Mania with depressive symptoms: A pathophysiological review

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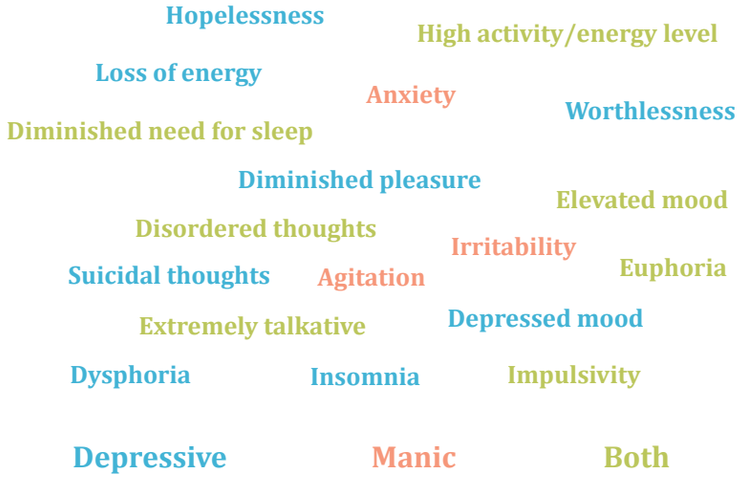

ABSTRACT

Key messages

- Bipolar disorder (BD) is a common, complex, and costly psychiatric illness that can be devastating for the affected individual and their families. Suicide is an important risk across the life span of bipolar patients.
- Accurate diagnosis is not easy, particularly in mixed states. Psychotic symptoms may suggest schizophrenia, and a major depressive episode may appear to be unipolar depression. Comorbid anxiety and substance/alcohol abuse often confuse the diagnostic picture. These factors contribute to under-diagnosis of BD.
- Incorrect diagnosis may worsen prognosis and increase hospital stay and the overall costs of treatment and patient management.
- There is a significant clinical need for more effective and better-tolerated drug treatments for BD. Although the pathophysiology and neurobiological processes responsible for BD are not fully understood, a greater understanding of the causative underlying mechanisms is emerging.
- Identification of new drug targets driven by recent research should help define a more tailored and potentially more successful approach to the treatment of BD. Future advances are expected based on the ability to manipulate and redress the fundamental disease processes and neurobiological dysfunction that underlie BD.
- To describe BD as alternating periods of mania and depression is an oversimplification. Mania can present with associated depressive symptoms and features leading to complicated, problematic, and difficult-to-treat mixed states.

Key words: mania, manic, depressive symptoms, depression, anxiety, bipolar disorder, psychiatric, psychotic, schizophrenia

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INTRODUCTION

Bipolar disorder (BD) is a chronic, episodic mental illness characterized by periods of mania, depression, and/or 'mixed episodes' where patients experience irritability, anxiety, and agitation. In this state, patients experience one or more depressive symptoms during a manic episode, or restlessness and over-activity during a depressive episode [1]. In particular, the emergence of characteristic non-mood symptoms, notably irritability, agitation, anxiety, and insomnia, may represent an overlap between depression and mania that manifests as a mixed episode in

BD [2]. BD is biologically complex, with abnormalities at the molecular level, as well as within neural networks and within the brain structure [3]. International data indicate a total worldwide lifetime prevalence of BD and the broader bipolar spectrum of 2.4% [4].

BD is one of the top 10 most severely disabling illnesses worldwide and is associated with significant morbidity and mortality [5]. In particular, in mixed states, the combination of manic and depressive states has recently been reported to be associated with a more severe form of BD, with a worse course of illness, and higher rates of comorbid conditions [6]. Cycles of mania and depression are reported to increase in frequency with disease duration, and to have shorter inter-episode intervals, suggesting disease progression [7]. An increasingly held view is that BD may be considered a systemic disease, frequently associated with cardiovascular disease, diabetes, obesity, and thyroid disease [5]. Notably, BD has a high risk of suicide [8,9], reported to be greater than with unipolar depression [10,11]. The suicide rate associated with BD is 5–17 times higher than in the general population, attaining a lifetime risk of 10–20% [12]. Consequently, for a majority of affected individuals, outcome can be poor [13].

