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Future Directions for Pharmacotherapies for Treatment-resistant Bipolar Disorder

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Abstract: Current pharmacological treatments for bipolar disorder (BD) are limited and efficacy has historically been discovered through serendipity. There is now scope for new drug development, focused on the underlying biology of BD that is not targeted by current therapies. The need for novel treatments is urgent when considering treatment resistant BD, where current therapies have failed. While established drugs targeting the monoamine systems continue to be worthwhile, new biological targets including inflammatory and oxidative an nitrosative pathways, apoptotic and neurotrophic pathways, mitochondrial pathways, the N-methyl-D-aspartate (NMDA)–receptor complex, the purinergic system, neuropeptide system, cholinergic system and melatonin pathways are all being identified as potential anchors for the discovery of new agents. Many agents are experimental and efficacy data is limited, however further investigation may provide a new line for drug discovery, previously stalled by lack of corporate interest.

Keywords: Bipolar disorder, inflammation, nitrosative stress, oxidative stress, pathways, pharmacotherapy, receptors, treatment targets.

MAIN TEXT

Greater understanding the biological basis of bipolar disorder (BD) has uncovered a complex web of perturbed systems and genetic risk. Genome-wide association studies have identified numerous risk alleles, overlapping with other pathologies that may have similar biological alterations [1]. In addition, neurobiological differences have been demonstrated between bipolar cases and health controls, longitudinally between people at the early stages of bipolar illness and those with a long history of illness, and between euthymic individuals compared to those experiencing an acute episode [2].

This complex biological underpinning suggests a potential for targeted interventions, however conventional pharmacotherapies for BD are limited in their number and scope. Other than lithium, most conventional drugs currently indicated for the treatment of BD were originally developed for the treatment of other disorders; anticonvulsants for seizure control and antipsychotics for psychoses. Moreover, these agents have limited efficacy, and may work well for some individuals but not for others. Many individuals experience relapse in spite of conventional maintenance treatments [3]. There are also those who do not respond to current therapies, considered treatment resistant. Given this, there is an urgent need for new treatments for BD which focus on these biological targets.

The drugs available to treat BD predominantly come from two classes, with overlapping mechanisms of action. Most conventional mood stabilisers are anticonvulsant agents that block voltage-sensitive sodium and calcium channels, and also have downstream effects on monoamine regulation. Second generation (a typical) antipsychotics are common treatments for an acutemanic episode, with some atypical antipsychotics also used in maintenance and depressive phase of the illness. These agentsbind to a range of receptorsand most of these agents target multiple mechanisms and downstream effects. Although the pharmacodynamics of these agents have been studied and reported, the mechanisms of action that makes them effective as mood stabilisers or for manic or depressive episodes is, for most cases, not fully known.

Novel therapies offer opportunities for improving outcomes for people with treatment resistant bipolar disorder. In recent years there has been significant progress in identifying biological differences associated with bipolar disorder, creating the possibility for developing new treatments that may directly target the underlying biology of the disorder. Studies of peripheral biomarkers have revealed the role of inflammatory [4], oxidative and nitrosative [5] stressin bipolar disorder. Changes in inflammatory cytokines, corticosteroids, neurotrophins, mitochondrial

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energy generation, oxidative stress and neurogenesis have also been documented [6]. Further insights have been obtained from genome wide association studies (GWAS) implicating several genes in susceptibility to the disorder [1]. All of these biological factors are of interest as potential drug targets.

A fruitful approach has been to repurpose drugs used primarily for indications other than psychiatric illness. All anticonvulsant drugs commonly used for the treatment of epilepsy have been trialled for efficacy in bipolar disorder, sometimes successfully (*e.g*. lamotrigine) and sometimes unsuccessfully (*e.g*. gabapentin, topiramate and phenytoin), suggesting that any new anticonvulsants are likely to also be trialled for bipolar disorder. Similarly, most atypical antipsychotic agents have demonstrating some success for the treatment of maniainbipolar disorder. There is some efficacy during maintenance treatment with atypical antipsychotic and agents including quetiapine and lurisidone [7, 8] have been effective in the depressive phases of the illness [9]. While there may be a continuation of agents being repurposed for use in bipolar disorder, these do not provide targeted treatment, specifically designed for bipolar disorder. Instead, if repurposing is to be more greatly effective, agent selection should be based on known pharmacology and married to our understanding of the biology of bipolar disorder. In this respect, anti-inflammatory agents, for example, may have some potential and, if efficacious, can also provide a reverse-engineering loop for further agent development.

