility genes for BD and schizophrenia [20]. The catechol-O-methyltransferase (COMT) gene, which is responsible for controlling the metabolism of dopamine in the prefrontal cortex, appears to be associated with both schizophrenia and BD [21]. Norepinephrine, dopamine, and serotonin are the three major neurotransmitters that are responsible for the disorder of mood (Figure 3).

A failure of regulation of a neurotransmitter noradrenaline (NA) is currently implicated in depression/depression episodes [13]. More recent evidence, however, has reported that normal or elevated levels of NA activity are evident in depression, suggesting that the situation is more complicated [22]. For symptom stabilization, the time course of drug responses shows more changes in receptor sensitivity as compared to shifts in absolute neurotransmitter levels [23]. To produce symptoms of mood disorders, it is widely believed that the deficits in other neurotransmitter systems such as GABA and Substance P are interacted by the dysregulation in dopamine and serotonin systems [24].

It can be observed that people suffering from BD even in the absence of increased binding of dopamine to the receptors tend to show pronounced behavioral effects to amphetamine [25]. Some theories place emphasis on links between mood disorders and dopamine receptors within specific regions of the brain believed to be involved in reward motivation, including the nucleus accumbens, the ventral tegmentum, and the striatum [26]. Behavioral sensitization refers to the finding that organisms exposed to repeated intermittent doses of psychomotor stimulants become more responsive to their effects, given certain conditions of intermittency and dosage [27]. This increased sensitivity may be a result of the enhanced sustained release of dopamine [28], particularly within pathways involved in modulating reward motivation [29].

Drugs for bipolar disorder

The treatment of Bipolar disorder includes psychosocial therapies as well as pharmacotherapy. Currently available psychosocial treat-

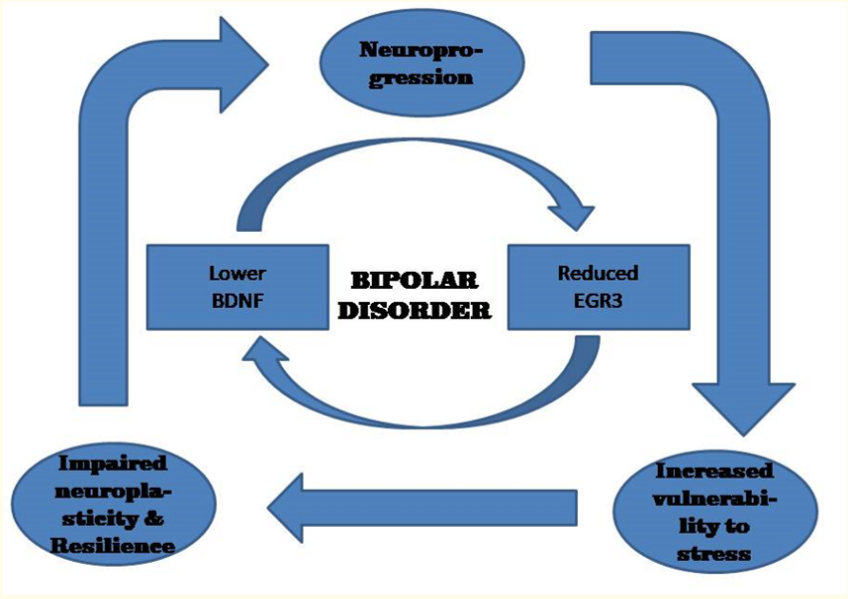

Figure 3: *Pathophysiology of bipolar disorder.*

ments differ in their presumed mechanisms of action, whether they are initiated during the period after an episode or after a period of remission and whether they are delivered in individual versus group modalities [17]. To successfully deal with the patients of bipolar disorder, the pharmacological treatment is necessary. Few medical classes of drugs that are used to treat the bipolar disorder are mood stabilizers, atypical antipsychotics and conventional anti-depressants [30].

Mood stabilizers

The first agent to be used in the treatment of bipolar disorder was lithium. Although it has many limitations, including a delayed onset of action in the treatment of acute mania, limited efficacy in the treatment of bipolar depression, and a narrow therapeutic window, lithium still has an important role today [11,31]. The most commonly used mood stabilizer is Sodium valproate. It has a more rapid onset of action than lithium for the acute treatment of mania, and was superior to placebo as an acute therapy in the largest study performed to date [11], but the evidence for its efficacy as a maintenance treatment for mania is not so robust [32]. The table below (Table 1) represents the list of all mood stabilizers that are recommended as per the condition of the patient (Source: https://psycheducation.org/treatment/mood-stabilizers/).

