



REVIEW

Recent advances in the understanding and management of bipolar disorder in adults [version 1; referees: 2 approved]

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Abstract

This article focuses on some aspects of recent progress in the neurobiology and treatment of bipolar disorder (BD) in adults. A molecular-genetic approach to the etiopathogenesis of the illness resulted in the findings of a genetic overlap between BD and other major psychiatric disorders. Furthermore, a poly-gene-environmental interaction in the development of the illness has been demonstrated. For the management of BD, new drugs with putative mood-stabilizing properties have been introduced in the past two decades. However, none of these can surpass lithium, the prototype mood-stabilizer, still considered the most specific drug for BD. Recent research on lithium, besides providing new data on the neurobiology of BD, has confirmed anti-suicidal, immunomodulatory, and neuroprotective properties of this drug.

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Introduction

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5)¹ classifies bipolar disorder (BD) as a separate category of mental illness. BD is a recurrent and often chronic condition that is generally characterized by episodes of mania, hypomania, depression, and mixed affective states. BD is estimated to have a worldwide prevalence rate of 2–5%, and the prevalence of type I BD (that is, BD with mania) is estimated at 1–2% and type II BD (that is, BD without mania) is estimated at 3–4%². BD causes significant suffering for patients and their families and has an estimated 10–20% lifetime suicide rate³. Genetic predisposition for BD is high, the heritability index is estimated at 0.85⁴, and drugs with mood-stabilizing properties make the most important pharmacological modality in the treatment of BD⁵.

This article aims to briefly review some of the latest advances in understanding the genetics of BD and in the use of mood stabilizers (MSs) in its treatment, with a special focus on lithium. Recent results of the molecular-genetic studies of BD show, on the one hand, a genetic overlap between BD and a number of psychiatric disorders and, on the other hand, the effect of epigenetic and environmental factors on the genetic predisposition to the illness. New drugs with putative mood-stabilizing properties, mainly atypical anti-psychotics, have been introduced in the past two decades. Also, new discoveries have appeared concerning lithium, the prototype of mood-stabilizing drugs, still considered the most specific for BD. Recent research using lithium as a research tool has provided new data on the neurobiology of BD and also provides evidence of the anti-suicidal, immunomodulatory, and neuroprotective properties of lithium.

Genetic overlap of bipolar disorder

A significant role of genetic factors in the pathogenesis of BD was presented by Craddock and Sklar⁶ in their review, published in 2013. In recent decades, previous findings from family and twin studies have been supported by linkage and genetic association research, using mainly the candidate gene approach. The latest evidence comes from the genome-wide association studies (GWASs) showing and replicating the association of BD with numerous gene polymorphisms such as CACNA1C, ODZ4, and NSAN. A polygenic contribution to the risk of illness has been postulated (that is, many risk alleles of small effect).

An important message coming from recent molecular-genetic research is that genetic susceptibility to BD can be shared with other psychiatric disorders. A report from the Cross-Disorder Group of the Psychiatric Genomic Consortium, after performing a GWAS for the five disorders—autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), BD, major depressive disorder, and schizophrenia (SCH)—in 33,332 cases and 27,888 controls, showed that single-nucleotide polymorphisms (SNPs) at four loci (regions on chromosomes 3p21 and 10q24, SNPs within CACNA1C and CACNB2) attained genome-wide significance for several of these disorders⁷.

The most relevant genetic overlap can occur between BD and SCH. In 2009, Lichtenstein *et al.*⁸, searching more than 2 million nuclear families in Sweden, showed that first-degree relatives of probands

with either SCH or BD were at increased risk of both these disorders. In the same year, the GWAS from the International Schizophrenia Consortium confirmed a substantial overlap of common polygenic variation between these two illnesses⁹. It seems that the polygenic risk score of BD can influence the clinical dimension of mania in SCH while such a score of SCH can influence the clinical dimension of psychosis in BD¹⁰. It was also found that a lesser contribution of very large copy number variations in BD, compared with SCH, makes a significant difference between two disorders¹¹.