Limited treatment options and a lack of relevantly targeted agents both contribute to the likelihood of treatment resistance. In mental illness, the term "resistance" is often used synonymously with "non-response", "treatment failure" or "break-through illness", when describing the outcome of a pharmacological intervention. Although these terms are not synonymous, all of these terms describe failed or suboptimal treatment outcomes for people with bipolar disorder. In this paper we will be reviewing treatment targets for emerging or novel therapies that may benefit people with BD who do not have adequate outcomes with conventional treatments.

Conventional pharmacotherapeutic options for treatment resistance include dose increases or combination mood stabilisers, such as lithium plus valproate [10]. Further, clinicians may add other psychotropic agents such as an atypical antipsychotic or antidepressants to an individual's treatment regimen in an attempt to improve outcomes. While this may be effective for some, many individuals will still not achieve symptomatic improvement, or may not tolerate drug combinations or dose increases, or may improve and then relapse. Even where conventional pharmacotherapy is considered adequate for acute symptom improvement, many individuals will show impaired functioning and quality of life and continue to experience significant mood instability over the long term [11]. Consequently, there is an urgent need to develop new treatments for bipolar disorder, especially treatment with novel mechanisms of action.

MONOAMINE TARGETS

Established drug targets; serotonin, dopamine and noradrenaline are still central to the production of new therapies for bipolar disorder. There is evidence that norepinephrine alpha-1, dopamine D1 and histamine antagonism are important targets for bipolar depression, with weaker evidence for 5-HT2A, muscarinic and dopamine D2 and D3 antagonism and less evidence norepinephrine reuptake inhibition and 5HT-1A agonism [12]. Conversely, antidepressants that augmentserotonin reuptake are controversial treatments for BD [13].

Dopamine regulation may be critical to mood stability in BD [14]. This is supported by reports that the concomitant use of cocaine and amphetamine (that enhance dopamine release) is associated with pooreroutcomes for people with bipolar disorder. Excessive dopamine is associated with mania and dopamine deficiency with depression.

Regarding experimental treatments for BD, targeting monoaomine pathways, pramipexole (a D2/D3 agonist used for the treatment of Parkinson's disease) is associated with reduced metabolic activity in several regions of the frontal cortex that are reportedly overactive during depression [15]. Cariprazine (a dopamine D2/3 receptor partial agonist) has demonstrated efficacy for the treatment of mania [16]. Modafinil and its isomer armodafinil, (weak inhibitors of the dopamine transporter) andare effective as an adjunctive agents for depressive episodes of BD and are better tolerated than pramipexole [17-19].

N-METHYL-D-ASPARTATE (NMDA) RECEPTOR

The N-methyl-D-aspartate (NMDA)–receptor complex is an ion channel receptor regulated endogenously by glutamate non-specifically and aspartate specifically. Dysfunction of the glutamatergic system has been identified in BD [20]. Polymorphisms of the GRIN1 gene and the GRIN2B gene, which coding for the NR1 and NR2B receptor subunits of the NMDA receptor have been associated with BD [21, 22].

Ketamine is an NMDA antagonist that has been shown to have rapid antidepressant and anti-suicidal effects when administered to individuals experiencing bipolar depression. In one study, these effects were reported to last for 3 days [23]. Further studies determined that the greatest improvements were seen in those with no prior history of suicide attempt potentially indicating a link between NMDA and suicidality [24].

PURINERGIC SYSTEM

Purinergic receptors include both ion channels and G protein-coupled receptors and bind adenosine (P1 receptors) or adenosine triphosphate (P2 receptors). They are further divided into numerous subclasses. The P2RX7 gene, which codes for the purinergic ion channelP2X purinoceptor7 is found in microglia and is associated with the inflammatory response [25]. P2X purinoceptor7 has been shown to have a single nucleotide polymorphism (SNP) rs2230912 that is significantly associated with unipolar depression and BD [26] and a further SNP, rs1718119, which is associated with symptoms of mania [27]. Allopurinol blocks the conversion of the oxypurines hypoxanthine and xanthine to uric acid and inhibits purine synthesis. Given this allopurinol may be a possible agent for the treatment ofmania [28, 29].

CHOLINERGIC SYSTEM

Depressive symptoms can be induced in currently manic individuals with BD by administering the anticholinesterase inhibitor physostigmine [30]. The antimuscarinic scopolamine has been associated with a rapid, robust antidepressant in patients with recurrent unipolar depression or BD [31]. There may be scope to explore cholinergic agents for the treatment of BD.