Differential diagnosis is not easy, particularly in mixed states, which can afflict up to 64% of bipolar patients [14]. A correct diagnosis of BD may be hindered by the presence of psychotic symptoms suggestive of schizophrenia. A BD patient presenting with a major depressive episode, but no mania, may appear indistinguishable from a patient with unipolar depression. Comorbid anxiety and particularly substance/alcohol abuse often confuse the diagnostic picture [15]. Because the pathophysiology and biological basis for BD are not well understood, patients with BD are often misdiagnosed, incorrectly treated, or undertreated. Incorrect BD diagnosis may worsen prognosis and increase hospital stay and the associated overall costs of treatment/patient management [16].

Current empirical treatments for BD are largely directed toward ameliorating symptoms and preventing relapse. A greater understanding of pathophysiological processes is now required to identify biological markers for BD, and provide research direction for better diagnosis and new personalized treatment approaches [3]. Specific-targeted therapies capable of affecting the underlying disease processes that manifest as BD may prove to be more effective, faster acting, and better tolerated than existing therapies, with better outcomes for individuals affected by this devastating condition [17]. This brief review attempts to summarize current thinking on disease mechanisms responsible for BD and the implications for identifying new approaches to the treatment of BD.

INDIVIDUAL NEUROTRANSMITTER DEFICITS VERSUS THE BIGGER PICTURE

Early neurobiological investigations in mood disorders concentrated on characterizing individual monoaminergic neurotransmitters and any associated changes evident with the illness. The impact of mood stabilizing and antidepressant medications on any neurotransmitter deficit or abnormality was then assessed. The catecholamine hypothesis [18] neatly stated that depression resulted from low levels of norepinephrine, and mania resulted from high levels; however, verification of the hypothesis proved difficult to document. Investigative thinking quickly expanded to incorporate the view that neurotransmitter dysregulation and related signal transduction in BD may occur on different levels [19]. Manji [20] subsequently posed the question: rather than all of the neurotransmitters being independently abnormal, maybe there is something in common that regulates all of them? Unlike schizophrenia, most BD patients retain the capacity to return to a state of relative normality, even in the absence of treatment. This strongly suggests alterations in a modulatory mechanism [21].

More recent research on the underlying biological causes of mood disorders has undergone a paradigm shift: from a focus on monoamines with assessment of absolute changes in, e.g., monoamines and neuropeptides, subsequently recognizing evidence of changes in intracellular second messenger systems, to a more complex and inter-connected picture encompassing progressive changes in corticosteroids, neurotrophins, mitochondrial energy generation, oxidative stress, and neurogenesis that provides a more comprehensive model capable of explaining some of the clinical features of BD [22].

There is now increasing consensus that the pathophysiology of BD features changes and abnormalities in neuronal circuits and synapses, intracellular signaling cascades, and neural plasticity processes, leading to aberrant information processing in critical synapses and circuits [17,23]. In a recent review, it was suggested that BD manifests from impairments in neurotrophic, cellular plasticity, and resilience pathways and impairment of neuroprotective processes. Hence, the efficacy of mood stabilizing agents such as lithium may be explained by restoration/reversal of these impairments and pathophysiological changes [24].

An in-depth and comprehensive assessment of the putative disease mechanisms thought to underpin BD is beyond the scope of this review; however, a number of important hypotheses that have been/are being explored experimentally are summarized here.

The Hypothalamic–Pituitary–Adrenal (HPA) Axis

Dysregulation within the HPA physiological system has been reported in patients with BD [25]. Furthermore, a genetic predisposition is suggested by the observation that increased cortisol secretion, which reflects HPA axis dysfunction, occurs and persists in adolescent offspring of parents with BD [26]. Whether dysfunction in the HPA axis is a cause or a consequence of BD is yet to be firmly established; however, a recent publication [27] hypothesizes that HPA dysfunction plays a causal role in BD pathophysiology. Delivery of cholesterol from the outer to the inner mitochondrial membrane is necessary for the synthesis of all steroids, and an 18 kDa translocator protein (TSPO) is responsible for binding and importing

cholesterol across the membrane (Papadopoulos, et al. 2006, Fan, et al. 2009, Batarseh, et al. 2010). A common single nucleotide polymorphism (rs6971) in the TSPO gene leads to an amino acid substitution, Ala147Thr, which dramatically alters the affinity with which TSPO binds drug ligands (Owen 2012). This substitution may also impair the ability of TSPO to bind or import cholesterol, thereby affecting steroid synthesis and HPA function (Rupprecht, et al. 2010).

