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Review

Emergent treatments based on the pathophysiology of bipolar disorder: A selective review

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ABSTRACT

Bipolar disorder is a chronic psychiatric disorder that is a cause of significant symptomatology even in the setting of optimal treatment. Most current treatments are developed from serendipity, and not based on known pathophysiology. In this review we examine a number of somatic and pharmacologic therapies that are poised to become part of the armamentarium of interventions to treat bipolar illness. As a group, these interventions are derived from a growing understanding of the biological underpinnings of bipolar disorders. We will look at emergent treatments based on our understanding of the molecular biology, neuroanatomy, and the genetics of bipolar disorder.

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1. Introduction

Bipolar disorder is a debilitating psychiatric disorder estimated to affect between 2% and 5% of the population (Merikangas et al., 2007). For many patients this diagnosis is associated with a chronic and lifelong risk of mood episodes (Angst et al., 2003). In addition to psychiatric symptomatology, this diagnosis is associated with significant risk for suicide, medical comorbidities and increased risk of death from chronic medical illness (Crump et al., 2013). At a societal level, bipolar disorder is associated with tremendous losses in work place productivity (Kessler et al., 2006), and health care spending (Parker et al., 2013).

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Options for the pharmacologic and somatic treatment of bipolar disorder include multiple interventions in the treatment or prevention of mood episodes as recently reviewed by (Geddes and Miklowitz, 2013). To summarize in brief, longstanding clinical experience and evidence support the use of lithium in both the prevention and treatment of mood episodes. Other anticonvulsant medications may have roles in acute treatment or prophylaxis but the evidence for these medications can be contradictory. The use of antipsychotic medications in the acute treatment in mania is accepted but the role of these medications in other phases of illness remains a subject of investigation. Despite these options for pharmacologic treatment, there remains an undeniable need for more effective and better tolerated treatments for these disorders. Even under a program of regular psychopharmacology and psychosocial intervention, a person diagnosed with bipolar disorder type I may only experience months of full remission of symptoms between mood episodes (Perlis et al., 2006). For many patients diagnosed with this disorder, treatment for the depressive phase of illness remains a particularly intractable challenge (see Tondo et al., 2013 for review). For patients with treatment resistant episodes of depression even somatic therapies such as ECT may have a poor chance of achieving remission (Schoeyen et al., 2014).

Many of our current options for treatment of bipolar disorder owe their discovery to combination of fortune, intellectual rigor, and the careful observation of human and animal phenotypes e.g. the discovery of lithium's clinical utility (reviewed in Mitchell and Hadzi-Pavlovic, 2000). This careful observation of behavior is increasingly being supplemented with an improved understanding of the biology of bipolar disorder. Our understanding of the biological underpinnings of bipolar disorder is increasingly reflected in the treatments moving into clinical trials. To reflect this development, we here survey clinical trials of pharmacologic and somatic therapies in bipolar disorder that are based on our understanding of the pathophysiology of bipolar disorder. We define "emergent" therapies as those that do not fall into classes of medications with an established role in the treatment of bipolar disorder (e.g. lithium, antipsychotics, and anti-convulsant medications).

As scientific discoveries in bipolar disorder increase in number, several reviews have attempted to integrate these findings into models of the pathophysiology of bipolar disorder. Recent examples include Maletic and Raison (2014) and Strakowski (2012). Drawing on these reviews, we performed a literature search using NCBI Pubmed searching for MeSH Term "bipolar disorder" AND publication type "clinical trial or controlled clinical trial or randomized trial" plus terms derived from these reviews such as signaling, transcranial magnetic stimulation, glutamate, GABA, neurotrophin, mitochondria, and oxidative. These publications and publications referenced or referenced by them were reviewed and grouped into the major themes described below. We limited our scope to published results of clinical trials of bipolar mood episodes in human subjects because the time gap between animal models and clinical application is significant and will likely render any current review outdated by the time this bench to bedside translation is successful. Although we did not limit our review to trials in symptomatic populations, it was notable that only two of the studies reviewed here explored the maintenance phase of treatment.

We have divided this review to three sections based on themes derived from this literature search: Emergent treatments based on (1) The molecular biology of bipolar disorder, (2) the neuroanatomy of bipolar disorder, and (3) the genetics of bipolar disorder (Table 1).

2. Emergent treatments based on the molecular biology of bipolar disorder

Here we review several clinical studies that are driven by our understanding of how bipolar disorder pathophysiology is influenced by glutamatergic neurotransmission, signal transduction cascades (protein kinase C and estrogen), mitochondrial dysfunction, and oxidative stress.

2.1. Glutamatergic neurotransmission

In recent years a growing body of literature has illuminated the specific role of glutamatergic neurotransmission in the pathophysiology of bipolar mood states. In brief, evidence from in vivo imaging of glutamate and its metabolites as well as postmortem studies of glutamate receptor and glutamate transporter expression implicate glutamate signaling in the pathophysiology of mood disorders (as reviewed in Zarate et al., 2010). The development of the NMDA receptor antagonist ketamine as an antidepressant has attracted considerable interest for both its speed and efficacy in ameliorating depressive episodes. While the bulk of the evidence for ketamine's efficacy as an antidepressant is in studies of unipolar depression, there are now controlled studies demonstrating its utility in treating bipolar disorder. In the first of these studies Diazgranados et al. conducted a randomized placebo-controlled double-blind study of ketamine ability to augment mood stabilizer treatment in 18 bipolar depressed subjects. They observed a significant improvement in depressive symptoms that persisted days after the infusion (Diazgranados et al., 2010). In a follow on study Zarate et al. (2012) replicated these results in another cohort of 15 bipolar depressed subjects. The ability of ketamine to alleviate suicidality has received particular attention and in the latter study the authors noted that suicidality (measured by Montgomery–Asberg Depression Rating Scale) was significantly decreased for several days following treatment.

Other compounds to modify glutamatergic transmission have been studied for clinical use in bipolar disorder. Zarate et al. (2005) conducted an open label study of adding riluzole, which inhibits glutamate release (though it may also be a direct antagonist at NMDA or AMPA receptors) to lithium in a cohort of depressed bipolar patients. In this trial patients were originally treated with lithium for at least one month before having riluzole added to their regimen. The authors noted a significant improvement in depressive symptoms but only 8 subjects were able to complete the 8-week trial. More recently Brennan at al. also conducted an open label study of treating depressed bipolar subjects with riluzole (Brennan et al., 2010). Notably, the subjects of this study also underwent magnetic resonance spectroscopy (MRS) to measure brain glutamate and another metabolite in response to treatment. Concerns about medication effects on glutamate levels led the authors to exclude subjects being treated with lithium. Despite these differences in study population, the authors observed a similar significant improvement in depressive symptoms over the six weeks of treatment with riluzole.

2.2. Protein kinase C signal transduction

Modulation of signal transduction via protein kinase C (PKC) has been implicated in the treatment of bipolar disorder. This idea is in part based on the observation that the mood stabilizers lithium and valproic acid both reduce PKC levels in vivo. Several studies have now tested the hypothesis that direct inhibition of PKC signal transduction using the medication tamoxifen might also have similar efficacy in mood stabilization. Babchuk et al. administered tamoxifen to seven manic subjects, most of whom were not on other psychiatric medications (Bebchuk et al., 2000).