For many years, clinicians have discussed diagnostic difficulties in differentiating BD with ADHD¹² as well as with borderline personality disorders¹³. These problems were recently substantiated in GWASs. In the first of them, a significant genetic overlap between BD and ADHD was demonstrated¹⁴, and in the second, an overlap of borderline personality disorder with BD, major depression, and SCH was reported¹⁵.

O'Donovan and Owen¹⁶ believe that the shared genetics of psychiatric disorders, demonstrated in numerous studies, points to extensive genic and allelic pleiotropy. According to them, the existence of risk alleles specific to a single diagnostic category, including BD, is unlikely.

Gene-environmental interaction in bipolar disorder

An emerging paradigm for the pathogenesis of psychiatric disorders, including BD, has been a model of gene-environment interaction, linking the genome, epigenetic regulation, and environmental factors. Epigenetic mechanisms such as DNA methylation and histone modification can modulate gene expression in response to the environment, therefore exerting an effect on the pathophysiology and development of BD^{17,18}. Epigenetic findings in BD were mostly obtained by means of peripheral blood and postmortem brain studies. In BD, abnormal DNA methylation can make a trait marker. Sugawara *et al.*¹⁹ when studying monozygotic twins discordant for BD found promotor hypermethylation of the serotonin transporter gene in the twin with BD. The most prominent candidate gene for methylation studies in BD is the brain-derived neurotrophic factor (*BDNF*) gene. Among patients with BD, the more pronounced *BDNF* exon I hypermethylation was found in type II compared with type I of the disorder²⁰. In a postmortem study of patients with BD, Rao *et al.*²¹ found increased global histone H3 acetylation and hypermethylation of the promotor region for the drebrin-like protein gene. Interestingly, many abnormal epigenetic mechanisms, similar to the multiple polygenic variations mentioned above, can be comparable in patients with psychotic BD and SCH. For example, Dong *et al.*²² showed increased DNA-methyltransferase1 binding to GABA-ergic and *BDNF* promoters in postmortem brain of both patients with BD and those with SCH. It seems that psychosis can also be a shared epigenetic trait.

Epidemiological studies have identified multiple environmental factors that can be associated with BD^{23,24}. Many of these are akin to those operating in SCH and major depressive disorder. Among factors occurring during pregnancy, the most important could be an intrauterine infection with influenza. Canetta *et al.*²⁵ demonstrated

that maternal serological influenza exposure was related to a five-fold greater risk of adult BD with psychotic features but not without such features, and this may suggest that prenatal influenza can be a risk factor for psychosis. The same group reported that the offspring exposed *in utero* to maternal smoking exhibited a twofold greater risk for BD in adulthood²⁶.

Among psychological factors associated with the onset and course of BD, childhood trauma and life events should be listed. Negative experiences in childhood, such as physical, sexual, and emotional abuse; physical and emotional neglect; and separation from parents, occur in patients with BD significantly more frequently than in the control population. In these patients, such events are associated with an earlier onset and more severe course of the illness, suicidal behavior, substance abuse, and somatic diseases²⁷. In adulthood, stressful life events can trigger manic or depressive episodes. A prospective study of 222 patients with BD shows that more than 60% of them experienced at least one life event 6 months before a new episode²⁸.

Seasonal and climate factors can also exert an effect on the onset and course of BD. Recently, an association of seasonal variation and BD symptoms was summarized in a systematic review by Geoffroy *et al.*²⁹. Also, a relationship between sunlight and the age of onset of BD was demonstrated in an international multisite study³⁰.

Mood stabilizers

The concept of MSs as the main drugs used in BD treatment has evolved in the last half century. MSs can be defined as drugs that (1) reduce or ameliorate manic or depressive symptoms or both, (2) act prophylactically to prevent recurrent manic or depressive episodes or both, and (3) do not induce or worsen manic or depressive episodes.