Following a large-scale case–control study, a nominal association between this TSPO polymorphism and the diagnosis of BD has been reported. This polymorphism may alter cholesterol handling by TSPO, steroid synthesis or its regulation, and if subsequently confirmed, would provide the first direct evidence that HPA dysregulation may have a causal role in BD. Hence, if TSPO is identified as having a causal role in BD, it is highly likely to become an important target in developing new drug treatments for BD [27].

The Arachidonic Acid (AA) Cascade Hypothesis

This hypothesis was derived from animal studies and asserts that mood-stabilizing drugs (lithium, carbamazepine, and sodium valproate) alleviate BD symptoms, particularly bipolar mania, by downregulating brain arachidonic acid (AA) metabolism and the formation of prostaglandin E_2 and AA cascade enzymes [28,29]. Of note, topiramate, investigated as a mood stabilizer, is ineffective in BD and does not modify the rat brain AA cascade. Downregulation of the AA cascade by mood stabilizers is believed to be linked to inhibition of AA neurotransmission via dopaminergic D_2-like and glutamatergic NMDA (N-methyl-D-aspartate) receptors. In contrast with mood stabilizers, antidepressants that increase switching of bipolar depression to mania are reported to upregulate the rat brain AA cascade. These observations point to a conclusion that bipolar symptoms, particularly mania, are associated with an upregulated cascade and excessive signaling via D_2-like and NMDA receptors. The presence of an upregulated AA cascade in BD patients could potentially be assessed by regional brain imaging using positron emission tomography, as increased AA incorporation associated with neuroinflammation has been measured using this methodology in Alzheimer's Disease [7].

Neuroprotective Effects

Impairment of synaptic strength and cellular plasticity in mood disorders has been shown to involve changes in pathways regulating neurotrophic factors and neuroprotective proteins [24]. The neuroprotective effects of lithium are considered key to its therapeutic actions. Lithium has been shown to reduce the oxidative stress that occurs with multiple episodes of mania and depression. Furthermore, lithium increases availability of cytoprotective proteins such as brain-derived neurotrophic factor (BDNF) and B-cell lymphoma 2 (Bcl-2), and reduces apoptotic processes through inhibition of glycogen synthase kinase 3 (GSK-3) and autophagy of dysfunctional cellular constituents [30].

Mitochondrial Dysfunction and Calcium Dynamics

A disturbance of energy metabolism is frequently observed in BD, and an underlying dysfunction of mitochondria has been implicated and reviewed [31]. The calcium ion (Ca^{2+}) is a ubiquitous intracellular messenger controlling diverse critical functions in the CNS. Ca^{2+} ions influence the synthesis and release of neurotransmitters and second-messenger cascades, thereby affecting plasticity, activation, intracellular signaling, and energy metabolism. Ca^{2+} homeostasis is impaired in both BD and schizophrenia, and impaired regulation of Ca^{2+} cascades is reported to be one of the most reproducible biological abnormalities described in BD research [24,31]. Both lithium and sodium valproate induce increases in mitochondrial oxygen consumption and mitochondrial membrane potential, and normalized mitochondrial function after a methamphetamine-induced insult. This indicates that mood-stabilizing drugs may alleviate some of the symptoms of BD by improving mitochondrial function [31]. Animal data indicate that lithium and sodium valproate affect and stabilize intracellular Ca^{2+}; for example, rat brain mitochondria incubated in lithium-containing media maintained their membrane potential better after a Ca^{2+}–mediated insult than mitochondria incubated in normal media [32].

Lithium: An Observational Window?

Lithium is a salt and does not have a receptor in the brain to bind to. When a neuron depolarizes, the sodium channel opens allowing ingress of sodium and lithium. Inside the cell lithium appears to modulate several secondary messenger systems including cyclic adenosine monophosphate (cAMP) and phosphoinositol (PI) pathways. Rather than causing noticeably large changes in baseline cellular activity, lithium seems to attenuate responsivity to other neurotransmitters including serotonin, dopamine, and γ-amino-butyric acid (GABA) [21]. Among lithium's several targets under investigation, GSK-3 inhibition, effects on the PI cycle and protein kinase C (PKC) have been identified as contributing to lithium's neurotrophic, antimanic, and antidepressant effects [33]. Continued work to decipher these effects will hopefully lead to the development of improved therapeutics for BD. Consequently, the available evidence indicates that lithium's efficacy in BD is likely to be related to wide-ranging neurobiological effects mediated via intracellular signaling cascades rather than a single mechanism.