NEUROPEPTIDE SYSTEMS

Neuropeptides are cell signalling molecules secreted by neurons and glia that differ from conventional neuro-transmitters in structure and function. Neurotransmitters are short acting, influencing neuron polarisation and firing. In contrast, neuropeptides have longer lasting, diverse effects that include influencing gene expression. Neuropeptide-y (NPY) operates on a G protein-coupled receptor and has been implicated in post-traumatic stress disorder [32], alcoholism [33] and depression and anxiety [34]. Further, quetiapine is a modulator of NPY and this mechanism may contribute to the efficacy seen inBD [34].

Opioid neuropeptide systems dysregulation occurs in people with bipolar disorder. Antagonism of the kappa opioid receptor has antidepressant effects and partial agonism of the kappa opioid receptor was shown to have antimanic effects. Delta and mu opioid receptor agonists have antidepressant like effects in animal models [35].

In the tachykinin neuropeptide system, substance P, which binds to the neurokinin 1 (NK1) receptor, is associated with mood dysregulation. There is some evidence that NK1 and NK2 receptor antagonism has antidepressant effects [35].

NOVEL TARGETS FROM GENETIC STUDIES

Linkage and GWAS studies have identified genes associated with catechol-O-aminotransferase (COMPT), brain derived neurotrophic factor (BDNF), cyclic-AMP response element binding (CREB)and ankyrin-G to be associated withBD [2]. Some of the genes that has been associated with bipolar disorder included *CACNA1C* that encodes for the voltage-dependant calcium channel α-1 subunit and the apoptotic genes *FAS, BAK* and *APAF-1*[2]. The $Val^{66}Met$ brain-derived neurotrophic factor (BDNF) polymorphism has been associated with suicidal behaviorin BD [36]. Lithium has been suggested to alter the gene expression of CREB genes associated with BD and valproate modulates gene expression by inducing DNA demethylation [2].

APOPTOTIC AND NEUROTROPHIC PATHWAYS

Dysregulation of pro- and anti-apoptotic factors is also associated with bipolar disorder. The central process triggeringapoptosis is caspase activation, which has three major pathways; the extrinsic or death receptor pathway, the intrinsic or apoptosome pathway, triggered by the release of cytochrome c from the mitochondria, and the cytotoxic lymphocyte-initiated granzyme B pathway [37]. There are at least 12 mammalian caspases, including apoptotic caspases (caspase-2, -3) and inflammatory caspases (caspase-1) [38]. A complex array of molecular pathways involving upstream and downstream processes isinvolved in apoptosis. Caspase-8 can initiate a mitochondrial pathway to apoptosis. Caspase-2-initiated apoptosis can be triggered by processes including DNA damage [37]. DNA damage can also be caused by immuno-inflammatory processes and oxidative or nitrosative stress. Caspase inhibitors are potent neuroprotective agents in hypoxic brain injury [39], but there is limited evidence supporting these agents as treatments for bipolar disorder. Minocycline is a caspase-1 inhibitor that has some evidence of efficacy in bipolar disorder, however it has multiple mechanisms of action and it is not possible to disentangle which actions of this drug contribute to its possible efficacy [40].

Glutamate excitotoxicity-induced apoptosis is another potential mechanism for therapeutic targeting. Glutamate-induced apoptosis may be caspase-dependent or –independent therefore efficacy would potentially not be limited to caspase augmentation. Agents that may reduce glutatmate excitotoxicity such as oestrogen or N-acetyl cysteine may therefore be potentially efficacious for BD [41, 42].

Modulation of B cell lymphoma-2 (bcl-2) protein, a regulator of apoptosis, is already achieved by some current pharmacotherapies for bipolar disorder. Lithiumand lamotrigine both upregulate bcl-2 and protect against glutamate excitotoxicity. Atypical antipsychotics increase the gene expression of superoxide dismutase andhave demonstrated anti-apoptotic properties inPC12 cell cultures [43].

Neurotrophins are cell signalling proteins that induce the survival, development, and function of neurons. A cascade that modifies gene expression and protein synthesis is triggered by the binding of neurotrophin to the Trk receptor [44]. Brain-derived neurotrophic factor (BDNF) and the tropomyosin related kinase B (TrkB) receptor, are critical for neuronal growth and survival and promote dendritic connectivity [45]. Neurotrophinsupregulation is achieved by agents including lithium and some atypical antipsychotics. BDNF is upregulated by some atypical antipsychotics, but not the conventional antipsychotic haloperidol. Neurotrophinschange other apoptotic and neurotrophic factors such as bcl-2, glycogen synthase kinase 3β (GSK-3β) and β-catenin. Lithium inhibits GSK-3β and induces BDNF.