Atypical antipsychotics

The atypical antipsychotics were developed in the modern era of psychopharmacology; all agents in this class have been studied by randomized controlled trials in the treatment of BD [53]. However, very few atypical antipsychotics have shown efficacy for the treatment of Bipolar disorder. Only quetiapine (immediate-release [IR] and extended-release [XR] formulations) has proven efficacy as monotherapy for treating acute depressive episodes of BD I or BD II [55,56]. A recent meta-analysis of trials of the atypical antipsychotics in maintenance treatment concluded that aripiprazole, olanzapine, quetiapine (IR or XR), and risperidone LAI monotherapy were statistically superior to placebo for treating manic or mixed episodes, while quetiapine alone was also significantly effective against recurrence of depressive episodes [57].

Medication	Why you might choose it	References
Lamotrigine/Lamictal	• Depression is the dominant symptom • Rapid cycling • Need all the antidepressant you can get • Afraid of weight gain	[33,34]
Low-dose lithium	• Lamotrigine alone not sufficient • Need all the antidepressant you can get • Suicide risk is a concern (not full dose lithium; that's practically a different drug)	[35,36]
Quetiapine/Seroquel	• Depression and agitation are both severe • Severe sleep problems • Anxiety is a significant symptom also • No family history of diabetes	[37,38]
Divalproex/Depakote	• Need something strong and fast • Male (so not at risk of PCOS) and not afraid of weight gain • Rapid cycling • Significant manic or mixed state symptoms	[36,39]
Carbamazepine/Tegretol	• Rapid cycling • Severe sleep problems • Can't take divalproex (e.g. female, or afraid of weight gain risk) • Depression is not the main problem: cycling or agitation	[40,41]
Olanzapine/Zyprexa	• Emergency-level symptoms • Need help really fast • Can use on "as-needed" basis • (If you continue to use it regularly) Not afraid of weight gain	[42,43]
Oxcarbazepine/Trileptal	• Milder symptoms, can risk a using a probably-weaker agent • Significant manic symptoms • Alternative to divalproex as a starting place • Slightly lower long-term risk appealing	[44,45]
Omega-3 fatty acids/fish oil	• "Natural"; most common problem is "seal burps" (put the pills in the fridge) • Milder symptoms, can risk a weaker agent • You want to add a possible mood stabilizer without adding more medication • Depression is a major symptom • Willing to multiple pills, or swallow (flavored) fish oil	[46-48]
Lurasidone	• Most expensive of all, for a few years yet • Clearly helps in mixed states; yet not always, and occasionally induces manic symptoms • Not as weight-neutral as the manufacturer wants you to think	[49,50]

Clozapine	• Tried everything else • Severe symptoms • Ready for major weight gain, weekly blood tests • Ready for one of the most effective medications we have	[51,52]
Atypical antipsychotics	Low-dose boosters for specific problems (as add-ons to "real" mood stabilizers?) • Quetiapine: For sleep and agitation; has weight gain risk • Risperidone: For elderly, at very low doses; or BPI perhaps - tricky antidepressant effects in some • Aripiprazole: Strong antimanic. At low doses it's more like an antidepressant; seems like it can induce subtle mixed states, and can be hard to stop • Ziprasidone: No clear role; but hey, it causes less weight gain than olanzapine, and really helps an occasional patient (lurasidone got it's own category above as it's pretty clearly different)	[53,54]

Table 1: *Mood stabilizers.*

The table below (Table 2) represents the suitable drug for a particular condition as stated by the FDA.

Generic Name	Trade Name	Manic	Mixed	Maintenance	Depression	References
Valproate	Depakote	X				[58,59]
Carbamazepine extended release	Equestro	X	X			
Lamotrigine	Lamictal			X		
Lithium		X		X		
Aripiprazole	Abilify	X	X	X		[60,61]
Ziprasidone	Geodon	X	X			[62,63]
Risperidone	Risperdal	X	X			[64,65]
Quetiapine	Seroquel	X			X	
Chlorpromazine	Thorazine	X				[66]
Olanzapine	Zyprexa	X	X	X		
Olanzapine/fluoxetine combination	Symbyax				X	[67,68]

Table 2: *FDA approved drugs for Bipolar Disorder. It represents the suitable drug for a particular condition. (Source: https://www.medscape.org/viewarticle/554128).*

Conventional antidepressants

It is an area of controversy to use these antidepressants for bipolar depressants. The main concern in using antidepressants as monotherapy in patients with bipolar depression is the risk of precipitating a switch to mania/hypomania, which is estimated to occur in between 3% and 15% of cases [69-71]. If conventional antidepressants are used, it is recommended to combine them with a mood stabilizer or an atypical antipsychotic, and to taper the antidepressant dose following remission of the episode [72,73]. Contemporary guidelines recommend selective serotonin reuptake inhibitors (SSRIs) or bupropion rather than selective serotonin-norepinephrine reuptake inhibitors (SNRIs) or tricyclics, as SSRIs and bupropion are less likely to cause manic switch [74].