WHAT CAN ANIMAL STUDIES TELL US?

Currently there are no animal models that fully encompass BD [34]. BD is problematic to model in animals since there are no well-established biomarkers for the

illness or the effects of treatment [35]. In particular, animal models have struggled to capture the hallmark cyclical nature of BD. However, new models based on the concept of "reverse translation" are being developed. This approach shifts focus from creating abnormal animal behaviors that resemble aspects of psychiatric disorders (i.e., animal models) to using what has been learned about the mechanisms of disease in humans, to develop animals that have the molecular and cellular abnormalities found in patients with BD (i.e., model animals) [34]. Specific examples of animal studies taking this approach are summarized below.

Example of an Animal Investigation Modeling Facets of Mania

Glutamate receptor 6 (GluR6)

The GluR6 (also known as GRIK2) gene resides in a genetic linkage region (6q21) associated with BD. In genetically engineered GluR6 knock out (KO) mice, a battery of specific tests showed that the KO mice, compared with control mice, exhibited less anxious and more risk taking behavior/aggression. They were more responsive to amphetamine. Chronic lithium treatment reduced hyperactivity, aggressive displays, and some risk-taking behavior. The attenuation of these behaviors is similar to the effects of lithium in patients with BD. These observations suggest that GLuR6 may play a unique role in regulating some of the symptoms of mania, e.g., hyperactivity/psychomotor agitation, aggressiveness, driven or increased goal-directed pursuits, risk taking, and supersensitivity to psychostimulants [36].

Example of an animal investigation modeling facets of depression

Point mutation D1881A of mouse mtDNA polymerase (POLG)

Altered mitochondrial function appears to play a role in the pathophysiology of BD [37,38]. Following the hypothesis that mitochondrial dysfunction is key to the etiology of BD, researchers have developed a transgenic (Tg) mouse carrying brain mtDNA deletions—specifically POLG, to act as a model for BD. Kasahara, et al. [39] report that POLG Tg mice exhibit a depression-like phenotype based on reduced wheel-running activity, and altered intra-day activity rhythms thought to echo the altered circadian rhythms often seen in mood disorders. These abnormal behaviors, resembling mood disorder, were worsened by tricyclic antidepressant treatment and improved by the mood stabilizing effects of lithium. Antidepressant-induced mania-like behavior and long-lasting irregularity of activity in some mutant animals were also reported. These data suggest accumulation of mtDNA defects in the brain caused mood disorder-like mental symptoms, with similar treatment responses to those seen in BD. These findings are compatible with a mitochondrial dysfunction hypothesis of BD and the behavioral phenotype of these animals is more akin to BD than major depressive disorder [34,39].

Although animal models have obvious limitations in their ability to reflect human mood states, they can help to derive valid hypotheses regarding causative mechanisms of BD worthy of human pharmacological and clinical investigation. Animal models have already contributed substantially toward understanding the genetic, molecular, and cellular basis of BD pathophysiology [34].

DEPRESSION IN BD: DISTINCT FROM UNIPOLAR DEPRESSION

Literature comparing unipolar depression with depression in BD is sparse. Although some authorities consider BD and unipolar major depressive disorder as part of an overlying spectrum [40], the prevailing model is that depressions within unipolar and BDs are qualitatively different in etiology and phenomenology. This distinction is exemplified in the DSM-5 diagnostic system.

Patients with BD spend proportionally more time in depression than in manic phases. Additionally, depressive episodes in BD are associated with the greatest degree of psychosocial impairment and disability [41]. Depressive episodes in BD, generally, have different symptom profiles to unipolar depression, notably prominent fatigue, hypersomnia, and reverse diurnal mood variability, in contrast to the insomnia associated with unipolar depression. Early functional imaging studies reported that bipolar patients with depression had significantly lower cortical metabolism than either control or patients with unipolar depression (42,43). The observed changes were state dependent and the anomalies disappeared following patients' recovery from depression.