IMMUNO-INFLAMMATORY PATHWAYS

Psychiatric research has expanded its understanding of psychiatric disorders as ‘whole-body’ disorders, not specific to the brain. BD is a systemic illness associated with increased levels of pro-inflammatory cytokines, suggesting a chronic, low grade activation of the immune system [46]. Activation of the immune system is not specific to BD but appears to be a common factor also documented in depression, schizophrenia, and autism. Increased inflammation, measured by increases in pro-inflammatory peripheral biomarkers such as interleukin-6 and tumor necrosis factor (TNF), as well as the acute-phase biomarker c-reactive protein (CRP), have been observed to be higher in treatment-resistant depression (unresponsive to antidepressant therapy) compared to treatment-responsive depression [47]. Although

results are limited, inhibitors of inflammatory cytokines have been trialled in treatment-resistant depression. The TNF antagonist infliximab was compared to placebo in a small study ofindividuals with treatment-resistant depression (N=60). Although there was no overall change inHAM-D scores between treatment groups across time, infliximab was superior to placebo for participants with high baseline inflammatory biomarkers [48].

Activation of the immune system in BD may be associated with stress and allostatic load [49]. There is an association between stress and the immune system which has evolved as an adaptive advantage. Acute stress primes the immune response to injury and infection. However, stress has a bidirectional impact on the immune system. Susceptibility to infections and cancer is increased by stress which also increases the likelihood of allergic, autoimmune and inflammatory diseases. Chronic stress causes a dysregulation of the immune system. An upregulation of pro-inflammatory cytokines including interleukin-1 (IL-1), IL-6, IL-2, tumour necrosis factor (TNF)-α, and interferon (INF)-γis characterised by chronic stress [50]. This may result in an imbalance between pro and anti-inflammatory cytokine as well as changes in immune cell counts, trafficking and function [51]. Immune activation may be depressogenic, for example, interferon treatments may cause depression [52]. Stress is a ubiquitous part of the life of every individual, however different individuals may have differences in resilience and sensitisation to stressors. Greater stress is associated with a more adverse course of illness [53]. Medical comorbidity, including obesity and metabolic and endocrine disorders, is common in BD and is further associated with immune system activation [54], suggesting that treatments targeting weight control and comorbidities may be useful treatment targets for some people with treatment resistant bipolar disorder.

Adjunctive therapy using established anti-inflammatory agents or agents that downregulate or inhibit pro-inflammatory cytokines have been considered as novel therapies. Immuno-inflammatory signalling is downregulated by lithium and valproate, and some atypical antipsychotics [55]. The net benefit of these agents on inflammatory mechanisms is not known as weight gain and metabolic syndrome associated with these conventional agents can produce inflammatory stress. There have been promising results from trials of anti-inflammatory agents as adjunctive treatments. Some preliminary data suggests that cyclooxygenase-2 (COX-2) inhibitors, celecoxib, rofecoxib and cimicoxib, may reduce depressive symptoms [56]. COX-2 initiates prostaglandin E_2 (PGE_2) synthesis, regulating cytokine production. Aspirin inhibits both COX-1 and COX-2 and may be beneficial for people with BD [56]. Statins inhibit guanosine triphosphatase and nuclear factor-κB mediated activation of inflammatory pathways [57] and in a study of patients with cardiovascular disease were associated with reduced risk of depression [58].

Despite a strong theoretical and evidence base associating inflammation with mental health, no anti-inflammatory agents are currently indicated for the treatment of BD and their use remains experimental. This may be due to mechanistic limitations of current anti-inflammatory pharmaceuticals that modulate acute inflammatory pathways. BD is associated with chronic, low grade immune activation and there are no known treatments that target this form of immune dysregulation. Rather than suppressing the immune response, treatment are required that balance the numerous biological pathways and factors involved. Some health foods and supplements claim to 'restore immune system naturally' but are supported by limited or no evidence. Some evidence exists to suggest that changes in gut microbiota may impact the host immune system, however research into gut microbiota as a treatment target in mental health is in its infancy [59]. Despite limited evidence, immunomodulation remains an important therapeutic target and requires further investigation.

