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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.

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).

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

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Conflict of Interest

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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. replicated these results in another cohort of 15 bipolar depressed subjects (Zarate et al., 2012). 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. 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 (Zarate et al., 2005). 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). In this study tamoxifen was associated with a significant reduction in manic symptoms. In a larger follow on study, a cohort of 16 manic subjects was divided into tamoxifen and placebo treatment groups (Zarate et al., 2007). In this study none of the patients were prescribed psychiatric medications other than benzodiazepines. Tamoxifen was significantly more efficacious than placebo in treating manic symptoms. Yildiz et al. conducted a similar, larger study of 66 patients currently in a manic or mixed state randomized to treatment with either tamoxifen or placebo (Yildiz et al., 2008). They observed a similar anti-manic effect. More recently Amrollahi et al. conducted a randomized placebo controlled trial of adding either tamoxifen or placebo to lithium in the treatment of mania (Amrollahi et al., 2011). Tamoxifen did have a significant additive effect when combined with lithium which is particularly notable given the hypothesis that both medications might exert their clinical effect via PKC signaling.

2.3 Hormonal Signaling

In the studies described above tamoxifen was selected for clinical trial use on the basis of its inhibition of PKC and its ability to cross the blood brain barrier. Tamoxifen is much more extensively studied and used clinically as an estrogen receptor antagonist in the treatment of breast cancer. Given tamoxifen's effects on multiple molecular targets, could its anti-manic effect be via estrogen signaling? Kulkarni et al. conducted a study to evaluate these different potential mechanisms of action (Kulkarni et al., 2006). Specifically, they studied a group of women diagnosed with bipolar mania and compared treatment with tamoxifen to medroxyprogesterone (MPA), a progesterone agent known to modulate estrogen production without affecting protein kinase C signal transduction. Kulkarni et al. observed an antimanic effect from both tamoxifen and MPA in the small initial trial. In a larger follow on study comparing the two drugs, only MPA demonstrated significant improvement in manic symptoms and tamoxifen did not separate from placebo (Kulkarni et al., 2014). Of note, the dose of tamoxifen used in the study was lower than that used in studies demonstrating tamoxifen's efficacy in the treatment of mania.

2.4 Mitochondrial function and Oxidative Stress

A growing body of evidence implicates mitochondrial dysfunction in the etiology of bipolar disorder (reviewed in (Clay et al., 2011). This work dovetails with older clinical studies suggesting that enhancing mitochondrial function and energy production can have an antidepressant effect (reviewed in (Wang et al., 2014). Acetyl-L-carnitine (ALCAR) is a highly bioavailable compound that is converted to lcarnitine which facilitates lipid metabolism and energy production in mitochondria. The idea that bipolar disorder may be a disorder of mitochondrial dysfunction (and low energy production) led Brennan et al. to test ALCAR's efficacy in subjects with bipolar depression (Brennan et al., 2013). Brennan et al. conducted a randomized, placebo controlled clinical trial of adding either Acetyl-L-carnitine and α-lipoic acid (to minimize the creation of reactive oxygen species with ALCAR) or placebo to the medication regimen of subjects diagnosed with bipolar disorder (type I or II) that were currently depressed. In this trial ALCAR/ALA treatment did not separate from placebo (Brennan et al., 2013).

Another proposed mechanism for mitochondrial dysfunction giving rise to the pathophysiology of psychiatric illness is via oxidative damage. There is evidence of both decreased mitochondrial activity as well as protein oxidation in postmortem tissues from subjects with bipolar disorder (Andreazza et al., 2010). This finding joins a large body of evidence that oxidative stress may be a common factor in multiple psychiatric disorders (reviewed in (Ng et al., 2008). One hypothesis is that psychiatric disease is associated with oxidative damage incurred in the absence of normal levels of the major antioxidant glutathione. Cysteine is the rate limiting precursor to glutathione. Berk et al. hypothesized that providing n-acetyl cysteine (NAC), a highly bioavailable precursor to cysteine, to bipolar subjects might have a clinical benefit in the amelioration of mood symptoms (Berk et al., 2008). They conducted a double blinded, placebo controlled trial of adding NAC to the current medication regimen of subjects with bipolar depression. In this trial, treatment with NAC was associated with a significant improvement in depressive symptoms (Berk et al., 2008). This trial was followed by larger multi-phase trial: First an open label phase of treatment with NAC, then a double blinded trial in which half the subjects would be switched to placebo. The open label phase of treatment with NAC was associated with a decrease in depressive symptoms (Berk et al., 2011). In this subsequent double blinded study, no significant differences were found between subjects randomized to placebo versus NAC (Berk et al., 2012). An exploratory, placebo controlled study of NAC versus placebo as augmentation to standard medications in the treatment of mania in an outpatient setting favored NAC(Magalhaes et al., 2013).