Phytochemical treatment

Since a very long time, we have known well that herbal plants have potential source of curing ailments. In the coming time the health-care system will become more expensive. Thus, it is more important to know that introduction of herbal medicines will be beneficial for humans' health and economy. Traditional medicines are used by about 60 percent of the world population in rural areas in the developing countries as well as in the developed countries where use of modern medicine predominates [75]. Though the use of herbal medicine is steadily increasing in western world [76], the major hindrance in the amalgamation of herbal medicine into medical practice is the lack of sufficient scientific and clinical data and better understanding of efficacy and safety of the herbal products [77].

Aromatherapy is an alternative health practice that uses highly concentrated essential oils that are extracted from plants and are used to stimulate healing process including anxiety reduction. Numerous essential oils are used in aromatherapy, including eucalyptus, geranium, lavender, orange, citrus, and rosewood [78]. The chemical components of essential oils, such as ketones, aldehydes, and esters, determine the specific effects of the essential oils. Essential oils may be administered by inhalation, bathing, or massage to decrease anxiety, pain, fatigue, and improve wound healing. Although aromatherapy is pleasant, inexpensive, and has little side effects (except for rare allergies), there is little evidence that it is effective in patients undergoing medical interventions [79-81].

Here is a list of important plants (Table 3) that have been investigated and have shown some effects in treatment of bipolar disorder.

Phytochemical	Description	Reference
Black cohosh (*Cimicifuga racemosa*)	A nervous system depressant and sedative sometimes used by people with autoimmune conditions for its anti-inflammatory effects. Its active ingredient appears to bind to estrogen receptor sites, so it may cause hormonal activity.	[82]
Damiana (*Turnera aphrodisiaca*)	A traditional remedy for depression. As its Latin name indicates, it is also believed to have aphrodisiac properties. Whatever the case may be there, it does seem to act on the hormonal system. Its energizing quality might be dangerous for bipolar patients.	[83]
Ginkgo biloba	An extract of the ginkgo tree, advertised as an herb that can improve your memory. There is some clinical evidence for this claim. It is an antioxidant, and is prescribed in Germany for treatment of dementia. It is believed to increase blood flow to the brain.	[84]
Ginseng (*Panax quinquefolium*)	Has an energizing effect that may be helpful to people whose depression is accompanied by extreme fatigue and lethargy.	[85]
Gotu kola (*Centella asiatica, Hydrocotyl asiatica*)	An Ayurvedic herbal stimulant sometimes recommended for depression and anxiety.	[86]
St. John's Wort (*Hypericum perforatum*)	Has gained popularity as an herbal antidepressant. It has the backing of a decent amount of research. Those choosing to use this remedy should follow the same precautions as with SSRIs and MAOIs, two families of pharmaceutical antidepressants. It can also cause increased sensitivity to light. It is available by prescription in Germany, where it is the most widely used antidepressant. It is potentially dangerous to use St. John's Wort with prescription antidepressants or any other medication that could affect serotonin.	[87,88]

Table 3: *List of herbal plants effective in the treatment of bipolar disorder.*

Conclusion and Future Perspective

The Bipolar symptoms may are close enough to those of depression and hypomania. The episodes of mood and changes in the state of a person should be closely observed. It is not recommended to neglect such identifications as they can be serious in the later course of

the life. The best way to avoid such a disorder is to have a healthy and lively atmosphere around you. The positivity and the strength that is needed from oneself should be considered appropriate and relevant.

The unipolar and bipolar symptoms of this disorder should not be blended in each other as the distinct methods to diagnose the bipolar symptoms are discussed in this article. The therapies and the drugs approved for treatment of bipolar syndrome are basically meant for the balance of neurotransmitters that are responsible for our mental health. However, the true help lies in the willingness and the person's surroundings. Dealing with the person of this disorder is both an art as well as science. Sympathy and empathy are must to tackle such a person.

Further studies should be conducted to determine the true cause of this syndrome. Based on hypothesis and clinical studies, up till now no clear and accurate treatment has been established for the syndrome. However, Mood Stabilizers have shown some remarkable efficacy in context to this syndrome. The study of conventional antidepressants should be continued as they have shown fruitful results in this field. They might turn out to be a better therapy for the same. Dose ranges and drug interactions for the Bipolar disorder must be studied and examined with utmost importance.

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