OXIDATIVE AND NITROSATIVE STRESS

Oxidative and nitrosativehomeostasis is achieved through the balance of pro-oxidative and nitrosative factors, such as free radical, with anti-oxidative and nitrosative factors, such as anti-oxidants and free radical scavenger. Oxidative and nitrosative stress are documented in BD may be important therapeutic targets. Oxidative and nitrosative stress cause damage to lipids, proteins and DNA and are often associated with inflammatory stress [50]. Antioxidative and anti-nitrosative pathways maintain homeostasis by eliminating oxidant and nitrosative compounds. Oxidative and nitrosative stress has been observed from biomarker studies of people with BD, suggesting that these systems. People with BD may benefit from agents that supplement the production antioxidant and anti-nitrosative factors. Treatments that target oxidative and nitrosative pathways have been investigated for bipolar disorder, including N-acetylcysteine (NAC) which was shown to be superior to placebo for BD in a randomised, placebo controlled trial [60]. Ginkgo biloba, selenium, zinc, ascorbic acid, coenzyme Q10, beta-carotene, tocopherol and methionineincrease antioxidant capacity and have also been suggested as possible treatment for BD.

MITOCHONDRIAL DYSFUNCTION

There is evidence of impairment in complex I of the mitochondrial electron transport chain in BD that may result in increased protein oxidation and nitration in the prefrontal cortex [61]. Further evidence has come from studies that have demonstrated that BD can be a common comorbidity with mitochondrial cytopathies [62]. Mitochondria are energy generating organelles whereoxidative and nitro-sativeproducts are formed in as a consequence of normal function. Endogenous free radical scavengers and antioxidants maintain homeostasis. Mitochondria are susceptible to oxidative stress and in turn, people with BD may have an impaired capacity to manage oxidative and nitrosative stress in the mitochondria. Current pharmacotherapies can affect mitochondrial function. Haloperidol and fluphenazine inhibit mitochondrial complex I activity [63], whereas lithium and paroxetine increase mitochondrial energy generation [64].

Conventional therapies for mitochondrial cytopathies are largely supportive and include supplements such as co-enzyme Q10, carnitine, creatine, cysteine, dichloroacetate, dimethylglycine, supplement combinationsand physical

activity interventions [65]. Notably, many of these supplements have antioxidative properties. There is no evidence that targeting of mitochondrial pathways may be an effective treatment for bipolar disorder, however at least only clinical trial of a supplement combination designed to enhance mitochondrial function in depression is underway (Australian clinical trial registry number ACTRN12612000830897).

MELATONIN

Melatonin has a core role in maintaining circadian rhythm and is decreased in BD [66]. Melatonergic pathway activity in CNS may be another new and significant treatment target. BD has been associated with altered rhythmicity in body temperature and melatonin rhythms, greater day-to-day variability in activity and sleep timing, and disturbances of sleep or wake cycles and sleep continuity [67]. Melatonin increases the activity of the mitochondrial oxidative phosphorylation, increases the activity of the complexes I and IV dose-dependently, and increases the production of ATP [68]. Moreover, melatonin has antioxidant and anti-inflammatory properties [66].

In a study 8-week trial, participants treated with second generation antipsychotics (N=44), including participants with BD (n=20), were administered melatonin (5mg/day) or placebo. Melatonin treatment associated with less weight gain and lower diastolic blood pressure, especially for the participants with BD [69]. The melatoninprecursor N-acetylserotonin activates TrkB receptors and shows antidepressant like properties in the forced swim test [70].

OTHER TARGETS

New drug targets may be discovered from emerging data from laboratory techniques that analyse data across whole populations (genomics, proteomics, metabolomics). So far they have mainly reconfirmed previously known targets, however as more data is acquired and powerful statistical techniques are applied to the datasets generated by these studies some novel targets may arise. New data is confirming the association between mental health and gut microbiota [71] and modulation of gut microbiota by supplementation or by faecal transplant is a possible future treatment [72]. Intestinal permeability is associated with gut microbiota and inflammation and may also be a potential treatment target [73].

The field of biological psychiatry has exploded and novel targets have resulted. The interactions between a multitude of factors including inflammation, oxidative stress, impaired energy production and decreased neurogenesis are all now implicated in bipolar disorder, in addition to monoamine dysregulation. This biological understanding allows the exploration of new treatments for bipolar disorder. Moreover, the complexity of these factors and their interactions suggests that multi-targeted treatments, covering all of these aspects, may provide the complete relief from symptoms those with BD are desperately seeking.

CONCLUSION

There are many interesting drug targets for BD with even more new targets likely to emerge in the near future. These targets are currently of considerable interest to research. With time some of this research may yield important new treatments and some drug targets that are now considered to be of research interest only will become important targets for drugs used in routine clinical practice. Other drug targets of current interest may ultimately not provide useful new treatments and will cease being of interest. Current research into the biological basis of BD may uncover new drug targets that will be of interest in the future.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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