In 1963, a British psychiatrist, Geoffrey Hartigan, published the first report describing the long-term mood-stabilizing properties of lithium carbonate³¹. At the turn of the 1960s/1970s, other publications described possible mood-stabilizing effects of anti-convulsant drugs such as valproate^{32,33} and carbamazepine^{34,35}. The first observation that the atypical anti-psychotic drug clozapine may exert MS effects was advanced in the 1990s³⁶. Subsequently, other atypical anti-psychotics (for example, olanzapine, quetiapine, aripiprazole, and risperidone) have been found to have MS properties³⁷⁻³⁹. A suggestion that the anti-convulsant lamotrigine can also have MS characteristics was proposed in 2002⁴⁰. Because lithium and the classic anti-convulsant drugs preceded the introduction of newer MS agents by several decades, a proposal was made to group lithium, valproate, and carbamazepine as first-generation MSs and atypical anti-psychotics and lamotrigine as second-generation MSs³⁷.

Another classification of MSs can take into account the concept of “predominant polarity” (that is, manic or depressive) as the prevailing prophylactic effect of an MS⁴⁰. Clozapine, which exerts a predominant anti-manic and anti-psychotic action, might be placed at the extreme anti-manic end of the polarity continuum, being the MS with the greatest effect during mania (especially psychotic mania). Similarly, atypical anti-psychotics like olanzapine,

aripiprazole, and risperidone may also be placed along the anti-manic end of the polarity continuum. While first-generation MSs like lithium, carbamazepine, and valproate also demonstrate greater anti-manic than anti-depressant activity, lithium appears to produce the greatest anti-depressant action. It appears that quetiapine may exert a balance of anti-manic and anti-depressant effectiveness and might best be considered to occupy the mid-position along the polarity continuum. Finally, lamotrigine may best be placed on the anti-depressant pole of the continuum⁴¹. The use of both old and new MSs for the best therapeutic and prophylactic effect in BD has been elaborated in recent guidelines for BD treatment, such as those of the World Federation of Societies of Biological Psychiatry⁴², the Canadian Network for Mood and Anxiety Treatments (CANMAT)⁴³, the British Association of Psychopharmacology⁴⁴, and the Collegium Internationale Neuropsychopharmacologicum (CINP)⁴⁵.

Lithium – for bipolar disorder and beyond

Lithium, the first drug with reported mood-stabilizing properties³¹, is still regarded as the first choice for prevention of mood episodes in BD. A recent meta-analysis of lithium’s prophylactic efficacy was performed by Severus *et al.*⁴⁶. A comparison of lithium with valproate in this respect made in the framework of the BALANCE (Bipolar Affective Disorder: Lithium/Anticonvulsant Evaluation) study showed a superiority of lithium⁴⁷. Lithium is also the drug with the longest history of use for mood stabilization in mood disorders. Recently, we described a series of BD patients receiving lithium continually for 40 or more years with excellent results⁴⁸.

In 1999, a Canadian psychiatrist, Paul Grof, introduced the term “excellent lithium responders” for patients responding to lithium monotherapy by not having further recurrences of the illness and thus able to live a totally normal life. He suggested that in such patients the illness runs a course with distinct affective episodes and periods of complete remission and have low psychiatric comorbidity and frequent bipolar family history⁴⁹. This could reflect a “classic” form of the BDs, whose features are similar to those described by Kraepelin⁵⁰ as “manisch-depressives Irresein”. In our study on bipolar patients entering lithium prophylaxis in the 1970s (60 patients) and in the 1980s (49 patients), the percentages of patients not experiencing affecting episodes over a 10-year period were 35% and 27%, respectively, roughly one third of lithium-treated subjects⁵¹.

The response to lithium can be regarded as an endophenotype of BD and therefore has been a subject of molecular-genetic studies. The review of the association between lithium prophylactic efficacy and the SNPs of numerous candidate genes was done by the author of this article⁵². In 2008, the International Consortium of Lithium Genetic (ConLiGen) was founded with the aim of performing the GWAS of lithium response. Recently, the first results were published including 2,563 patients from 22 centers. The association between lithium response and a chromosome 21 region, containing two long, non-coding RNA genes, playing a role in gene expression regulation in the brain, was reported⁵³.