3. Emergent treatment based on the neuroanatomy of bipolar disorder

Here we review several studies that are driven by our understanding of the neuroanatomical basis of the pathophysiology of bipolar disorder. In brief, a number of experiments in human subjects have suggested dysfunction in neural circuits underlying reward processing, emotion regulation and emotion processing. These findings (reviewed in(Phillips and Swartz, 2014)) suggest dysfunction in a venterolateral prefrontal cortex- hippocampal-amygdala circuit as well as a striatal- obitofrontal and venterolateral prefrontal cortex circuit. In clinical practice, the studies of somatic therapies reviewed below have focused on the the prefrontal cortex as a target of intervention.

3.1 Transcranial Magnetic Stimulation in the treatment of bipolar mania

The development of repetitive transcranial magnetic stimulation (rTMS) has been groundbreaking in its ability to study neuroanatomy and neuroplasticity *in vivo* in human subjects. With the extension of these studies to clinical application, rTMS represents one of the most novel approaches to treating psychiatric illness in decades. While the application of rTMS to the treatment of unipolar depression is becoming widely known and accepted, its use in bipolar disorder has been less studied. Its first use was as adjunctive treatment in subjects with mania. Grisaru et al. conducted the first trial of rTMS to treat patients with bipolar mania as an adjuvant to pharmacologic treatment. Reflecting the uncertainty regarding relevant anatomical targets in this disorder, they compared rTMS directed to the right pre-frontal cortex (PFC) versus left PFC (Grisaru et al., 1998). Their Initial results suggested a beneficial effect to treatment with right prefrontal rTMS A follow-up study

comparing right prefrontal cortex rTMS to sham rTMS treatment did not demonstrate a significant difference and the authors suggested that the initial efficacy observed in Grisaru et al. may actually have been due to left prefrontal TMS treatment worsening mania symptoms instead of right rTMS improving symptoms (Kaptsan et al., 2003). Two other groups reported that right PFC rTMS treatment was associated with improvement in manic symptoms in open label trials without a sham control (Michael and Erfurth, 2004; Saba et al., 2004). Most recently Praharaj et al. conducted a sham controlled trial of right PFC rTMS in bipolar mania and demonstrated significant efficacy in the rTMS group when compared to the sham treatment group (Praharaj et al., 2009). It is worth noting that all of these studies have focused on PFC stimulation with high frequency stimulation thought to increase cortical activity. Studies of other cortical areas and studies using low frequency rTMS (<1Hz) to inhibit cortical activity in bipolar mania have not been published as of this writing.