In clinical practice, depression in BD is often more difficult to treat; typically, conventional antidepressants do not work well and can precipitate the development of mania or mixed states [21]. The reasons for the departure between the two conditions have not been fully elucidated; however, serotonin uptake, unlike unipolar depression, does not appear to play a significant role in bipolar depression. Despite this, many clinicians treat depressive episodes in BD in the same way as unipolar depression [44].

In an extensive review [44], the receptor-binding profiles of pharmacological agents with proven efficacy in bipolar depression (quetiapine, olanzapine-fluoxetine combination) were compared with the profiles of agents categorized as ineffective in acute bipolar depression (aripiprazole, buproprion, lamotrigine, paroxetine, ziprasidone, fluoxetine). Initially, the strong predictors for antidepressant efficacy in bipolar depression that emerged from this review were norepinephrine alpha-1, dopamine D_1, and histamine receptor antagonism. However, agents lacking efficacy in bipolar depression also showed this required mix of receptor antagonism. Further analyses revealed a unique combination of additional receptor effects, specifically indicative of antidepressant efficacy in BD. These were identified as follows: 5-HT_{2A}, muscarinic and dopamine D_2 and D_3 antagonism, $5HT_{1A}$ agonism, and norepinephrine reuptake inhibition. These findings would suggest that serotonin is less critically involved in

BD than unipolar depression, and norepinephrine activity rather than serotonin reuptake is more predictive of antidepressant effects in bipolar depression.

CONCLUSIONS

Recent progress in developing novel pharmacological treatments for BD has been limited. Most pharmacological treatments currently in use have emerged from a discovery process that owes much to serendipity. New approaches based on an increased understanding of the pathophysiology/neurobiology of BD are required to construct a better diagnostic system, and to develop the next generation of drugs with greater manipulative leverage within the disease processes of BD.

Alterations in signal transduction and abnormalities in the regulation of cellular plasticity cascades appear to offer a viable explanation for the range of symptoms associated with BD. However, it is currently difficult to specify exactly which mechanisms in the cascade of events associated with BD are the most important key drivers of this illness. Compared with developing receptor-specific drugs, the design of novel agents to affect secondary messenger systems, selectively, is much more highly challenging. Despite this, increased effort in conceptualizing and validating new biomarkers is potentially very important for developing new treatments.

There are grounds for further cautious optimism in that treatments with targets based on identified pathways in one disorder may well be valid candidate treatments in disorders with overlapping pathophysiology and biomarker data. Secondary improvements in comorbid conditions may result with interventions that target pathways that are common to psychiatric disorders and common medical disorders that are highly comorbid with psychiatric disorders, e.g., cardiovascular disease and diabetes.

Recent novel insights into the mechanisms of action of drugs with established efficacy in BD, notably lithium, are helping to identify and understand clinically relevant pathophysiological targets for the treatment of BD. Such development offers hope with respect to potentially "fixing the broken bipolar brain" via:

- prevention/prophylaxis (intervention to prevent onset of molecular and cellular changes);
- treatment (minimizing the severity of deficits over time);
- rectification/repair (to reverse molecular and cellular deficits) [24].

Finally, early intervention with optimal therapy may reduce the disability associated with disease progression and may modify the course of BD into a more treatment-responsive pattern [22].