The response to lithium may also serve as a tool to elucidate the pathogenesis of BD. Among numerous studies performed in

recent years, interesting results were obtained by using induced pluripotent stem cells (iPSCs) acquired from lithium-responsive patients with BD. In 2015, Mertens *et al.*⁵⁴ investigated the cellular phenotypes in hippocampal dentate gyrus-like neurons derived from iPSCs of patients with BD. In this model, the authors observed hyperactive action potential firing, which was selectively reversed by lithium only in neurons derived from patients who also responded to lithium treatment. The findings were confirmed by Stern *et al.*⁵⁵ in a similar model. They showed that neurons derived from patients with BD divide into intrinsically different subpopulations, according to patients' lithium response. Recently, Tobe *et al.*⁵⁶, profiling the iPSC proteomics, showed that lithium alters the phosphorylation of collapsing response mediator protein-2 (CRMP2). We investigated the effect of long-term lithium treatment on very small embryonic-like stem cells (VSELs) and the mRNA expression of pluripotency and glial markers, in peripheral blood, in patients with BD. In patients not taking lithium, an increased number of VSELs, correlating with the duration of illness, and higher expression of markers were found. Long-term treatment with lithium reduced the number of VSELs and attenuated the expression of some markers, thus suppressing hyperactive regenerative and inflammatory processes occurring in the illness. The results may also show that VSELs in patients not treated with lithium provide a biological marker of the illness and its clinical progress⁵⁷.

Several decades of using lithium in BD have demonstrated some unique properties of this ion. In the early 1990s, we showed that long-term treatment with lithium can suppress labial herpes infections⁵⁸. Also, at that time, a multicenter study established that lithium can decrease mortality by reducing the occurrence of suicide⁵⁹. The anti-suicidal effect of lithium was fully confirmed in a recent meta-analysis⁶⁰, and lithium is currently regarded as a MS with the most pronounced anti-suicidal activity. Furthermore, intriguing results have been obtained in studies performed in Japan and Austria. They point to an inverse relationship between lithium concentration in drinking water and suicide rate in a given area^{61,62}. This may suggest that even very low levels of lithium in drinking water play a role in reducing suicide risk within the general population.

A topic of great interest is a possible neuroprotective effect of lithium. Recent neuroimaging studies have indicated an increase in gray matter of prefrontal cortex and left cingulate in lithium-treated healthy persons and bipolar patients, mostly lithium responders⁶³⁻⁶⁵. Also, an increase of hippocampal volume of lithium-treated bipolar patients has been reported^{66,67}. The biochemical underpinnings of lithium's neuroprotective effect have been proposed, especially the inhibition by lithium of glycogen synthase kinase-3 (GSK-3)⁶⁸. Based on these findings, a postulate to use lithium as a therapeutic agent in neurodegenerative conditions such as Alzheimer's disease (AD), Huntington's disease (HD), multiple system atrophy (MSA), and amyotrophic lateral sclerosis (ALS) has been voiced in recent years⁶⁹. Data from large cohort studies suggest an association between lithium treatment and dementia risk reduction or reduced dementia severity⁷⁰. In a few clinical trials, lithium showed some therapeutic effect in amnesic mild cognitive impairment and AD, even with doses lower than those used for mood stabilization. On the other hand, studies of lithium in HD, MSA, and ALS were mostly negative⁷¹.

Conclusions

Recent research has brought about a paradigm change as to the role of genetic factors in the pathogenesis of BD, demonstrating a genetic overlap between bipolar and other major psychiatric disorders and a poly-gene-environmental interaction in the development of the illness. New drugs with MS properties have found their place in the treatment guidelines for BD. Recently, we have also witnessed a revival of interest in lithium as a tool for the elucidation of the pathogenesis of the illness and in its unique biological properties. Some of these properties (for example, neuroprotective) may prompt its use beyond psychiatry.



Competing interests

The author declares that he has no competing interests.

Grant information

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