3.2 Transcranial Magnetic Stimulation in bipolar depression and euthymia

An initial brief report using sham controlled rTMS and a crossover study design demonstrated efficacy of rTMS in the treatment of bipolar depression (Dolberg et al., 2002). Details about the cortical target and the frequency of the stimulus used were unavailable. A study using left PFC excitatory rTMS in a population of patients with bipolar depression demonstrated safety but failed to demonstrated efficacy when comparing sham to actual rTMS treatment (Nahas et al., 2003). More recently Harel et al reported success in an open trial of excitatory TMS delivered by an H-coil “deep TMS” device to the prefrontal cortex to treat bipolar depression (Harel et al., 2011). It remains to be determined if this treatment is significantly more effective than sham treatment. Reports of slow (inhibitory) rTMS targeting the right dorso-lateral pre-frontal cortex (DLPFC) treating unipolar depression prompted Tamas et al. to study a small number of bipolar depressed subjects using this technique(Tamas et al., 2007). This study demonstrated efficacy but was limited in its study size (4 subjects receiving rTMS, one sham control). A larger study of low frequency (inhibitory) right PFC rTMS in treatment resistant depressed bipolar subjects did show some efficacy but this study lacked a sham treatment group (Dell'Osso et al., 2009). These subjects were subsequently followed longitudinally for a year and the authors found that an initial response to rTMS was associated with continued remission at one year to rTMS predicted continued response, albeit in a very small number of subjects. (Dell'osso et al., 2011). Only one study has been published to date using maintenance rTMS in bipolar disorder. Li et al. did a study of using qWeek left PFC stimulatory rTMS in bipolar patients who previously responded to rTMS treatment for depression (Li et al., 2004). The authors were unable to make conclusions about the efficacy of this method given the small number of subjects in the trial.

4. Emergent Treatments based on the genetics of bipolar disorder

With the advent of genome wide association studies (GWAS) for genetic polymorphisms conferring risk for bipolar disorder, our understanding of the genetics of this disorder has improved. These studies have identified a number of common genetic varients in genes that are linked to an increased risk of bipolar disorder. An underlying hope is that these studies

will not simply inform bipolar genetics but the genes identified will lead to an understanding of the molecular pathogenesis of this disorder. These loci of increased risk are linked to polymorphisms in several genes such as *CACNa1c* which encodes a voltage gated calcium channel, *ODZ4* which encodes a cell surface signalling protein, and *NCAN* which encodes a extracellular glycoprotein (reviewed in (Craddock and Sklar, 2013). Work remains to be done to establish a direct link between these polymorphism and increased risk of developing bipolar disorder. Once this is established, we anticipate that an understanding of the function of these proteins and how function is altered by the identified polymorphisms will inform an understanding of the biology of this disorder and lead to improved interventions. In this section we discuss pilot work into a pharmacologic intervention informed directly from these GWAS studies. We also describe the impact of pharmacogenetics- the way an individual's genetic code informs our choice of medication and our expectations about the efficacy of the treatment.

4.1 Therapeutic targets derived from GWAS studies

In 2008 it was demonstrated that a single nucleotide polymorphism (SNP) in an intron of the *CACNa1c* gene conveyed an increased risk for developing bipolar disorder(Ferreira et al., 2008; Sklar et al., 2008). This was the first SNP discovered that met genome-wide significance for the development of bipolar disorder. The *CACNa1c* gene encodes a voltage gated calcium channel and this result dovetailed with pre-existing hypotheses suggesting a role for calcium channel dysfunction in the pathogenesis of bipolar disorder (reviewed in (Casamassima et al., 2010). This initial result has been followed by further studies exploring the role of this SNP in the development of other psychiatric disorders (Green et al., 2010). While an exciting finding, the identification of this SNP did not suggest a specific mechanism linking channel activity to disease pathology. Fundamental questions such as “does this SNP contribute to the pathogenesis of bipolar disorder via an inappropriate increase or decrease in calcium influx?” remain unanswered. A recent trial of the calcium channel blocker isradipine in bipolar depression represents an initial effort to explore these questions in a clinical setting (Ostacher et al., 2014). This study was designed to establish the safety of this medication with respect to mood symptoms in a cohort of subjects with bipolar disorder. While not a controlled study and with a low completion (only 4 participants completed the study), the preliminary data was suggestive that isradipine was safe and possibly efficacious in treating bipolar depression. At the time of this writing, the study authors are currently recruiting for a larger, controlled trial of adding isradipine to lithium or valproic acid for the treatment of bipolar depression (NCT01784666 at www.clinicaltrials.gov).