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REFERENCES

1. González-Pinto A, Aldama A, Mosquera F, González Gómez C. Epidemiology, diagnosis and management of mixed mania. CNS Drugs. 2007;21(8):611–26.
2. Swann AC, Lafer B, Perugi G, et al. Bipolar mixed states: an international society for bipolar disorders task force report of symptom structure, course of illness and diagnosis. American Journal of Psychiatry. 2013;170:31–42.
3. Yang H. Decoding the biology of bipolar disorder: an update on recent findings in genetics, imaging and immunology. Focus. 2011;IX(4);423–27.
4. Merikangas KR, Jin R, He J-P, et al. Prevalence and correlates of bipolar disorder on the World Mental Health Survey Initiative. Archives of General Psychiatry. 2011;69(3):241–51.
5. Kupfer DJ. The increasing medical burden in bipolar disorder. JAMA 2005;293(20):2528–30.
6. Vieta E, Valenti M. Mixed states in DSM-5: implications for clinical care, education and research. Journal of Affective Disorders. 2013;148:28–36.
7. Rapoport SI, Basselin M, yung-Wook Kim H, Rao JS. Bipolar disorder and mechanisms of action of mood stabilizers. Brain Research Reviews.2009;61(2):185–209.
8. Baldessarini RJ, Pompili M, Tondo L. Suicide in bipolar disorder: risks and management. CNS Spectrums. 2006 Jun; 11(6): 465–71.
9. Fountoulakis KN, Gonda X, Siamouli M, Rihmer Z. Psychotherapeutic intervention and suicide risk reduction in bipolar disorder: a review of the evidence. Journal of Affective Disorders 2009;113:21–9.
10. Rihmer Z, Kiss K. Bipolar disorders and suicide risk. Clinical Approach to Bipolar Disorder. 2002;1:15–21. Abstract.
11. Øiesvold, et al. Classification of bipolar disorder in psychiatric hospital. a prospective cohort study. BMC Psychiatry 2012;12:13.
12. Bostwick JM, Pankratz VS. Affective disorders and suicide risk: a reexamination. American Journal of Psychiatry. 2000;157(12): 1925–32.
13. Belmaker RH. Bipolar disorder. New England Journal of Medicine. 2004;351:476–86.
14. Vieta E, Grunze H, Azorin J-M, Fagolini A. Phenomenology of manic episodes according to the presence or absence of depressive features as defined in DSM-5: results from the IMPACT self-reported online survey. Journal of Affective Disorder 2014;156:206–13.
15. Nery FG. Comorbid bipolar disorder and substance abuse. Current Psychiatry 2011;10(4):57–67.
16. Sing T, Rajput M. Misdiagnosis of Bipolar Disorder. Psychiatry. 2006;October:57–63.
17. Zarate CA, Singh J, Manji HK. Cellular Plasticity cascades: targets for the development of novel therapeutics for bipolar disorder. Biological Psychiatry. 2006;59:1006–20.
18. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. American Journal of Psychiatry. 1965; 122: 509–22.
19. Ackenheil M. Neurotransmitters and signal transduction processes in bipolar affective disorders: a synopsis. Journal of Affective Disorders. 2001;62(1–2):101–11.
20. Manji HK. Neurobiology and bipolar disorder: beyond the synapse. Advanced Studies in Medicine. 2006;6(6A):S417–29.
21. Berns GS, Nemeroff CB. The neurobiology of bipolar disorder. American Journal of Medical Genetics Part C 2003;123C:76–84.
22. Berk M, Kapczinski F, Andreazza AC, et al. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotropic factors. Neuroscience and Behavioural Reviews. 2011;35(3):804–17.
23. Schloesser RJ, Huang J, Klein PS, Manji HK. Cellular plasticity cascades in the pathophysiology and treatment of bipolar disorder. Neuropsychopharmacology. 2008;33:110–33.
24. Soeiro-de-Souza MG, Dias VV, Figueueira ML, et al. Translating neurotrophic and cellular plasticity: from pathophysiology to improved therapeutics for bipolar disorder. Acta Psychiatrica Scandinavica. 2012;1–10.
25. Watson S, Gallagher P, Ritchie JC, Ferrier IN, Young AH. Hypothalamic-pituitary-adrenal axis function in patients with bipolar disorder. British Journal of Psychiatry. 2004;184:496–502.