4.2 Pharmacogenomics

A less popularly publicized effort to translate genetic research from bench to the bedside is the ongoing effort to understand the genetic determinants of response to existing medications. The current progress in this endeavor is extensively reviewed in (Geoffroy et al., 2014) and (Rybakowski, 2013) and are only briefly summarized here. The overwhelming majority of these studies have to date focused on finding genetic contributors to lithium responsiveness and have typically used a candidate gene approach reviewed in (Rybakowski, 2013). A handful of studies have applied this candidate gene approach to

studies of other mood stabilizers and atypical antipsychotics (reviewed in (Geoffroy et al., 2014)). More recently a number of GWAS studies have been published look for polygenic contributors to lithium response. Perlis et al. identified several genetic loci with an association to lithium response in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study (Perlis et al., 2009). Squassina et al. identified several SNPs with an association to lithium response and particularly highlighted the identification of a SNP located in an intron of the *ACCN1* gene that encodes a lithium permeable ion channel (Squassina et al., 2011). Very recently a report from Chen et al. identified two SNPs in patients of Han Chinese ancestry that were strongly associated with lithium response. These SNPs are located in introns of *GADL1*, the gene encoding glutamic acid decarboxylase-like protein 1(Chen et al., 2014). As with many other GWAS studies, these results were published with a replication sample but replication by an independent group has yet to be achieved e.g.(Consortium on Lithium et al., 2014).

5. Conclusion

In this review we have attempted to review medications and somatic therapies that are poised to become treatment options for bipolar disorder in the near future. Looking over the studies cited there is a clear trend towards small sample sizes and heterogeneous study design.. It remains unclear which of these new therapeutic approaches will prove efficacious in the replication studies necessary to become accepted treatments in the field.

This review is organized around the principle that our understanding of bipolar disorder as a disease is informing the development of new therapeutics. We could also imagine a variation on this principle: that the next stage of development of these therapies will be based upon our understanding of bipolar disorder as a spectrum of illnesses influenced by a multitude of factors. In every study in which individual responses to an intervention were reported, one observes subjects who responded robustly, those with a small response and even some subjects who worsened clinically. Inherent in these data is the fact that unmeasured variables allowed some subjects to respond robustly. It could be imagined that the next stage in therapeutic development will actually be not in new or different drugs but rather in the discovery of those unmeasured variables. The pharmacogenomics section above may be the best existing model of how this discovery process could interact with existing treatments but this is just one of many ways of characterizing bipolar illnesses. It may be that future studies will demonstrate that riluzole is an effective antidepressant in subjects who showed the best response to ketamine infusion. We may learn that all of the depressed bipolar rTMS responders are characterized by abnormal connectivity between the DLPFC and other brain regions while depressed. In the laboratory, research to elucidate unmeasured variables that have a biological basis (biomarkers) is the subject of intense effort from many different approaches. The promise of these efforts is to better understand the illness being treated but also to focus efforts to develop future therapeutics. The stratification of patient populations by biomarkers could allow hypothesis / clinical intervention testing with smaller sample sizes. Moving away from the research study and into the clinic, we can think of this idea broadly as “personalized medicine”. It many ways psychiatry has fully embraced how an individual's developmental history, personal circumstances, social structure and other factors deeply influence clinical presentation. The medication or somatic therapy prescribed

may be the least individual-specific part of a psychiatric visit. It seems likely that the future will be one of psychopharmacology and somatic therapies catching up to the already highly personal psychiatric visit.

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Highlights

- Emergent treatments draw upon advances in our understanding of bipolar disorder.
- Several neuroscience based interventions have entered clinical trials.
- New medications target glutamate, oxidative damage, PKC and hormonal signaling.
- TMS has been evaluated for the treatment of both bipolar depression and depression.
- GWAS studies have led to a novel clinical trial of a calcium channel blocker.

Study	Intervention	Subject Number & Trial Design	Subject Population
		Clinical Trials Based on Molecular Biology	
Diazgranados et al., 2010	ketamine 0.5mg/kg versus placebo	18 subjects in crossover trial	8 BPD type I, 10 BPD type II, all depressed
Zarate et al., 2012	ketamine 0.5mg/kg versus placebo	15 subjects in crossover trial	9 BPD type I, 6 BPD type II, all depressed
Zarate et al., 2005	riluzole 50mg-200mg daily	14 subjects in open label trial	6 BPD type I, 8 BPD type II, all depressed
Brennan et al., 2010	riluzole 100mg-200mg daily	14 subjects in open label trial	4 BPD type I, 10 type II, all depressed
Bebchuk et al., 2000	tamoxifen 80mg daily	7 subjects in open label trial	7 BPD, all manic
Zarate et al., 2007	tamoxifen 20-140mg/day	16 subjects in placebo controlled trial (8 in placebo arm)	16 BPD, all manic or mixed
Yildiz et al., 2008	tamoxifen 80mg daily	66 subjects in placebo controlled trial (31 in placebo arm)	66 BPD, type I, all manic or mixed
Amrollahi et al., 2011	lithium plus tamoxifen 80mg vs lithium plus placebo	40 subjects in placebo controlled trial (20 each arm)	40 subjects diagnosed with mania
Kulkarni et al., 2006	tamoxifen 40mg vs MPA 20mg vs placebo	13 subjects in placebo controlled trial (5 tamoxifen, 4 MPA, 4 placebo)	13 BPD subjects, all manic or hypomanic
Kulkarni et al., 2014	tamoxifen 40mg vs MPA 20mg vs placebo	51 subjects in placebo controlled trial (15 tamoxifen, 18 MPA, 18 placebo)	42 BPD subjects, 9 schizoaffective subjects, all manic
Brennan et al., 2013	plus ALA 600 to 1800 mg daily versus placebo	40 subjects in placebo controlled trial (20 each arm)	30 BPD type I, 10 BPD type II, all depressed
Berk et al., 2008	NAC 1g BID vs placebo	75 subjects in placebo controlled trial (37 placebo)	75 BPD type I or II, varoius mood states
Berk et al., 2011	NAC 1g BID	148 subjects in open label trial	103 BPD type I, 44 BPD type II, 1 BPD NOS, all depressed
Berk et al., 2012	NAC 2g / day vs placebo	148 subjects in placebo controlled trial (76 NAC, 72 placebo)	103 BPD type I, 44 BPD type II, 1 BPD NOS, all depressed
Magalhaes et al., 2013	NAC 2g / day vs placebo	15 subjects in placebo controlled trial (7 placebo)	15 BPD type I or II, all hypomanic or manic
		Clinical Trials Based on Neuroanatomy	
Grisaru et al., 1998	right vs left prefrontal rapid TMS	16 subjects in open study (7 right, 9 left)	16 subjects with mania
Kapstan et al., 2003	right prefrontal rapid TMS vs sham	19 subjects in sham controlled trial (11 tMS, 8 sham)	19 subjects with mania
Michael and Erfurth, 2004	right prefrontal rapid TMS	9 subjects in open study	9 BPD type I, all manic
Saba et al., 2004	right DLPFC rapid TMS	8 subjects in open study	8 BPD type I, all manic
Praharaj et al., 2009	right DLPFC rapid TMS vs sham	41 subjects in sham controlled trial (21 TMS, 20 sham)	41 BPD subjects, all manic
Dolberg et al., 2002	TMS vs sham TMS	20 subjects in sham controlled trial (10 TMS, 10 sham then TMS)	20 BPD subjects, all depressed
Nahas et al., 2003	left prefrontal rapid TMS vs sham	23 subjects in sham controlled trial (11 TMS, 12 sham)	23 subjects (12 BPI depressed, 9 BPII depressed, 2 BPI mixed)
Tamas et al., 2007	right DLPFC slow TMS vs sham	5 subjects in sham controlled trial (4 TMS, 1 sham)	5 BPD type I, all depressed
Dell'Osso et al., 2009	right DLPFC slow TMS	11 subjects in open study	11 subjects (5 type I, 6 type II)

Study	Intervention	Subject Number & Trial Design	Subject Population
Li et al., 2004	weekly left prefrontal rapid TMS	7 subjects in open study	7 subjects (3 type I, 1 type II)
Harel et al., 2011	left prefrontal rapid “deep” TMS	19 subjects in open study	19 Bipolar subjects, all depressed
		Clinical Trials Based on Genetics	
Ostacher et al., 2014	isradipine 10mg BID	10 subjects in open study	7 BPD type I, 3 BPD type II, all depressed