26. Ellenbogen MA, Hodgins S, Walker CD, Couture S, Adam S. Daytime cortisol and stress reactivity in the offspring of parents with bipolar disorder. Psychoneuroendocrinology 2006;31:1164–80.
27. Chang MC, Grange E, Rabin O, Bell JM, Allen DD, Rapoport SI. Lithium decreases turnover of arachidonate in several brain phospholipids. Neuroscience Letters. 1996;220:171–4. [http://www.ncbi.nlm.nih.gov/pubmed/11331408].
28. Chang MC, Contreras MA, Rosenberger TA, Rintala JJ, Bell JM, Rapoport SI. Chronic valproate treatment decreases the in vivo turnover of arachidonic acid in brain phospholipids: a possible common effect of mood stabilizers. Journal of Neurochemistry. 2001;77:796–803. [PubMed: 11331408].
29. Malhi GS, Tanious M, Das P, Coulston CM, Berk M. Potential mechanisms of action of lithium in bipolar disorder. Current understanding. CNS Drugs 2013;27(2):135–53.
30. Clay H, Sullivan S, Konradi C. Mitochondrial dysfunction and pathology in bipolar disorder and schizophrenia. International Journal of Developmental Neuroscience. 2011;29(3):311–24.
31. Shalbuyeva N, Brustovetsky T, Brustovetsky N. Lithium desensitizes brain mitochondria to calcium, antagonizes permeability transition, and diminishes cytochrome C release. Journal of Biological Chemistry. 2007;282(25):18057–68.
32. Machado-Viera R, Manji HK, Zarate CA. The role of lithium in the treatment of bipolar disorder: convergent evidence for neurotrophic effects as a unifying hypothesis. Bipolar Disorder. 2009;11(Suppl 2):92–109.
33. Malkesman O, Austin DR, Chen G, Manji HK. Reverse translational strategies for developing animal models of bipolar disorder. Disease Models and Mechanisms. 2009;2:238–45.
34. Gould TD, Einat H. Animal models of bipolar disorder and mood stabilizer efficacy: a critical need for improvement. Neuroscience and Biobehavioral Reviews. 2007;31(6):825–31.
35. Shaltiel G, Ma eng S, Ikesman O Ma, et al. Evidence for the involvement of the kainite receptor subunit GluR6 (GRIK2) in mediating behavioural displays related to behavioural symptoms of mania. Molecular Psychiatry. 2008;13(9):858–72.
36. Stork C, Renshaw PF. Mitochondrial dysfunction in bipolar disorder: evidence from magnetic resonance spectroscopy research 2005;10(10):900–19.
37. Quiroz JA, Gray NA, Kato T, Manji HK. Mitochondrially mediated plasticity in the pathophysiology and treatment of bipolar disorder. Neuropsychopharmacology. 2008;33(11):2551–65.
38. Kasahara T, Kubota M, Miyauchi T, et al. Mice with neuron-specific accumulation of mitochondrial DNA mutations show mood disorder-like phenotypes. Molecular Psychiatry. 2006;11(6):577–93, 523.
39. Judd LL, Akiskal HS. The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. Journal of Affective Disorders. 2003;73(1–2):123–31.
40. Calabrese J, Hirschfeld RM, Frye MA. Impact of depressive symptoms compared with manic symptoms in bipolar disorder: results of a US community-based sample. Journal of Clinical Psychiatry. 2004;65:1499–504.
41. Baxter LR Jr., Phelps ME, Mazziotta JC, et al. Cerebral metabolic rates for glucose in mood disorders. Studies with positron emission tomography and fluorodeoxyglucose F 18. Archives of General Psychiatry. 1985;42(5):441–7.
42. Buchsbaum MS, Wu J, De Lisi LE. Frontal cortex and basal ganglia metabolic rates assessed by positron emission tomography with [^{18}F]2-deoxyglucose in affective illness. Journal of Affective Disorders. 1986;10(2):137–52.
43. Fountoulakis KN, Kelsoe JR, Akiskal H. Receptor targets for antidepressant therapy in bipolar disorder: an overview. Journal of Affective Disorders 2012;138:222–38.
44. Batarseh A, Papadopoulos V. Regulation of translocator protein 18 kDa (TSPO) expression in health and disease states. Molecular and Cellular Endocrinology. 2010;327(1–2):1–12. [http://www.ncbi.nlm.nih.gov/pubmed/20600583].
45. Cuellar AK, Johnson SL, Winters R. Distinctions between bipolar and unipolar depression. Clinical Psychology Review. 2005;25(3):307–39.
46. Fan J, Rone MB, Papadopoulos V. Translocator protein 2 is involved in cholesterol redistribution during erythropoiesis. Journal of Biological Chemistry. 2009;284(44):30484–97. doi: 10.1074/jbc.M109.029876.
47. Owen DR, Yeo AJ Gunn RN, et al. An 18-kDa ranslocator protein (TSPO) polymorphism explains differences in binding affinity of the PET radioligand PBR28. Journal of Cerebral Blood Flow & Metabolism. 2012;32: 1–5.
48. Papadopoulos V, et al. Translocator protein (18kDa): new nomenclature for the peripheral-type benzodiazepine receptor based on its structure and molecular function. Trends in Pharmacological Sciences. 2006;27(8):402–9.